Medicines Information Services
Information on any aspect of drug therapy can be obtained from Regional and District Medicines Information Services. Details regarding the local services provided within your Region can be obtained by telephoning the following numbers.

England
Birmingham: (0121) 424 7298
Bristol: (0117) 342 2867
Ipswich: (01473) 704 431
Leeds: (0113) 206 5377
Leicester: (0116) 255 779/258 6491
Liverpool: (0151) 794 8113/4/5/7, or (0151) 795 8206
London:
  Guy’s Hospital (020) 7188 8750, or (020) 7188 3849, or (020) 7188 3855
  Northwick Park Hospital (020) 8869 2761, or (020) 8869 3973
Newcastle: (0191) 282 4631
Southampton: (023) 8120 6908/9

Wales
Cardiff: (029) 2074 2979, or (029) 2074 2251

Scotland
Aberdeen: (01224) 552 316
Dundee: (01382) 632 351, or (01382) 660 111 Extn 32351
Edinburgh: (0131) 242 2920
Glasgow: (0141) 211 4407

Northern Ireland
Belfast: (028) 9063 2032, or (028) 9063 3847

Republic of Ireland
Dublin: (Dublin) 473 0589, or (Dublin) 453 7941 Extn 2348

United Kingdom Medicines Information Pharmacists Group (UKMIPG) website
www.ukmi.nhs.uk

Telephone numbers and email addresses of manufacturers listed in BNF Publications are shown in Index of Proprietary Manufacturers

UK Teratology Information Service
Information on drug and chemical exposures in pregnancy. Tel: 0844 892 0909

Information on drug therapy relating to dental treatment can be obtained by telephoning
Liverpool: (0151) 794 8206

Driver and Vehicle Licensing Agency (DVLA)
Information on the national medical guidelines of fitness to drive is available from: www.gov.uk/government/publications/at-a-glance

Patient Information Lines
NHS Urgent Care Services 111

Poisons Information Services
UK National Poisons Information Service 0844 892 0111

Sport
Information on substances currently permitted or prohibited is provided in a card supplied by UK Anti-doping. Further information regarding medicines in sport is available from: www.ukad.org.uk
Tel: (020) 7766 7350 information@ukad.org.uk

Travel Immunisation
Up-to-date information on travel immunisation requirements may be obtained from:
National Travel Health Network and Centre (for healthcare professionals only) 0845 602 6712 (09.00–12.00 and 14.00–16.30 hours weekdays)
Travel Medicine Team, Health Protection Scotland (0141) 300 1130 (14.00–16.00 hours weekdays)
www.travax.nhs.uk (for registered users of the NHS website Travax only)
Welsh Government Switchboard English language 0300 0603300 (09.00–17.30 hours weekdays only)
Welsh Government Switchboard Yr laith Gymraeg 0300 0604400 (09.00–17.30 hours weekdays only)
Department of Health and Social Services (Belfast) (028) 9052 2118 (weekdays)

List of Registered Medical Practitioners
Details on whether doctors are registered and hold a licence to practise medicine in the UK can be obtained from the General Medical Council.
Tel: (0161) 923 6602
www.gmc-uk.org/register

Travel Immunisation
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Tel: (0161) 923 6602
www.gmc-uk.org/register
Access the BNF your way

The *British National Formulary* (BNF) and *BNF for Children* are updated monthly online via MedicinesComplete, ensuring healthcare professionals always have the latest prescribing advice.

You can be alerted to all the latest updates by signing up to the BNF eNewsletter at www.bnf.org/newsletter.

**ONLINE**

- **BNF on MedicinesComplete**
  Access BNF and *BNF for Children* on MedicinesComplete and receive the very latest drug information through monthly online updates.

- **BNF on FormularyComplete**
  Create, edit and manage your own local formulary content built upon the trusted prescribing advice of the BNF and *BNF for Children*.

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- **BNF app** – Stay up to date anywhere with the BNF app available for iOS, Android and Blackberry.
- **BNF eBook** – Available as an ePDF via a range of suppliers. See www.pharmpress.com/bnf.
- **BNF on MedicinesComplete** – Now mobile responsive.

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- **BNF subscription** – if you prefer to access BNF in print, take advantage of our subscription option. We will send you the new BNF as soon as the book is published. One or two year packages (including or excluding BNFC) are available. Discounted pricing is also available on bulk sales.

**BNF on Evidence Search**
Search the BNF and *BNF for Children* alongside other authoritative clinical and non-clinical evidence and best practice at http://evidence.nhs.uk from NICE.
How to purchase

Purchase direct from Pharmaceutical Press by visiting
www.pharmpress.com/bnf

For enquiries about the BNF or BNFC in print, contact
direct@macmillan.co.uk
Tel: +44 (0) 1256 302 699

For enquiries concerning MedicinesComplete, BNF on FormularyComplete, or bulk orders of the print edition, contact
pharmpress@rpharms.com
Tel: +44 (0) 20 7572 2266

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For pricing information please visit the website at
www.pharmpress.com/bnf

For international sales contact your local sales agent. Contact details at www.pharmpress.com/agents

Stay up to date – sign up to the BNF eNewsletter at
www.bnf.org/newsletter

NICE have altered their distribution arrangement for England, and eligible health professionals will now receive one free print copy of BNF a year - the September issue - to supplement online access. To buy your copy/ies of the March BNF direct, go to www.pharmpress.com/bnf.
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September 2015
–March 2016

ROYAL PHARMACEUTICAL SOCIETY

BMA
Preface

The BNF is a joint publication of the British Medical Association and the Royal Pharmaceutical Society. It is published under the authority of a Joint Formulary Committee which comprises representatives of the two professional bodies, the UK Health Departments, the Medicines and Healthcare products Regulatory Agency, and a national guideline producer. The Dental Advisory Group overseas the preparation of advice on the drug management of dental and oral conditions; the Group includes representatives of the British Dental Association and a representative from the UK Health Departments. The Nurse Prescribers’ Advisory Group advises on the content relevant to nurses and includes representatives from different parts of the nursing community and from the UK Health Departments.

The BNF aims to provide prescribers, pharmacists, and other healthcare professionals with sound up-to-date information about the use of medicines.

The BNF includes key information on the selection, prescribing, dispensing and administration of medicines. Medicines generally prescribed in the UK are covered and those considered less suitable for prescribing are clearly identified. Little or no information is included on medicines promoted for purchase by the public.

Information on drugs is drawn from the manufacturers’ product literature, medical and pharmaceutical literature, UK health departments, regulatory authorities, and professional bodies. Advice is constructed from clinical literature and reflects, as far as possible, an evaluation of the evidence from diverse sources. The BNF also takes account of authoritative national guidelines and emerging safety concerns. In addition, the editorial team receives advice on all therapeutic areas from expert clinicians; this ensures that the BNF’s recommendations are relevant to practice.

The BNF is designed as a digest for rapid reference and it may not always include all the information necessary for prescribing and dispensing. Also, less detail is given on areas such as obstetrics, malignant disease, and anaesthesia since it is expected that those undertaking treatment will have specialist knowledge and access to specialist literature. BNF for Children should be consulted for detailed information on the use of medicines in children. The BNF should be interpreted in the light of professional knowledge and supplemented as necessary by specialised publications and by reference to the product literature. Information is also available from medicines information services, see Medicines Information Services.

It is important to use the most recent BNF information for making clinical decisions. The print edition of the BNF is updated in March and September each year. Monthly updates are provided online via Medicines Complete and the NHS Evidence portal. The more important changes are listed under Changes; changes listed online are cumulative (from one print edition to the next), and can be printed off each month to show the main changes since the last print edition as an aide memoire for those using print copies.

The BNF Publications website (www.bnf.org) includes additional information of relevance to healthcare professionals. Other digital formats of the BNF—including versions for mobile devices and integration into local formularies—are also available.
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Acknowledgements

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How BNF publications are constructed

The BNF is unique in bringing together authoritative, independent guidance on best practice with clinically validated drug information, enabling healthcare professionals to select safe and effective medicines for individual patients.

Information in the BNF has been validated against emerging evidence, best-practice guidelines, and advice from a network of clinical experts.

Hundreds of changes are made between print editions, and are published monthly in some digital formats. The most clinically significant updates are listed under Changes p. xv.

Joint Formulary Committee
The Joint Formulary Committee (JFC) is responsible for the content of the BNF. The JFC includes doctors appointed by the BMJ Group, pharmacists appointed by the Royal Pharmaceutical Society, nursing and lay representatives; there are also representatives from the Medicines and Healthcare products Regulatory Agency (MHRA), the UK Health Departments, and a national guideline producer. The JFC decides on matters of policy and reviews amendments to the BNF in the light of new evidence and expert advice.

Dental Advisory Group
The Dental Advisory Group oversees the preparation of advice on the drug management of dental and oral conditions; the group includes representatives from the British Dental Association and a representative from the UK Health Departments.

Nurse Prescribers’ Advisory Group
The Nurse Prescribers’ Advisory Group oversees the list of drugs approved for inclusion in the Nurse Prescribers’ Formulary; the group includes representatives from a range of nursing disciplines and stakeholder organisations.

Editorial Team
BNF clinical writers have all worked as pharmacists and have a sound understanding of how drugs are used in clinical practice. Each clinical writer is responsible for editing, maintaining, and updating BNF content. During the publication cycle the clinical writers review information in the BNF against a variety of sources.

Amendments to the text are drafted when the clinical writers are satisfied that any new information is reliable and relevant. The draft amendments are passed to expert advisers for comment and then presented to the Joint Formulary Committee for consideration. Additionally, sections are regularly chosen for thorough review. These planned reviews aim to verify all the information in the selected sections and to draft any amendments to reflect the current best practice.

Clinical writers prepare the text for publication and undertake a number of checks on the knowledge at various stages of the production.

Expert advisers
The BNF uses about 60 expert clinical advisers (including doctors, pharmacists, nurses, and dentists) throughout the UK to help with clinical content. The role of these expert advisers is to review existing text and to comment on amendments drafted by the clinical writers. These clinical experts help to ensure that the BNF remains reliable by:
- commenting on the relevance of the text in the context of best clinical practice in the UK;
- checking draft amendments for appropriate interpretation of any new evidence;
- providing expert opinion in areas of controversy or when reliable evidence is lacking;
- advising on areas where the BNF diverges from summaries of product characteristics;
- providing independent advice on drug interactions, prescribing in hepatic impairment, renal impairment, pregnancy, breast-feeding, children, the elderly, palliative care, and the emergency treatment of poisoning.

In addition to consulting with regular advisers, the BNF calls on other clinical specialists for specific developments when particular expertise is required.

The BNF works closely with a number of expert bodies that produce clinical guidelines. Drafts or pre-publication copies of guidelines are routinely received for comment and for assimilation into the BNF.

Sources of BNF information
The BNF uses a variety of sources for its information; the main ones are shown below.

Summaries of product characteristics
The BNF receives summaries of product characteristics (SPCs) of all new products as well as revised SPCs for existing products. The SPCs are the principal source of product information and are carefully processed, despite the ever-increasing volume of information being issued by the pharmaceutical industry. Such processing involves:
- verifying the approved names of all relevant ingredients including ‘non-active’ ingredients (the BNF is committed to using approved names and descriptions as laid down by the Human Medicines Regulations 2012);
- comparing the indications, cautions, contra-indications, and side-effects with similar existing drugs. Where these are different from the expected pattern, justification is sought for their inclusion or exclusion;
- seeking independent data on the use of drugs in pregnancy and breast-feeding;
- incorporating the information into the BNF using established criteria for the presentation and inclusion of the data;
- checking interpretation of the information by a second clinical writer before submitting to a content manager; changes relating to doses receive an extra check;
- identifying potential clinical problems or omissions and seeking further information from manufacturers or from expert advisers;
- careful validation of any areas of divergence of the BNF from the SPC before discussion by the Committee (in the light of supporting evidence);
- constructing, with the help of expert advisers, a comment on the role of the drug in the context of similar drugs.

Much of this processing is applicable to the following sources as well.

Literature
Clinical writers monitor core medical and pharmaceutical journals. Research papers and reviews relating to drug therapy are carefully processed. When a difference between the advice in the BNF and the paper is noted, the new information is assessed for reliability and relevance to UK clinical practice. If necessary, new text is drafted and discussed with expert advisers and the Joint Formulary Committee. The BNF enjoys a close working relationship with a number of national information providers.

Systematic reviews
The BNF has access to various databases of systematic reviews (including the Cochrane Library and various web-
based resources). These are used for answering specific queries, for reviewing existing text, and for constructing new text. Clinical writers receive training in critical appraisal, literature evaluation, and search strategies. Reviews published in Clinical Evidence are used to validate BNF advice.

**Consensus guidelines**

The advice in the BNF is checked against consensus guidelines produced by expert bodies. A number of bodies make drafts or pre-publication copies of the guidelines available to the BNF; it is therefore possible to ensure that a consistent message is disseminated. The BNF routinely processes guidelines from the National Institute for Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC), and the Scottish Intercollegiate Guidelines Network (SIGN).

**Reference sources**

Textbooks and reference sources are used to provide background information for the review of existing text or for the construction of new text. The BNF team works closely with the editorial team that produces *Martindale: The Complete Drug Reference*. The BNF has access to *Martindale* information resources and each team keeps the other informed of significant developments and shifts in the trends of drug usage.

**Statutory information**

The BNF routinely processes relevant information from various Government bodies including Statutory Instruments and regulations affecting the Prescriptions only Medicines Order. Official compendia such as the British Pharmacopoeia and its addenda are processed routinely to ensure that the BNF complies with the relevant sections of the Human Medicines Regulations 2012.

The BNF maintains close links with the Home Office (in relation to controlled drug regulations) and the Medicines and Healthcare products Regulatory Agency (including the British Pharmacopoeia Commission). Safety warnings issued by the Commission on Human Medicines (CHM) and guidelines on drug are issued by the UK health departments are processed as a matter of routine.

Relevant professional statements issued by the Royal Pharmaceutical Society are included in the BNF as are guidelines from bodies such as the Royal College of General Practitioners.

The BNF reflects information from the Drug Tariff, the Scottish Drug Tariff, and the Northern Ireland Drug Tariff.

**Medicines and devices**

NHS Prescription Services (from the NHS Business Services Authority) provides non-clinical, categorical information (including prices) on the medicines and devices included in the BNF.

**Comments from readers**

Readers of the BNF are invited to send in comments. Numerous letters and emails are received by the BNF team. Such feedback helps to ensure that the BNF provides practical and clinically relevant information. Many changes in the presentation and scope of the BNF have resulted from comments sent in by users.

**Comments from industry**

Close scrutiny of BNF by the manufacturers provides an additional check and allows them an opportunity to raise issues about BNF’s presentation of the role of various drugs; this is yet another check on the balance of BNF’s advice. All comments are looked at with care and, where necessary, additional information and expert advice are sought.

**Market research**

Market research is conducted at regular intervals to gather feedback on specific areas of development, such as drug interactions or changes to the way information is presented in digital formats.

**Overview**

The BNF is an independent professional publication that is kept up-to-date and addresses the day-to-day prescribing information needs of healthcare professionals. Use of this resource throughout the health service helps to ensure that medicines are used safely, effectively, and appropriately.
How to use the BNF

This edition of the BNF marks a fundamental change to the structure of the content. The changes have been made to bring consistency and clarity to BNF content, and to the way that the content is arranged within print and digital products, increasing the ease with which information can be found.

For this print edition, the most notable changes include:
— Drug monographs – where possible, all information that relates to a single drug is now contained within its drug monograph, moving information previously contained in the prescribing notes. Drug monographs have also changed structurally: additional sections have been added, ensuring greater regularity around where information is located within the publication.
— Drug-class monographs – where substantial amounts of information is common to all drugs within a drug class (e.g. macrolides, p. 469), a drug-class monograph has been created to contain the common information.
— Medicines – categorical information about marketed medicines, such as price and pack size, continues to be sourced directly from the Dictionary of Medicines and Devices provided by the NHS Business Services Authority. However, clinical information curated by the BNF team has been clearly separated from the categorical pricing and pack size information and is included in the relevant section of the drug monograph.
— Section numbering – the BNF section numbering has been removed. This section numbering tied the content to a rigid structure and enforced the retention of defunct classifications, such as mercurial diuretics, and hindered the relocation of drugs where therapeutic use had altered. It also caused constraints between the BNF and BNF for Children, where drugs had different therapeutic uses in children.
— Appendix 4 – the content has been moved to individual drug monographs. The introductory notes have been replaced with a new guidance section, Guidance on intravenous infusions, p. 14.

Introduction

In order to achieve the safe, effective, and appropriate use of medicines, healthcare professionals must be able to use the BNF effectively, and keep up to date with significant changes in the BNF that are relevant to their clinical practice. This How to Use the BNF is key in introducing the new structure of the BNF to all healthcare professionals involved with prescribing, monitoring, supplying, and administering medicines, as well as supporting the learning of students training to join these professions.

Structure of the BNF

This new BNF broadly follows the high-level structure of previous editions:
Front matter, comprising information on how to use the BNF, the significant content changes in each edition, and guidance on various prescribing matters (e.g. prescription writing, the use of intravenous drugs, particular considerations for special patient populations);
Chapters, containing drug monographs describing the uses, doses, safety issues and other considerations involved in the use of drugs; class monographs; and treatment summaries, covering guidance on the selection of drugs. Monographs and treatment summaries are divided into chapters based on specific aspects of medical care, such as Chapter 5, Infections, or Chapter 16, Emergency treatment of poisoning; or drug use related to a particular system of the body, such as Chapter 2, Cardiovascular.
Within each chapter, content is organised alphabetically by therapeutic use (e.g. Respiratory disease, obstructive), with the treatment summaries first (e.g. asthma), followed by the monographs of the drugs used to manage the conditions discussed in the treatment summary. Within each therapeutic use, the drugs are organised alphabetically by classification (e.g. Antimuscarinics, Beta,-agonist bronchodilators) and then alphabetically within each classification (e.g. Acetylcholine, Glycopyrronium bromide, Ipratropium bromide).

Appendices, covering interactions, borderline substances, cautionary and advisory labels, and woundcare.
Back matter, covering the lists of medicines approved by the NHS for Dental and Nurse Practitioner prescribing, proprietary and specials manufacturer’s contact details, and the index. Yellow cards are also included, to facilitate the reporting of adverse events, as well as quick reference guides for life support and key drug doses in medical emergencies, for ease of access.

Navigating the BNF

The contents page provides the high-level layout of information within the BNF; and in addition, each chapter begins with a small contents section, describing the therapeutic uses covered within that chapter. Once in a chapter, location is guided by the side of the page showing the chapter number (the thumbnail), alongside the chapter title. The top of the page includes the therapeutic use (the running head) alongside the page number.

On one page, visual cues aid navigation: treatment summary information is in black type, with therapeutic use titles similarly styled in black, whereas the use of colour indicates drug-related information, including drug classification titles, class monographs, and drug monographs.
Although navigation is possible by browsing, primarily access to the information is via the index, which covers the titles of drug class monographs, drug monographs, and treatment summaries; as well as the names of branded medicines and other topics of relevance, such as abbreviations, guidance sections, tables, and images.

Content types
Treatment summaries

Treatment summaries are of three main types;
— an overview of delivering a drug to a particular body system (e.g. Skin conditions, management, p. 998),
— a comparison between a group or groups of drugs (e.g. Beta-adrenoceptor blocking drugs, p. 139),
— an overview of the drug management or prophylaxis of common conditions intended to facilitate rapid appraisal of options (e.g. Hypertension, p. 121, or Malaria, prophylaxis, p. 528).

In order to select safe and effective medicines for individual patients, information in the treatment summaries must be used in conjunction with other prescribing details about the drugs and knowledge of the patient’s medical and drug history.

Monographs

Overview

In previous editions, a systemically administered drug with indications for use in different body systems was split across the chapters relating to those body systems body systems. So, for example, codeine phosphate was found in chapter 1, for its antiemetic effects and chapter 4 for its analgesic effects. However, the monograph in chapter 1 contained only the dose and some selected safety precautions.

In this new BNF all of the information for the systemic use of a drug is contained within one monograph, so codeine phosphate is now included in chapter 4. This
carries the advantage of providing all of the information in one place, so the user does not need to flick back and forth across several pages to find all of the relevant information for that drug. Cross references are included in chapter 1, where the management of diarrhoea is discussed, to the drug monograph to assist navigation.

Where drugs have systemic and local uses, for example, chloramphenicol, and the considerations around drug use are markedly different according to the route of administration, the monograph is split, as with previous editions, into the relevant chapters.

This means that the majority of drugs will still be placed in the same chapters and sections as previous editions, and although there may be some variation in order, all of the relevant information will be easier to locate.

One of the most significant changes to the monograph structure is the increased granularity, with a move from around 9 sections over 20 sections; sections are only included when relevant information has been identified. The following information describes these sections and their uses in more detail.

**Nomenclature**

Monograph titles follow the convention of recommended international non-proprietary names (rINNs), or, in the absence of a rINN, British Approved Names. Relevant synonyms are included below the title, and in some instances a brief description of the drug action is included. Over future editions these drug action statements will be rolled out for all drugs.

In some monographs, immediately below the nomenclature or drug action, there are a number of cross references or flags used to signpost the user to any additional information they need to consider about a drug. This is most common for drugs formulated in combinations, where users will be signposted to the monographs for the individual ingredients (e.g. Ispaghula husk with senna, p. 54) or for drugs that are related to a class monograph (see Class monographs, below).

**Indication and dose**

User feedback has highlighted that one of the main uses of the BNF is identifying indications and doses of drugs. Therefore in this edition, indication and dose information has been promoted to the top of the monograph and highlighted by a coloured panel to aid quick reference.

The indication and dose section is more highly structured than in previous editions, giving greater clarity around which doses should be used for which indications and by which route. In addition, if the dose varies with a specific indication and dose panel, under a heading of the preparation name.

Doses are either expressed in terms of a definite frequency (e.g. 1 g 4 times daily) or in the total daily dose format (e.g. 6 g daily in 3 divided doses); the total daily dose should be divided into individual doses (in the second example, the patient should receive 2 g 3 times daily).

Doses for specific patient groups (e.g. the elderly) may be included if they are different to the standard dose. Doses for children can be identified by the relevant age range and may vary according to their age or body-weight.

In previous editions of the BNF, age ranges and weight ranges overlapped. For clarity and to aid selection of the correct dose, wherever possible the age and weight ranges now do not overlap. When interpreting age ranges it is important to understand that a patient is considered to be 64 up until the point of their 65th birthday, meaning that an age range of adult 18 to 64 is applicable to a patient from the day of their 18th birthday until the day before their 65th birthday. All age ranges should be interpreted in this way. Similarly, when interpreting weight ranges, it should be understood that a weight range of 35 to 59kg is applicable to a patient as soon as they tip the scales at 35kg right up until, but not including, the point that the scales tip to 60kg. All weight ranges should be interpreted in this way.

In all circumstances, it is important to consider the patient in question and their physical condition, and select the dose most appropriate for the individual.

**Other information relevant to indication and dose**

The dose panel also contains, where known, an indication of pharmacokinetic considerations that may affect the choice of dose, and dose equivalence information, which may aid the selection of dose when switching between drugs or preparations.

The BNF includes unlicensed use of medicines when the clinical need cannot be met by licensed medicines; such use should be supported by appropriate evidence and experience. When the BNF recommends an unlicensed medicine or the ‘off-label’ use of a licensed medicine, this is shown below the indication and dose panel in the unlicensed use section.

**Minimising harm and drug safety**

The drug chosen to treat a particular condition should minimise the patient’s susceptibility to adverse effects and, where co-morbidities exist, have minimal detrimental effects on the patient’s other diseases. To achieve this, the Contra-indications, Cautions and Side-effects of the relevant drug should be reviewed.

The information under Cautions can be used to assess the risks of using a drug in a patient who has co-morbidities that are also included in the Cautions for that drug—if a safer alternative cannot be found, the drug may be prescribed while monitoring the patient for adverse-effects or deterioration in the co-morbidity. Contra-indications are far more restrictive than Cautions and mean that the drug should be avoided in a patient with a condition that is contra-indicated.

The impact that potential side-effects may have on a patient’s quality of life should also be assessed. For instance, in a patient who has difficulty sleeping, it may be preferable to avoid a drug that frequently causes insomnia.

Clinically relevant Side-effects for drugs are included in the monographs or class monographs. Side-effects are listed in order of frequency, where known, and arranged alphabetically. The frequency of side-effects follows the regulatory standard:

- Very common — occurs more frequently than 1 in 10 administrations of a drug
- Common — occurs between 1 in 10 and 1 in 100 administrations of a drug
- Uncommon — between 1 in 100 and 1 in 1,000 administrations of a drug
- Rare — between 1 in 1,000 and 1 in 10,000 administrations of a drug
- Very rare — occurs less than 1 in 10,000 administrations of a drug
- Frequency not known

An exhaustive list of side-effects is not included, particularly for drugs that are used by specialists (e.g. cytotoxic drugs and drugs used in anaesthesia). The BNF also omits effects that are likely to have little clinical consequence (e.g. transient increase in liver enzymes). Recognising that hypersensitivity reactions can occur with virtually all medicines, this effect is generally not listed, unless the drug carries an increased risk of such reactions, when the information is included under Allergy and cross sensitivity.

The Important safety advice section in the BNF, delineated by a coloured outline box, highlights important safety concerns, often those raised by regulatory authorities or guideline producers. Safety warnings issued by the Commission on Human Medicines (CHM) or Medicines and
Healthcare products Regulatory Agency (MHRA) are found here. Drug selection should aim to minimise drug interactions. If it is necessary to prescribe a potentially serious combination of drugs, patients should be monitored appropriately. The mechanisms underlying drug interactions are explained in Appendix 1 p. 1137, followed by details of drug interactions.

**Use of drugs in specific patient populations**

Drug selection should aim to minimise the potential for drug accumulation, adverse drug reactions, and exacerbation of pre-existing hepatic or renal disease. If it is necessary to prescribe drugs whose effect is altered by hepatic or renal disease, appropriate drug dose adjustments should be made, and patients should be monitored adequately. The general principles for prescribing are outlined under Prescribing in Hepatic Impairment p. 17, and Prescribing in Renal Impairment p. 17. Information about drugs that should be avoided or used with caution in hepatic disease or renal impairment can be found in drug monographs under Hepatic impairment and Renal impairment (e.g. fluconazole p. 518).

Similarly, drug selection should aim to minimise harm to the fetus, nursing infant, and mother. The infant should be monitored for potential side-effects of drugs used by the mother during pregnancy or breast-feeding. The general principles for prescribing are outlined under Prescribing in Pregnancy p. 19 and Prescribing in Breast-feeding p. 19. The Treatment Summaries provide guidance on the drug treatment of common conditions that can occur during pregnancy and breast-feeding (e.g. asthma p. 210).

Information about the use of specific drugs during pregnancy and breast-feeding can be found in their drug monographs under Pregnancy, and Breast-feeding (e.g. fluconazole p. 518).

In this edition a new section, Conception and contraception, containing information around considerations for females of childbearing potential or men who might father a child (e.g. isotretinoin p. 1045) has been included.

**Administration and monitoring**

When selecting the most appropriate drug, it may be necessary to screen the patient for certain genetic markers or metabolic states. This information is included within a section called Pre-treatment screening (e.g. abacavir, p. 561). This section covers one-off tests required to assess the suitability of a patient for a particular drug.

Once the drug has been selected, it needs to be given in the most appropriate manner. A new Directions for administration section contains the information about intravenous administration previously located in Appendix 4. This provides practical information on the preparation of intravenous drug infusions, including compatibility of drugs with standard intravenous infusion fluids, method of dilution or reconstitution, and administration rates. In addition, general advice relevant to other routes of administration is provided within this section (e.g. fentanyl, p. 362).

After selecting and administering the most appropriate drug by the most appropriate route, patients should be monitored to ensure they are achieving the expected benefits from drug treatment without any unwanted side-effects. The Monitoring section specifies any special monitoring requirements, including information on monitoring the plasma concentration of drugs with a narrow therapeutic index (e.g. theophylline, p. 238). Monitoring may, in certain cases, be affected by the impact of a drug on laboratory tests (e.g. hydroxocobalamin, p. 837), and this information is included in Effects on laboratory tests.

In some cases, when a drug is withdrawn, further monitoring or precautions may be advised (e.g. clonidine, p. 137): these are covered under Treatment cessation.

**Choice and supply**

The prescriber and the patient should agree on the health outcomes that the patient desires and on the strategy for achieving them (see Taking Medicines to Best Effect, p. 1). Taking the time to explain to the patient (and carers) the rationale and the potential adverse effects of treatment may improve adherence. For some medicines there is a special need for counselling (e.g. appropriate posture during administration of doxycycline, p. 496); this is shown in Patient and carer advice.

Other information contained in the latter half of the monograph also helps prescribers and those dispensing medicines choose medicinal forms (by indicating information such as flavour or when branded products may not be interchangeable e.g. Dilatazem, p. 149), assess the suitability of a drug for prescribing, understand the NHS funding status for a drug (e.g. sildenafil, p. 656, or assess when a patient may be able to purchase a drug without prescription (e.g. loperamide hydrochloride, p. 56).

**Medicinal forms**

In the BNF, preparations follow immediately after the monograph for the drug that is their main ingredient. In previous editions, when a particular preparation had safety information, dose advice or other clinical information specific to the product, it was contained within the preparations record. This information has now been moved to the relevant section in the main body of the monograph under a heading of the name of the specific medicinal form (e.g. peppermint oil), p. 40.

In the new BNF, the medicinal forms (formerly preparations) record provides information on the type of formulation (e.g. tablet), the amount of active drug in a solid dosage form, and the concentration of active drug in a liquid dosage form. The legal status is shown for prescription-only medicines and controlled drugs, as well as pharmacy medicines and medicines on the general sales list. Practitioners are reminded, by a statement at the top of the monograph that not all products containing a specific drug ingredient may be similarly licensed. To be clear on the precise licensing status of specific medicinal forms, practitioners should check the product literature for the particular product being prescribed or dispensed.

Patients should be prescribed a preparation that complements their daily routine, and that provides the right dose of drug for the right indication and route of administration. When dispensing liquid preparations, a sugar-free preparation should always be used in preference to one containing sugar. Patients receiving medicines containing cariogenic sugars should be advised of appropriate dental hygiene measures to prevent caries. Previously the BNF only included excipients and electrolyte information for proprietary medicines. This information is now covered at the level of the dose form (e.g. tablet). It is not possible to keep abreast of all the changes in the UK market, and so this information serves as a reminder to the healthcare professional that, if the presence of a particular excipient is of concern, they should check the product literature for the particular product being prescribed or dispensed.

Cautionary and advisory labels that pharmacists are recommended to add when dispensing are included in the medicinal forms (formerly Preparations) record. Details of these labels can be found in Appendix 3, p. 1291. As these labels have now been applied at the level of the dose form, a full list of medicinal products with their relevant labels would be extensive. This list has therefore been removed, but the information is retained within the monograph.
In the case of compound preparations, the prescribing information for all constituents should be taken into account.

**Prices in the BNF**

Basic NHS net prices are given in the BNF to provide an indication of relative cost. Where there is a choice of suitable preparations for a particular disease or condition the relative cost may be used in making a selection. Cost-effective prescribing must, however, take into account other factors (such as dose frequency and duration of treatment) that affect the total cost. The use of more expensive drugs is justified if it will result in better treatment of the patient, or a reduction of the length of an illness, or the time spent in hospital.

Prices are regularly updated using the Drug Tariff and proprietary price information published by the NHS dictionary of medicines and devices (dm+d, www.dmd.nhs.uk). The weekly updated dm+d data (including prices) can be accessed using the dm+d browser of the NHS Business Services Authority (www.ppa.org.uk/systems/pccdbrowserv2.3new/browser.jsp). Prices have been calculated from the net cost used in pricing NHS prescriptions in June 2015 and generally reflect whole dispensing packs. Prices for extemporaneously prepared preparations are not provided in the BNF as prices vary between different manufacturers.

In Appendix 5 prices stated are per dressing or bandage. BNF prices are not suitable for quoting to patients seeking private prescriptions or contemplating over-the-counter purchases because they do not take into account VAT, professional fees, and other overheads.

A fuller explanation of costs to the NHS may be obtained from the Drug Tariff. Separate drug tariffs are applicable to England and Wales (www.ppa.org.uk/ppa/edt_intro.htm), Scotland (www.isdsclot.org/HealthTopics/Prescribing-and-Medicines/Scottish-Drug-Tariff/), and Northern Ireland (www.dhsspsni.gov.uk/pas-tariff); prices in the different tariffs may vary.

**Drug-class monographs**

In previous editions of the BNF, information relating to a class of drug sharing the same properties (e.g. tetracyclines, p. 496), was contained within the prescribing notes. In this new edition, drug-class monographs have been created to contain the common information; this ensures such information is easier to find, and has a more regularised structure.

For consistency and ease of use, the class monograph follows the same structure as a drug monograph. Class monographs are indicated by the presence of a flag (e.g. Beta blockers, systemic, p. 140). If a drug monograph has a corresponding class monograph, that needs to be considered in tandem, in order to understand the full information about a drug, the monograph is also indicated by a flag (e.g. metoprolol, p. 144). Where the drug monographs run on from a class monograph no further cross referencing is given. However, occasionally, due to differences in therapeutic use, the drug monograph may not directly follow the class monograph. In this situation the need to consider a class monograph is still indicated by a flag, but a cross reference is also provided to help navigate the user to the class monograph (e.g. sotalol, p. 93).

**Other content**

**Nutrition**

Appendix 2, p. 1260 includes tables of ACBS-approved enteral feeds and nutritional supplements based on their energy and protein content. There are separate tables for specialised formulae for specific clinical conditions. Classified sections on foods for special diets and nutritional supplements for metabolic diseases are also included.

**Wound dressings**

A table on wound dressings in Appendix 4 (previously Appendix 5), p. 1294 allows an appropriate dressing to be selected based on the appearance and condition of the wound. Further information about the dressing can be found by following the cross-reference to the relevant classified section in the Appendix.

Advanced wound contact dressings have been classified in order of increasing absorbency.

**Other useful information**

**Finding significant changes in the BNF**

— **Changes**, p. xv, provides a list of significant changes, dose changes, classification changes, new names, and new preparations that have been incorporated into the BNF, as well as a list of preparations that have been discontinued and removed from the BNF. Changes listed online are cumulative (from one print edition to the next), and can be printed off each month to show the main changes since the last print edition as an aide memoire for those using print copies. So many changes are made for each update of the BNF, that not all of them can be accommodated in the Changes section. We encourage healthcare professionals to review regularly the prescribing information on drugs that they encounter frequently.

— **Changes to the Dental Practitioners’ Formulary**, p. 27, are located at the end of the Dental List.

— **E-newsletter**, the BNF & BNFC e-newsletter service is available free of charge. It alerts healthcare professionals to details of significant changes in the clinical content of these publications and to the way that this information is delivered. Newsletters also review clinical case studies, provide tips on using these publications effectively, and highlight forthcoming changes to the publications. To sign up for e-newsletters go to www.bnf.org.

— An e-learning programme developed in collaboration with the Centre for Pharmacy Postgraduate Education (CPPE), enables pharmacists to identify and assess how significant changes in the BNF affect their clinical practice. The module can be found at www.cppe.ac.uk.

**Using other sources for medicines information**

The BNF is designed as a digest for rapid reference. Less detail is given on areas such as obstetrics, malignant disease, and anaesthesia since it is expected that those undertaking treatment will have specialist knowledge and access to specialist literature. **BNF for Children** should be consulted for detailed information on the use of medicines in children. The BNF should be interpreted in the light of professional knowledge and supplemented as necessary by specialised publications and by reference to the product literature. Information is also available from medicines information services.
Changes

Monthly updates are provided online via MedicinesComplete and the NHS Evidence portal. The changes listed below are cumulative (from one print edition to the next).

**Significant changes**

Significant changes made since release of data for the print edition of BNF 69 (March–September 2015):

- Accelexfenac p. 916: updated cardiovascular advice—new contra-indications in certain established cardiovascular diseases [MHRA advice].
- Apixaban p. 108 for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism [NICE guidance].
- Axitinib p. 802 for treating advanced renal cell carcinoma after failure of prior systemic treatment [NICE guidance].
- Codeine phosphate p. 360 for cough and cold: restricted use in children [MHRA advice].
- Dabigatran etexilate p. 117 for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism [NICE guidance].
- Diclofenac potassium p. 920, 12.5 mg tablets no longer available over the counter [MHRA advice].
- Dimethyl fumarate p. 727: risk of lymphopenia and potential risk of progressive multifocal leukoencephalopathy [MHRA advice].
- Empagliflozin p. 610 in combination therapy for treating type 2 diabetes [NICE guidance].
- Hydroxyzine hydrochloride p. 248: risk of QT interval prolongation and Torsade de Pointes [MHRA advice].
- Indinavir p. 906, adalimumab p. 901 and golimumab p. 904 for treating moderately to severely active ulcerative colitis after the failure of conventional therapy [NICE guidance].
- Obinutuzumab p. 739 in combination with chlorambucil for untreated chronic lymphocytic leukaemia [NICE guidance].
- Ofatumumab p. 740 in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia [NICE guidance].
- Omalizumab p. 235 for previously treated chronic spontaneous urticaria [NICE guidance].
- Pomalidomide p. 797 for relapsed and refractory multiple myeloma previously treated with lenalidomide p. 796 and bortezomib p. 801 [NICE guidance].
- Rivaroxaban p. 109 for preventing adverse outcomes after acute management of acute coronary syndrome [NICE guidance].
- Rifaximin p. 495 for preventing episodes of overt hepatic encephalopathy [NICE guidance].
- Simeprevir p. 548 in combination with peginterferon alfa p. 542 and ribavirin p. 545 for treating genotypes 1 and 4 chronic hepatitis C [NICE guidance].
- Sofosbuvir p. 546 for treating chronic hepatitis C [NICE guidance].
- Ustekinumab p. 899 for treating active psoriatic arthritis [NICE guidance].

**Dose changes**

Changes in dose statements made since release of data for the print edition of BNF 69 (March–September 2015):

- Eprosartan p. 133
- Lisdxemafetamine mesilate p. 271 [dose in renal impairment]
- Tetrastarch p. 854 [Volulyte®]
- Tetrastarch p. 854 [Volufen®]
- Tramadol hydrochloride p. 373 [oral dose for acute and chronic pain]

**Classification changes**

Classification changes made since release of data for the print edition of BNF 69 (March–September 2015):

**New names**

Name changes introduced since release of data for the print edition of BNF 69 (March–September 2015):

**Deleted preparations**

Preparations discontinued since release of data for the print edition of BNF 69 (March–September 2015):

**New preparations**

New preparations included since release of data for the print edition of BNF 69 (March–September 2015):

- Anafranil SR®
- BindRen®
- Brexidol®
- Calcium-Sandoz®
- Calmurl HC®
- Didronel®
- Eporatio®
- Fluarix®
- Froben®
- Ortho-Gynelet®
- Penbritin® syup
- Pneumovax® II
- Rienso®
- Rupafin®
- Vantas®
- Vistabel®
- Jaydess® [levonorgestrel p. 692]
- Ketoconazole HRA® [ketocanazole p. 587]
- Lonquex® [lipefilgrastim p. 842]
- Salofalk® 1 g suppositories [mesalazine p. 34]
Guidance on prescribing

General guidance
Medicines should be prescribed only when they are necessary, and in all cases the benefit of administering the medicine should be considered in relation to the risk involved. This is particularly important during pregnancy, when the risk to both mother and fetus must be considered. It is important to discuss treatment options carefully with the patient to ensure that the patient is content to take the medicine as prescribed. In particular, the patient should be helped to distinguish the adverse effects of prescribed drugs from the effects of the medical disorder. When the beneficial effects of the medicine are likely to be delayed, the patient should be advised of this.

Taking medicines to best effect
Difficulties in adherence to drug treatment occur regardless of age. Factors contributing to poor compliance with prescribed medicines include:

- prescription not collected or not dispensed;
- purpose of medicine not clear;
- perceived lack of efficacy;
- real or perceived adverse effects;
- patients’ perception of the risk and severity of side-effects may differ from that of the prescriber;
- instructions for administration not clear;
- physical difficulty in taking medicines (e.g. swallowing the medicine, handling small tablets, or opening medicine containers);
- unattractive formulation (e.g. unpleasant taste);
- complicated regimen.

The prescriber and the patient should agree on the health outcomes that the patient desires and on the strategy for achieving them (‘concordance’). The prescriber should be sensitive to religious, cultural, and personal beliefs that can affect a patient’s acceptance of medicines. Taking the time to explain to the patient (and relatives) the rationale and the potential adverse effects of treatment may improve adherence. Reinforcement and elaboration of the physician’s instructions by the pharmacist and other members of the healthcare team also helps. Advising the patient of the possibility of alternative treatments may encourage the patient to seek advice rather than merely abandon unacceptable treatment.

Simplifying the drug regimen may help; the need for abandonment of unacceptable treatment.

Biosimilar medicines
A biosimilar medicine is a new biological product that is similar to a medicine that has already been authorised to be marketed (the biological reference medicine) in the European Union. The active substance of a biosimilar medicine is similar, but not identical, to the biological reference medicine. Biological products are different from standard chemical products in terms of their complexity and although theoretically there should be no important differences between the biosimilar and the biological reference medicine in terms of safety or efficacy, when prescribing biological products, it is good practice to use the brand name. This will ensure that substitution of a biosimilar medicine does not occur when the medicine is dispensed.

Biosimilar medicines have black triangle status at the time of initial marketing. It is important to report suspected adverse reactions to biosimilar medicines using the Yellow Card Scheme. For biosimilar medicines, adverse reaction reports should clearly state the brand name and the batch number of the suspected medicine.

Complementary and alternative medicine
An increasing amount of information on complementary and alternative medicine is becoming available. The scope of the BNF is restricted to the discussion of conventional medicines but reference is made to complementary treatments if they affect conventional therapy (e.g. interactions with St John’s wort). Further information on herbal medicines is available at www.mhra.gov.uk.

Abbreviation of titles
In general, titles of drugs and preparations should be written in full. Unofficial abbreviations should not be used as they may be misinterpreted.

Non-proprietary titles
Where non-proprietary (‘generic’) titles are given, they should be used in prescribing. This will enable any suitable product to be dispensed, thereby saving delay to the patient and sometimes expense to the health service. The only exception is where there is a demonstrable difference in clinical effect between each manufacturer’s version of the formulation, making it important that the patient should always receive the same brand; in such cases, the brand name or the manufacturer should be stated. Non-proprietary titles should not be invented for the purposes of prescribing generically since this can lead to confusion, particularly in the case of compound and modified-release preparations.

Titles used as headings for monographs may be used freely in the United Kingdom but in other countries may be subject to restriction.

Many of the non-proprietary titles used in this book are titles of monographs in the European Pharmacopoeia, British Pharmacopoeia, or British Pharmaceutical Codex 1973. In such cases the preparations must comply with the standard (if any) in the appropriate publication, as required by the Human Medicines Regulations 2012.

Proprietary titles
Names followed by the symbol ® are or have been used as proprietary names in the United Kingdom. These names may in general be applied only to products supplied by the owners of the trade marks.

Marketing authorisation and BNF advice
In general the doses, indications, cautions, contra-indications, and side-effects in the BNF reflect those in the manufacturers’ data sheets or Summaries of Product Characteristics (SPCs) which, in turn, reflect those in the corresponding marketing authorisations (formerly known as Product Licences). The BNF does not generally include proprietary medicines that are not supported by a valid Summary of Product Characteristics or when the marketing authorisation holder has not been able to supply essential information. When a preparation is available from more than one manufacturer, the BNF reflects advice that is the most clinically relevant regardless of any variation in the marketing authorisations. Unlicensed products can be obtained from ‘special-order’ manufacturers or specialist importing companies.

Where an unlicensed drug is included in the BNF, this is indicated in square brackets after the entry. When the BNF
Guidance on prescribing

2 Guidance on prescribing

s suggests a use (or route) that is outside the licensed indication of a product (‘off-label’ use), this too is indicated. Unlicensed use of medicines becomes necessary if the clinical need cannot be met by licensed medicines; such use should be supported by appropriate evidence and experience.

The doses stated in the BNF are intended for general guidance and represent, unless otherwise stated, the usual range of doses that are generally regarded as being suitable for adults.

Prescribing unlicensed medicines

Prescribing medicines outside the recommendations of their marketing authorisation alters (and probably increases) the prescriber’s professional responsibility and potential liability. The prescriber should be able to justify and feel competent in using such medicines, and also inform the patient or the patient’s carer that the prescribed medicine is unlicensed.

Oral syringes

An oral syringe is supplied when oral liquid medicines are prescribed in doses other than multiples of 5 mL. The oral syringe is marked in 0.5 mL divisions from 1 to 5 mL to measure doses of less than 5 mL (other sizes of oral syringe may also be available). It is provided with an adaptor and an instruction leaflet. The 5–5 mL spoon is used for doses of 5 mL (or multiples thereof).

Important To avoid inadvertent intravenous administration of oral liquid medicines, only an appropriate oral or enteral syringe should be used to measure an oral liquid medicine (if a medicine spoon or graduated measure cannot be used); these syringes should not be compatible with intravenous or other parenteral devices. Oral or enteral syringes should be clearly labelled 'Oral' or 'Enteral' in a large font size; it is the healthcare practitioner’s responsibility to label the syringe with this information if the manufacturer has not done so.

Excipients

Branded oral liquid preparations that do not contain fructose, glucose, or sucrose are described as ‘sugar-free’ in the BNF. Preparations containing hydrogenated glucose syrup, mannitol, maltitol, sorbitol, or xylitol are also marked ‘sugar-free’ since there is evidence that they do not cause dental caries. Patients receiving medicines containing cariogenic sugars should be advised of appropriate dental hygiene measures to prevent caries. Sugar-free preparations should be used whenever possible.

Where information on the presence of aspartame, gluten, sulfites, tartrazine, arachis (peanut) oil or sesame oil is available, this is indicated in the BNF against the relevant preparation.

Information is provided on selected excipients in skin preparations, in vaccines, and on selected preservatives and excipients in eye drops and injections.

The presence of benzyl alcohol and polyoxyl castor oil (polyethoxylated castor oil) in injections is indicated in the BNF. Benzyl alcohol has been associated with a fatal toxic syndrome in preterm neonates, and therefore, parenteral preparations containing the preservative should not be used in neonates. Polyoxyl castor oils, used as vehicles in intravenous injections, have been associated with severe anaphylactoid reactions.

The presence of propylene glycol in oral or parenteral medicines is indicated in the BNF; it can cause adverse effects if its elimination is impaired, e.g. in renal failure, in neonates and young children, and in slow metabolisers of the substance. It may interact with disulfiram p. 428 and metronidazole p. 475. The lactose content in most medicines is too small to cause problems in most lactose-intolerant patients. However in severe lactose intolerance, the lactose content should be determined before prescribing. The amount of lactose varies according to manufacturer, product, formulation, and strength.

Important In the absence of information on excipients in the BNF and in the product literature (available at www.medicines.org.uk/emc), contact the manufacturer (see Index of Proprietary Manufacturers) if it is essential to check details.

Extemporaneous preparation

A product should be dispensed extemporaneously only when no product with a marketing authorisation is available.

The BP direction that a preparation must be freshly prepared indicates that it must be made not more than 24 hours before it is issued for use. The direction that a preparation should be recently prepared indicates that deterioration is likely if the preparation is stored for longer than about 4 weeks at 15–25°C.

The term water used without qualification means either potable water freshly drawn direct from the public supply and suitable for drinking or freshly boiled and cooled purified water. The latter should be used if the public supply is from a local storage tank or if the potable water is unsuitable for a particular preparation (Water for injections).

Drugs and driving

Prescribers and other healthcare professionals should advise patients if treatment is likely to affect their ability to perform skilled tasks (e.g. driving). This applies especially to drugs with sedative effects; patients should be warned that these effects are increased by alcohol. General information about a patient’s fitness to drive is available from the Driver and Vehicle Licensing Agency at www.dvla.gov.uk.

A new offence of driving, attempting to drive, or being in charge of a vehicle, with certain specified controlled drugs in excess of specified limits, came into force on 2nd March 2015. This offence is an addition to the existing rules on drug impaired driving and fitness to drive, and applies to two groups of drugs—commonly abused drugs, including cannabis, cocaine, and ketamine p. 1110, and drugs used mainly for medical reasons, such as opioids and benzodiazepines. Amphetamines are also expected to be added to the legislation later in 2015. Anyone found to have any of the drugs (including related drugs, for example, apomorphine hydrochloride p. 332) above specified limits in their blood will be guilty of an offence, whether their driving was impaired or not. This also includes prescribed drugs which metabolise to those included in the offence, for example, selegiline hydrochloride p. 340. However, the legislation provides a statutory “medical defence” for patients taking drugs for medical reasons in accordance with instructions, if their driving was not impaired—it continues to be an offence to drive if actually impaired. Patients should therefore be advised to continue taking their medicines as prescribed, and when driving, to carry suitable evidence that the drug was prescribed, or sold, to treat a medical or dental problem, and that it was taken according to the instructions given by the prescriber, or information provided with the medicine (e.g. a repeat prescription form or the medicine’s patient information leaflet). Further information is available from the Department for Transport at www.gov.uk/government/collections/drug-driving.

Patents

In the BNF, certain drugs have been included notwithstanding the existence of actual or potential patent rights. In so far as such substances are protected by Letters
Patent, their inclusion in this Formulary neither conveys, nor implies, licence to manufacture.

**Health and safety**
When handling chemical or biological materials particular attention should be given to the possibility of allergy, fire, explosion, radiation, or poisoning. Substances such as corticosteroids, some antimicrobials, phenothiazines, and many cytotoxics, are irritant or very potent and should be handled with caution. Contact with the skin and inhalation of dust should be avoided.

**Safety in the home**
Patients must be warned to keep all medicines out of the reach of children. All solid dose and all oral and external liquid preparations must be dispensed in a reclosable child-resistant container unless:
- the medicine is in an original pack or patient pack such as to make this inadvisable;
- the patient will have difficulty in opening a child-resistant container;
- a specific request is made that the product shall not be dispensed in a child-resistant container;
- no suitable child-resistant container exists for a particular liquid preparation.

All patients should be advised to dispose of unwanted medicines by returning them to a supplier for destruction.

**Labelling of prescribed medicines**
There is a legal requirement for the following to appear on the label of any prescribed medicine:
- name of the patient;
- name and address of the person dispensing the medicine;
- date of dispensing;
- name of the medicine;
- directions for use of the medicine;
- precautions relating to the use of the medicine.

The Royal Pharmaceutical Society recommends that the following also appears on the label:
- the words ‘Keep out of the sight and reach of children’;
- where applicable, the words ‘Use this medicine only on your skin’.

A pharmacist can exercise professional skill and judgement to amend or include more appropriate wording for the name of the medicine, the directions for use, or the precautions relating to the use of the medicine.

**Non-proprietary names of compound preparations**
Non-proprietary names of compound preparations which appear in the BNF are those that have been compiled by the British Pharmacopoeia Commission or another recognised body; whenever possible they reflect the names of the active ingredients.

Prescribers should avoid creating their own compound names for the purposes of generic prescribing; such names do not have an approved definition and can be misinterpreted.

Special care should be taken to avoid errors when prescribing compound preparations; in particular the hyphen in the prefix ‘co’ should be retained.

Special care should also be taken to avoid creating generic names for modified-release preparations where the use of these names could lead to confusion between formulations with different lengths of action.

**EEA and Swiss prescriptions**
Pharmacists can dispense prescriptions issued by doctors and dentists from the European Economic Area (EEA) or Switzerland (except prescriptions for controlled drugs in Schedules 1, 2, or 3, or for drugs without a UK marketing authorisation). Prescriptions should be written in ink or otherwise so as to be indelible, should be dated, should state the name of the patient, should state the address of the prescriber, should contain particulars indicating whether the prescriber is a doctor or dentist, and should be signed by the prescriber.

**Security and validity of prescriptions**
The Councils of the British Medical Association and the Royal Pharmaceutical Society have issued a joint statement on the security and validity of prescriptions. In particular, prescription forms should:
- not be left unattended at reception desks;
- not be left in a car where they may be visible; and
- when not in use, be kept in a locked drawer within the surgery and at home.

Where there is any doubt about the authenticity of a prescription, the pharmacist should contact the prescriber. If this is done by telephone, the number should be obtained from the directory rather than relying on the information on the prescription form, which may be false.

**Patient group direction (PGD)**
In most cases, the most appropriate clinical care will be provided on an individual basis by a prescriber to a specific individual patient. However, a Patient Group Direction for supply and administration of medicines by other healthcare professionals can be used where it would benefit patient care without compromising safety.

A Patient Group Direction is a written direction relating to the supply and administration (or administration only) of a licensed prescription-only medicine (including some Controlled Drugs in specific circumstances) by certain classes of healthcare professionals; the Direction is signed by a doctor (or dentist) and by a pharmacist. Further information on Patient Group Directions is available in Health Service Circular HSC 2000/026 (England), HDL (2001) 7 (Scotland), and WHC (2000) 116 (Wales); see also the Human Medicines Regulations 2012.

**NICE and Scottish Medicines Consortium**
Advice issued by the National Institute for Health and Care Excellence (NICE) is included in the BNF when relevant. The BNF also includes advice issued by the Scottish Medicines Consortium (SMC) when a medicine is restricted or not recommended for use within NHS Scotland. If advice within a NICE Single Technology Appraisal differs from SMC advice, the Scottish Executive expects NHS Boards within NHS Scotland to comply with the SMC advice. Details of the advice together with updates can be obtained from www.nice.org.uk and from www.scottishmedicines.org.uk.
Prescription writing

Shared care

In its guidelines on responsibility for prescribing (circular EL (S1) 127) between hospitals and general practitioners, the Department of Health has advised that legal responsibility for prescribing lies with the doctor who signs the prescription.

Prescriptions should be written legibly in ink or otherwise so as to be indelible (it is permissible to issue carbon copies of NHS prescriptions as long as they are signed in ink), should be dated, should state the name and address of the patient, the address of the prescriber, an indication of the type of prescriber, and should be signed in ink by the prescriber (computer-generated facsimile signatures do not meet the legal requirement). The age and the date of birth of the patient should preferably be stated, and it is a legal requirement in the case of prescription-only medicines to state the age for children under 12 years. These recommendations are acceptable for prescription-only medicines. Prescriptions for controlled drugs have additional legal requirements.

Wherever appropriate the prescriber should state the current weight of the child to enable the dose prescribed to be checked. Consideration should also be given to including the dose per unit mass e.g. mg/kg or the dose per m² body-surface area e.g. mg /m² where this would reduce error.

The following should be noted:

- The strength or quantity to be contained in capsules, lozenges, tablets etc. should be stated by the prescriber. In particular, strength of liquid preparations should be clearly stated (e.g. 125 mg/5 mL).
- The unnecessary use of decimal points should be avoided, e.g. 3 mg, not 3.0 mg. Quantities of 1 gram or more should be written as 1 g etc.
- Quantities less than 1 gram should be written in milligrams, e.g. 500 mg, not 0.5 g. Quantities less than 1 mg should be written in micrograms, e.g. 100 micrograms, not 0.1 mg. When decimals are unavoidable a zero should be written in front of the decimal point where there is no other figure, e.g. 0.5 mL, not .5 mL. Use of the decimal point is acceptable to express a range, e.g. 0.5 to 1 g.
- Micrograms and ‘nanograms’ should not be abbreviated. Similarly ‘units’ should not be abbreviated.
- The term ‘millilitre’ (ml or mL) is used in medicine and pharmacy, and cubic centimetre, c.c., or cm³ should not be used. (The use of capital ‘L’ in mL is a printing convention throughout the BNF; both ‘ml’ and ‘mL’ are recognised SI abbreviations).
- Dose and dose frequency should be stated; in the case of preparations to be taken ‘as required’ a minimum dose interval should be specified. Care should be taken to ensure children receive the correct dose of the active drug. Therefore, the dose should normally be stated in terms of the mass of the active drug (e.g. ‘125 mg 3 times daily’); terms such as ‘5 mL’ or ‘1 tablet’ should be avoided except for compound preparations.

When doses other than multiples of 5 mL are prescribed for oral liquid preparations the dose-volume will be provided by means of an oral syringe, (except for preparations intended to be measured with a pipette). Suitable quantities:

- Elixir, Linctuses, and Paediatric Mixtures (5-mL dose), 50, 100, or 150 mL
- Adult Mixtures (10 mL dose), 200 or 300 mL

Ear Drops, Eye drops, and Nasal Drops, 10 mL (or the manufacturer’s pack)

- Eye Lotions, Gargles, and Mouthwashes, 200 mL
- The names of drugs and preparations should be written clearly and not abbreviated, using approved titles only; avoid creating generic titles for modified-release preparations.
- The quantity to be supplied may be stated by indicating the number of days of treatment required in the box provided on NHS forms. In most cases the exact amount will be supplied. This does not apply to items directed to be used as required—if the dose and frequency are not given then the quantity to be supplied needs to be stated. When several items are ordered on one form the box can be marked with the number of days of treatment provided the quantity is added for any item for which the amount cannot be calculated.
- Although directions should preferably be in English without abbreviation, it is recognised that some Latin abbreviations are used, for details, see Inside Back Cover.

Sample prescription

Ear Drops, Eye drops, and Nasal Drops, 10 mL (or the manufacturer’s pack)

Eye Lotions, Gargles, and Mouthwashes, 200 mL

Prescribing by dentists

Until new prescribing arrangements are in place for NHS prescriptions, dentists should use form FP10D (GP14 in Scotland, WP10D in Wales) to prescribe only those items listed in the Dental Practitioners’ Formulary. The Human Medicines Regulations 2012 does not set any limitations upon the number and variety of substances which the dentist may administer to patients in the surgery or may order by private prescription—provided the relevant legal requirements are observed the dentist may use or order whatever is required for the clinical
situation. There is no statutory requirement for the dentist to communicate with a patient’s medical practitioner when prescribing for dental use. There are, however, occasions when this would be in the patient’s interest and such communication is to be encouraged.

Computer-issued prescriptions

For computer-issued prescriptions the following advice, based on the recommendations of the Joint GP Information Technology Committee, should also be noted:

1. The computer must print out the date, the patient’s surname, one forename, other initials, and address, and may also print out the patient’s title and date of birth. The age of children under 12 years and of adults over 60 years must be printed in the box available; the age of children under 5 years should be printed in years and months. A facility may also exist to print out the age of patients between 12 and 60 years.

2. The doctor’s name must be printed at the bottom of the prescription form; this will be the name of the doctor responsible for the prescription (who will normally sign it). The doctor’s surgery address, reference number, and Primary Care Trust (PCT, Health Board in Scotland, Local Health Board in Wales) are also necessary. In addition, the surgery telephone number should be printed.

3. When prescriptions are to be signed by general practitioner registrars, assistants, locums, or deputising doctors, the name of the doctor printed at the bottom of the form must still be that of the responsible principal.

4. Names of medicines must come from a dictionary held in the computer memory, to provide a check on the spelling and to ensure that the name is written in full. The computer can be programmed to recognise both the non-proprietary and the proprietary name of a particular drug and to print out the preferred choice, but must not print out both names. For medicines not in the dictionary, separate checks are required—the user must be warned that no check was possible and the entire prescription must be entered in the lexicon.

5. The dictionary may contain information on the usual doses, formulations, and pack sizes to produce standard predetermined prescriptions for common preparations, and to provide a check on the validity of an individual prescription on entry.

6. The prescription must be printed in English without abbreviation; information may be entered or stored in abbreviated form. The dose must be in numbers, the frequency in words, and the quantity in numbers in brackets, thus: 40 mg four times daily (112). It must also be possible to prescribe by indicating the length of treatment required.

7. The BNF recommendations should be followed as listed above.

8. Checks may be incorporated to ensure that all the information required for dispensing a particular drug has been filled in. For instructions such as ‘as directed’ and ‘when required’, the maximum daily dose should normally be specified.

9. Numbers and codes used in the system for organising and retrieving data must never appear on the form.

10. Supplementary warnings or advice should be written in full, should not interfere with the clarity of the prescription itself, and should be in line with any warnings or advice in the BNF; numerical codes should not be used.

11. A mechanism (such as printing a series of nonspecific characters) should be incorporated to cancel out unused space, or wording such as ‘no more items on this prescription’ may be added after the last item.

Otherwise the doctor should delete the space manually.

12. To avoid forgery the computer may print on the form the number of items to be dispensed (somewhere separate from the box for the pharmacist). The number of items per form need be limited only by the ability of the printer to produce clear and well-demarcated instructions with sufficient space for each item and a spacer line before each fresh item.

13. Handwritten alterations should only be made in exceptional circumstances—it is preferable to print out a new prescription. Any alterations must be made in the doctor’s own handwriting and countersigned; computer records should be updated to fully reflect any alteration. Prescriptions for drugs used for contraceptive purposes (but which are not promoted as contraceptives) may need to be marked in handwriting with the symbol ′♀′, (or endorsed in another way to indicate that the item is prescribed for contraceptive purposes).

14. Prescriptions for controlled drugs can be printed from the computer, but the prescriber’s signature must be handwritten (See Controlled Drugs and Drug Dependence; the prescriber may use a date stamp).

15. The strip of paper on the side of the FP10SS (GP10SS in Scotland, WP10SS in Wales) may be used for various purposes but care should be taken to avoid including confidential information. It may be advisable for the patient’s name to appear at the top, but this should be preceded by ‘confidential’.

16. In rural dispensing practices prescription requests (or details of medicines dispensed) will normally be entered in one surgery. The prescriptions (or dispensed medicines) may then need to be delivered to another surgery or location; if possible the computer should hold up to 10 alternatives.

17. Prescription forms that are reprinted or issued as a duplicate should be labelled clearly as such.
Emergency supply of medicines

Emergency supply requested by member of the public

Pharmacists are sometimes called upon by members of the public to make an emergency supply of medicines. The Human Medicines Regulations 2012 allows exemptions from the Prescription Only requirements for emergency supply to be made by a person lawfully conducting a retail pharmacy business provided:

a) that the pharmacist has interviewed the person requesting the prescription-only medicine and is satisfied:
   i) that there is immediate need for the prescription-only medicine and that it is impracticable in the circumstances to obtain a prescription without undue delay;
   ii) that treatment with the prescription-only medicine has on a previous occasion been prescribed for the person requesting it;
   iii) as to the dose that it would be appropriate for the person to take;

b) that no greater quantity shall be supplied than will provide 5 days' treatment of phenobarbital p. 409, phenobarbital sodium, or Controlled Drugs in Schedules 4 or 5 (doctors or dentists from the European Economic Area and Switzerland, or their patients, cannot request an emergency supply of Controlled Drugs in Schedules 1, 2, or 3, or drugs that do not have a UK marketing authorisation) or 30 days' treatment for other prescription-only medicines, except when the prescription-only medicine is:
   i) insulin, an ointment or cream, or a preparation for the relief of asthma in an aerosol dispenser when the smallest pack can be supplied;
   ii) an oral contraceptive when a full cycle may be supplied;
   iii) an antibiotic in liquid form for oral administration when the smallest quantity that will provide a full course of treatment can be supplied;

c) that an entry shall be made by the pharmacist in the prescription book stating:
   i) the date of supply;
   ii) the name, quantity and, where appropriate, the pharmaceutical form and strength;
   iii) the name and address of the patient;
   iv) the nature of the emergency;

d) that the container or package must be labelled to show:
   i) the date of supply;
   ii) the name, quantity and, where appropriate, the pharmaceutical form and strength;
   iii) the name of the patient;
   iv) the name and address of the pharmacy;
   v) the words 'Emergency supply';
   vi) the words 'Keep out of the reach of children' (or similar warning);

e) that the prescription-only medicine is not a substance specifically excluded from the emergency supply provision, and does not contain a Controlled Drug specified in Schedules 1, 2, or 3 to the Misuse of Drugs Regulations 2001 except for phenobarbital p. 409 or phenobarbital sodium for the treatment of epilepsy: for details see Medicines, Ethics and Practice, London, Pharmaceutical Press (always consult latest edition); (Doctors or dentists from the European Economic Area and Switzerland, or their patients, cannot request an emergency supply of Controlled Drugs in Schedules 1, 2, or 3, or drugs that do not have a UK marketing authorisation).

f) that an entry shall be made in the prescription book stating:
   i) the date of supply;
   ii) the name, quantity and, where appropriate, the pharmaceutical form and strength;
   iii) the name and address of the practitioner requesting the emergency supply;
   iv) the name and address of the patient;
   v) the date on the prescription;
   vi) when the prescription is received the entry should be amended to include the date on which it is received.

Emergency supply requested by prescriber

Emergency supply of a prescription-only medicine may also be made at the request of a doctor, a dentist, a supplementary prescriber, a community practitioner nurse prescriber, a nurse, pharmacist, or optometrist independent prescriber, or a doctor or dentist from the European Economic Area or Switzerland, provided:

a) that the pharmacist is satisfied that the prescriber by reason of some emergency is unable to furnish a prescription immediately;

b) that the prescriber has undertaken to furnish a prescription within 72 hours;

c) that the medicine is supplied in accordance with the directions of the prescriber requesting it;

d) that the medicine is not a Controlled Drug specified in Schedules 1, 2, or 3 to the Misuse of Drugs Regulations 2001 except for phenobarbital p. 409 or phenobarbital sodium for the treatment of epilepsy: for details see Medicines, Ethics and Practice, London, Pharmaceutical Press (always consult latest edition); (Doctors or dentists from the European Economic Area and Switzerland, or their patients, cannot request an emergency supply of Controlled Drugs in Schedules 1, 2, or 3, or drugs that do not have a UK marketing authorisation).

e) that an entry shall be made in the prescription book stating:
   i) the date of supply;
   ii) the name, quantity and, where appropriate, the pharmaceutical form and strength;
   iii) the name and address of the practitioner requesting the emergency supply;
   iv) the name and address of the patient;
   v) the date on the prescription;
   vi) when the prescription is received the entry should be amended to include the date on which it is received.

Royal Pharmaceutical Society’s guidelines

1. The pharmacist should consider the medical consequences of not supplying a medicine in an emergency.

2. If the pharmacist is unable to make an emergency supply of a medicine the pharmacist should advise the patient how to obtain essential medical care.

For conditions that apply to supplies made at the request of a patient see Medicines, Ethics and Practice, London Pharmaceutical Press, (always consult latest edition).
The Misuse of Drugs Act, 1971 prohibits certain activities in relation to ‘Controlled Drugs’, in particular their manufacture, supply, and possession. The penalties applicable to offences involving the different drugs are graded broadly according to the harmfulness attributable to a drug when it is misused and for this purpose the drugs are defined in the following three classes:


**Class C** includes: certain drugs related to the amphetamines such as benzphetamine and chlorphentermine, butenafine p. 434, diethylpropion, mazindol, meoraphosphate p. 265 pemoline, pipradrol, most benzodiazepines, tramadol hydrochloride p. 373, zaleplon p. 422, zolpidem tarrate p. 423, zopiclone p. 423, and non-human chorionic gonadotrophin (HCG), non-human chorionic gonadotrophin, somatotropin, somatrem, and somatropin p. 642.

The Misuse of Drugs Regulations 2001 (and subsequent amendments) define the classes of person who are authorised to supply and possess controlled drugs while acting in their professional capacities and lay down the conditions under which these activities may be carried out. In the regulations drugs are divided into five schedules each specifying the requirements governing such activities as import, export, production, supply, possession, prescribing, and record keeping which apply to them.

**Schedule 1** includes drugs such as lysergide which is not used medicinally. Possession and supply are prohibited except in accordance with Home Office authority.

**Schedule 2** includes drugs such as diamorphine hydrochloride p. 361 (heroin), morphine p. 367, nabilone p. 346, remifentanil p. 1108, pethidine hydrochloride p. 372, secobarbital, glutethimide, the amphetamines, sodium oxybate and cocaine and are subject to the full controlled drug requirements relating to prescriptions, safe custody (except for secobarbital), the need to keep registers, etc. (unless exempted in Schedule 5).

**Schedule 3** includes the barbiturates (except secobarbital, now Schedule 2), butenafine p. 434, diethylpropion, mazindol, meoraphosphate p. 265, midazolam p. 414, pentazocine p. 371, phenmetrazine, temazepam p. 420, and tramadol hydrochloride p. 373. They are subject to the special prescription requirements (except for temazepam p. 420) and to the safe custody requirements (except for any 5,5 disubstituted barbituric acid (e.g. phenobarbital), mazindol, meoraphosphate p. 265, midazolam p. 414, pentazocine p. 371, phenmetrazine, tramadol hydrochloride p. 373, or any stereoisomeric form or salts of the above). Records in registers do not need to be kept (although there are requirements for the retention of invoices for 2 years).

**Schedule 4** includes in Part 1 benzodiazepines (except temazepam p. 420 and midazolam p. 414, which are in Schedule 3), zaleplon p. 422, zolpidem tarrate p. 423, and zopiclone p. 423 which are subject to minimal control. Part II includes androgenic and anabolic steroids, clenbuterol, chonic gonadotrophin (HCG), non-human chonic gonadotrophin, somatotropin, somatrem, and somatropin p. 642. Controlled drug prescription requirements do not apply and Schedule 4 Controlled Drugs are not subject to safe custody requirements.

**Schedule 5** includes those preparations which, because of their strength, are exempt from virtually all Controlled Drug requirements other than retention of invoices for two years.

### Prescriptions

Preparations in Schedules 1, 2, 3, and 4 of the Misuse of Drugs Regulations 2001 (and subsequent amendments) are identified throughout the BNF and BNF for children using the following symbols:

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Schedule</th>
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<tr>
<td>CD1</td>
<td>for preparations in Schedule 1</td>
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<tr>
<td>CD2</td>
<td>for preparations in Schedule 2</td>
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<tr>
<td>CD3</td>
<td>for preparations in Schedule 3</td>
</tr>
<tr>
<td>CD4-1</td>
<td>for preparations in Schedule 4 (Part I)</td>
</tr>
<tr>
<td>CD4-2</td>
<td>for preparations in Schedule 4 (Part II)</td>
</tr>
</tbody>
</table>

The principal legal requirements relating to medical prescriptions are listed below.

**Prescription requirements** Prescriptions for Controlled Drugs that are subject to prescription requirements, (all preparations in Schedules 2 and 3, except temazepam p. 420), must be indelible, (a machine-written prescription is acceptable; the prescriber’s signature must be handwritten), and must be signed by the prescriber, be dated, and specify the prescriber’s address. The prescription must always state:

- the name and address of the patient;
- in the case of a preparation, the form, (the dosage form e.g. tablets must be included on a Controlled Drugs prescription irrespective of whether it is implicit in the proprietary name e.g. MST Continus or whether only one form is available), and where appropriate the strength of the preparation (when more than one strength of a preparation exists the strength required must be specified);
- for liquids, the total volume in millilitres (in both words and figures) of the preparation to be supplied; for dosage units, the number (in both words and figures) of dosage units to be supplied; in any other case, the total quantity (in both words and figures) of the Controlled Drug to be supplied;
- the dose (the instruction ‘one as directed’ constitutes a dose but ‘as directed’ does not);
- the words ‘for dental treatment only’ if issued by a dentist.

A pharmacist is **not** allowed to dispense a Controlled Drug unless all the information required by law is given on the prescription. In the case of a prescription for a Controlled Drug in Schedule 2 or 3, a pharmacist can amend the prescription if it specifies the total quantity only in words or
in figures or if it contains minor typographical errors, provided that such amendments are indelible and clearly attributable to the pharmacist (implementation date for N. Ireland not confirmed). Failure to comply with the regulations concerning the writing of prescriptions will result in inconvenience to patients and carers and delay in supplying the necessary medicine. A prescription for a Controlled Drug in Schedules 2, 3, or 4 is valid for 28 days from the date stated thereon (the prescriber may forward-date the prescription; the start date may also be specified in the body of the prescription).

Instalments and ‘repeats’
A prescription may order a Controlled Drug to be dispensed by instalments; the amount of instalments and the intervals to be observed must be specified. A total of 14 days’ treatment by instalment of any drug listed in Schedule 2 of the Misuse of Drugs Regulations, buprenorphine p. 434, and diazepam p. 267 may be prescribed in England. In England, forms FP10(MDA) (blue) and FP10H(MDA) (blue) should be used. In Scotland, forms GP10 (peach), HBP (blue), or HBPA (pink) should be used. In Wales a total of 14 days’ treatment by instalment of any drug listed in Schedules 2–5 of the Misuse of Drugs Regulations may be prescribed. In Wales, form WP10(MDA) or form WP10HP(AD) should be used. Instalment prescriptions must be dispensed in accordance with the directions in the prescription. However, the Home Office has approved specific wording which may be included in an instalment prescription to cover certain situations; for example, if a pharmacy is closed on the day when an instalment is due. For details, see Medicines, Ethics and Practice, London, Pharmaceutical Press (always consult latest edition) or see Drug Misuse and Dependence: UK Guidelines on Clinical Management (2007), available at www.nta.nhs.uk/uploads/clinical_guidelines_2007.pdf.

Private prescriptions
Private prescriptions for Controlled Drugs in Schedules 2 and 3 must be written on specially designated forms provided by Primary Care Trusts in England, Health Boards in Scotland, Local Health Boards in Wales, or the Northern Ireland Central Services Agency; in addition, prescriptions must specify the prescriber’s identification number. Prescriptions to be supplied by a pharmacist in hospital are exempt from the requirements for private prescriptions.

Department of Health guidance
Guidance (June 2006) issued by the Department of Health in England on prescribing and dispensing of Controlled Drugs requires:
• In general, prescriptions for Controlled Drugs in Schedules 2, 3, and 4 to be limited to a supply of up to 30 days’ treatment; exceptionally, to cover a justifiable clinical need and after consideration of any risk, a prescription can be issued for a longer period, but the reasons for the decision should be recorded on the patient’s notes;
• the patient’s identifier to be shown on NHS and private prescriptions for Controlled Drugs in Schedules 2 and 3. Further information is available at www.gov.uk/dh.

See sample prescription:

Dependence and misuse
The most serious drugs of addiction are cocaine, diamorphine hydrochloride p. 361 (heroin), morphine p. 367, and the synthetic opioids. For arrangements for prescribing of diamorphine, dipipanone, or cocaine for addicts, see Prescribing of diamorphine (heroin), dipipanone, and cocaine for addicts. Despite marked reduction in the prescribing of amphetamines, there is concern that abuse of illicit amphetamine and related compounds is widespread. Benzodiazepines are commonly misused. However, the misuse of barbiturates is now uncommon, in line with declining medicinal use and consequent availability. Cannabis (Indian hemp) has no approved medicinal use and cannot be prescribed by doctors. Its use is illegal but widespread. Cannabis is a mild hallucinogen seldom accompanied by a desire to increase the dose; withdrawal symptoms are unusual. However, cannabis extract is licensed as a medicinal product. Lysergide (lysergic acid diethylamide, LSD) is a much more potent hallucinogen; its use can lead to severe psychotic states which can be life-threatening. There are concerns over increases in the availability and misuse of other drugs with variously combined hallucinogenic, anaesthetic, or sedative properties. These include ketamine p. 1110 and gamma-hydroxybutyrate (sodium oxybate, GHB).

Supervised consumption
Individuals prescribed opioid substitution therapy can take their daily dose under the supervision of a doctor, nurse, or pharmacist during the dose stabilisation phase (usually the first 3 months of treatment), after a relapse or period of
instability, or if there is a significant increase in the dose of methadone. Supervised consumption should continue (in accordance with local protocols) until the prescriber is confident that the patient is compliant with their treatment.

**Prescribing drugs likely to cause dependence or misuse**

The prescriber has three main responsibilities:

- To avoid creating dependence by introducing drugs to patients without sufficient reason. In this context, the proper use of the morphine-like drugs is well understood. The dangers of other Controlled Drugs are less clear because recognition of dependence is not easy, and its effects, and those of withdrawal, are less obvious.
- To see that the patient does not gradually increase the dose of a drug, given for good medical reasons, to the point where dependence becomes more likely. This tendency is seen especially with hypnotics and anxiolytics. The prescriber should keep a close eye on the amount prescribed to prevent patients from accumulating stocks. A minimal amount should be prescribed in the first instance, or when seeing a new patient for the first time.
- To avoid being used as an unwitting source of supply for addicts and being vigilant to methods for obtaining medicines. Methods include visiting more than one doctor, fabricating stories, and forging prescriptions.

Patients under temporary care should be given only small supplies of drugs unless they present an unequivocal letter from their own doctor. Doctors should also remember that their own patients may be attempting to collect prescriptions from other prescribers, especially in hospitals. It is sensible to reduce dosages steadily or to issue weekly or even daily prescriptions for small amounts if it is apparent that dependence is occurring.

The stealing and misuse of prescription forms could be minimised by the following precautions:

- do not leave unattended if called away from the consulting room or at reception desks; do not leave in a car where they may be visible; when not in use, keep in a locked drawer within the surgery and at home;
- draw a diagonal line across the blank part of the form under the prescription;
- write the quantity in words and figures when prescribing drugs prone to abuse; this is obligatory for controlled drugs;
- alterations are best avoided but if any are made they should be clear and unambiguous; add initials against altered items;
- if prescriptions are left for collection they should be left in a safe place in a sealed envelope.

**Travelling abroad**

Prescribed drugs listed in Schedule 4 Part II (CD Anab) and Schedule 5 of the Misuse of Drugs Regulations 2001 are not subject to export or import licensing. However, patients intending to travel abroad for more than 3 months carrying any amount of drugs listed in Schedules 2, 3, or 4 Part I (CD Benz) will require a personal export/import licence. Further details can be obtained at www.gov.uk/controlled-drugs-licences-fees-andreturns or from the Home Office by contacting licensing_enquiry.aadu@homeoffice.gsi.gov.uk

In cases of emergency, telephone (020) 7035 6330

Applications must be supported by a covering letter from the prescriber and should give details of:

- the patient’s name and address;
- the quantities of drugs to be carried;
- the strength and form in which the drugs will be dispensed;
- the country or countries of destination;

- the dates of travel to and from the United Kingdom.

Applications for licences should be sent to the Home Office, Drugs Licensing & Compliance Unit, Fry Building, 2 Marsham Street, SW1P 4DF. Alternatively, completed application forms can be emailed to dlcucommsofficer@homeoffice.gsi.gov.uk with a copy of the covering letter from the prescriber as a pdf. A minimum of two weeks should be allowed for processing the application.

Patients travelling for less than 3 months do not require a personal export/import licence for carrying Controlled Drugs, but are advised to carry a letter from the prescribing doctor. Those travelling for more than 3 months are advised to make arrangements to have their medication prescribed by a practitioner in the country they are visiting.

Doctors who want to take Controlled Drugs abroad while accompanying patients may similarly be issued with licences. Licences are not normally issued to doctors who want to take Controlled Drugs abroad solely in case a family emergency should arise.

Personal export/import licences do not have any legal status outside the UK and are issued only to comply with the Misuse of Drugs Act and to facilitate passage through UK Customs and Excise control. For clearance in the country to be visited it is necessary to approach that country’s consulat in the UK.

**Notification of patients receiving structured drug treatment for substance dependence**

In England, doctors should report cases where they are providing structured drug treatment for substance dependence to their local National Drug Treatment Monitoring System (NDTMS) Team. General information about NDTMS can be found at www.nta.nhs.uk/ndtms.aspx.

Enquiries about NDTMS, and how to submit data, should initially be directed to:

Malcolm Roxburgh, NTA Information Manager
Tel: (020) 7972 1964
malcolm.roxburgh@nta-nhs.org.uk

In Scotland, doctors should report cases to the Substance Misuse Programme (SMP).
Tel: (0131) 275 6348

In Northern Ireland, the Misuse of Drugs (Notification of Supply to Addicts) (Northern Ireland) Regulations 1973 require doctors to send particulars of persons whom they consider to be addicted to certain controlled drugs to the Chief Medical Officer of the Department of Health and Social Services. The Northern Ireland contacts are:

Medical contact:
Dr Ian McMaster,
C3 Castle Buildings
Belfast BT4 3FQ
Tel: (028) 9052 2421
Fax: (028) 9052 0718
ian.mcmaster@dhsspsni.gov.uk

Administrative contact:
Public Health Information & Research Branch
Annex 2
Castle Building
Belfast, BT4 3SQ
Tel: (028) 9052 2520

Public Health Information & Research Branch also maintains the Northern Ireland Drug Misuse Database (NIDMD) which collects detailed information on those presenting for treatment, on drugs misused and injecting behaviour; participation is not a statutory requirement.

In Wales, doctors should report cases where they are providing structured drug treatment for substance...
dependence on the Welsh National Database for Substance Misuse; enquiries should be directed to: substance.misuse-queries@wales.nhs.uk.

**Prescribing of diamorphine (heroin), dipipanone, and cocaine for addicts**

The Misuse of Drugs (Supply to Addicts) Regulations 1997 require that only medical practitioners who hold a special licence issued by the Home Secretary may prescribe, administer, or supply diamorphine hydrochloride p. 361, dipipanone (Diconal®), or cocaine in the treatment of drug addiction; other practitioners must refer any addict who requires these drugs to a treatment centre. Whenever possible the addict will be introduced by a member of staff from the treatment centre to a pharmacist whose agreement has been obtained and whose pharmacy is conveniently sited for the patient. Prescriptions for weekly supplies will be sent to the pharmacy by post and will be dispensed on a daily basis as indicated by the doctor. If any alterations of the arrangements are requested by the addict, the portion of the prescription affected must be represcribed and not merely altered.

General practitioners and other doctors do not require a special licence for prescribing diamorphine hydrochloride p. 361, dipipanone, and cocaine for patients (including addicts) for relieving pain from organic disease or injury.
Adverse reactions to drugs

Any drug may produce unwanted or unexpected adverse reactions. Rapid detection and recording of adverse drug reactions is of vital importance so that unrecognised hazards are identified promptly and appropriate regulatory action is taken to ensure that medicines are used safely. Healthcare professionals and coroners are urged to report suspected adverse drug reactions directly to the Medicines and Healthcare products Regulatory Agency (MHRA) through the Yellow Card Scheme using the electronic form at www.mhra.gov.uk/yellowcard. Alternatively, prepaid Yellow Cards for reporting are available from the address below and are also bound in the inside back cover of the BNF.

Send Yellow Cards to:
FREEPOST YELLOW CARD
(No other address details required).
Tel: 0800 731 6789

Suspected adverse drug reactions to any therapeutic agent should be reported, including drugs (self-medication as well as those prescribed), blood products, vaccines, radiographic contrast media, complementary and herbal products. For biosimilar medicines and vaccines, adverse reaction reports should clearly state the brand name and the batch number of the suspected medicine or vaccine.

Suspected adverse drug reactions should be reported through the Yellow Card Scheme at www.mhra.gov.uk/yellowcard. Yellow Cards can be used for reporting suspected adverse drug reactions to medicines, vaccines, herbal or complementary products, whether self-medicated or prescribed. This includes suspected adverse drug reactions associated with misuse, overdose, medication errors or from use of unlicensed and off-label medicines. Yellow Cards can also be used to report medical device incidents, defective medicines, and suspected fake medicines.

Spontaneous reporting is particularly valuable for recognising possible new hazards rapidly. An adverse reaction should be reported even if it is not certain that the drug has caused it, or if the reaction is well recognised, or if other drugs have been given at the same time. Reports of overdoses (deliberate or accidental) can complicate the assessment of adverse drug reactions, but provide important information on the potential toxicity of drugs.

A freephone service is available to all parts of the UK for advice and information on suspected adverse drug reactions; contact the National Yellow Card Information Service at the MHRA on 0800 731 6789. Outside office hours a telephone-answering machine will take messages. The following Yellow Card Centres can be contacted for further information:

Yellow Card Centre West Midlands
City Hospital
Dudley Road
Birmingham B18 7QH
Tel: (0121) 507 5672

Yellow Card Centre Scotland
CARDS, Royal Infirmary of Edinburgh
51 Little France Crescent
Old Dalkeith Road
Edinburgh EH16 4SA
Tel: (0131) 242 2919
YCCScotland@luht.scot.nhs.uk

The MHRA’s database facilitates the monitoring of adverse drug reactions. More detailed information on reporting and a list of products currently under additional monitoring can be found on the MHRA website: www.mhra.gov.uk.

MHRA Drug Safety Update

Drug Safety Update is a monthly newsletter from the MHRA and the Commission on Human Medicines (CHM); it is available at www.mhra.gov.uk/drugsafetyupdate.

Self-reporting

Patients and their carers can also report suspected adverse drug reactions to the MHRA. Reports can be submitted directly to the MHRA through the Yellow Card Scheme using the electronic form at www.mhra.gov.uk/yellowcard, by telephone on 0808 100 3352, or by downloading the Yellow Card form from www.mhra.gov.uk. Alternatively, patient Yellow Cards are available from pharmacies and GP surgeries. Information for patients about the Yellow Card Scheme is available in other languages at www.mhra.gov.uk/yellowcard.

Prescription-event monitoring

In addition to the MHRA’s Yellow Card Scheme, an independent scheme monitors the safety of new medicines using a different approach. The Drug Safety Research Unit identifies patients who have been prescribed selected new medicines and collects data on clinical events in these patients. The data are submitted on a voluntary basis by general practitioners on green forms. More information about the scheme and the Unit’s educational material is available from www.dsru.org.

Newer drugs and vaccines

Only limited information is available from clinical trials on the safety of new medicines. Further understanding about the safety of medicines depends on the availability of information from routine clinical practice. The black triangle symbol identifies newly licensed medicines that require additional monitoring by the European Medicines Agency. Such medicines include new active substances, biosimilar medicines, and medicines that the European Medicines Agency consider require additional monitoring. The black triangle symbol also appears in the Patient Information Leaflets for relevant medicines, with a brief explanation of what it means. Products usually retain a black triangle for 5 years, but this can be extended if required.

Spontaneous reporting is particularly valuable for recognising possible new hazards rapidly. For medicines showing the black triangle symbol, the MHRA asks that all suspected reactions (including those considered not to be serious) are reported through the Yellow Card Scheme. An adverse reaction should be reported even if it is not certain that the drug has caused it, or if the reaction is well...
Adverse reactions to drugs

Established drugs and vaccines
Healthcare professionals and coroners are asked to report all suspected reactions to established drugs (including over-the-counter, herbal, and unlicensed medicines and medicines used off-label) and vaccines that are serious, medically significant, or result in harm. Serious reactions include those that are fatal, life-threatening, disabling, incapacitating, or which result in or prolong hospitalisation, or a congenital abnormality; they should be reported even if the effect is well recognised. Examples include anaphylaxis, blood disorders, endocrine disturbances, effects on fertility, haemorrhage from any site, renal impairment, jaundice, ophthalmic disorders, severe CNS effects, severe skin reactions, reactions in pregnant women, and any drug interactions. Reports of serious adverse reactions are required to enable comparison with other drugs of a similar class. Reports of overdoses (deliberate or accidental) can complicate the assessment of adverse drug reactions, but provide important information on the potential toxicity of drugs.

For established drugs there is no need to report well-known, relatively minor side-effects, such as dry mouth with tricyclic antidepressants or constipation with opioids.

Medication errors
Adverse drug reactions where harm occurs as a result of a medication error are reportable as a Yellow Card or through the local risk management systems into the National Reporting and Learning System (NRLS). If reported to the NRLS, these will be shared with the MHRA. If the NRLS is not available and harm occurs, report using a Yellow Card.

Adverse reactions to medical devices
Suspected adverse reactions to medical devices including dental or surgical materials, intra-uterine devices, and contact lens fluids should be reported. Information on reporting these can be found at: www.mhra.gov.uk.

Side-effects in the BNF
The BNF includes clinically relevant side-effects for most drugs; an exhaustive list is not included for drugs that are used by specialists (e.g. cytotoxic drugs and drugs used in anaesthesia). Where causality has not been established, side-effects in the manufacturers’ literature may be omitted from the BNF.

Recognising that hypersensitivity reactions can occur with virtually all medicines, this effect is not generally listed, unless the drug carries an increased risk of such reactions. The BNF also omits effects that are likely to have little clinical consequence (e.g. transient increase in liver enzymes).

Side-effects are generally listed in order of frequency and arranged broadly by body systems. Occasionally a rare side-effect might be listed first if it is considered to be particularly important because of its seriousness.

In the product literature the frequency of side-effects is generally described as follows:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>greater than 1 in 10</td>
</tr>
<tr>
<td>Common</td>
<td>1 in 100 to 1 in 10</td>
</tr>
<tr>
<td>Uncommon</td>
<td>1 in 1000 to 1 in 100</td>
</tr>
<tr>
<td>Rare</td>
<td>less than 1 in 10 000</td>
</tr>
</tbody>
</table>

Special problems

Delayed drug effects Some reactions (e.g. cancers, chloroquine retinopathy, and retroperitoneal fibrosis) may become manifest months or years after exposure. Any suspicion of such an association should be reported directly to the MHRA through the Yellow Card Scheme.

The elderly Particular vigilance is required to identify adverse reactions in the elderly.

Congenital abnormalities When an infant is born with a congenital abnormality or there is a malformed aborted fetus doctors are asked to consider whether this might be an adverse reaction to a drug and to report all drugs (including self-medication) taken during pregnancy.

Children Particular vigilance is required to identify and report adverse reactions in children, including those resulting from the unlicensed use of medicines; all suspected reactions should be reported directly to the MHRA through the Yellow Card Scheme (see also Adverse Drug Reactions in Children).

Prevention of adverse reactions
Adverse reactions may be prevented as follows:
- never use any drug unless there is a good indication. If the patient is pregnant do not use a drug unless the need for it is imperative;
- allergy and idiosyncrasy are important causes of adverse drug reactions. Ask if the patient had previous reactions to the drug or formulation;
- ask if the patient is already taking other drugs including self-medication drugs, health supplements, complementary and alternative therapies; interactions may occur;
- age and hepatic or renal disease may alter the metabolism or excretion of drugs, so that much smaller doses may be needed. Genetic factors may also be responsible for variations in metabolism, and therefore for the adverse effect of the drug; notably of isoniazid p. 506 and the tricyclic antidepressants;
- prescribe as few drugs as possible and give very clear instructions to the elderly or any patient likely to misunderstand complicated instructions;
- whenever possible use a familiar drug; with a new drug, be particularly alert for adverse reactions or unexpected events;
- consider if excipients (e.g. colouring agents) may be contributing to the adverse reaction. If the reaction is minor, a trial of an alternative formulation of the same drug may be considered before abandoning the drug;
- warn the patient if serious adverse reactions are liable to occur.

Oral side-effects of drugs
Drug-induced disorders of the mouth may be due to a local action on the mouth or to a systemic effect manifested by oral changes. In the latter case urgent referral to the patient’s medical practitioner may be necessary.
Oral mucosa Medicaments left in contact with or applied directly to the oral mucosa can lead to inflammation or ulceration; the possibility of allergy should also be borne in mind. Aspirin p. 104 tablets allowed to dissolve in the sulcus for the treatment of toothache can lead to a white patch followed by ulceration.

Flavouring agents, particularly essential oils, may sensitise the skin, but mucosal swelling is not usually prominent. The oral mucosa is particularly vulnerable to ulceration in patients treated with cytotoxic drugs, e.g. methotrexate p. 762. Other drugs capable of causing oral ulceration include ACE inhibitors, gold, nicoardil p. 185, NSAIDs, pancreatin p. 81, penicillamine p. 896, proguanil hydrochloride p. 539, and protease inhibitors. Erythema multiforme or Stevens-Johnson syndrome may follow the use of a wide range of drugs including antibacterials, antiretrovirals, sulphonamide derivatives, and anticonvulsants; the oral mucosa may be extensively ulcerated, with characteristic target lesions on the skin. Oral lesions of toxic epidermal necrolysis have been reported with a similar range of drugs. Lichenoid eruptions are associated with ACE inhibitors, NSAIDs methylprednisoil p. 138, chloroquine p. 536, oral antidiabetics, thiazide diuretics, and gold. Candidiasis can complicate treatment with antibacterials and immunosuppressants and is an occasional side-effect of corticosteroid inhalers.

Teeth and jaw Brown staining of the teeth frequently follows the use of chlorhexidine p. 989 mouthwash, spray or gel, but can readily be removed by polishing. Iron salts in liquid form can stain the enamel black. Superficial staining has been reported rarely with co-amoxiclav p. 484 suspension. Intrinsic staining of the teeth is most commonly caused by tetracyclines. They will affect the teeth if given at any time from about the fourth month in utero until the age of twelve years; they are contra-indicated during pregnancy, in breast-feeding women, and in children under 12 years. All tetracyclines can cause permanent, unsightly staining in children, the colour varying from yellow to grey. Excessive ingestion of fluoride leads to dental fluorosis with mottling of the enamel and areas of hypoplasia or pitting; fluoride supplements occasionally cause mild mottling (white patches) if the dose is too large for the child’s age (taking into account the fluoride content of the local drinking water and of toothpaste). The risk of osteonecrosis of the jaw is substantially greater for patients receiving intravenous bisphosphonates in the treatment of cancer than for patients receiving oral bisphosphonates for osteoporosis or Fagate’s disease. All patients receiving bisphosphonates should have a dental check-up (and any necessary remedial work should be performed) before bisphosphonate treatment, or as soon as possible after starting treatment. Patients with cancer receiving bevacizumab p. 736 or sunitinib p. 817 may also be at risk of osteonecrosis of the jaw. Periodontium Gingival overgrowth (gingival hyperplasia) is a side-effect of phenytoin p. 398 and sometimes of ciclosporin p. 717 or of nifedipine p. 154 (and some other calcium-channel blockers). Thrombocytopenia may be drug related and may cause bleeding at the gingival margins, which may be spontaneous or may follow mild trauma (such as toothbrushing).

Salivary glands The most common effect that drugs have on the salivary glands is to reduce flow (xerostomia). Patients with a persistently dry mouth may have poor oral hygiene; they are at an increased risk of dental caries and oral infections (particularly candidiasis). Many drugs have been implicated in xerostomia, particularly antimuscarinics (anticholinergic), antidepressants (including tricyclic antidepressants, and selective serotonin re-uptake inhibitors), alpha-blockers, antihistamines, antipsychotics, baclofen p. 914, bupropion hydrochloride p. 433, clonidine hydrochloride p. 137, 5HT; agonists, opioids, and tizanidine p. 913. Excessive use of diuretics can also result in xerostomia. Some drugs (e.g. clozapine p. 313, neostigmine p. 912) can increase saliva production but this is rarely a problem unless the patient has associated difficulty in swallowing. Pain in the salivary glands has been reported with some antihypertensives (e.g. clonidine hydrochloride p. 137, methylprednisoil p. 138) and with vinca alkaloids. Swelling of the salivary glands can occur with iodides, antithyroid drugs, phenothiazines, and sulphonamides.

Taste There may be decreased taste acuity or alteration in taste sensation. Many drugs are implicated, including amiodarone hydrochloride p. 88, calcitonin, ACE inhibitors, carbimazole p. 664, clarithromycin p. 470, gold, griseofulvin p. 1012, lithium salts, metformin hydrochloride p. 594, metronidazole p. 475, penicillamine p. 896, phenindione p. 129, propafenone hydrochloride p. 92, protease inhibitors, terbinafine p. 514, and zopiclone p. 423.

Defective medicines During the manufacture or distribution of a medicine an error or accident may occur whereby the finished product does not conform to its specification. While such a defect may impair the therapeutic effect of the product and could adversely affect the health of a patient, it should not be confused with an Adverse Drug Reaction where the product conforms to its specification. The Defective Medicines Report Centre assists with the investigation of problems arising from licensed medicinal products thought to be defective and co-ordinates any necessary protective action. Reports on suspect defective medicinal products should include the brand or the non-proprietary name, the name of the manufacturer or supplier, the strength and dosage form of the product, the product licence number, the batch number or numbers of the product, the nature of the defect, and an account of any action already taken in consequence. The Centre can be contacted at:

The Defective Medicines Report Centre
Medicines and Healthcare products Regulatory Agency
151 Buckingham Palace Road
London SW1W 9SZ
Tel: (020) 3080 6588
info@mhra.gsi.gov.uk
Guidance on intravenous infusions

Intravenous additives policies
A local policy on the addition of drugs to intravenous fluids should be drawn up by a multi-disciplinary team in each Strategic Health Authority (or equivalent) and issued as a document to the members of staff concerned. Centralised additive services are provided in a number of hospital pharmacy departments and should be used in preference to making additions on wards.

The information that follows should be read in conjunction with local policy documents.

Guidelines
- Drugs should only be added to infusion containers when constant plasma concentrations are needed or when the administration of a more concentrated solution would be harmful.
- In general, only one drug should be added to any infusion container and the components should be compatible. Ready-prepared solutions should be used whenever possible. Drugs should not normally be added to blood products, mannitol, or sodium bicarbonate.
- Only specially formulated additives should be used with fat emulsions or amino-acid solutions.
- Solutions should be thoroughly mixed by shaking and checked for absence of particulate matter before use.
- Strict asepsis should be maintained throughout and in general the giving set should not be used for more than 24 hours (for drug admixtures).
- The infusion container should be labelled with the patient’s name, the name and quantity of additives, and the date and time of addition (and the new expiry date or time). Such additional labelling should not interfere with information on the manufacturer’s label that is still valid. When possible, containers should be retained for a period after use in case they are needed for investigation.
- It is good practice to examine intravenous infusions from time to time while they are running. If cloudiness, crystallisation, change of colour, or any other sign of interaction or contamination is observed the infusion should be discontinued.

Problems
Microbial contamination The accidental entry and subsequent growth of micro-organisms converts the infusion fluid pathway into a potential vehicle for infection with micro-organisms, particularly species of Candida, Enterobacter, and Klebsiella. Ready-prepared infusions containing the additional drugs, or infusions prepared by an additive service (when available) should therefore be used in preference to making extemporaneous additions to infusion containers on wards etc. However, when this is necessary strict aseptic procedure should be followed.

Incompatibility Physical and chemical incompatibilities may occur with loss of potency, increase in toxicity, or other adverse effect. The solutions may become opalescent or precipitation may occur, but in many instances there is no visual indication of incompatibility. Interaction may take place at any point in the infusion fluid pathway, and the potential for incompatibility is increased when more than one substance is added to the infusion fluid.

Common incompatibilities Precipitation reactions are numerous and varied and may occur as a result of pH, concentration changes, ‘sinking-out’ effects, complexation or other chemical changes. Precipitation or other particle formation must be avoided since, apart from lack of control of dosage on administration, it may initiate or exacerbate adverse effects. This is particularly important in the case of drugs which have been implicated in either thrombophlebitis (e.g. diazepam) or skin sloughing or necrosis caused by extravasation (e.g. sodium bicarbonate and certain cytotoxic drugs). It is also especially important to effect solution of colloidal drugs and to prevent their subsequent precipitation in order to avoid a pyrogenic reaction (e.g. amphotericin).

It is considered undesirable to mix beta-lactam antibiotics, such as semi-synthetic penicillins and cephalosporins, with proteinaceous materials on the grounds that immunogenic and allergic conjugates could be formed.

A number of preparations undergo significant loss of potency when added singly or in combination to large volume infusions. Examples include ampicillin in infusions that contain glucose or lactates. The breakdown products of dacarbazine have been implicated in adverse effects.

Blood Because of the large number of incompatibilities, drugs should not normally be added to blood and blood products for infusion purposes. Examples of incompatibility with blood include hypertonic mannitol solutions (irreversible crenation of red cells), dextran (formation and interference with cross-matching), glucose (clumping of red cells), and oxytocin (interaction with blood include hypertonic mannitol solutions (irreversible crenation of red cells), dextran (formation and interference with cross-matching), glucose (clumping of red cells), and oxytocin (interaction with blood). If the giving set is not changed after the administration of blood, but used for other infusion fluids, a fibrin clot may form which, apart from blocking the set, increases the likelihood of microbial growth.

Intravenous fat emulsions These may break down with coalescence of fat globules and separation of phases when additions such as antibacterials or electrolytes are made, thus increasing the possibility of embolism. Only specially formulated products such as Vitlipid N® may be added to appropriate intravenous fat emulsions.

Other infusions Infusions that frequently give rise to incompatibility include amino acids, mannitol, and sodium bicarbonate.

Bactericides Bactericides such as chlorocresol 0.1% or phenylmercuric nitrate 0.001% are present in some injection solutions. The total volume of such solutions added to a container for infusion on one occasion should not exceed 15 ml.

Method
Ready-prepared infusions should be used whenever available. Potassium chloride is usually available in concentrations of 20, 27, and 40 mmol/litre in sodium chloride intravenous infusion (0.9%), glucose intravenous infusion (5%) or sodium chloride and glucose intravenous infusion. Lidocaine hydrochloride is usually available in concentrations of 0.1 or 0.2% in glucose intravenous infusion (5%).

When addition is required to be made extemporaneously, any product reconstitution instructions such as those relating to concentration, vehicle, mixing, and handling precautions should be strictly followed using an aseptic technique throughout. Once the product has been reconstituted, addition to the infusion fluid should be made immediately in order to minimise microbial contamination and, with certain products, to prevent degradation or other formulation change which may occur; e.g. reconstituted ampicillin injection degrades rapidly on standing, and also may form polymers which could cause sensitivity reactions. It is also important in certain instances that an infusion fluid of specific pH be used (e.g. furosemide injection requires dilution in infusions of pH greater than 5.5). When drug additions are made it is important to mix thoroughly; additions should not be made to an infusion container that has been connected to a giving set, as mixing
is hampered. If the solutions are not thoroughly mixed a concentrated layer of the additive may form owing to differences in density. Potassium chloride is particularly prone to this ‘layering’ effect when added without adequate mixing to infusions packed in non-rigid infusion containers; if such a mixture is administered it may have a serious effect on the heart.

A time limit between addition and completion of administration must be imposed for certain admixtures to guarantee satisfactory drug potency and compatibility. For admixtures in which degradation occurs without the formation of toxic substances, an acceptable limit is the time taken for 10% decomposition of the drug. When toxic substances are produced stricter limits may be imposed. Because of the risk of microbial contamination a maximum time limit of 24 hours may be appropriate for additions made elsewhere than in hospital pharmacies offering central additive service.

Certain injections must be protected from light during continuous infusion to minimise oxidation, e.g. dacarbazine and sodium nitroprusside.

Dilution with a small volume of an appropriate vehicle and administration using a motorised infusion pump is advocated for preparations such as unfractionated heparin where strict control over administration is required. In this case the appropriate dose may be dissolved in a convenient volume (e.g. 24–48 mL) of sodium chloride intravenous infusion (0.9%).

Information provided in the BNF

The BNF gives information about preparations given by three methods:

- continuous infusion;
- intermittent infusion;
- addition via the drip tubing.

Drugs for continuous infusion must be diluted in a large volume infusion. Penicillins and cephalosporins are not usually given by continuous infusion because of stability problems and because adequate plasma and tissue concentrations are best obtained by intermittent infusion. Where it is necessary to administer them by continuous infusion, detailed literature should be consulted.

Drugs that are both compatible and clinically suitable may be given by intermittent infusion in a relatively small volume of infusion over a short period of time, e.g. 100 mL in 30 minutes. The method is used if the product is incompatible or unstable over the period necessary for continuous infusion; the limited stability of ampicillin or amoxicillin in large volume glucose or lactate infusions may be overcome in this way.

Intermittent infusion is also used if adequate plasma and tissue concentrations are not produced by continuous infusion as in the case of drugs such as dacarbazine, gentamicin, and ticarcillin. An in-line burette may be used for intermittent infusion techniques in order to achieve strict control over the time and rate of administration, especially for infants and children and in intensive care units. Intermittent infusion may also make use of the ‘piggy-back’ technique provided that no additions are made to the primary infusion. In this method the drug is added to a small secondary container connected to a Y-type injection site on the primary infusion giving set; the secondary solution is usually infused within 30 minutes.

Addition via the drip tubing is indicated for a number of cytotoxic drugs in order to minimise extravasation. The preparation is added aseptically via the rubber septum of the injection site of a fast-running infusion. In general, drug preparations intended for a bolus effect should be given directly into a separate vein where possible. Failing this, administration may be made via the drip tubing provided that the preparation is compatible with the infusion fluid when given in this manner.

Drugs given by intravenous infusion

The BNF includes information on addition of drugs to Glucose intravenous infusion 5 and 10%, and Sodium chloride intravenous infusion 0.9%. Compatibility with glucose 5% and with sodium chloride 0.9% indicates compatibility with Sodium chloride and glucose intravenous infusion. Infusion of a large volume of hypotonic solution should be avoided therefore care should be taken if water for injections is used. The information relates to the proprietary preparations indicated; for other preparations suitability should be checked with the manufacturer.
Prescribing for children

For detailed advice on medicines used for children, consult BNF for Children.

Children, and particularly neonates, differ from adults in their response to drugs. Special care is needed in the neonatal period (first 28 days of life) and doses should always be calculated with care. At this age, the risk of toxicity is increased by reduced drug clearance and differing target organ sensitivity. Whenever possible, intramuscular injections should be avoided in children because they are painful. Where possible, medicines for children should be prescribed within the terms of the marketing authorisation (product licence). However, many children may require medicines not specifically licensed for paediatric use. Although medicines cannot be promoted outside the limits of the licence, the Human Medicines Regulations 2012 does not prohibit the use of unlicensed medicines. It is recognised that the informed use of unlicensed medicines or of licensed medicines for unlicensed applications (‘off-label’ use) is often necessary in paediatric practice.

Adverse drug reactions in children

Suspected adverse drug reactions in children and young adults under 18 years should be reported through the Yellow Card Scheme. Yellow cards can be used for reporting suspected adverse drug reactions to medicines, vaccines, herbal or complementary products, whether self-medicated or prescribed. This includes suspected adverse drug reactions associated with misuse, overdose, medication errors or from use of unlicensed and off-label medicines. Yellow Cards can also be used to report medical device incidents, defective medicines, and suspected fake medicines.

Report all suspected adverse drug reactions that are:

- serious, medically significant or result in harm.
- associated with newer drugs and vaccines; the most up to date list of black triangle medicines is available at: www.mhra.gov.uk/blacktriangle

If in doubt whether to report a suspected adverse drug reaction, please complete a Yellow Card. The identification and reporting of adverse reactions to drugs in children and neonates is particularly important because:

- the action of the drug and its pharmacokinetics in children (especially in the very young) may be different from that in adults;
- many drugs are not specifically licensed for use in children and are used either ‘off-label’ or as unlicensed products;
- drugs may affect the way a child grows and develops or may cause delayed adverse reactions which do not occur in adults;
- suitable formulations may not be available to allow precise dosing in children or they may contain excipients that should be used with caution in children;
- the nature and course of illnesses and adverse drug reactions may differ between adults and children.

Even if reported through the British Paediatric Surveillance Unit’s Orange Card Scheme, any identified suspected adverse drug reactions should also be submitted to the Yellow Card Scheme.

Adverse drug reactions where harm occurs as a result of a medication error are reportable as a Yellow Card or through the local risk management systems into the National Reporting and Learning System (NRLS). If reported to the NRLS, these will be shared with the MHRA. If the NRLS is not available and harm occurs, report using a Yellow Card.

Prescription writing

Prescriptions should be written according to the guidelines in Prescription Writing. Inclusion of age is a legal requirement in the case of prescription-only medicines for children under 12 years of age, but it is preferable to state the age for all prescriptions for children. It is particularly important to state the strengths of capsules or tablets. Although liquid preparations are particularly suitable for children, they may contain sugar which encourages dental decay. Sugar-free medicines are preferred for long-term treatment.

Many children are able to swallow tablets or capsules and may prefer a solid dose form; involving the child and parents in choosing the formulation is helpful. When a prescription for a liquid oral preparation is written and the dose ordered is smaller than 5 mL an oral syringe will be supplied. Parents should be advised not to add any medicines to the infant’s feed, since the drug may interact with the milk or other liquid in it; moreover the ingested dosage may be reduced if the child does not drink all the contents. Parents must be warned to keep all medicines out of reach of children.

Rare paediatric conditions

Information on substances such as biotin and sodium benzoate used in rare metabolic conditions is included in BNF for Children; further information can be obtained from:

Alder Hey Children’s Hospital
Drug Information Centre
Liverpool L12 2AP
Tel: (0151) 252 5381

Great Ormond Street Hospital for Children
Pharmacy
Great Ormond St
London WC1N 3JH
Tel: (020) 7405 9200

Dosage in children

Children’s doses in the BNF are stated in the individual drug entries or a cross-reference is provided to BNF for Children. Doses are generally based on body-weight (in kilograms) or specific age ranges, e.g. first month (neonate), 1–5 years, 6–11 years, 12–17 years.

Dose calculation

Many children’s doses are standardised by weight (and therefore require multiplying by the body-weight in kilograms to determine the child’s dose); occasionally, the doses have been standardised by body surface area (in m²). These methods should be used rather than attempting to calculate a child’s dose on the basis of doses used in adults. For most drugs the adult maximum dose should not be exceeded. For example if the dose is stated as 8 mg/kg (max. 300 mg), a child weighing 10 kg should receive 80 mg but a child weighing 40 kg should receive 300 mg (rather than 320 mg).

Young children may require a higher dose per kilogram than adults because of their higher metabolic rates. Other problems need to be considered. For example, calculation by body-weight in the overweight child may result in much higher doses being administered than necessary; in such cases, dose should be calculated from an ideal weight, related to height and age.

Body surface area (BSA) estimates are sometimes preferable to body-weight for calculation of paediatric doses.
since many physiological phenomena correlate better with body surface area. Body surface area can be estimated from weight. For more information, refer to BNF for Children. Where the dose for children is not stated, prescribers should consult BNF for Children or seek advice from a medicines information centre.

**Dose frequency**
Antibacterials are generally given at regular intervals throughout the day. Some flexibility should be allowed in children to avoid waking them during the night. For example, the night-time dose may be given at the child’s bedtime. Where new or potentially toxic drugs are used, the manufacturers’ recommended doses should be carefully followed.

**Prescribing in hepatic impairment**
Liver disease may alter the response to drugs in several ways as indicated below, and drug prescribing should be kept to a minimum in all patients with severe liver disease. The main problems occur in patients with jaundice, ascites, or evidence of encephalopathy.

**Impaired drug metabolism**
Metabolism by the liver is the main route of elimination for many drugs, but hepatic reserve is large and liver disease has to be severe before important changes in drug metabolism occur. Routine liver-function tests are a poor guide to the capacity of the liver to metabolise drugs, and in the individual patient it is not possible to predict the extent to which the metabolism of a particular drug may be impaired.
A few drugs, e.g. rifampicin p. 508 and fusidic acid p. 463, are excreted in the bile unchanged and can accumulate in patients with intrahepatic or extrahepatic obstructive jaundice.

**Hypoproteinaemia**
The hypoalbuminaemia in severe liver disease is associated with reduced protein binding and increased toxicity of some highly protein-bound drugs such as phenytoin p. 398 and prednisolone p. 585.

**Reduced clotting**
Reduced hepatic synthesis of blood-clotting factors, indicated by a prolonged prothrombin time, increases the sensitivity to oral anticoagulants such as warfarin sodium p. 121 and phenindione p. 120.

**Hepatic encephalopathy**
In severe liver disease many drugs can further impair cerebral function and may precipitate hepatic encephalopathy. These include all sedative drugs, opioid analgesics, those diuretics that produce hypokalaemia, and drugs that cause constipation.

**Fluid overload**
Oedema and ascites in chronic liver disease can be exacerbated by drugs that give rise to fluid retention e.g. NSAIDs and corticosteroids.

**Hepatotoxic drugs**
Hepatotoxicity is either dose-related or unpredictable (idiosyncratic). Drugs that cause dose-related toxicity may do so at lower doses in the presence of hepatic impairment than in individuals with normal liver function, and some drugs that produce reactions of the idiosyncratic kind do so more frequently in patients with liver disease. These drugs should be avoided or used very carefully in patients with liver disease.
Where care is needed when prescribing in hepatic impairment, this is indicated under the relevant drug in the BNF.

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**Prescribing in renal impairment**
The use of drugs in patients with reduced renal function can give rise to problems for several reasons:

- reduced renal excretion of a drug or its metabolites may cause toxicity;
- sensitivity to some drugs is increased even if elimination is unimpaired;
- many side-effects are tolerated poorly by patients with renal impairment;
- some drugs are not effective when renal function is reduced.

Many of these problems can be avoided by reducing the dose or by using alternative drugs.

**Principles of dose adjustment in renal impairment**
The level of renal function below which the dose of a drug must be reduced depends on the proportion of the drug eliminated by renal excretion and its toxicity. For many drugs with only minor or no dose-related side-effects very precise modification of the dose regimen is unnecessary and a simple scheme for dose reduction is sufficient. For more toxic drugs with a small safety margin or patients at extremes of weight, dose regimens based on creatinine clearance should be used. When both efficacy and toxicity are closely related to plasma-drug concentration, recommended regimens should be regarded only as a guide to initial treatment; subsequent doses must be adjusted.
Prescribing in renal impairment

according to clinical response and plasma-drug concentration. Renal function declines with age; many elderly patients have renal impairment but, because of reduced muscle mass, this may not be indicated by a raised serum creatinine. It is wise to assume at least mild impairment of renal function when prescribing for the elderly. The total daily maintenance dose of a drug can be reduced either by reducing the size of the individual doses or by increasing the interval between doses. For some drugs, although the size of the maintenance dose is reduced it is important to give a loading dose if an immediate effect is required. This is because it takes about five times the half-life of the drug to achieve steady-state plasma concentrations. Because the plasma half-life of drugs excreted by the kidney is prolonged in renal impairment it can take many doses for the reduced dosage to achieve a therapeutic plasma concentration. The loading dose should usually be the same size as the initial dose for a patient with normal renal function. Nephrotoxic drugs should, if possible, be avoided in patients with renal disease because the consequences of nephrotoxicity are likely to be more serious when renal reserve is already reduced. Dose recommendations are based on the severity of renal impairment. Renal function is measured either in terms of estimated glomerular filtration rate (eGFR) calculated from a formula derived from the Modification of Diet in Renal Disease study (‘MDRD formula’ that uses serum creatinine, age, sex, and race (for Afro-Caribbean patients)) or it can be expressed as creatinine clearance (best derived from a 24-hour urine collection but often calculated from the Cockcroft and Gault formula (CG)).

Cockcroft and Gault Formula

\[
\text{Estimated Creatinine Clearance} = \frac{(140 - \text{Age}) \times \text{Weight} \times \text{Constant}}{\text{Serum creatinine}} \quad \text{in mL/minute}
\]

Age in years
Weight in kilograms; use ideal body-weight
Serum creatinine in micromol/litre
Constant = 1.23 for men; 1.04 for women

The serum-creatinine concentration is sometimes used instead as a measure of renal function but it is only a rough guide to drug dosing.

Important Renal function in adults is increasingly being reported on the basis of estimated glomerular filtration rate (eGFR) normalised to a body surface area of 1.73 m² and derived from the Modification of Diet in Renal Disease (MDRD) formula. However, published information on the effects of renal impairment on drug elimination is usually stated in terms of creatinine clearance as a surrogate for glomerular filtration rate (GFR). The information on dosage adjustment in the BNF is expressed in terms of eGFR, rather than creatinine clearance, for most drugs (exceptions include toxic drugs and patients at extremes of weight). Although the two measures of renal function are not interchangeable, in practice, for most drugs and for most patients (over 18 years) of average build and height, eGFR (MDRD ‘formula’) can be used to determine dosage adjustments in place of creatinine clearance. An individual’s absolute glomerular filtration rate can be calculated from the eGFR as follows:

\[
\text{GFR Absolute} = \text{eGFR} \times (\text{individual’s body surface area}/1.73)
\]

Toxic drugs For potentially toxic drugs with a small safety margin, creatinine clearance (calculated from the Cockcroft and Gault formula) should be used to adjust drug dosages in addition to plasma-drug concentration and clinical response.

Patients at extremes of weight In patients at both extremes of weight (BMI of less than 18.5 kg/m² or greater than 30 kg/m²) the absolute glomerular filtration rate or creatinine clearance (calculated from the Cockcroft and Gault formula) should be used to adjust drug dosages.

In the BNF, values for eGFR, creatinine clearance (for toxic drugs), or another measure of renal function are included where possible. However, where such values are not available, the BNF reflects the terms used in the published information.

### Chronic kidney disease in adults: UK guidelines for identification, management and referral (March 2006) define renal function as follows:

<table>
<thead>
<tr>
<th>Degree of impairment</th>
<th>eGFR mL/minute/1.73 m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal - Stage 1</td>
<td>More than 90 (with other evidence of kidney damage)</td>
</tr>
<tr>
<td>Mild - Stage 2</td>
<td>60–89 (with other evidence of kidney damage)</td>
</tr>
<tr>
<td>Moderate - Stage 3</td>
<td>30–59</td>
</tr>
<tr>
<td>Severe - Stage 4</td>
<td>15–29</td>
</tr>
<tr>
<td>Established renal failure - Stage 5</td>
<td>Less than 15</td>
</tr>
</tbody>
</table>

1. NICE clinical guideline 73 (September 2008) — Chronic kidney disease: Stage 3a eGFR 45–59, Stage 3b eGFR 30–44

Dialysis

For prescribing in patients on continuous ambulatory peritoneal dialysis (CAPD) or haemodialysis, consult specialist literature.

Drug prescribing should be kept to the minimum in all patients with severe renal disease. If even mild renal impairment is considered likely on clinical grounds, renal function should be checked before prescribing any drug which requires dose modification. Where care is needed when prescribing in renal impairment, this is indicated under the relevant drug in the BNF.
Prescribing in pregnancy

Drugs can have harmful effects on the embryo or fetus at any time during pregnancy. It is important to bear this in mind when prescribing for a woman of childbearing age or for men trying to father a child.

During the first trimester drugs can produce congenital malformations (teratogenesis), and the period of greatest risk is from the third to the eleventh week of pregnancy. During the second and third trimesters drugs can affect the growth or functional development of the fetus, or they can have toxic effects on fetal tissues.

Drugs given shortly before term or during labour can have adverse effects on labour or on the neonate after delivery. Not all the damaging effects of intra-uterine exposure to drugs are obvious at birth, some may only manifest later in life. Such late-onset effects include malignancy, e.g. adenocarcinoma of the vagina after puberty in females exposed to diethylstilbestrol in the womb, and adverse effects on intellectual, social, and functional development.

The BNF and BNF for Children identifies drugs which:
- may have harmful effects in pregnancy and indicates the trimester of risk
- are not known to be harmful in pregnancy

The information is based on human data, but information from animal studies has been included for some drugs when its omission might be misleading. Maternal drug doses may require adjustment during pregnancy due to changes in maternal physiology but this is beyond the scope of the BNF and BNF for Children.

Where care is needed when prescribing in pregnancy, this is indicated under the relevant drug in the BNF and BNF for Children.

Important Drugs should be prescribed in pregnancy only if the expected benefit to the mother is thought to be greater than the risk to the fetus, and all drugs should be avoided if possible during the first trimester. Drugs which have been extensively used in pregnancy and appear to be usually safe should be prescribed in preference to new or untried drugs; and the smallest effective dose should be used. Few drugs have been shown conclusively to be teratogenic in humans, but no drug is safe beyond all doubt in early pregnancy.

Screening procedures are available when there is a known risk of certain defects.

Absence of information does not imply safety. It should be noted that the BNF and BNF for Children provide independent advice and may not always agree with the product literature.

Information on drugs and pregnancy is also available from the UK Teratology Information Service. Tel: 0844 892 0909 (09:00–17:00 Monday to Friday; urgent enquiries only outside these hours).

Prescribing in breast-feeding

Breast-feeding is beneficial; the immunological and nutritional value of breast milk to the infant is greater than that of formula feeds.

Although there is concern that drugs taken by the mother might affect the infant, there is very little information on this. In the absence of evidence of an effect, the potential for harm to the infant can be inferred from:
- the amount of drug or active metabolite of the drug delivered to the infant (dependent on the pharmacokinetic characteristics of the drug in the mother);
- the efficiency of absorption, distribution, and elimination of the drug by the infant (infant pharmacokinetics);
- the nature of the effect of the drug on the infant (pharmacodynamic properties of the drug in the infant).

The amount of drug transferred in breast milk is rarely sufficient to produce a discernible effect on the infant. This applies particularly to drugs that are poorly absorbed and need to be given parenterally. However, there is a theoretical possibility that a small amount of drug present in breast milk can induce a hypersensitivity reaction. A clinical effect can occur in the infant if a pharmacologically significant quantity of the drug is present in milk. For some drugs (e.g. fluvastatin p. 180), the ratio between the concentration in milk and that in maternal plasma may be high enough to expose the infant to adverse effects. Some infants, such as those born prematurely or who have jaundice, are at a slightly higher risk of toxicity. Some drugs inhibit the infant’s sucking reflex (e.g. phenobarbital p. 409) while others can affect lactation (e.g. bromocriptine p. 333).
Prescribing in palliative care

Palliative care is an approach that improves the quality of life of patients and their families facing life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual. Careful assessment of symptoms and needs of the patient should be undertaken by a multidisciplinary team. Specialist palliative care is available in most areas as day hospice care, home-care teams (often known as Macmillan teams), in-patient hospice care, and hospital teams. Many acute hospitals and teaching centres now have consultative, hospital-based teams. Hospice care of terminally ill patients has shown the importance of symptom control and psychosocial support of the patient and family. Families should be included in the care of the patient if they wish. Many patients wish to remain at home with their families. Although some families may at first be afraid of caring for the patient at home, support can be provided by community nursing services, social services, voluntary agencies and hospices together with the general practitioner. The family may be reassured by the knowledge that the patient will be admitted to a hospital or hospice if the family cannot cope.

Drug treatment

The number of drugs should be as few as possible, for even the taking of medicine may be an effort. Oral medication is usually satisfactory unless there is severe nausea and vomiting, dysphagia, weakness, or coma, when parenteral medication may be necessary.

Pain

Pain management in palliative care is focused on achieving control of pain by administering the right drug in the right dose at the right time. Analgesics can be divided into three broad classes: non-opioid (paracetamol p. 354, NSAID), opioid (e.g. codeine phosphate p. 360 ‘weak’, morphine p. 367 ‘strong’) and adjuvant (e.g. antidepressants, antiepileptics). Drugs from the different classes are used alone or in combination according to the type of pain and response to treatment. Analgesics are more effective in preventing pain than in the relief of established pain; it is important that they are given regularly.

Paracetamol or a NSAID given regularly will often be sufficient to manage mild pain. If non-opioid analgesics alone are not sufficient, then an opioid analgesic alone or in combination with a non-opioid analgesic at an adequate dosage, may be helpful in the control of moderate pain. Codeine phosphate or tramadol hydrochloride p. 373 can be considered for moderate pain. If these preparations do not control the pain then morphine is the most useful opioid analgesic. Alternatives to morphine, including transdermal buprenorphine p. 434, transdermal fentanyl p. 362, hydromorphone hydrochloride p. 366, methadone hydrochloride p. 436, or oxycodone hydrochloride p. 369, should be initiated by those with experience in palliative care. Initiation of an opioid analgesic should not be delayed by concern over a theoretical likelihood of psychological dependence (addiction).

Bone metastases

In addition to the above approach, radiotherapy, bisphosphonates, and radioactive isotopes of strontium ranelate p. 626 (Metastron® available from GE Healthcare) may be useful for pain due to bone metastases.

Neuropathic pain

Patients with neuropathic pain may benefit from a trial of a tricyclic antidepressant. An antiepileptic may be added or substituted if pain persists; gabapentin p. 392 and pregabalin p. 400 are licensed for neuropathic pain. Ketamine p. 1110 is sometimes used under specialist supervision for neuropathic pain that responds poorly to opioid analgesics. Pain due to nerve compression may be reduced by a corticosteroid such as dexamethasone p. 947, which reduces oedema around the tumour, thus reducing compression. Nerve blocks or regional anaesthesia techniques (including the use of epidural and intrathecal catheters) can be considered when pain is localised to a specific area.

Pain management with opioids

Oral route

Treatment with morphine p. 367 is given by mouth as immediate-release or modified-release preparations. During the titration phase the initial dose is based on the previous medication used, the severity of the pain, and other factors such as presence of renal impairment, increasing age, or frailty. The dose is given either as an immediate-release preparation 4-hourly or as a modified-release preparation 12-hourly, in addition to rescue doses.

If pain occurs between regular doses of morphine (‘breakthrough pain’), an additional dose (‘rescue dose’) of immediate-release morphine should be given. An additional dose should also be given 30 minutes before an activity that causes pain, such as wound dressing. The standard dose of a strong opioid for breakthrough pain is usually one-tenth to one-sixth of the regular 24-hour dose, repeated every 2–4 hours as required (up to hourly may be needed if pain is severe or in the last days of life). Review pain management if rescue analgesic is required frequently (twice daily or more). Each patient should be assessed on an individual basis. Formulations of fentanyl p. 362 that are administered nasally, buccally or sublingually are also licensed for breakthrough pain.

When adjusting the dose of morphine, the number of rescue doses required and the response to them should be taken into account; increments of morphine should not exceed one-third to one-half of the total daily dose every 24 hours. Thereafter, the dose should be adjusted with careful assessment of the pain, and the use of adjuvant analgesics should also be considered. Upward titration of the dose of morphine stops when either the pain is relieved or unacceptable adverse effects occur, after which it is necessary to consider alternative measures. Morphine immediate-release 30mg 4-hourly (or modified-release 100mg 12-hourly) is usually adequate for most patients; some patients require morphine immediate-release up to 200mg 4-hourly (or modified-release 600mg 12-hourly), occasionally more is needed.

Once their pain is controlled, patients started on 4-hourly immediate-release morphine can be transferred to the same total 24-hour dose of morphine given as the modified-release preparation for 12-hourly or 24-hourly administration. The first dose of the modified-release preparation is given with, or within 4 hours of, the last dose of the immediate-release preparation. For preparations suitable for 12-hourly or 24-hourly administration see modified-release preparations under morphine p. 367. Increments should be made to the dose, not to the frequency of administration. The patient must be monitored closely for efficacy and side-effects, particularly constipation, and nausea and vomiting. A suitable laxative should be prescribed routinely.
Oxycodone hydrochloride p. 369 can be used in patients who require an opioid but cannot tolerate morphine. If the patient is already receiving an opioid, oxycodone hydrochloride should be started at a dose equivalent to the current analgesic (see below). Oxycodone hydrochloride immediate-release preparations can be given for breakthrough pain.

**Equivalent doses of opioid analgesics**

This table is only an approximate guide (doses may not correspond with those given in clinical practice); patients should be carefully monitored after any change in medication and dose titration may be required.

<table>
<thead>
<tr>
<th>Analgesic</th>
<th>Route</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>PO</td>
<td>100 mg</td>
</tr>
<tr>
<td>Diamorphine</td>
<td>IM, IV, SC</td>
<td>3 mg</td>
</tr>
<tr>
<td>Dihydromorphone</td>
<td>PO</td>
<td>100 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>PO</td>
<td>2 mg</td>
</tr>
<tr>
<td>Morphine</td>
<td>IM, IV, SC</td>
<td>5 mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>PO</td>
<td>6.6 mg</td>
</tr>
<tr>
<td>Tramadol</td>
<td>PO</td>
<td>100 mg</td>
</tr>
</tbody>
</table>

PO = by mouth; IM = intramuscular; IV = intravenous; SC = subcutaneous

**Parenteral route** The equivalent parenteral dose of morphine p. 367 (subcutaneous, intramuscular, or intravenous) is about half of the oral dose. If the patient becomes unable to swallow, generally morphine is administered as a continuous subcutaneous infusion (for details, see Continuous Subcutaneous Infusions below). Diamorphine hydrochloride p. 361 is sometimes preferred, because being more soluble, it can be given in a smaller volume. The equivalent subcutaneous dose of diamorphine hydrochloride is about one-third of the oral dose of morphine.

If the patient can resume taking medicines by mouth, then oral morphine may be substituted for subcutaneous infusion of morphine or diamorphine hydrochloride, see table above of approximate equivalent doses of morphine and diamorphine hydrochloride. The infusion is discontinued when the first oral dose of morphine is given.

**Rectal route** Morphine p. 367 is also available for rectal administration as suppositories; alternatively oxycodone hydrochloride suppositories p. 369 can be obtained on special order.

**Transdermal route** Transdermal preparations of fentanyl p. 362 and buprenorphine p. 434 are available, they are not suitable for acute pain or in patients whose analgesic requirements are changing rapidly because the long time to steady state prevents rapid titration of the dose. Prescribers should ensure that they are familiar with the correct use of transdermal preparations, see under buprenorphine p. 434 and fentanyl p. 362 (inappropriate use has caused fatalities). Immediate-release morphine can be given for breakthrough pain.

The following 24-hour oral doses of morphine are considered to be approximately equivalent to the buprenorphine and fentanyl patches shown, however when switching due to possible opioid-induced hyperalgesia, reduce the calculated equivalent dose of the new opioid by one-quarter to one-half.

**Buprenorphine patches are approximately equivalent to the following 24-hour doses of oral morphine**

<table>
<thead>
<tr>
<th>Morphine Salt</th>
<th>BuTrans®</th>
<th>7-day patches</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 mg daily</td>
<td>BuTrans®</td>
<td>5’ patch</td>
</tr>
<tr>
<td>24 mg daily</td>
<td>BuTrans®</td>
<td>10’ patch</td>
</tr>
<tr>
<td>48 mg daily</td>
<td>BuTrans®</td>
<td>20’ patch</td>
</tr>
<tr>
<td>84 mg daily</td>
<td>Transtec®</td>
<td>35’ patch</td>
</tr>
<tr>
<td>126 mg daily</td>
<td>Transtec®</td>
<td>70’ patch</td>
</tr>
<tr>
<td>168 mg daily</td>
<td>Transtec®</td>
<td>72.5’ patch</td>
</tr>
</tbody>
</table>

72-hour Fentanyl patches are approximately equivalent to the following 24-hour doses of oral morphine

<table>
<thead>
<tr>
<th>Morphine Salt</th>
<th>Fentanyl</th>
<th>7-day patches</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg daily</td>
<td>fentanyl ‘12’ patch</td>
<td></td>
</tr>
<tr>
<td>60 mg daily</td>
<td>fentanyl ‘25’ patch</td>
<td></td>
</tr>
<tr>
<td>120 mg daily</td>
<td>fentanyl ‘50’ patch</td>
<td></td>
</tr>
<tr>
<td>180 mg daily</td>
<td>fentanyl ‘75’ patch</td>
<td></td>
</tr>
<tr>
<td>240 mg daily</td>
<td>fentanyl ‘100’ patch</td>
<td></td>
</tr>
</tbody>
</table>

Conversion ratios vary and these figures are a guide only. Morphine equivalences for transdermal opioid preparations have been approximated to allow comparison with available preparations of oral morphine.

**Symptom control**

Several recommendations in this section involve unlicensed indications or routes.

**Anorexia** Anorexia may be helped by prednisolone p. 979 or dexamethasone p. 947.

**Bowel colic and excessive respiratory secretions** Bowel colic and excessive respiratory secretions may be reduced by a subcutaneous injection of hyoscine hydrobromide p. 344, hyoscine butylbromide p. 73, or glycopyrronium bromide p. 1100. These antimuscarinics are generally given every 4 hours when required, but hourly use is occasionally necessary, particularly in excessive respiratory secretions. If symptoms persist, they can be given regularly via a continuous infusion device. Care is required to avoid the discomfort of dry mouth.

**Capillary bleeding** Capillary bleeding can be treated with tranexamic acid p. 95 by mouth; treatment is usually discontinued one week after the bleeding has stopped, or, if necessary, it can be continued at a reduced dose. Alternatively, gauze soaked in tranexamic acid 100 mg/mL p. 95 or adrenaline/epinephrine solution 1 mg/mL (1 in 1000) p. 196 can be applied to the affected area. Vitamin K may be useful for the treatment and prevention of bleeding associated with prolonged clotting in liver.
disease. In severe chronic cholestasis, absorption of vitamin K may be impaired; either parenteral or water-soluble oral vitamin K (see phytomenadione p. 889) should be considered.

**Constipation** Constipation is a common cause of distress and is almost invariable after administration of an opioid analgesic. It should be prevented if possible by the regular administration of laxatives; a faecal softener with a peristaltic stimulant (e.g. co-danthramer p. 52) or lactulose p. 47 solution with a seppa p. 53 preparation should be used. Methylalazine bromide p. 47 is licensed for the treatment of opioid-induced constipation.

**Convulsions** Patients with cerebral tumours or uraemia may be susceptible to convulsions. Prophylactic treatment with phenytoin p. 398 or carbamazepine p. 387 should be considered. When oral medication is no longer possible, diazepam p. 267 given rectally, or phenobarbital p. 409 by injection is continued as prophylaxis. For the use of midazolam p. 414 by subcutaneous infusion using a continuous infusion device see below.

**Dry mouth** Dry mouth may be relieved by good mouth care and measures such as chewing sugar-free gum, sucking ice or pineapple chunks, or the use of artificial saliva, dry and measures such as chewing sugar-free gum, sucking ice butylbromide p. 73 may also be helpful if there is bronchospasm or partial obstruction.

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**Dysphagia** A corticosteroid such as dexamethasone p. 947 may help, temporarily, if there is an obstruction due to tumour. See also ‘Dry mouth’, above.

**Dyspnoea** Breathlessness at rest may be relieved by regular oral morphine p. 367 in carefully titrated doses. Diazepam p. 267 may be helpful for dryness or association with anxiety. A corticosteroid, such as dexamethasone p. 947, may also be helpful if there is bronchospasm or partial obstruction.

**Fungating tumours** Fungating tumours can be treated by regular dressing and antibacterial drugs; systemic treatment with metronidazole p. 475 is often required to reduce malodour but topical metronidazole is also used.

**Gastro-intestinal pain** The pain of bowel colic may be reduced by loperamide hydrochloride p. 56. Hyoscine butylbromide may also be helpful, given sublingually as 5wells® tablets. Subcutaneous injections of hyoscine butylbromide p. 73, hyoscine hydrobromide p. 344, and glycopyrrocol bromide p. 1100 can also be used to treat bowel colic.

**Hiccups** Hiccups may be due to gastric distension and may be treated by a preparation incorporating an antacid with an antiflatulent and a prokinetic such as domperidone p. 346 before meals.

**Insomnia** Patients with advanced cancer may not sleep because of discomfort, cramps, night sweats, joint stiffness, or fear. There should be appropriate treatment of these problems before hypnotics are used. Benzodiazepines, such as temazepam p. 420, may be useful.

**Intractable cough** Intractable cough may be relieved by moist inhalations or by regular administration of oral morphine p. 367. Methadone hydrochloride p. 436 linctus should be avoided because it has a long duration of action and tends to accumulate.

**Muscle spasm** The pain of muscle spasm can be helped by a muscle relaxant such as diazepam p. 267 or baclofen p. 914.

**Nausea and vomiting** Nausea and vomiting are common in patients with advanced cancer. Ideally, the cause should be determined before treatment with an antiemetic is started. A prokinetic antiemetic may be a preferred choice for first-line therapy.

**Nausea and vomiting** Nausea and vomiting may occur with opioid therapy particularly in the initial stages but can be prevented by giving an antiemetic such as haloperidol p. 306 or metoclopramide hydrochloride p. 347. An antiemetic is usually necessary only for the first 4 or 5 days and therefore combined preparations containing an opioid with an antiemetic are not recommended because they lead to unnecessary antiemetic therapy (and associated side-effects when used long-term). Metoclopramide hydrochloride has a prokinetic action and is used by mouth for nausea and vomiting associated with gastritis, gastric stasis, and functional bowel obstruction. Drugs with antimuscarinic effects antagonise prokinetic drugs and, if possible, should not be used concurrently. Haloperidol is used by mouth for most metabolic causes of vomiting (e.g. hypercalcaemia, renal failure). Cyclizine p. 343 is given by mouth. It is used for nausea and vomiting due to mechanical bowel obstruction, raised intracranial pressure, and motion sickness. Levomepromazine p. 345 is used as an antiemetic; it is given by mouth or by subcutaneous injection at bedtime. For the dose by subcutaneous infusion see below. Dexamethasone p. 947 by mouth can be used as an adjunct. Antiemetic therapy should be reviewed every 24 hours; it may be necessary to substitute the antiemetic or to add another one.

**Pruritus** Pruritus, even when associated with obstructive jaundice, often responds to simple measures such as application of emollients. In the case of obstructive jaundice, further measures include administration of colestyramine p. 173).

**Raised intracranial pressure** Headache due to raised intracranial pressure often responds to a high dose of a corticosteroid, such as dexamethasone p. 947 and should be given before 6 p.m. to reduce the risk of insomnia.

**Restlessness and confusion** Restlessness and confusion may require treatment with an antipsychotic, e.g. haloperidol p. 306 or levomepromazine p. 345, by mouth or by subcutaneous injection, both repeated every 2 hours if required. The dose and frequency is adjusted according to the level of patient distress and the response. A regular maintenance dose should also be considered, given twice daily either by mouth or by subcutaneous injection; alternatively use a continuous infusion device. Levomepromazine is licensed to treat pain in palliative care—this use is reserved for distressed patients with severe pain unresponsive to other measures (seek specialist advice).
Continuous subcutaneous infusions

Although drugs can usually be administered by mouth to control the symptoms of advanced cancer, the parenteral route may sometimes be necessary. Repeated administration of intramuscular injections can be difficult in a cachectic patient. This has led to the use of portable continuous infusion devices, such as syringe drivers, to give a continuous subcutaneous infusion, which can provide good control of symptoms with little discomfort or inconvenience to the patient.

Indications for the parenteral route are:

- the patient is unable to take medicines by mouth owing to nausea and vomiting, dysphagia, severe weakness, or coma
- there is malignant bowel obstruction in patients for whom further surgery is inappropriate (avoiding the need for an intravenous infusion or for insertion of a nasogastric tube)
- occasionally when the patient does not wish to take regular medication by mouth.

Syringe driver rate settings Staff using syringe drivers should be adequately trained and different rate settings should be clearly identified and differentiated; incorrect use of syringe drivers is a common cause of medication errors.

Bowel colic and excessive respiratory secretions Hyoscine butylbromide p. 344 effectively reduces respiratory secretions and bowel colic and is sedative (but occasionally causes paradoxical agitation). Hyoscine butylbromide p. 72 is used for bowel colic and for excessive respiratory secretions, and is less sedative than hyoscine hydrobromide.

Glycopyrronium bromide p. 1100 may also be used to treat bowel colic or excessive respiratory secretions.

Confusion and restlessness Haloperidol p. 306 has little sedative effect.

Levomepromazine p. 345 has a sedative effect. Levomepromazine p. 414 is a sedative and an antiepileptic that may be used in addition to an antipsychotic drug in a very restless patient. Midazolam is also used for myoclonus.

Convulsions If a patient has previously been receiving an antiepileptic drug or has a primary or secondary cerebral tumour or is at risk of convulsion (e.g. owing to uraemia) antiepileptic medication should not be stopped. Midazolam is the benzodiazepine antiepileptic of choice for continuous subcutaneous infusion.

Nausea and vomiting Haloperidol p. 306 and levomepromazine p. 345 can both be given as a subcutaneous infusion but sedation can limit the dose of levomepromazine.

Cyclizine is particularly likely to precipitate if mixed with diamorphine or other drugs (see under Mixing and Compatibility, below).

Metoclopramide hydrochloride p. 304, prochlorperazine p. 309, and diazepam p. 267 are contra-indicated as they cause skin reactions at the injection site; to a lesser extent cyclizine p. 343 and levomepromazine p. 345 also sometimes cause local irritation.

In theory injections dissolved in water for injections are more likely to be associated with pain (possibly owing to their hypotonicity). The use of physiological saline (sodium chloride 0.9% p. 953) however increases the likelihood of precipitation when more than one drug is used; moreover subcutaneous injection rates are so slow (0.1–0.3 mL/hour) that pain is not usually a problem when water is used as a diluent.

Diamorphine can be given by subcutaneous infusion in a strength of up to 250 mg/mL; up to a strength of 40 mg/mL either water for injections or physiological saline (sodium chloride 0.9%) is a suitable diluent—above that strength only water for injections is used (to avoid precipitation). The following can be mixed with diamorphine:

- Cyclizine, may precipitate at concentrations above 10 mg/mL or in the presence of sodium chloride 0.9% or as the concentration of diamorphine relative to cyclizine increases; mixtures of diamorphine and cyclizine are also likely to precipitate after 24 hours.
- Dexamethasone, special care is needed to avoid precipitation of dexamethasone when preparing it.
- Haloperidol, mixtures of haloperidol and diamorphine are likely to precipitate after 24 hours if haloperidol concentration is above 2 mg/mL.
- Hyoscine butylbromide
- Hyoscine hydrobromide
- Levomepromazine
- Metoclopramide, under some conditions infusions containing metoclopramide become discoloured; such solutions should be discarded.
- Midazolam

Subcutaneous infusion solution should be monitored regularly both to check for precipitation (and discoulouration) and to ensure that the infusion is running at the correct rate.

Problems encountered with syringe drivers The following are problems that may be encountered with syringe drivers and the action that should be taken:

- if the subcutaneous infusion runs too quickly check the rate setting and the calculation;
- if the subcutaneous infusion runs too slowly check the start button, the battery, the syringe driver, the cannula, and make sure that the injection site is not inflamed;
- if there is an injection site reaction make sure that the site does not need to be changed—firmness or swelling at the site of injection is not in itself an indication for change, but pain or obvious inflammation is.

Mixing and compatibility The general principle that injections should be given into separate sites (and should not be mixed) does not apply to the use of syringe drivers in palliative care. Provided that there is evidence of compatibility, selected injections can be mixed in syringe drivers. Not all types of medication can be used in a subcutaneous infusion. In particular, chlorpromazine hydrochloride p. 304, prochlorperazine p. 309, and diazepam p. 267 are contra-indicated as they cause skin reactions at the injection site; to a lesser extent cyclizine p. 343 and levomepromazine p. 345 also sometimes cause local irritation.

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Equivalent doses of morphine sulfate and diamorphine hydrochloride given over 24 hours

These equivalences are *approximate only* and should be adjusted according to response

<table>
<thead>
<tr>
<th>MORPHINE</th>
<th>PARENTERAL DIAMORPHINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral morphine sulfate</td>
<td>Subcutaneous infusion of morphine sulfate</td>
</tr>
<tr>
<td>over 24 hours</td>
<td>over 24 hours</td>
</tr>
<tr>
<td>30 mg</td>
<td>15 mg</td>
</tr>
<tr>
<td>60 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>90 mg</td>
<td>45 mg</td>
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<td>600 mg</td>
<td>300 mg</td>
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<tr>
<td>780 mg</td>
<td>390 mg</td>
</tr>
<tr>
<td>960 mg</td>
<td>480 mg</td>
</tr>
<tr>
<td>1200 mg</td>
<td>600 mg</td>
</tr>
</tbody>
</table>

If breakthrough pain occurs give a subcutaneous (preferable) or intramuscular injection equivalent to one-tenth to one-sixth of the total 24-hour subcutaneous infusion dose. It is kinder to give an intermittent bolus injection subcutaneously—absorption is smoother so that the risk of adverse effects at peak absorption is avoided (an even better method is to use a subcutaneous butterfly needle). To minimise the risk of infection no individual subcutaneous infusion solution should be used for longer than 24 hours.
Prescribing for the elderly

Old people, especially the very old, require special care and consideration from prescribers. Medicines for Older People, a component document of the National Service Framework for Older People (Department of Health. National Service Framework for Older People. London: Department of Health, March 2001), describes how to maximise the benefits of medicines and how to avoid excessive, inappropriate, or inadequate consumption of medicines by older people.

Appropriate prescribing
Elderly patients often receive multiple drugs for their multiple diseases. This greatly increases the risk of drug interactions as well as adverse reactions, and may affect compliance. The balance of benefit and harm of some medicines may be altered in the elderly. Therefore, elderly patients’ medicines should be reviewed regularly and medicines which are not of benefit should be stopped. Non-pharmacological measures may be more appropriate for symptoms such as headache, sleeplessness, and light-headedness when associated with social stress as in widowhood, loneliness, and family dispersal.

In some cases prophylactic drugs are inappropriate if they are likely to complicate existing treatment or introduce unnecessary side-effects, especially in elderly patients with poor prognosis or with poor overall health. However, elderly patients should not be denied medicines which may help them, such as anticoagulants or antiplatelet drugs for atrial fibrillation, antihypertensives, statins, and drugs for osteoporosis.

Form of medicine
Frail elderly patients may have difficulty swallowing tablets; if left in the mouth, ulceration may develop. They should always be encouraged to take their tablets or capsules with enough fluid, and whilst in an upright position to avoid the possibility of oesophageal ulceration. It can be helpful to discuss with the patient the possibility of taking the drug as a liquid if available.

Manifestations of ageing
In the very old, manifestations of normal ageing may be mistaken for disease and lead to inappropriate prescribing. In addition, age-related muscle weakness and difficulty in maintaining balance should not be confused with neurological disease. Disorders such as light-headedness not associated with postural or postprandial hypotension are unlikely to be helped by drugs.

Sensitivity
The nervous system of elderly patients is more sensitive to many commonly used drugs, such as opioid analgesics, benzodiazepines, antipsychotics, and anti-parkinsonian drugs, all of which must be used with caution. Similarly, other organs may also be more susceptible to the effects of drugs such as anti-hypertensives and NSAIDs.

Pharmacokinetics
Pharmacokinetic changes can markedly increase the tissue concentration of a drug in the elderly, especially in debilitated patients. The most important effect of age is reduced renal clearance. Many aged patients thus excrete drugs slowly, and are highly susceptible to nephrotoxic drugs. Acute illness can lead to rapid reduction in renal clearance, especially if accompanied by dehydration. Hence, a patient stabilised on a drug with a narrow margin between the therapeutic and the toxic dose (e.g. digoxin p. 94) can rapidly develop adverse effects in the aftermath of a myocardial infarction or a respiratory-tract infection. The hepatic metabolism of lipid soluble drugs is reduced in elderly patients because there is a reduction in liver volume. This is important for drugs with a narrow therapeutic window.

Adverse reactions
Adverse reactions often present in the elderly in a vague and non-specific fashion. Confusion is often the presenting symptom (caused by almost any of the commonly used drugs). Other common manifestations are constipation (with antimuscarinics and many tranquillisers) and postural hypotension and falls (with diuretics and many psychotropics).

Hypnotics
Many hypnotics with long half-lives have serious hangover effects, including drowsiness, unsteady gait, slurred speech, and confusion. Hypnotics with short half-lives should be used but they too can present problems. Short courses of hypnotics are occasionally useful for helping a patient through an acute illness or some other crisis but every effort must be made to avoid dependence. Benzodiazepines impair balance, which can result in falls.

Diuretics
Diuretics are overprescribed in old age and should not be used on a long-term basis to treat simple gravitational oedema which will usually respond to increased movement, raising the legs, and support stockings. A few days of diuretic treatment may speed the clearing of the oedema but it should rarely need continued drug therapy.

NSAIDs
Bleeding associated with aspirin and other NSAIDs is more common in the elderly who are more likely to have a fatal or serious outcome. NSAIDs are also a special hazard in patients with cardiac disease or renal impairment which may again place older patients at particular risk. Owing to the increased susceptibility of the elderly to the side-effects of NSAIDs the following recommendations are made:

- for osteoarthritis, soft-tissue lesions, and back pain, first try measures such as weight reduction (if obese), warmth, exercise, and use of a walking stick;
- for osteoarthritis, soft-tissue lesions, back pain, and pain in rheumatoid arthritis, paracetamol p. 354 should be used first and can often provide adequate pain relief;
- alternatively, a low-dose NSAID (e.g. ibuprofen p. 927 up to 1.2 g daily) may be given;
- for pain relief when either drug is inadequate, paracetamol in a full dose plus a low-dose NSAID may be given;
- if necessary, the NSAID dose can be increased or an opioid analgesic given with paracetamol p. 354;
- do not give two NSAIDs at the same time.

Prophylaxis of NSAID-induced peptic ulcers may be required if continued NSAID treatment is necessary see, NSAID-associated ulcers under Peptic ulceration p. 61.

Other drugs
Other drugs which commonly cause adverse reactions are antiparkinsonian drugs, antihypertensives, psychotropics, and digoxin p. 94. The usual maintenance dose of digoxin p. 94 in very old patients is 125 micrograms daily (62.5 micrograms in those with renal disease); lower doses are often inadequate but toxicity is common in those given 250 micrograms daily.

Drug-induced blood disorders are much more common in the elderly. Therefore drugs with a tendency to cause bone marrow depression (e.g. co-trimoxazole p. 461, mianserin
hydrochloride p. 290) should be avoided unless there is no acceptable alternative. The elderly generally require a lower maintenance dose of warfarin sodium p. 121 than younger adults; once again, the outcome of bleeding tends to be more serious.

**Guidelines**

Always consider whether a drug is indicated at all.

**Limit range** It is a sensible policy to prescribe from a limited range of drugs and to be thoroughly familiar with their effects in the elderly.

**Reduce dose** Dosage should generally be substantially lower than for younger patients and it is common to start with about 50% of the adult dose. Some drugs (e.g. long-acting antidiabetic drugs such as glibenclamide p. 611) should be avoided altogether.

**Review regularly** Review repeat prescriptions regularly. In many patients it may be possible to stop some drugs, provided that clinical progress is monitored. It may be necessary to reduce the dose of some drugs as renal function declines.

**Simplify regimens** Elderly patients benefit from simple treatment regimens. Only drugs with a clear indication should be prescribed and whenever possible given once or twice daily. In particular, regimens which call for a confusing array of dosage intervals should be avoided.

**Explain clearly** Write full instructions on every prescription (including repeat prescriptions) so that containers can be properly labelled with full directions. Avoid imprecisions like ‘as directed’. Child-resistant containers may be unsuitable.

**Repeats and disposal** Instruct patients what to do when drugs run out, and also how to dispose of any that are no longer necessary. Try to prescribe matching quantities. If these guidelines are followed most elderly people will cope adequately with their own medicines. If not then it is essential to enrol the help of a third party, usually a relative or a friend.

**Drugs and sport**

UK Anti-Doping, the national body responsible for the UK’s anti-doping policy, advises that athletes are personally responsible should a prohibited substance be detected in their body. An advice card listing examples of permitted and prohibited substances is available from:

UK Anti-doping
Oceanic House
1a Cockspur Street
London SW1Y 5BG
Tel: (020) 7766 7350
information@ukad.org.uk
www.ukad.org.uk

**General Medical Council’s advice** Doctors who prescribe or collude in the provision of drugs or treatment with the intention of improperly enhancing an individual’s performance in sport contravene the GMC’s guidance, and such actions would usually raise a question of a doctor’s continued registration. This does not preclude the provision of any care or treatment where the doctor’s intention is to protect or improve the patient’s health.
Prescribing in dental practice

Advice on the drug management of dental and oral conditions has been integrated into the main text. For ease of access, guidance on such conditions is usually identified by means of a relevant heading (e.g. Dental and Orofacial Pain) in the appropriate sections of the BNF. The following is a list of topics of particular relevance to dentists.

**General guidance**
- Prescribing by dentists, see Prescription writing p. 4
- Oral side-effects of drugs, see Adverse reactions to drugs p. 11
- Medical emergencies in dental practice (below)
- Medical problems in dental practice p. 30

**Drug management of dental and oral conditions**

**Dental and orofacial pain, see Analgesics p. 352**
- Neuropathic pain p. 382
- Non-opioid analgesics and compound analgesic preparations, see Analgesics p. 352
- Opioid analgesics, see Analgesics p. 352
- Non-steroidal anti-inflammatory drugs p. 915

**Oral infections**
- Bacterial infections, see Antibacterials, principles of therapy p. 438
- Phenoxymethylpenicillin p. 481
- Broad-spectrum penicillins (amoxicillin p. 482 and ampicillin p. 483)
- Cephalosporins (cefalexin p. 456 and cefradine p. 458)
- Tetracyclines p. 496
- Macrolides (clarithromycin p. 470, erythromycin p. 471 and azithromycin p. 955)
- Clindamycin p. 467
- Metronidazole p. 475
- Fusidic acid p. 956

**Fungal infections**
- Local treatment, Oropharynx infections, fungal p. 996
- Systemic treatment, Antifungals, systemic use p. 512
- Viral infections
- Herpetic gingivostomatitis, local treatment, see Oropharynx infections, viral p. 997
- Herpetic gingivostomatitis, systemic treatment, see Oropharynx infections, viral p. 997
- Herpes labialis

**Anaesthetics, anxiolytics and hypnotics**
- Anaesthesia, sedation, and resuscitation in dental practice p. 1094
- Hypnotics, see Hypnotics and anxiolytics p. 416
- Sedation for dental procedures, see Hypnotics and anxiolytics p. 416
- Local anaesthesia p. 1111
- Oral ulceration and inflammation p. 992
- Mouthwashes, gargles and dentifrices, see Mouthwashes and other preparations for oropharyngeal use p. 989
- Dry mouth, see Treatment of dry mouth p. 987
- Aromatic inhalations, see Aromatic inhalations, cough preparations and systemic nasal decongestants p. 258
- Nasal decongestants, see Aromatic inhalations, cough preparations and systemic nasal decongestants p. 258

**Dental Practitioners’ Formulary p. 1520**

**Changes to Dental Practitioners’ Formulary, see Dental Practitioners’ Formulary p. 1520**

**Medical emergencies in dental practice**

This section provides guidelines on the management of the more common medical emergencies which may arise in dental practice. Dentists and their staff should be familiar with standard resuscitation procedures, but in all circumstances it is advisable to summon medical assistance as soon as possible. See also **algorithm** of the procedure for Cardiopulmonary resuscitation p. 195.

**The drugs referred to in this section include:**
- Adrenaline/epinephrine Injection, adrenaline 1 in 1000, (adrenaline 1 mg/mL as acid tartrate), 1 mL amp p. 196
- Aspirin Dispersible Tablets 300 mg p. 104
- Glucagon Injection, glucagon (as hydrochloride), 1-unit vial (with solvent) p. 618
- Glucose (for administration by mouth) p. 852
- Glyceryl trinitrate Spray p. 190
- Midazolam Oromucosal Solution, midazolam 5 mg/mL p. 414
- Oxygen
- Salbutamol Aerosol Inhalation, salbutamol 100 micrograms/metered inhalation p. 222

**Adrenal insufficiency**

Adrenal insufficiency may follow prolonged therapy with corticosteroids and can persist for years after stopping. A patient with adrenal insufficiency may become hypotensive under the stress of a dental visit (important: see also Adrenal suppression for details of corticosteroids (systemic) p. 579 cover before dental surgical procedures under general anaesthesia).

**Management**
- **Lay the patient flat**
- **Give oxygen**
- Transfer patient urgently to hospital

**Anaphylaxis**

A severe allergic reaction may follow oral or parenteral administration of a drug. Anaphylactic reactions in dentistry may follow the administration of a drug or contact with substances such as latex in surgical gloves. In general, the more rapid the onset of the reaction the more profound it tends to be. Symptoms may develop within minutes and rapid treatment is essential. Anaphylactic reactions may also be associated with additives and excipients in foods and medicines. Refined arachis (peanut) oil, which may be present in some medicinal products, is unlikely to cause an allergic reaction—nevertheless it is wise to check the full formula of preparations which may contain allergens (including those for topical application, particularly if they are intended for use in the mouth or for application to the nasal mucosa).

**Symptoms and signs**
- Paraesthesia, flushing, and swelling of face
- Generalised itching, especially of hands and feet
- Bronchospasm and laryngospasm (with wheezing and difficulty in breathing)
- Rapid weak pulse together with fall in blood pressure and pallor; finally cardiac arrest

**Management**

First-line treatment includes securing the airway, restoration of blood pressure (laying the patient flat and raising the feet, or in the recovery position if unconscious or nauseous and at risk of vomiting), and administration of adrenaline/epinephrine injection p. 196. This is given intramuscularly in a dose of 500 micrograms (0.5 mL adrenaline injection 1 in 1000); a dose of 300 micrograms (0.3 mL adrenaline injection 1 in 1000) may be appropriate for immediate self-administration. The dose is repeated if
Prescribing in dental practice

necessary at 5-minute intervals according to blood pressure, pulse, and respiratory function. Oxygen administration is also of primary importance. Arrangements should be made to transfer the patient to hospital urgently.

**Asthma**

Patients with asthma may have an attack while at the dental surgery. Most attacks will respond to 2 puffs of the patient’s short-acting beta, agonist inhaler such as salbutamol 100 micrograms/puff p. 222; further puffs are required if the patient does not respond rapidly. If the patient is unable to use the inhaler effectively, further puffs should be given through a large-volume spacer device (or, if not available, through a plastic or paper cup with a hole in the bottom for the inhaler mouthpiece). If the response remains unsatisfactory, or if further deterioration occurs, then the patient should be transferred urgently to hospital. Whilst awaiting transfer, oxygen should be given with salbutamol 5 mg or terbutaline sulfate 10 mg p. 225 by nebuliser; if a nebuliser is unavailable, then 2–10 puffs of salbutamol 100 micrograms/metered inhalation should be given (preferably by a large-volume spacer), and repeated every 10–20 minutes if necessary. If asthma is part of a more generalised anaphylactic reaction, an intramuscular injection of adrenaline/epinephrine p. 196 (as detailed under Anaphylaxis) should be given.

Patients with severe chronic asthma or whose asthma has deteriorated previously during a dental procedure may require an increase in their prophylactic medication before a dental procedure. This should be discussed with the patient’s medical practitioner and may include increasing the dose of inhaled or oral corticosteroid.

**Cardiac emergencies**

If there is a history of angina the patient will probably carry isosorbide dinitrate spray or tablets p. 190 (or isosorbide dinitrate tablets p. 191) and should be allowed to use them. Hospital admission is not necessary if symptoms are mild and resolve rapidly with the patient’s own medication. See also Coronary Artery Disease p. 29.

Arrhythmias may lead to a sudden reduction in cardiac output with loss of consciousness. Medical assistance should be summoned. For advice on pacemaker interference, see also Pacemakers p. 30.

The pain of myocardial infarction is similar to that of angina but generally more severe and more prolonged.

**Symptoms and signs of myocardial infarction**

- Progressive onset of severe, crushing pain across front of chest; pain may radiate towards the shoulder and down arm, or into neck and jaw
- Skin becomes pale and clammy
- Nausea and vomiting are common
- Pulse may be weak and blood pressure may fall
- Breathlessness

**Initial management of myocardial infarction**

Call immediately for medical assistance and an ambulance, as appropriate. Allow the patient to rest in the position that feels most comfortable; in the presence of breathlessness this is likely to be sitting position, whereas the syncopal patient should be laid flat; often an intermediate position (dictated by the patient) will be most appropriate. Oxygen may be administered.

Sublingual glyceryl trinitrate p. 190 may relieve pain. Intramuscular injection of drugs should be avoided because absorption may be too slow (particularly when cardiac output is reduced) and pain relief is inadequate. Intramuscular injection also increases the risk of local bleeding into the muscle if the patient is given a thrombolytic drug.

Reassure the patient as much as possible to relieve further anxiety. If available, aspirin p. 104 in a single dose of 300 mg should be given. A note (to say that aspirin has been given) should be sent with the patient to the hospital. For further details on the initial management of myocardial infarction, see Management of ST-Segment Elevation Myocardial Infarction p. 186.

If the patient collapses and loses consciousness attempt standard resuscitation measures. See also algorithm of the procedure for Cardiopulmonary resuscitation p. 195.

**Epileptic seizures**

Patients with epilepsy must continue with their normal dosage of anticonvulsant drugs when attending for dental treatment. It is not uncommon for epileptic patients not to volunteer the information that they are epileptic but there should be little difficulty in recognising a tonic-clonic (grand mal) seizure.

**Symptoms and signs**

- There may be a brief warning (but variable)
- Sudden loss of consciousness, the patient becomes rigid, falls, may give a cry, and becomes cyanotic (tonic phase)
- After 30 seconds, there are jerking movements of the limbs; the tongue may be bitten (clonic phase)
- There may be frothing from mouth and urinary incontinence
- The seizure typically lasts a few minutes; the patient may then become flaccid but remain unconscious. After a variable time the patient regains consciousness but may remain confused for a while

**Management**

During a convulsion try to ensure that the patient is not at risk from injury but make no attempt to put anything in the mouth or between the teeth (in mistaken belief that this will protect the tongue). Give oxygen to support respiration if necessary. Do not attempt to restrain convulsive movements. After convulsive movements have subsided place the patient in the coma (recovery) position and check the airway.

After the convulsion the patient may be confused (postictal confusion) and may need reassurance and sympathy. The patient should not be sent home until fully recovered. Seek medical attention or transfer the patient to hospital if it was the first episode of epilepsy, or if the convulsion was atypical, prolonged (or repeated), or if injury occurred. Medication should only be given if convulsive seizures are prolonged (convulsive movements lasting 5 minutes or longer) or repeated rapidly.

**Midazolam** oromucosal solution p. 414 can be given by the buccal route in adults as a single dose of 10 mg [unlicensed]. For further details on the management of status epilepticus, including details of paediatric doses of midazolam, see Drugs used in status epilepticus (Epilepsy p. 383).

Focal seizures similarly need very little active management (in an automatism only a minimum amount of restraint should be applied to prevent injury). Again, the patient should be observed until post-ictal confusion has completely resolved.

**Hypoglycaemia**

Insulin-treated diabetic patients attending for dental treatment under local anaesthesia should inject insulin and eat meals as normal. If food is omitted the blood glucose will fall to an abnormally low level (hypoglycaemia). Patients can often recognise the symptoms themselves and this state responds to sugar in water or a few lumps of sugar. Children may not have such prominent changes but may appear unduly lethargic.

**Symptoms and signs**

- Shaking and trembling
- Sweating
Unconsciousness

Convulsions

Medical problems in dental practice

Individuals presenting at the dental surgery may also suffer from an unrelated medical condition; this may require modification to the management of their dental condition.

If the patient has systemic disease or is taking other medication, the matter may need to be discussed with the patient’s general practitioner or hospital consultant.

Allergy

Patients should be asked about any history of allergy; those with a history of atopic allergy (asthma, eczema, hay fever, etc.) are at special risk. Those with a history of a severe allergy or of anaphylactic reactions are at high risk—it is essential to confirm that they are not allergic to any medication, or to any dental materials or equipment (including latex gloves). See also Anaphylaxis p. 242.

Arrhythmias

Patients, especially those who suffer from heart failure or who have sustained a myocardial infarction, may have irregular cardiac rhythm. Atrial fibrillation is a common arrhythmia even in patients with normal hearts and is of little concern except that dentists should be aware that such patients may be receiving anticoagulant therapy. The patient’s medical practitioner should be asked whether any special precautions are necessary. Premedication (e.g. with temazepam p. 420) may be useful in some instances for very anxious patients.

See also Cardiac emergencies and Dental Anaesthesia (Local anaesthesia p. 1111).

Cardiac prostheses

For an account of the risk of infective endocarditis in patients with prosthetic heart valves, see Infective Endocarditis p. 29. For advice on patients receiving anticoagulants, see Thromboembolic disease p. 30.

Coronary artery disease

Patients are vulnerable for at least 4 weeks following a myocardial infarction or following any sudden increase in the symptoms of angina. It would be advisable to check with the patient’s medical practitioner before commencing treatment. See also Cardiac Emergencies p. 28.

Treatment with low-dose aspirin (75 mg daily), clopidogrel p. 106, or dipyrindamole p. 107 should not be stopped routinely nor should the dose be altered before dental procedures.

A Working Party of the British Society for Antimicrobial Chemotherapy has not recommended antibiotic prophylaxis for patients following coronary artery bypass surgery.

Cyanotic heart disease

Patients with cyanotic heart disease are at risk in the dental chair, particularly if they have pulmonary hypertension. In such patients a syncopal reaction increases the shunt away from the lungs, causing more hypoxia which worsens the syncopal reaction—a vicious circle that may prove fatal. The advice of the cardiologist should be sought on any patient with congenital cyanotic heart disease. Treatment in hospital is more appropriate for some patients with this condition.

Hypertension

Patients with hypertension are likely to be receiving antihypertensive drugs. Their blood pressure may fall dangerously low under general anaesthesia, see also under Dental Anaesthesia (Local anaesthesia p. 1111).

Immunosuppression and indwelling intraperitoneal catheters

Advice of a Working Party of the British Society for Antimicrobial Chemotherapy is that patients who are immunosuppressed (including transplant patients) and patients with indwelling intraperitoneal catheters do not require antibiotic prophylaxis for dental treatment provided there is no other indication for prophylaxis.

Prescribing in dental practice
Prescribing in dental practice

The Working Party has commented that there is little evidence that dental treatment is followed by infection in immunosuppressed and immunodeficient patients nor is there evidence that dental treatment is followed by infection in patients with indwelling intraperitoneal catheters.

**Infecive endocarditis**

While almost any dental procedure can cause bacteraemia, there is no clear association with the development of infective endocarditis. Routine daily activities such as tooth brushing also produce a bacteraemia and may present a greater risk of infective endocarditis than a single dental procedure.

Antibacterial prophylaxis and chlorhexidine p. 989 mouthwash are not recommended for the prevention of endocarditis in patients undergoing dental procedures. Such prophylaxis may expose patients to the adverse effects of antimicrobials when the evidence of benefit has not been proven.

**Reduction of oral bacteraemia**

Patients at risk of endocarditis include those with valve replacement, acquired valvular heart disease with stenosis or regurgitation, structural congenital heart disease (including surgically corrected or palliated structural conditions, but excluding isolated atrial septal defect, fully repaired ventricular septal defect, fully repaired patent ductus arteriosus, and closure devices considered to be endothelialised), hypertrophic cardiomyopathy, or a previous episode of infective endocarditis, should be advised to maintain the highest possible standards of oral hygiene in order to reduce the:

- need for dental extractions or other surgery;
- chances of severe bacteraemia if dental surgery is needed;
- possibility of ‘spontaneous’ bacteraemia.

**Postoperative care**

Patients at risk of endocarditis include those with valve replacement, acquired valvular heart disease with stenosis or regurgitation, structural congenital heart disease (including surgically corrected or palliated structural conditions, but excluding isolated atrial septal defect, fully repaired ventricular septal defect, fully repaired patent ductus arteriosus, and closure devices considered to be endothelialised), hypertrophic cardiomyopathy, or a previous episode of infective endocarditis, should be warned to report to the doctor or dentist any unexplained illness that develops after dental treatment.

Any infection in patients at risk of endocarditis should be investigated promptly and treated appropriately to reduce the risk of endocarditis.

**Patients on anticoagulant therapy**

For general advice on dental surgery in patients receiving oral anticoagulant therapy see Thromboembolic Disease (below).

**Joint prostheses**

Advice of a Working Party of the British Society for Antimicrobial Chemotherapy is that patients with prosthetic joint implants (including total hip replacements) do not require antibiotic prophylaxis for dental treatment. The Working Party considers that it is unacceptable to expose patients to the adverse effects of antibiotics when there is no evidence that such prophylaxis is of any benefit, but that those who develop any intercurrent infection require prompt treatment with antibiotics to which the infecting organisms are sensitive.

The Working Party has commented that joint infections have rarely been shown to follow dental procedures and are even more rarely caused by oral streptococci.

**Pacemakers**

Pacemakers prevent asystole or severe bradycardia. Some ultrasonic scalers, electronic apex locators, electro-analgesic devices, and electrocautery devices interfere with the normal function of pacemakers (including shielded pacemakers) and should not be used. The manufacturer’s literature should be consulted whenever possible. If severe bradycardia occurs in a patient fitted with a pacemaker, electrical equipment should be switched off and the patient placed supine with the legs elevated. If the patient loses consciousness and the pulse remains slow or is absent, cardiopulmonary resuscitation may be needed. Call immediately for medical assistance and an ambulance, as appropriate.


**Thromboembolic disease**

Patients receiving a heparin or an oral anticoagulant such as warfarin sodium p. 121, acenocoumarol p. 120 (nicoumalone), phenindione p. 120, apixaban p. 108, dabigatran etexilate p. 117 or rivaroxaban p. 109 may be liable to excessive bleeding after extraction of teeth or other dental surgery. Often dental surgery can be delayed until the anticoagulant therapy has been completed.

For a patient requiring long-term therapy with warfarin sodium, the patient’s medical practitioner should be consulted and the International Normalised Ratio (INR) should be assessed 72 hours before the dental procedure. This allows sufficient time for dose modification if necessary. In those with an unstable INR (including those who require weekly monitoring of their INR, or those who have had some INR measurements greater than 4.0 in the last 2 months), the INR should be assessed within 24 hours of the dental procedure. Patients requiring minor dental procedures (including extractions) who have an INR below 4.0 may continue warfarin sodium without dose adjustment. There is no need to check the INR for a patient requiring a non-invasive dental procedure.

If it is necessary to remove several teeth, a single extraction should be done first; if this goes well further teeth may be extracted at subsequent visits (two or three at a time). Measures should be taken to minimise bleeding during and after the procedure. This includes the use of sutures and a haemostatic such as oxidised cellulose, collagen sponge or resorbable gelatin sponge. Scaling and root planing should initially be restricted to a limited area to assess the potential for bleeding.

For a patient on long-term warfarin sodium, the advice of the clinician responsible for the patient’s anticoagulation should be sought if:

- the INR is unstable, or if the INR is greater than 4.0;
- the patient has thrombocytopenia, haemophilia, or other disorders of haemostasis, or suffers from liver impairment, alcoholism, or renal failure;
- the patient is receiving antiplatelet drugs, cytotoxic drugs or radiotherapy.

Intramuscular injections are contra-indicated in patients taking anticoagulants with an INR above the therapeutic range, and in those with any disorder of haemostasis. In patients taking anticoagulants who have a stable INR within the therapeutic range, intramuscular injections should be avoided if possible; if an intramuscular injection is necessary, the patient should be informed of the increased risk of localised bleeding and monitored carefully.

A local anaesthetic containing a vasoconstrictor should be given by infiltration, or by intraligamentary or mental nerve injection if possible. If regional nerve blocks cannot be avoided the local anaesthetic should be given cautiously using an aspirating syringe.
Drugs which have potentially serious interactions with anticoagulants include aspirin and other NSAIDs, carbamazepine p. 387, imidazole and triazole antifungals (including miconazole p. 1011), erythromycin p. 471, clarithromycin p. 470, and metronidazole p. 475; for details of these and other interactions with anticoagulants, see Appendix 1 (dabigatran etexilate, heparins, phenindione, rivaroxaban, and coumarins).

Although studies have failed to demonstrate an interaction, common experience in anticoagulant clinics is that the INR can be altered following a course of an oral broad-spectrum antibiotic, such as ampicillin p. 483 or amoxicillin p. 482. Information on the treatment of patients who take anticoagulants is available at www.npsa.nhs.uk/patientsafety/alerts-and-directives/alerts/anticoagulant.

Liver disease
Liver disease may alter the response to drugs and drug prescribing should be kept to a minimum in patients with severe liver disease. Problems are likely mainly in patients with jaundice, ascites, or evidence of encephalopathy. For guidance on prescribing for patients with hepatic impairment, see Prescribing in hepatic impairment p. 17. Where care is needed when prescribing in hepatic impairment, this is indicated under the relevant drug in the BNF.

Renal impairment
The use of drugs in patients with reduced renal function can give rise to many problems. Many of these problems can be avoided by reducing the dose or by using alternative drugs. Special care is required in renal transplantation and immunosuppressed patients; if necessary such patients should be referred to specialists. For guidance on prescribing in patients with renal impairment, see Prescribing in renal impairment p. 17. Where care is needed when prescribing in renal impairment, this is indicated under the relevant drug in the BNF.

Pregnancy
Drugs taken during pregnancy can be harmful to the fetus and should be prescribed only if the expected benefit to the mother is thought to be greater than the risk to the fetus; all drugs should be avoided if possible during the first trimester. For guidance on prescribing in pregnancy, see Prescribing in pregnancy p. 19. Where care is needed when prescribing in pregnancy, this is indicated under the relevant drug in the BNF.

Breast-feeding
Some drugs taken by the mother whilst breast-feeding can be transferred to the breast milk, and may affect the infant. For guidance on prescribing in breast-feeding, see Prescribing in breast-feeding p. 19. Where care is needed when prescribing in breast-feeding, this is indicated under the relevant drug in the BNF.
1 Chronic bowel disorders

Chronic bowel disorders

Once tumours are ruled out individual symptoms of chronic bowel disorders need specific treatment including dietary manipulation as well as drug treatment and the maintenance of a liberal fluid intake.

Clostridium difficile infection

Clostridium difficile infection is caused by colonisation of the colon with Clostridium difficile and production of toxin. It often follows antibiotic therapy and is usually of acute onset, but may become chronic. It is a particular hazard of ampicillin, amoxicillin, co-amoxiclav, second- and third-generation cephalosporins, clindamycin, and quinolones, but few antibiotics are free of this side-effect. Treatment options include metronidazole p. 475, vancomycin p. 465, and fidaxomicin p. 468.

Diverticular disease

Diverticular disease is treated with a high-fibre diet, bran supplements, and bulk-forming drugs. Antispasmodics may provide symptomatic relief when colic is a problem. Antibacterials are used only when the diverticula in the intestinal wall become infected. Antimotility drugs which slow intestinal motility, e.g. codeine phosphate p. 360, diphenoxylate, and loperamide hydrochloride p. 56 could possibly exacerbate the symptoms of diverticular disease and are contra-indicated.

Irritable bowel syndrome

Irritable bowel syndrome can present with pain, constipation, or diarrhea. In some patients there may be important psychological aggravating factors which respond to reassurance and possibly specific treatment e.g. with an antidepressant.

The fibre intake of patients with irritable bowel syndrome should be reviewed. If an increase in dietary fibre is required, soluble fibre (e.g. ispaghula husk p. 45, sterculia p. 46, or oats) is recommended; insoluble fibre (e.g. bran) may exacerbate symptoms and its use should be discouraged. A laxative can be used to treat constipation. An osmotic laxative, such as a macrogl, is preferred; lactulose p. 47 may cause bloating. Linaclotide p. 40 is licensed for the treatment of moderate to severe irritable bowel syndrome associated with constipation. Stimulant laxatives should be avoided or used only occasionally. Loperamide hydrochloride p. 56 may relieve diarrhoea and antispasmodic drugs may relieve pain. Opioids with a central action, such as codeine phosphate p. 360, are better avoided because of the risk of dependence.

A tricyclic antidepressant can be used for abdominal pain or discomfort [unlicensed indication] in patients who have not responded to laxatives, loperamide hydrochloride p. 56, or antispasmodics. A selective serotonin reuptake inhibitor may be considered in those who do not respond to a tricyclic antidepressant [unlicensed indication].

Malabsorption syndromes

Individual conditions need specific management and also general nutritional consideration. Coeliac disease (gluten enteropathy) usually needs a gluten-free diet and pancreatic insufficiency needs pancreatin supplements.

See further information on foods for special diets (ACBS), see Borderline substances p. 1260.

1.1 Inflammatory bowel disease

Inflammatory bowel disease

Chronic inflammatory bowel diseases include ulcerative colitis and Crohn’s disease. Effective management requires drug therapy, attention to nutrition, and in severe or chronic active disease, surgery.

Aminosalicylates (balsalazide sodium p. 34, mesalazine p. 34, olsalazine sodium p. 37, and sulfasalazine p. 37), corticosteroids (hydrocortisone p. 583, beclometasone dipropionate p. 38, budesonide p. 38, and prednisolone p. 585), and drugs that affect the immune response are used in the treatment of inflammatory bowel disease.

Treatment of acute ulcerative colitis and Crohn’s disease

Acute mild to moderate disease affecting the rectum (proctitis) or the recto-sigmoid is treated initially with local application of an aminosalicylate; alternatively, a local corticosteroid can be used but it is less effective. A combination of a local aminosalicylate and a local
corticosteroid can be used for proctitis that does not respond to a local aminosalicylate alone. Foam preparations and suppositories are especially useful when patients have difficulty retaining liquid enemas.

Diffuse inflammatory bowel disease or disease that does not respond to local therapy requires oral treatment. Mild disease affecting the proximal colon can be treated with an oral aminosalicylate alone; a combination of a local and an oral aminosalicylate can be used in proctitis or distal colitis. Refractory or moderate inflammatory bowel disease usually requires adjunctive use of an oral corticosteroid such as prednisolone for 4–8 weeks. Modified-release budesonide is licensed for Crohn’s disease affecting the ileum and the ascending colon; it causes fewer systemic side-effects than oral prednisolone but may be less effective. Beclometasone dipropionate by mouth is licensed as an adjunct to mesalazine for mild to moderate ulcerative colitis, but it is not known whether it is as effective as other corticosteroids.

Severe inflammatory bowel disease or disease that is not responding to an oral corticosteroid requires hospital admission and treatment with an intravenous corticosteroid (such as hydrocortisone p. 583 or methylprednisolone p. 584); other therapy may include intravenous fluid and electrolyte replacement, and possibly parenteral nutrition. Specialist supervision is required for patients who fail to respond adequately to these measures. Patients with severe ulcerative colitis that has not responded to intravenous corticosteroids, may benefit from a short course of intravenous ciclosporin p. 717 [unlicensed indication]. Patients with unresponsive or chronically active Crohn’s disease may benefit from azathioprine p. 716, mercaptopurine p. 762 [unlicensed indication], or once-weekly methotrexate p. 762 [unlicensed indication]; these drugs have a slower onset of action.

Infliximab p. 906 is licensed for the management of severe active Crohn’s disease and severe ulcerative colitis in patients whose condition has not responded adequately to treatment with a corticosteroid and a conventional drug that affects the immune response, or who are intolerant of them.

Adalimumab p. 901 is licensed for the treatment of severe active Crohn’s disease and severe ulcerative colitis in patients whose condition has not responded adequately to treatment with a corticosteroid and a conventional drug that affects the immune response, or who are intolerant of them. For inducing remission, adalimumab can be used in combination with a corticosteroid, but it may be given alone if a corticosteroid is inappropriate or is not tolerated. Adalimumab may also be used for Crohn’s disease in patients who have relapsed while taking infliximab or who cannot tolerate infliximab because of hypersensitivity reactions.

Golimumab p. 904 is licensed for the treatment of severe ulcerative colitis in patients whose condition has not responded adequately to conventional therapy, or who are intolerant of it.

Vedolizumab p. 39 is licensed for the treatment of moderate to severe active Crohn’s disease and ulcerative colitis in patients who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor alpha inhibitor.

Maintenance of remission of acute ulcerative colitis and Crohn’s disease

Smoking cessation reduces the risk of relapse in Crohn’s disease and should be encouraged. Aminosalicylates are efficacious in the maintenance of remission of ulcerative colitis, but there is no evidence of efficacy in the maintenance of remission of Crohn’s disease. Corticosteroids are not suitable for maintenance treatment because of their side-effects. In resistant or frequently relapsing cases either azathioprine p. 716 or mercaptopurine p. 762 [unlicensed indication], given under close supervision may be helpful. Methotrexate p. 762 is tried in Crohn’s disease if azathioprine or mercaptopurine cannot be used [unlicensed indication]. Maintenance therapy with infliximab p. 906 should be considered for patients with Crohn’s disease or ulcerative colitis who respond to the initial induction course of infliximab; fixed-interval dosing is superior to intermittent dosing. Adalimumab p. 901 is licensed for maintenance therapy in Crohn’s disease and ulcerative colitis. Golimumab p. 904 is licensed for maintenance therapy in ulcerative colitis.

Fistulating Crohn’s disease

Treatment may not be necessary for simple, asymptomatic perianal fistulas. Metronidazole p. 475 or ciprofloxacin p. 450 can improve symptoms of fistulating Crohn’s disease but complete healing occurs rarely [unlicensed indication]. Metronidazole is usually given for 1 month but no longer than 3 months because of concerns about peripheral neuropathy. Ciprofloxacin by mouth is given twice daily. Other antibacterials should be given if specifically indicated (e.g. sepsis associated with fistulas and perianal disease) and for managing bacterial overgrowth in the small bowel. Fistulas may also require surgical exploration and local drainage.

Either azathioprine p. 716 or mercaptopurine p. 762 is used as a second-line treatment for fistulating Crohn’s disease and continued for maintenance [unlicensed indication]. Infliximab p. 906 is used for fistulating Crohn’s disease refractory to conventional treatments; fixed-interval dosing is superior to intermittent dosing. Maintenance therapy with infliximab should be considered for patients who respond to the initial induction course of infliximab. Adalimumab p. 901 can be used if there is intolerance to infliximab p. 906 [unlicensed indication].

Adjuvantive treatment of inflammatory bowel disease

Due attention should be paid to diet; high-fibre or low-residue diets should be used as appropriate. Antimotility drugs such as codeine phosphate p. 360 and loperamide hydrochloride p. 56, and antisipasmic drugs may precipitate paralytic ileus and megacolon in active ulcerative colitis; treatment of the inflammation is more logical. An osmotic laxative, such as a macrogol, may be required in proctitis. Diarrhoea resulting from the loss of bile-salt absorption (e.g. in terminal ileal disease or bowel resection) may improve with colestyramine p. 173, which binds bile salts.

Drugs used in chronic bowel disorders

Aminosalicylates

Sulfasalazine p. 37 is a combination of 5-aminosalicylic acid (‘5-ASA’) and sulapyridine; sulapyridine acts only as a carrier to the colonic site of action but still causes side-effects. In the newer aminosalicylates, mesalazine p. 34 (5-aminosalicylic acid), balsalazide sodium p. 34 (a prodrug of 5-aminosalicylic acid) and olsalazine sodium p. 37 (a dimer of 5-aminosalicylic acid which cleaves in the lower bowel), the sulfonamide-related side-effects of sulfasalazine are avoided, but 5-aminosalicylic acid alone can still cause side-effects including blood disorders and lupus-like syndrome also seen with sulfasalazine.

Drugs affecting the immune response

Azathioprine p. 716, ciclosporin p. 717, mercaptopurine p. 762, and methotrexate p. 762 have a role in the treatment of inflammatory bowel disease. Folic acid p. 836 should be given to reduce the possibility of methotrexate toxicity [unlicensed indication]. Folic acid is usually given once weekly on a different day to the methotrexate; alternative regimens may be used in some settings.
Cytokine modulators
Infliximab p. 906, adalimumab p. 901, and golimumab p. 904 are monoclonal antibodies which inhibit the pro-inflammatory cytokine, tumour necrosis factor alpha. They should be used under specialist supervision. Adequate resuscitation facilities must be available when infliximab is used.

AMINOSALICYLATES

Aminosalicylates

- **SIDE-EFFECTS**
  - Rare Acute pancreatitis · agranulocytosis · alopecia · aplastic anaemia · arthralgia · blood disorders · eosinophilia · fibrosing alveolitis · hepatitis · interstitial nephritis · leukopenia · lung disorders · lupus erythematosus-like syndrome · methaemoglobinemia · myalgia · myocarditis · nephrotic syndrome · neutropenia · pericarditis · peripheral neuropathy · renal dysfunction · skin reactions · Stevens-Johnson syndrome · thrombocytopenia
  - Frequency not known Abdominal pain · diarrhoea · exacerbation of symptoms of colitis · headache · hypersensitivity reactions · nausea · rash · urticaria · vomiting

-BLOOD DISORDERS A blood count should be performed and the drug stopped immediately if there is suspicion of a blood dyscrasia.

- **ALLERGY AND CROSS-SENSITIVITY** Contraindicated in salicylate hypersensitivity.

- **RENAI IMPAIRMENT** Renal function should be monitored more frequently in renal impairment.

- **MONITORING REQUIREMENTS** Renal function should be monitored before starting an oral aminosalicylate, at 3 months of treatment, and then annually during treatment.

-PATIENT AND CARER ADVICE Blood disorders Patients receiving aminosalicylates, and their carers, should be advised to report any unexplained bleeding, bruising, purpura, sore throat, fever or malaise that occurs during treatment.

Balsalazide sodium

- **INDICATIONS AND DOSE**
  - **PENTASA® TABLETS**
    - Treatment of mild to moderate ulcerative colitis, acute attack
    - BY MOUTH
      - Adult: 2.25 g 3 times a day until remission occurs or for up to maximum of 12 weeks
    - **Maintenance of remission of ulcerative colitis**
      - By mouth
        - Adult: 1.5 g twice daily (max. per dose 3 g), adjusted according to response; maximum 6 g per day
  - **ASACOL® MR 800MG TABLETS**
    - Treatment of mild to moderate ulcerative colitis, acute attack
    - BY MOUTH
      - Adult: 2.4–4.8 g daily in divided doses
    - **Maintenance of remission of ulcerative colitis**
      - By mouth
        - Adult: Up to 2.4 g once daily, alternatively up to 2.4 g daily in divided doses
      - **Maintenance of remission of Crohn’s ileo-colitis**
        - By mouth
          - Adult: Up to 2.4 g daily in divided doses
    - **ASACOL® MR 400MG TABLETS**
      - Treatment of mild to moderate ulcerative colitis, acute attack
      - BY MOUTH
        - Child 12-17 years: 800 mg 3 times a day
        - Adult: 2.4 g daily in divided doses
    - **OCTASA®**
      - Treatment of mild to moderate ulcerative colitis, acute attack
      - BY MOUTH
        - Adult: 2.4–4.8 g once daily, alternatively 2.4–4.8 g daily in divided doses, dose over 2.4 g daily in divided doses only
      - **Maintenance of remission of ulcerative colitis and Crohn’s ileo-colitis**
        - By mouth
          - Adult: 1.2–2.4 g daily in divided doses
  
- **CAUTIONS** History of asthma
  - **SIDE-EFFECTS** Cholelithiasis
  - **PREGNANCY** Manufacturer advises avoid.
  - **BREAST FEEDING** Diarrhoea may develop in the infant. Monitor breast-fed infants for diarrhoea.
  - **HEPATIC IMPAIRMENT** Avoid in severe impairment.
  - **RENAI IMPAIRMENT** Manufacturer advises avoid in moderate to severe impairment.

Mesalazine

- **INDICATIONS AND DOSE**
  - **PENTASA® TABLETS**
    - Treatment of mild to moderate ulcerative colitis, acute attack
    - BY MOUTH
      - Adult: Up to 4 g once daily, alternatively up to 4 g daily in 2–3 divided doses
      - **Maintenance of remission of ulcerative colitis**
        - By mouth
          - Adult: 2.4 g once daily
      - **MEZAVANT® XL**
        - Treatment of mild to moderate ulcerative colitis, acute attack
        - BY MOUTH
          - Adult: 2.4 g once daily
      - **ASACOL® MR 400MG TABLETS**
        - Treatment of mild to moderate ulcerative colitis, acute attack
        - BY MOUTH
          - Adult: 2.4–4.8 g daily in divided doses
      - **Maintenance of remission of ulcerative colitis**
        - By mouth
          - Adult: Up to 2.4 g once daily, alternatively up to 2.4 g daily in divided doses
      - **Maintenance of remission of Crohn’s ileo-colitis**
        - By mouth
          - Adult: Up to 2.4 g daily in divided doses
  
- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

-Capsule
  - **CAUTIONARY AND ADVISORY LABELS**
    - Almirall Ltd
    - **Balsalazide disodium 750 mg** Colazide 750mg capsules | 130 capsule [P301] £30.42 DT price = £30.42

-BNF
**SALOFALK® TABLETS**

Treatment of mild to moderate ulcerative colitis, acute attack

**BY MOUTH**

- Child 5–17 years (body-weight up to 39 kg): 10–20 mg/kg 3 times a day
- Child 5–17 years (body-weight 40 kg and above): 0.5–1 g 3 times a day
- Adult: 0.5–1 g 3 times a day

**Maintenance of remission of ulcerative colitis**

**BY MOUTH**

- Child 5–17 years (body-weight up to 39 kg): 7.5–15 mg/kg twice daily, total daily dose may alternatively be given in 3 divided doses
- Child 5–17 years (body-weight 40 kg and above): 500 mg 3 times a day
- Adult: 500 mg 3 times a day

**IPOCOL®**

Treatment of mild to moderate ulcerative colitis, acute attack

**BY MOUTH**

- Adult: 2.4 g daily in divided doses

**PENTASA® GRANULES**

Treatment of mild to moderate ulcerative colitis, acute attack

**BY MOUTH**

- Child 5–17 years (body-weight up to 40 kg): 10–20 mg/kg 3 times a day
- Child 5–17 years (body-weight 41 kg and above): 1–2 g twice daily, total daily dose may alternatively be given in 3–4 divided doses
- Adult: Up to 4 g once daily, alternatively up to 4 g daily in 2–4 divided doses

**Maintenance of remission of ulcerative colitis**

**BY MOUTH**

- Child 5–17 years (body-weight up to 40 kg): 7.5–15 mg/kg twice daily, total daily dose may alternatively be given in 3 divided doses
- Child 5–17 years (body-weight 41 kg and above): 2 g once daily
- Adult: 2 g once daily

**SALOFALK® GRANULES**

Treatment of mild to moderate ulcerative colitis, acute attack

**BY MOUTH**

- Child 5–17 years (body-weight up to 40 kg): 30–50 mg/kg once daily, dose preferably given in the morning, alternatively 10–20 mg/kg 3 times a day
- Child 5–17 years (body-weight 41 kg and above): 1.5–3 g once daily, dose preferably given in the morning, alternatively 0.5–1 g 3 times a day
- Adult: 1.5–3 g once daily, dose preferably taken in the morning, alternatively 0.5–1 g 3 times a day

**Maintenance of remission of ulcerative colitis**

**BY MOUTH**

- Child 5–17 years (body-weight up to 40 kg): 7.5–15 mg/kg twice daily, total daily dose may alternatively be given in 3 divided doses
- Child 5–17 years (body-weight 41 kg and above): 500 mg 3 times a day
- Adult: 500 mg 3 times a day

**SALOFALK® RECTAL FOAM**

Treatment of mild ulcerative colitis affecting sigmoid colon and rectum

**BY RECTUM**

- Child 12–17 years: 2 g once daily, dose to be administered into the rectum at bedtime, alternatively 2 g daily in 2 divided doses
- Adult: 2 g once daily, dose to be administered into the rectum at bedtime, alternatively 2 g daily in 2 divided doses

**ASACOL® FOAM ENEMA**

Treatment of acute attack of mild to moderate ulcerative colitis, affecting the rectosigmoid region

**BY RECTUM**

- Adult: 1 g daily for 4–6 weeks, to be administered into the rectum

**SALOFALK® SUPPOSITORIES**

Treatment of acute attack of mild to moderate ulcerative colitis affecting the rectum, sigmoid colon and descending colon

**BY RECTUM**

- Adult: 0.5–1 g 2–3 times a day, adjusted according to response, dose to be given using 500 mg suppositories

**Treatment of acute attack of mild to moderate ulcerative colitis affecting the rectum**

**BY RECTUM**

- Adult: 1 g daily, preferably at bedtime, dose to be given using 1 g suppositories

**ASACOL® SUPPOSITORIES**

Treatment of acute attack of mild to moderate ulcerative colitis and maintenance of remission

**BY RECTUM**

- Adult: 0.75–1.5 g daily in divided doses, last dose to be administered at bedtime

**PENTASA® SUPPOSITORIES**

Treatment of acute attack, ulcerative proctitis

**BY RECTUM**

- Child 15–17 years: 1 g daily for 2–4 weeks
- Adult: 1 g daily for 2–4 weeks

**Maintenance, ulcerative proctitis**

**BY RECTUM**

- Child 15–17 years: 1 g daily
- Adult: 1 g daily

**PENTASA® RETENTION ENEMA**

Treatment of acute attack of mild to moderate ulcerative colitis or maintenance of remission

**BY RECTUM**

- Adult: 1 g once daily, dose to be administered at bedtime

**Treatment of acute attack of mild to moderate ulcerative colitis affecting the rectosigmoid region**

**BY RECTUM**

- Child 12–17 years: 1 g once daily, dose to be administered at bedtime

**SALOFALK® ENEMA**

Treatment of acute attack of mild to moderate ulcerative colitis or maintenance of remission

**BY RECTUM**

- Adult: 2 g once daily, dose to be administered at bedtime

**CAUTIONS**

- Elderly
- Pulmonary disease
Gastro-intestinal system

Mesalazine 800 mg Octasa 800mg MR gastro-resistant tablets | 90 tablet (£47.50) | 180 tablet (£95.00 DT price = £111.72
> Salofalk (Dr. Falk Pharma UK Ltd)
Mesalazine 250 mg Salofalk 250mg gastro-resistant tablets | 100 tablet (£36.19
Mesalazine 500 mg Salofalk 500mg gastro-resistant tablets | 100 tablet (£32.38

**Modified-release granules**

**CAUTIONARY AND ADVISORY LABELS 25**

> Pentasa (Ferring Pharmaceuticals Ltd)
Mesalazine 1 gram Pentasa 1g modified-release granules sachets (sugar-free) | 50 sachet (£30.74 DT price = £30.74
Mesalazine 2 gram Pentasa 2g modified-release granules sachets (sugar-free) | 60 sachet (£73.78 DT price = £73.78
Mesalazine 4 gram Pentasa 4g modified-release granules sachets (sugar-free) | 30 sachet (£71.78
> Salofalk (Dr. Falk Pharma UK Ltd)
Mesalazine 500 mg Salofalk 500mg gastro-resistant modified-release granules sachets (sugar-free) | 100 sachet (£28.74
Mesalazine 1 gram Salofalk 1g gastro-resistant modified-release granules sachets (sugar-free) | 50 sachet (£28.74 DT price = £28.74
Mesalazine 1.5 gram Salofalk 1.5g gastro-resistant modified-release granules sachets (sugar-free) | 60 sachet (£48.85 DT price = £48.85
Mesalazine 3 gram Salofalk 3g gastro-resistant modified-release granules sachets (sugar-free) | 60 sachet (£97.70 DT price = £97.70

**Foam**

EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), disodium edetate, hydroxybenzoates (parabens), polysorbates, propylene glycol, sodium metabisulphite

> MESAIZINE (Non-proprietary)
Mesalazine 1 gram per 1 application Mesalazine 1g/application foam enema | 14 dose (£62.70) no price available
Mesalazine 1 gram per 1 application Asacol 1g/application foam enema | 14 dose (£26.72)
> Salofalk (Dr. Falk Pharma UK Ltd)
Mesalazine 1 gram per 1 application Salofalk 1g/application foam enema | 14 dose (£30.17

**Suppository**

> MESAIZINE (Non-proprietary)
Mesalazine 250 mg Mesalazine 250mg suppositories | 20 suppository (£70) no price available
Mesalazine 500 mg Mesalazine 500mg suppositories | 10 suppository (£120) no price available | 20 suppository (£240) no price available
Asacol (Warner Chilcott UK Ltd)
Mesalazine 250 mg Asacol 250mg suppositories | 20 suppository (£4.82
Mesalazine 500 mg Asacol 500mg suppositories | 10 suppository (£4.82
> Pentasa (Ferring Pharmaceuticals Ltd)
Mesalazine 1 gram Pentasa 1g suppositories | 28 suppository (£40.01 DT price = £40.01
Salofalk (Dr. Falk Pharma UK Ltd)
Mesalazine 500 mg Salofalk 500mg suppositories | 30 suppository (£14.81
Mesalazine 1 gram Salofalk 1g suppositories | 30 suppository (£29.62

**Enema**

> MESAIZINE (Non-proprietary)
Mesalazine 33.9 mg per 1 ml Mesalazine 2g/59ml enema | 7 enema (£29.92
> Pentasa (Ferring Pharmaceuticals Ltd)
Mesalazine 10 mg per 1 ml Pentasa Mesalazine 1g/100ml enema | 7 enema (£17.73 DT price = £17.73
> Salofalk (Dr. Falk Pharma UK Ltd)
Mesalazine 33.9 mg per 1 ml Salofalk 2g/59ml enema | 7 enema (£29.92

**Gastro-resistant tablet**

CAUTIONARY AND ADVISORY LABELS 5, 25

> MESAIZINE (Non-proprietary)
Mesalazine 400 mg Mesalazine 400mg gastro-resistant tablets | 90 tablet (£29.41 DT price = £29.41 | 120 tablet (£39.21
Mesalazine 800 mg Mesalazine 800mg gastro-resistant tablets | 90 tablet (£58.81
Asacol MR (Warner Chilcott UK Ltd)
Mesalazine 400 mg Asacol 400mg MR gastro-resistant tablets | 90 tablet (£29.41 DT price = £29.41 | 120 tablet (£39.21
Mesalazine 800 mg Asacol 800mg MR gastro-resistant tablets | 180 tablet (£111.62 DT price = £111.62
Ipoloc (Sandz Ltd)
Mesalazine 400 mg Ipoloc 400mg gastro-resistant tablets | 120 tablet (£17.68
Octasa MR (Tillett’s Pharma Ltd)
Mesalazine 400 mg Octasa 400mg MR gastro-resistant tablets | 90 tablet (£19.50 DT price = £29.41 | 120 tablet (£26.00

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Modified-release tablet**

CAUTIONARY AND ADVISORY LABELS 21, 25

> Mezavant XL (Shire Pharmaceuticals Ltd)
Mesalazine 1.2 gram Mezavant XL 1200mg tablets | 60 tablet (£62.44 DT price = £62.44
> Pentasa (Ferring Pharmaceuticals Ltd)
Mesalazine 500 mg Pentasa 500mg modified-release tablets | 60 tablet (£36.89 DT price = £36.89

**INTERACTIONS**

The manufacturers of some mesalazine gastro-resistant and modified-release medicines (Asacol® MR tablets, Ipoloc®, Salofalk® granules) suggest that preparations that lower stool pH (e.g. lactulose) may prevent the release of mesalazine.

**SIDE-EFFECTS**

Rare Dizziness
Very rare Oligospermia (reversible)

**PREGNANCY**

Negligible quantities cross placenta.

**BREAST FEEDING**

Diarrhoea reported in breast-fed infants, but negligible amounts of mesalazine detected in breast milk. Monitor breast-fed infant for diarrhoea.

**HEPATIC IMPAIRMENT**

Avoid in severe impairment.

**RENAL IMPAIRMENT**

Use with caution. Avoid if eGFR less than 20 mL/minute/1.73 m².

**DIRECTIONS FOR ADMINISTRATION**

**PENTASA® TABLETS**

Tablets may be halved, quartered, or dispersed in water, but should not be chewed.

**PENTASA® GRANULES**

Granules should be placed on tongue and washed down with water or orange juice without chewing.

In children Contents of one sachet should be weighed and divided immediately before use; discard any remaining granules.

**SALOFALK® GRANULES**

Granules should be placed on tongue and washed down with water without chewing.

**PRESCRIBING AND DISPENSING INFORMATION**

Flavours of granule formulations of Salofalk® may include vanilla. There is no evidence to show that any one oral preparation of mesalazine is more effective than another; however, the delivery characteristics of oral mesalazine preparations may vary.

**PATIENT AND CARER ADVICE**

If it is necessary to switch a patient to a different brand of mesalazine, the patient should be advised to report any changes in symptoms. Some products may require special administration advice; patients and carers should be informed.
Olsalazine sodium

**INDICATIONS AND DOSE**

Treatment of acute attack of mild ulcerative colitis

**BY MOUTH**

- Adult: 1 g daily in divided doses, doses to be taken after meals, then increased if necessary up to 3 g daily in divided doses (max. per dose 1 g), dose to be increased over 1 week.

**Maintenance of remission of mild ulcerative colitis**

**BY MOUTH**

- Adult: Maintenance 500 mg twice daily, dose to be taken after food.

**SIDE-EFFECTS**

- **Common or very common** Watery diarrhoea
- **Frequency not known** Blurred vision • palpitation • photosensitivity • pyrexia • tachycardia
- **PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk.
- **BREAST FEEDING** Monitor breast-fed infants for diarrhoea.
- **RENAI IMPAIRMENT** Use with caution; manufacturer advises avoid in significant impairment.
- **DIRECTIONS FOR ADMINISTRATION** Capsules can be opened and contents sprinkled on food.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

- **Tablet**
  - CAUTIONARY AND ADVISORY LABELS 21
  - **Olsalazine sodium 500 mg** Olsalazine 500mg tablets | 60 tablet [PD] £85.00 DT price = £85.00
- **Capsule**
  - CAUTIONARY AND ADVISORY LABELS 21
  - **Olsalazine sodium 250 mg** Olsalazine 250mg capsules | 112 capsule [PD] £75.00 DT price = £75.00

Sulfasalazine (Sulphasalazine)

**INDICATIONS AND DOSE**

Treatment of acute attack of mild to moderate and severe ulcerative colitis | Active Crohn’s disease

**BY MOUTH**

- Adult: 1–2 g 4 times a day until remission occurs, corticosteroids may also be given, if necessary
- Adult: 0.5–1 g twice daily, administered alone or in conjunction with oral therapy, morning and night after a bowel movement

**Maintenance of remission of mild to moderate and severe ulcerative colitis**

**BY MOUTH**

- Adult: 500 mg 4 times a day

**BY RECTUM**

- Adult: 0.5–1 g twice daily, administered alone or in conjunction with oral therapy, morning and night after a bowel movement

**Active rheumatoid arthritis (administered on expert advice)**

**BY MOUTH**

- Adult: Initially 500 mg daily, increased in steps of 500 mg every 1 week, increased to 2–3 g daily in divided doses, enteric coated tablets to be administered

**CONTRA-INDICATIONS** Child under 2 years of age

**CAUTIONS** Acute porphyrias p. 864, G6PD deficiency • history of allergy • history of asthma • maintain adequate fluid intake • risk of haematological toxicity • risk of hepatic toxicity • slow acetylator status

**INTERACTIONS** → Appendix 1 (aminosalicylates).

**SIDE-EFFECTS**

- **Common or very common** Blood disorders • cough • dizziness • fever • Heinz body anaemia • insomnia • megaloblastic anaemia • proteinuria • pruritus • stomatitis • taste disturbances • tinnitus
- **Uncommon** Alopecia • convulsions • depression • dyspnoea • vasculitis
- **Frequency not known** Anaphylaxis • aseptic meningitis • ataxia • crystalluria • disturbances of smell • epidermal necrolysis • exfoliative dermatitis • gastro-intestinal intolerance • hallucinations • hypersensitivity reactions • leucopenia (especially in patients with rheumatoid arthritis) • loss of appetite • neutropenia (especially in patients with rheumatoid arthritis) • oligospermia • parotitis • photosensitivity • rashes • serum sickness • some soft contact lenses may be stained • thrombocytopenia (especially in patients with rheumatoid arthritis) • yellow-orange discoloration of other body fluids • yellow-orange discoloration of skin • yellow-orange discoloration of urine

**SID-EFFECTS, FURTHER INFORMATION**

**Gastro-intestinal side effects** Upper gastro-intestinal side-effects common over 4 g daily.

**Blood disorders** Haematological abnormalities occur usually in the first 3 to 6 months of treatment and are reversible on cessation of treatment.

**PREGNANCY** Theoretical risk of neonatal haemolysis in third trimester; adequate folate supplements should be given to mother.

**BREAST FEEDING** Small amounts in milk (1 report of bloody diarrhoea); theoretical risk of neonatal haemolysis especially in G6PD-deficient infants.

**HEPATIC IMPAIRMENT** Use with caution.

**RENAI IMPAIRMENT** Risk of toxicity, including crystalluria, in moderate impairment—ensure high fluid intake. Avoid in severe impairment.

**MONITORING REQUIREMENTS**

- Blood disorders Close monitoring of full blood counts (including differential white cell count and platelet count) is necessary initially, and at monthly intervals during the first 3 months.
- Renal function Although the manufacturer recommends renal function tests in rheumatic diseases, evidence of practical value is unsatisfactory.
- Liver function Liver function tests should be performed at monthly intervals for first 3 months.

**PATIENT AND CARER ADVICE**

Contact lenses Some soft contact lenses may be stained.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

- **Tablet**
  - CAUTIONARY AND ADVISORY LABELS 14
  - **SULFASALAZINE (Non-proprietary)**
    - Sulfasalazine 500 mg Sulfasalazine 500mg tablets | 112 tablet [PD] £18.00 DT price = £15.38
    - Sulfasalazine 1000 mg Sulfasalazine 1000mg tablets | 112 tablet [PD] £32.97 DT price = £28.38
  - **Salmazosprin (Pfizer Ltd)**
    - Sulfasalazine 500 mg Salazosprin 500mg tablets | 112 tablet [PD] £16.97 DT price = £15.38
Budesonide
The properties listed below are those particular to the drug only. For properties common to the class, see corticosteroids (systemic), p. 579.

INDICATIONS AND DOSE
ENTOCORT® CAPSULES
Mild to moderate Crohn’s disease affecting the ileum or ascending colon | Chronic diarrhoea due to collagenous colitis
BY MOUTH
▶ Adult: 3 mg 3 times a day for up to 8 weeks, reduce dose for the last 2 weeks of treatment
Autoimmune hepatitis, induction of remission
BY MOUTH
▶ Adult: 3 mg 3 times a day
Autoimmune hepatitis, maintenance
BY MOUTH
▶ Adult: 3 mg twice daily

BUDENOFALK® GRANULES
Mild to moderate Crohn’s disease affecting the ileum or ascending colon | Collagenous colitis
BY MOUTH
▶ Adult: 9 mg daily for up to 8 weeks, to be taken in the morning, dose to be reduced for the last 2 weeks of treatment

BUDENOFALK® RECTAL FOAM
Ulcerative colitis affecting sigmoid colon and rectum
BY RECTUM
▶ Adult: 1 metered application once daily for up to 8 weeks
Dose equivalence and conversion
1 metered application is equivalent to budesonide 2 mg.

ENTOCORT® ENEMA
Ulcerative colitis involving rectal and recto-sigmoid disease
BY RECTUM
▶ Adult: 1 enema daily for 4 weeks, to be administered at bedtime

● CAUTIONS
▶ With systemic use | Autoimmune hepatitis
▶ HEPATIC IMPAIRMENT
▶ With systemic use | When used in autoimmune hepatitis liver function tests should be monitored every 2 weeks for 1 month, then at least every 3 months.

DIRECTIONS FOR ADMINISTRATION
▶ With oral use | Granules should be placed on tongue and washed down with water without chewing.

BUDENOFALK® GRANULES
Granules should be placed on tongue and washed down with water without chewing.

● PRESCRIBING AND DISPENSING INFORMATION
Flavours of granule formulations may include lemon.

ENTOCORT® CAPSULES
Dispense in original container (contains dessicant).

PATIENT AND CARER ADVICE
▶ With oral use | Patients or carers should be given advice on how to administer budesonide granules.

NATIONAL FUNDING/ACCESS DECISIONS
BUDENOFALK® CAPSULES
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (April 2015) that Budenofalk® gastro-resistant capsules are accepted for restricted use within NHS Scotland for the treatment of autoimmune hepatitis in non-cirrhotic patients who are intolerant of conventional oral corticosteroids (prednisolone) with severe corticosteroid-related side effects (actual or anticipated) such as psychosis, poorly controlled diabetes or osteoporosis.

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
Modified-release tablet
▶ Cortisporin (Ferring Pharmaceuticals Ltd)
Budesonide 9 mg Cortisporin 9mg modified-release tablets | 30 tablet | £5.00

Modified-release capsule
CAUTIONARY AND ADVISORY LABELS 5, 10, 25
▶ Entocort CR (AstraZeneca UK Ltd)
Budesonide 3 mg Entocort CR 3mg capsules | 100 capsule | £95.00 DT price = £95.00

Gastro-resistant capsule
CAUTIONARY AND ADVISORY LABELS 5, 10, 22, 25
▶ Budenofalk (Dr. Falk Pharma UK Ltd)
Budesonide 3 mg Budenofalk 3mg gastro-resistant capsules | 100 capsule DT price = £75.05

Gastro-resistant granules
CAUTIONARY AND ADVISORY LABELS 5, 10, 22, 25
▶ Budenofalk (Dr. Falk Pharma UK Ltd)
Budesonide 9 mg Budenofalk 9mg gastro-resistant granules | 60 sachet | £135.00

Foam
EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), disodium edetate, propylene glycol, sorbic acid
Budesonide 2 mg per 1 actuation Budenofalk 2mg foam entema | 14 dose | £57.11

Enema
▶ Entocort (AstraZeneca UK Ltd)
Budesonide 20 microgram per 1 ml Entocort 2mg/100ml enema | 7 enema | £39.60

MONOCLONAL ANTIBODIES (ANTI-LYMPHOCYTE)
Vedolizumab

▶ DRUG ACTION Vedolizumab is a monoclonal antibody that binds specifically to the α4β7 integrin, which is preferentially expressed on gut homing T helper lymphocytes.

INDICATIONS AND DOSE
Moderate to severe active ulcerative colitis in patients who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor alpha inhibitor (under expert supervision)

BY INTRAVENOUS INFUSION
▶ Adult: Initially 300 mg, then 300 mg after 2 weeks, followed by 300 mg after 4 weeks, followed by 300 mg every 8 weeks, dose to be given over 30 minutes, if treatment is interrupted or response decreases, dosing frequency may be increased—consult product literature; review treatment if no response within 10 weeks of initial dose

Moderate to severe active Crohn’s disease in patients who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor alpha inhibitor (under expert supervision)

BY INTRAVENOUS INFUSION
▶ Adult: Initially 300 mg, then 300 mg after 2 weeks, followed by 300 mg after 4 weeks, followed by 300 mg every 8 weeks, dose to be given over 30 minutes, if treatment is interrupted or response decreases, dosing frequency may be increased—consult product literature; review treatment if no response within 14 weeks of initial dose

CONTRA-INDICATIONS Severe active infection

CAUTIONS Controlled chronic severe infection; history of recurring severe infection; previous treatment with natalizumab (wait at least 12 weeks between natalizumab use and initiation of vedolizumab unless potential benefit outweighs risk) • previous treatment with rituximab

CAUTIONS, FURTHER INFORMATION
Risk of infection Patients must be screened for tuberculosis before starting treatment; if latent tuberculosis is diagnosed, appropriate treatment must be initiated prior to vedolizumab treatment; if tuberculosis is diagnosed during treatment, discontinue vedolizumab until infection is resolved.

Patients should be brought up to date with current immunisation schedule before initiating treatment.

INTERACTIONS ▶ Appendix 1 (vedolizumab).

SIDE-EFFECTS
▶ Common or very common Acne • arthralgia • back pain • constipation • cough • dyspepsia • eczema • erythema • flatulence • gastroenteritis • headache • hypertension • infections • malaise • muscle spasms • muscular weakness • nasal congestion • nausea • night sweats • oropharyngeal pain • paraesthesia • pharyngitis • pruritus • pyrexia • rash • upper respiratory tract infection

▶ Uncommon Folliculitis • oral candidiasis • vulvovaginal candidiasis

SIDE-EFFECTS, FURTHER INFORMATION
Infusion-related reactions Infusion-related and hypersensitivity reactions have been reported. Patients should be observed continuously during each infusion for signs and symptoms of acute hypersensitivity reactions; they should also be observed for 2 hours after the initial two infusions, and for 1 hour after subsequent infusions. Discontinue treatment if a severe infusion-related or other severe reaction occurs and initiate appropriate treatment (e.g. adrenaline and antihistamines); if a mild to moderate infusion-related reaction occurs, interrupt infusion or reduce infusion rate and initiate appropriate treatment (if reaction subsides the infusion may be continued)—consider pretreatment with an antihistamine, hydrocortisone, and/or paracetamol prior to subsequent infusions in patients who experience mild to moderate infusion-related reactions.

CONCEPTION AND CONTRACEPTION Effective contraception required during and for at least 18 weeks after treatment.

PREGNANCY Manufacturer advises use only if potential benefit outweighs risk.

BREAST FEEDING Manufacturer advises avoid—present in milk in animal studies.

MONITORING REQUIREMENTS
Monitor closely for infection before, during and after treatment—potential increased risk of opportunistic infection.

Monitor for new onset or worsening neurological signs and symptoms (withhold treatment if progressive multifocal leukoencephalopathy (PML) is suspected).

DIRECTIONS FOR ADMINISTRATION For intravenous infusion (Entyvio®), give intermittently in Sodium chloride 0.9%; allow vial to reach room temperature then reconstitute with 4.8 mL of water for injection (using a syringe with a 21–25 gauge needle); gently swirl vial for at least 15 seconds, do not shake vigorously or invert; allow to stand for up to 20 minutes (gently swirl vial if needed), leave for an additional 10 minutes if not dissolved; gently invert vial three times, withdraw 5 mL of reconstituted solution (using a syringe with a 21–25 gauge needle), and add to 250 mL of infusion fluid; gently mix and give over 30 minutes.

PATIENT AND CARER ADVICE Patients should be provided with a patient alert card.
1.2 Irritable bowel syndrome

Drugs used for irritable bowel syndrome not listed below;
Alverine citrate, p. 74 • Mebeverine hydrochloride, p. 75

ANTISPASMODICS

Peppermint oil

INDICATIONS AND DOSE

COLPERMIN®
Relief of abdominal colic and distension, particularly in irritable bowel syndrome
BY MOUTH
- Child 15-17 years: 1–2 capsules 3 times a day for up to 3 months if necessary, capsule to be swallowed whole with water
- Adult: 1–2 capsules 3 times a day for up to 3 months if necessary, capsule to be swallowed whole with water

MINTEC®
Relief of abdominal colic and distension, particularly in irritable bowel syndrome
BY MOUTH
- Adult: 1–2 capsules 3 times a day for up to 2–3 months if necessary, dose to be taken before meals, swallowed whole with water

CAUTIONS
- Sensitivity to menthol

SIDE-EFFECTS
- Rare Allergic reactions • ataxia • bradycardia • headache • muscle tremor • rash
- Frequency not known Heartburn • perianal irritation
- PREGNANCY Not known to be harmful.
- BREAST FEEDING Significant levels of menthol in breast milk unlikely.
- DIRECTIONS FOR ADMINISTRATION Capsules should not be broken or chewed because peppermint oil may irritate mouth or oesophagus.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: enema

Modified-release capsule
CAUTIONARY AND ADVISORY LABELS 5, 22, 25
EXCIPIENTS: May contain Arachis (peanut) oil
- Colpermin (McNeil Products Ltd)
  Peppermint oil 200 microgram capsules Colpermin gastro-resistant modified-release capsules | 20 capsule [SSL] £3.33 | 100 capsule [SSL] £12.18 DT price = £12.18
Gastro-resistant capsule
CAUTIONARY AND ADVISORY LABELS 5, 22, 25
- PEPPERMINT OIL (Non-proprietary)
  Peppermint oil 0.2ml gastro-resistant capsules | 84 capsule [SSL] £7.04 DT price = £7.04
- Brands may include Apercap, Mintec

LIQUID

- PEPPERMINT OIL (Non-proprietary)
  Ethanol 90% 15 ml per 1 litre, Peppermint oil 0.5 ml per 1 litre, Purified water 9.5 ml per 1 litre Peppermint oil BP 1973 | 100 ml [SSL] £5.95 | 100 ml £19.50

GUANYLATE CYCLASE-C RECEPTOR AGONISTS

Linaclotide

INDICATIONS AND DOSE
Moderate to severe irritable bowel syndrome with constipation
BY MOUTH
- Adult: 290 micrograms once daily, review treatment if no response after 4 weeks

CONTRA-INDICATIONS
- Gastro-intestinal obstruction • inflammatory bowel disease

CAUTIONS
- Predisposition to fluid and electrolyte disturbances

SIDE-EFFECTS
- Common or very common Abdominal distension • abdominal pain • diarrhoea (if severe or prolonged, consider suspending treatment) • dizziness • flatulence
- Uncommon Decreased appetite • dehydration • hypokalaemia • orthostatic hypotension
- PREGNANCY Manufacturer advises avoid.
- BREAST FEEDING Unlikely to be present in milk in significant amounts, but manufacturer advises avoid.

PRESCRIBING AND DISPENSING INFORMATION
Dispense capsules in original container (contains desiccant); discard any capsules remaining 18 weeks after opening.

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (May 2013) that linaclotide (Constella®) is accepted for restricted use within NHS Scotland for moderate to severe irritable bowel syndrome in patients whose condition has not responded adequately to all other treatments, or who are intolerant of them.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Capsule
CAUTIONARY AND ADVISORY LABELS 22
- Constella (Almirall Ltd) ▼
  Linaclotide 290 microgram capsules | 28 capsule [POTS] £37.56

2 Constipation and bowel cleansing

2.1 Bowel cleansing

Drugs used for Bowel cleansing not listed below;
Bisacodyl, p. 52 • Docusate sodium, p. 52 • Macrogol 3350 with potassium chloride, sodium bicarbonate and sodium chloride, p. 48 • Magnesium sulfate, p. 858 • Phosphate, p. 861 • Sodium picosulfate, p. 54
MAGNESIUM-CONTAINING DRUGS

**Citric acid with magnesium carbonate**
(Formulated as a bowel cleansing preparation)

**INDICATIONS AND DOSE**
Bowel evacuation for surgery, colonoscopy or radiological examination

**BY MOUTH**
- Child 5-9 years: One-third of a sachet to be given at 8 a.m. the day before the procedure and, one-third of a sachet to be given between 2 and 4 p.m. the day before the procedure
- Child 10-17 years: 0.5–1 sachet, given at 8 a.m. the day before the procedure and 0.5–1 sachet, given between 2 and 4 p.m. the day before the procedure
- Adult: 1 sachet, given 8 a.m. the day before the procedure and 1 sachet, given between 2 and 4 p.m. the day before the procedure, use half the dose in frail elderly patients

**CONTRA-INDICATIONS**
Acute severe colitis • gastric retention • gastro-intestinal obstruction • gastro-intestinal perforation • toxic megacolon

**CAUTIONS**
Children • colitis (avoid if acute severe colitis) • debilitated • elderly • hypovolaemia (should be corrected before administration of bowel cleansing preparations) • impaired gag reflex or possibility of regurgitation or aspiration • patients with fluid and electrolyte disturbances

**CAUTIONS, FURTHER INFORMATION**
Adequate hydration should be maintained during treatment.

**INTERACTIONS**
Other oral drugs should not be taken one hour before or after administration of bowel cleansing preparations because absorption may be impaired. Consider withholding ACE inhibitors, angiotensin-II receptor antagonists, and NSAIDs on the day that bowel cleansing preparations are given and for up to 72 hours after the procedure. Also consider withholding diuretics on the day that bowel cleansing preparations are given.

**SIDE-EFFECTS**
- Common or very common Abdominal distention • abdominal pain • nausea • vomiting
- Uncommon Dehydration • dizziness • electrolyte disturbances • headache

**SIDE-EFFECTS, FURTHER INFORMATION**
Abdominal pain Abdominal pain is usually transient and can be reduced by taking preparation more slowly.

**PREGNANCY**
Use with caution.

**BREAST FEEDING**
Use with caution.

**HEPATIC IMPAIRMENT**
Avoid in hepatic coma if risk of renal failure.

**RENAL IMPAIRMENT**
- In adults Avoid if eGFR less than 30 mL/minute/1.73 m² — risk of hypermagnesaemia.
- In children Avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m² — risk of hypermagnesaemia.

**MONITORING REQUIREMENTS**
Renal function should be measured before starting treatment in patients at risk of fluid and electrolyte disturbances.

**DIRECTIONS FOR ADMINISTRATION**
One sachet should be reconstituted with 200 mL of hot water; the solution should be allowed to cool for approx. 30 minutes before drinking.

**PRESCRIBING AND DISPENSING INFORMATION**
Reconstitution of one sachet containing 11.57 g magnesium carbonate and 17.79 g anhydrous citric acid produces a solution containing magnesium citrate with 118 mmol Mg²⁺. Flavours of oral powders may include lemon and lime.

**PATIENT AND CARER ADVICE**
Low residue or fluid only diet (e.g. water, fruit squash, clear soup, black tea or coffee) recommended before procedure (according to prescriber’s advice) and copious intake of clear fluids recommended until procedure. Patient or carers should be given advice on how to administer oral powder.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Effervescent powder**

**ELECTROLYTES: Magnesium**
- Citramag (Sanochemia Diagnostics UK Ltd)
  Citric acid anhydrous 17.79 gram, Magnesium carbonate heavy 11.57 gram

**OSMOTIC LAXATIVES**

**Macrogol 3350 with anhydrous sodium sulfate, ascorbic acid, potassium chloride, sodium ascorbate and sodium chloride**
(Polyethylene glycols)

**INDICATIONS AND DOSE**
MOVIPREP®
Bowel evacuation for surgery, colonoscopy or radiological examination

**BY MOUTH**
- Adult: 1 litre daily for 2 doses: first dose of reconstituted solution taken on the evening before procedure and the second dose on the morning of procedure, alternatively 2 litres daily for 1 dose; reconstituted solution to be taken on the evening before the procedure, treatment should be completed at least 1 hour before colonoscopy

**CONTRA-INDICATIONS**
Acute severe colitis • G6PD deficiency • gastric retention • gastro-intestinal obstruction • gastro-intestinal perforation • toxic megacolon

**CAUTIONS**
Colitis (avoid if acute severe colitis) • debilitated patients • elderly • fluid and electrolyte disturbances • heart failure • hypovolaemia (should be corrected before administration of bowel cleansing preparations) • impaired gag reflex or possibility of regurgitation or aspiration

**INTERACTIONS**
Consider withholding ACE inhibitors, angiotensin-II receptor antagonists, and NSAIDs on the day that bowel cleansing preparations are given.

**SIDE-EFFECTS**
- Common or very common Abdominal distention • abdominal pain • nausea • vomiting
- Uncommon Dehydration • dizziness • electrolyte disturbances • headache
- Frequency not known Anal discomfort • fatigue • sleep disturbances

**SIDE-EFFECTS, FURTHER INFORMATION**
Abdominal pain Abdominal pain is usually transient and can be reduced by taking preparation more slowly.
Macrogol 3350 with anhydrous sodium sulfate, potassium chloride, sodium bicarbonate and sodium chloride (Formulated as a bowel cleansing preparation)

**INDICATIONS AND DOSE**
Bowel cleansing before radiological examination, colonoscopy, or surgery

**INITIALLY BY MOUTH**
- Adult: Initially 2 litres daily for 2 doses: first dose of reconstituted solution taken on the evening before procedure and the second dose on the morning of procedure, alternatively (by mouth) initially 250 mL every 10–15 minutes, reconstituted solution to be administered, alternatively (by nasogastric tube) initially 20–30 mL/minute, starting on the day before procedure until 4 litres have been consumed

**CONTRA-INDICATIONS** Acute severe colitis · gastric retention · gastro-intestinal obstruction · gastro-intestinal perforation · toxic megacolon

**CAUTIONS** Colitis (avoid if acute severe colitis) · debilitated patients · elderly · fluid and electrolyte disturbances · heart failure · hypovolaemia (should be corrected before administration of bowel cleansing preparations) · impaired gag reflex or possibility of regurgitation or aspiration

**INTERACTIONS** Consider withholding ACE inhibitors, angiotensin-II receptor antagonists, and NSAIDs on the day that bowel cleansing preparations are given and for up to 72 hours after the procedure. Also consider withholding diuretics on the day that bowel cleansing preparations are given.

**SIDE-EFFECTS**
- Common or very common Abdominal distension · abdominal pain · nausea · vomiting
- Uncommon Anal discomfort · dehydration · dizziness · electrolyte disturbances · fatigue · headache · sleep disturbances

**STIMULANT LAXATIVES**
Magnesium citrate with sodium picosulfate (Formulated as a bowel cleansing preparation)

**INDICATIONS AND DOSE**
Citraflex® SACHETS
Bowel evacuation on day before radiological examination, endoscopy, or surgery

**BY MOUTH**
- Adult: 1 sachet taken before 8 a.m., then 1 sachet after 6–8 hours

**PHARMACOKINETICS**
Acts within 3 hours of first dose.

**PICOLAX® SACHETS**
Bowel evacuation on day before radiological procedure, endoscopy, or surgery

**BY MOUTH**
- Child 1 year: 0.25 sachet taken before 8 a.m., then 0.25 sachet after 6–8 hours
- Child 2–3 years: 0.5 sachet taken before 8 a.m., then 0.5 sachet after 6–8 hours
- Child 4–8 years: 1 sachet taken before 8 a.m., then 0.5 sachet after 6–8 hours
- Child 9–17 years: 1 sachet taken before 8 a.m., then 1 sachet after 6–8 hours
- Adult: 1 sachet taken before 8 a.m., then 1 sachet after 6–8 hours
**PATIENT AND CARER ADVICE**

- **SIDE-EFFECTS**
  - Common or very common: Abdominal distention, abdominal pain (usually transient—reduced by taking more slowly), nausea, vomiting
  - Uncommon: Dehydration, dizziness, electrolyte disturbances, headache
  - Frequency not known: Anal discomfort, fatigue, rash, sleep disturbances

**CAUTIONS**

- **GENERAL CAUTIONS:**
  - Cardiac disease (avoid in congestive cardiac failure), children, colitis (avoid if acute severe colitis), debilitated patients, elderly, fluid and electrolyte disturbances, hypovolaemia (should be corrected before administration), impaired gag reflex or possibility of regurgitation or aspiration, recent gastro-intestinal surgery

- **CONTRA-INDICATIONS**
  - Acute severe colitis, ascites, congestive cardiac failure, gastric retention, gastro-intestinal obstruction, gastro-intestinal perforation, gastro-intestinal ulceration, toxic megacolon

- **BREAST FEEDING**

- **PREGNANCY**

- **HEPATIC IMPAIRMENT**

- **RENOV IMPAIRMENT**

**ELECTROLYTES:** May contain Magnesium, potassium

- **PATIENT AND CARER ADVICE**

**2.2 Constipation**

**Constipation**

Before prescribing laxatives it is important to be sure that the patient is constipated and that the constipation is not secondary to an underlying undiagnosed complaint. It is also important for those who complain of constipation to understand that bowel habit can vary considerably in frequency without doing harm. Some people tend to consider themselves constipated if they do not have a bowel movement every day. A useful definition of constipation is the passage of hard stools less frequently than the patient’s own normal pattern and this can be explained to the patient.

Misconceptions about bowel habits have led to excessive laxative use. Abuse may lead to hypokalaemia.

Thus, laxatives should generally be avoided except where straining will exacerbate a condition (such as angina) or increase the risk of rectal bleeding as in haemorrhoids. Laxatives are also of value in drug-induced constipation, for the expulsion of parasites after anthelmintic treatment, and to clear the alimentary tract before surgery and radiological procedures. Prolonged treatment of constipation is sometimes necessary. Also see the prevention of opioid-induced constipation in palliative care.

The laxatives that follow have been divided into 5 main groups. This simple classification disguises the fact that some laxatives have a complex action.

**Bulk-forming laxatives**

Bulk-forming laxatives are of value if the diet is deficient in fibre. Bulk-forming laxatives are of particular value in those with small hard stools, but should not be required unless fibre cannot be increased in the diet. A balanced diet, including adequate fluid intake and fibre is of value in preventing constipation.

Bulk-forming laxatives can be used in the management of patients with colostomy, ileostomy, haemorrhoids, anal fissure, chronic diarrhoea associated with diverticular disease, irritable bowel syndrome, and as adjuncts in ulcerative colitis. Adequate fluid intake must be maintained to avoid intestinal obstruction. Unprocessed wheat bran, taken with food or fruit juice, is a most effective bulk-forming preparation. Finely ground bran, though more palatable, has poorer water-retaining properties, but can be taken as bran bread or biscuits in appropriately increased quantities. Oat bran is also used.

Methylcellulose p. 45, ispaghula husk p. 45, and sterculia p. 46 are useful in patients who cannot tolerate bran. Methylcellulose also acts as a faecal softener.

**Stimulant laxatives**

Stimulant laxatives include bisacodyl p. 52, sodium picosulfate p. 54, and members of the anthraquinone group, senna p. 53, co-danthramer p. 52 and co-danthrusate p. 51. The indications for co-danthramer and
co-danthrusate are limited by its potential carcinogenicity (based on rodent carcinogenicity studies) and evidence of genotoxicity. Powerful stimulants such as cascara (an anthraquinone) and castor oil are obsolete. Docusate sodium p. 52 probably acts both as a stimulant and as a softening agent.

Stimulant laxatives increase intestinal motility and often cause abdominal cramp; they should be avoided in intestinal obstruction. Excessive use of stimulant laxatives can cause diarrhea and related effects such as hypokalaemia; however, prolonged use may be justifiable in some circumstances.

Glycerol p. 53 suppositories act as a lubricant and as a rectal stimulant by virtue of the mildly irritant action of glycerol.

Unstandardised preparations of cascara, fragula, rhubarb, and senna should be avoided as their laxative action is unpredictable. Aloes, colocynthis, and jalap should be avoided as they have a drastic purgative action.

The parasympathomimetics betanechol chloride p. 676, neostigmine p. 912, and pyridostigmine bromide p. 912 enhance parasympathetic activity in the gut and increase intestinal motility. They are rarely used for their gastro-intestinal effects. Organic obstruction of the gut must first be excluded and they should not be used shortly after bowel anastomosis.

Other stimulant laxatives
Unstandardised preparations of cascara, fragula, rhubarb, and senna should be avoided as their laxative action is unpredictable. Aloes, colocynthis, and jalap should be avoided as they have a drastic purgative action.

Faecal softeners
Liquid paraffin p. 49, the traditional lubricant, has disadvantages. Bulk laxatives and non-ionic surfactant ‘wetting’ agents e.g. docusate sodium p. 52 also have softening properties. Such drugs are useful for oral administration in the management of haemorrhoids and anal fissure; glycerol p. 53 is useful for rectal use.

Enemas containing arachis oil p. 51 (ground-nut oil, peanut oil) lubricate and soften impacted faeces and promote a bowel movement.

Osmotic laxatives
Osmotic laxatives increase the amount of water in the large bowel, either by drawing fluid from the body into the bowel or by retaining the fluid they were administered with. Lactulose p. 47 is a semi-synthetic disaccharide which is not absorbed from the gastro-intestinal tract. It produces an osmotic diarrhoea of low faecal pH, and discourages the proliferation of ammonia-producing organisms. It is therefore useful in the treatment of hepatic encephalopathy.

Macrogols are inert polymers of ethylene glycol which sequester fluid in the bowel; giving fluid with macrogols may reduce the dehydration effect sometimes seen with osmotic laxatives.

Saline purgatives such as magnesium hydroxide p. 46 are commonly abused but are satisfactory for occasional use; adequate fluid intake should be maintained. Magnesium salts, such as magnesium sulfate are useful where rapid bowel evacuation is required. Sodium salts should be avoided as they may give rise to sodium and water retention in susceptible individuals. Phosphate enemas are useful in bowel clearance before radiology, endoscopy, and surgery.

Other drugs used in constipation
Linaclotide p. 40 is a guanylate cyclase-C receptor agonist that is licensed for the treatment of moderate to severe irritable bowel syndrome associated with constipation. It increases intestinal fluid secretion and transit, and decreases visceral pain. It is metabolised within the gastro-intestinal tract and is virtually undetectable in the plasma after therapeutic doses.

Lubiprostone p. 46 is a chloride-channel activator that is licensed for the treatment of chronic idiopathic constipation in adults whose condition has not responded adequately to lifestyle changes (including dietary changes).

Prucacloride p. 50 is a selective serotonin 5HT4 receptor agonist with prokinetic properties. It is licensed for the treatment of chronic constipation in women, when other laxatives have failed to provide an adequate response.

Bowel cleansing preparations
Bowel cleansing preparations are used before colonic surgery, colonoscopy, or radiological examination to ensure the bowel is free of solid contents. They are not treatments for constipation.

Pregnancy
If dietary and lifestyle changes fail to control constipation in pregnancy, moderate doses of poorly absorbed laxatives may be used. A bulk-forming laxative should be tried first. An osmotic laxative, such as lactulose p. 47, can also be used. Bisacodyl p. 52 or senna p. 53 may be suitable, if a stimulant effect is necessary.

Constipation in children
Laxatives should be prescribed by a healthcare professional experienced in the management of constipation in children. Delays of greater than 3 days between stools may increase the likelihood of pain on passing hard stools leading to anal fissure, anal spasm and eventually to a learned response to avoid defaecation.

In infants, increased intake of fluids, particularly fruit juice containing sorbitol (e.g. prune, pear, or apple), may be sufficient to soften the stool. In infants under 1 year of age with mild constipation, lactulose p. 47 can be used to soften the stool; either an oral preparation containing macrogols or, rarely, glycerol p. 53 suppositories can be used to clear faecal impaction. The infant should be referred to a hospital paediatrician if these measures fail.

The diet of children over 1 year of age should be reviewed to ensure that it includes an adequate intake of fibre and fluid. An osmotic laxative containing macrogols can also be used, particularly in children with chronic constipation; lactulose p. 47 is an alternative in children who cannot tolerate a macrogol. If there is an inadequate response to the osmotic laxative, a stimulant laxative can be added.

Treatment of faecal impaction may initially increase symptoms of soiling and abdominal pain. In children over 1 year of age with faecal impaction, an oral preparation containing macrogols is used to clear faecal mass and to establish and maintain soft well-formed stools. If disimpaction does not occur after 2 weeks, a stimulant laxative can be added. If the impacted mass is not expelled following treatment with macrogols and a stimulant laxative, a sodium citrate p. 677 enema can be administered. Although rectal administration of laxatives may be effective, this route is frequently distressing for the child and may lead to persistence of withholding. A phosphate enema may be administered under specialist supervision if disimpaction does not occur after a sodium citrate enema; a bowel cleansing preparation is an alternative. Manual evacuation under anaesthetic may be necessary if disimpaction does not occur after oral and rectal treatment, or if the child is afraid.

Long-term regular use of laxatives is essential to maintain well-formed stools and prevent recurrence of faecal impaction; intermittent use may provoke relapses. In children with chronic constipation, laxatives should be continued for several weeks after a regular pattern of bowel movements or toilet training is established. The dose of laxatives should then be tapered gradually, over a period of
months, according to response. Some children may require laxative therapy for several years.

**Chronic constipation**
For children with chronic constipation, it may be necessary to exceed the licensed doses of some laxatives. Parents and carers of children should be advised to adjust the dose of laxative in order to establish a regular pattern of bowel movements in which stools are soft, well-formed, and passed without discomfort. Laxatives should be administered at a time that produces an effect that is likely to fit in with the child’s toilet routine.

**Bulk-forming laxatives**

**Indications and dose**

**ISPAGEL® ORANGE**

**Constitution**

**By mouth**

- Child 6-11 years: 2.5–5 mL twice daily, dose to be given as a half or whole level spoonful in water, preferably after meals
- Child 12-17 years: 1 sachet 1–3 times a day, dose to be given in water preferably after meals, alternatively 10 mL 1–3 times a day, dose to be given as level spoonfuls in water, preferably after meals
- Adult: 1 sachet 1–3 times a day, dose to be made up in water, preferably taken after food

**Dose equivalence and conversion**

1 sachet equivalent to 2 level 5 mL spoonfuls.

**Fybogel®**

**Constitution**

**By mouth**

- Child 6-11 years: 2.5–5 mL twice daily, dose to be given as a half or whole level spoonfuls in water, preferably after meals
- Child 12-17 years: 1 sachet twice daily, dose to be made up in water, preferably taken after food, alternatively 10 mL twice daily, dose to be made up in water, preferably taken after food
- Adult: 1 sachet twice daily, dose to be made up in water, preferably taken after food, alternatively 10 mL twice daily, dose to be made up in water, preferably taken after food

**Dose equivalence and conversion**

1 sachet equivalent to 2 level 5 mL spoonfuls.

**Contra-indications**

Colonic atony · difficulty in swallowing · faecal impaction · infective bowel disease · intestinal obstruction

**Caution**

Adequate fluid intake should be maintained to avoid intestinal obstruction

**Further information**

It may be necessary to supervise elderly or debilitated patients or those with intestinal narrowing or decreased motility to ensure adequate fluid intake.

**Side-effects**

Abdominal distension (especially during the first few days of treatment) · flatulence (especially during the first few days of treatment) · gastro-intestinal impaction · gastro-intestinal obstruction · hypersensitivity

**Prescribing and dispensing information**

Ispagel® Orange and Fybogel® effervescent granules are available as GSL medicines. Flavours of soluble granules formulations may include plain, lemon, or orange.

**Patient and carer advice**

Patients and their carers should be advised that the full effect may take some days to develop. Preparations that swell in liquid should always be carefully swallowed with water and should not be taken immediately before going to bed.

**Methylcellulose**

**Drug action**

Bulk-forming laxatives relieve constipation by increasing faecal mass which stimulates peristalsis.

**Indications and dose**

**Constitution**

**Diarrhoea**

**By mouth using tablets**

- Adult: 3–6 tablets twice daily

**Contra-indications**

Colonic atony · difficulty in swallowing · faecal impaction · infective bowel disease · intestinal obstruction

**Caution**

Adequate fluid intake should be maintained to avoid intestinal obstruction

**Further information**

It may be necessary to supervise elderly or debilitated patients or those with intestinal narrowing or decreased motility to ensure adequate fluid intake.

**Side-effects**

Abdominal distension (especially during the first few days of treatment) · flatulence (especially during the first few days of treatment) · gastro-intestinal impaction · gastro-intestinal obstruction · hypersensitivity

**Directions for administration**

In constipation the dose should be taken with at least 300 mL liquid. In diarrhoea, ileostomy, and colostomy control, avoid liquid intake for 30 minutes before and after dose.

**Patient and carer advice**

Patients and their carers should be advised that the full effect may take some days to develop. Preparations that swell in contact with liquid should always be carefully swallowed with water and should not be taken immediately before going to bed.

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug.

**Granules**

**Cautionary and advisory labels**

13 EXCIPMENTS: May contain Aspartame

- ISPAGHULA HUSK (Non-proprietary)
- Ispaghula husk 3.5 g granules sachets gluten free | 30 sachets GSL £2.29

**Effervescent granules**

**Cautionary and advisory labels**

13 EXCIPMENTS: May contain Aspartame

- ISPAGHULA HUSK (Non-proprietary)
- Ispaghula husk 3.5 g effervescent granules sachets gluten free sugar free (sugar-free) | 30 sachets no price available DT price = £2.29

**Powder**

**Cautionary and advisory labels**

13 EXCIPMENTS: May contain Aspartame

- ISPAGHULA HUSK (Non-proprietary)
- Ispaghula husk 1 mg per 1 mg Husk oral powder (sugar-free) | 200 gram GSL £1.24

Also available in combination with senna, p. 53
**Sterculia**

- **DRUG ACTION** Bulk-forming laxatives relieve constipation by increasing faecal mass which stimulates peristalsis.

### INDICATIONS AND DOSE

**Constipation**

**BY MOUTH**

- Child 6–11 years: 0.5–1 sachet 1–2 times a day, alternatively, half to one heaped 5–mL spoonful once or twice a day; washed down without chewing with plenty of liquid after meals.
- Child 12–17 years: 1–2 sachets 1–2 times a day, alternatively, one to two heaped 5–mL spoonfuls once or twice a day; washed down without chewing with plenty of liquid after meals.
- Adult: 1–2 sachets 1–2 times a day, alternatively, one to two heaped 5–mL spoonfuls once or twice a day; washed down without chewing with plenty of liquid after meals.

### CONTRA-INDICATIONS

Colonic atony - difficulty in swallowing - faecal impaction - intestinal obstruction.

### CAUTIONS

Adequate fluid intake should be maintained to avoid intestinal obstruction.

### SIDE-EFFECTS

- Abdominal distension (especially during the first few days of treatment).
- Flatulence (especially during the first few days of treatment).
- Gastro-intestinal obstruction.

### PREGNANCY

Manufacturer of Normacol Plus® advises avoid.

### BREAST FEEDING

Manufacturer of Normacol Plus® advises avoid.

### PATIENT AND CARER ADVICE

Patients and their carers should be advised that the full effect may take some days to develop. Preparations that swell in contact with liquid should always be carefully swallowed with water and should not be taken immediately before going to bed.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

#### Granules

**CAUTIONARY AND ADVISORY LABELS** 25, 27

- **Normacol** (Norgine Pharmaceuticals Ltd)
- **Sterculia** 620 mg per 1 gram (Normacol granules 7g sachets) [60 sachet | £5.77 DT price = £5.77]
- **Normacol granules** | 500 gram [53] | £6.85 DT price = £6.85

### CHLORIDE-CHANNEL ACTIVATORS

**Lubiprostone**

- **DRUG ACTION** A chloride-channel activator that acts in the gut to increase intestinal fluid secretion, which increases motility.

### INDICATIONS AND DOSE

**Chronic idiopathic constipation when response to lifestyle changes (including diet) inadequate**

**BY MOUTH**

- Adult: 24 micrograms twice daily for 2 weeks.

### CONTRA-INDICATIONS

Gastro-intestinal obstruction.

### SIDE-EFFECTS

- **Common or very common** Abdominal pain - diarrhoea - dizziness - dyspepsia - dysphoria - flatulence - headache - hot flush - hyperhidrosis - nausea - oedema - palpitation
- **Uncommon** Chest pain - muscle spasm - syncope - vomiting
- **Frequency not known** Influenza-like symptoms - rash - tachycardia

### PREGNANCY

Manufacturer advises avoid — toxicity in animal studies.

### BREAST FEEDING

Manufacturer advises avoid.

### HEPATIC IMPAIRMENT

In moderate to severe impairment initially 24 micrograms once daily; if tolerated, and if necessary, increased to 24 micrograms twice daily.

### PRESCRIBING AND DISPENSING INFORMATION

Dispense capsules in original container; discard any capsules remaining 4 weeks after opening.

### NATIONAL FUNDING/ACCESS DECISIONS

**NICE technology appraisals (TAs)**

- Lubiprostone for treating chronic idiopathic constipation (July 2014) NICE TA318

Lubiprostone is recommended as an option for treating chronic idiopathic constipation for adults in whom treatment with at least 2 laxatives from different classes, at the highest tolerated recommended doses for at least 6 months, has failed to provide adequate relief and for whom invasive treatment for constipation is being considered. If treatment with lubiprostone is not effective after 2 weeks, the patient should be re-examined and the benefit of continuing treatment reconsidered. Lubiprostone should only be prescribed by a clinician with experience of treating chronic idiopathic constipation, after careful review of the patient’s previous courses of laxative treatments. [www.nice.org.uk/TA318](www.nice.org.uk/TA318)

**Scottish Medicines Consortium (SMC) Decisions**

The **Scottish Medicines Consortium** has advised (July 2014) that lubiprostone (Amitiza®) is **not** recommended for use within NHS Scotland.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

#### Capsule

**CAUTIONARY AND ADVISORY LABELS** 21

- **Amitiza** (Sucampo Pharma Europe Ltd)

Lubiprostone 24 microgram | Amitiza 24microgram capsules | 28 capsule | £29.68 | 56 capsule | £53.48

### MAGNESIUM-CONTAINING DRUGS

**Magnesium hydroxide**

### INDICATIONS AND DOSE

**Constipation**

**BY MOUTH**

- Adult: 30–45 mL as required, dose to be given mixed with water at bedtime.

### CONTRA-INDICATIONS

Acute gastro-intestinal conditions.

### CAUTIONS

Debilitated patients - elderly.

### INTERACTIONS

Appendix 1 (antacids).

### SIDE-EFFECTS

Colic.

### HEPATIC IMPAIRMENT

Avoid in hepatic coma if risk of renal failure.

### RENAL IMPAIRMENT

Avoid or reduce dose. Increased risk of toxicity in renal impairment.

### PRESCRIBING AND DISPENSING INFORMATION

When prepared extemporaneously, the BP states Magnesium Hydroxide Mixture, BP consists of an aqueous suspension containing about 8% hydrated magnesium oxide.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.
Methylnaltrexone bromide

**DRUG ACTION** Peripherally acting opioid-receptor antagonist which does not alter the central analgesic effect of opioids.

**INDICATIONS AND DOSE**

Adjunct to other laxatives in opioid-induced constipation in terminally ill patients, when response to other laxatives is inadequate

**BY SUBCUTANEOUS INJECTION**

- Adult (body-weight up to 38 kg): 150 micrograms/kg once daily on alternate days for maximum duration of treatment 4 months, may be given less frequently depending on response; 2 consecutive doses may be given 24 hours apart if no response to treatment on the preceding day
- Adult (body-weight 38-62 kg): 8 mg once daily on alternate days for maximum duration of treatment 4 months, may be given less frequently depending on response; 2 consecutive doses may be given 24 hours apart if no response to treatment on the preceding day
- Adult (body-weight 62-114 kg): 12 mg once daily on alternate days for maximum duration of treatment 4 months, may be given less frequently depending on response; 2 consecutive doses may be given 24 hours apart if no response to treatment on the preceding day
- Adult (body-weight 115 kg and above): 150 micrograms/kg once daily on alternate days for maximum duration of treatment 4 months, may be given less frequently depending on response; 2 consecutive doses may be given 24 hours apart if no response to treatment on the preceding day

**PHARMACOKINETICS**

May act with 30–60 minutes.

- **CONTRA-INDICATIONS** Acute surgical abdominal conditions - gastro-intestinal obstruction
- **CAUTIONS** Diverticular disease - faecal impaction - patients with colostomy - patients with perineal catheter
- **SIDE-EFFECTS**
  - **Common or very common** Abdominal pain - diarrhoea - dizziness - flatulence - hyperhidrosis - injection site reactions - nausea
  - **Frequency not known** Gastro-intestinal perforation
- **PREGNANCY** Toxicity at high doses in *animal* studies - manufacturer advises avoid unless essential.
- **BREAST FEEDING** Manufacturer advises use only if potential benefit outweighs risk - present in milk in *animal* studies.
- **HEPATIC IMPAIRMENT** Manufacturer advises avoid in severe hepatic impairment - no information available.
- **RENAL IMPAIRMENT** If eGFR less than 30 ml/minute/1.73 m², reduce dose as follows: body-weight under 62 kg, 75 micrograms/kg on alternate days; body-weight 62–114 kg, 8 mg on alternate days; body-weight over 114 kg, 75 micrograms/kg on alternate days.
- **DIRECTIONS FOR ADMINISTRATION** Rotate injection site.

**OSMOTIC LAXATIVES**

**Lactulose**

**INDICATIONS AND DOSE**

- **Constipation**
  - **BY MOUTH**
    - Child 1–11 months: 2.5 mL twice daily, adjusted according to response
    - Child 1-4 years: 2.5–10 mL twice daily, adjusted according to response
    - Child 5–17 years: 5–20 mL twice daily, adjusted according to response
    - Adult: Initially 15 mL twice daily, adjusted according to response

- **Hepatic encephalopathy (portal systemic encephalopathy)**
  - **BY MOUTH**
    - Adult: Adjusted according to response to 30–50 mL 3 times a day, subsequently adjusted to produce 2–3 soft stools per day

**PHARMACOKINETICS**

Lactulose may take up to 48 hours to act.

- **UNLICENSED USE**
  - In children Not licensed for use in children for hepatic encephalopathy.
  - In adults Lactulose doses in the BNF may differ from those in product literature.
- **CONTRA-INDICATIONS** Galactosaemia - intestinal obstruction
- **CAUTIONS** Lactose intolerance
- **INTERACTIONS** [Appendix 1 (lactulose).
- **SIDE-EFFECTS**
  - **Common or very common** Abdominal discomfort - cramps - flatulence - nausea - vomiting
- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Nausea Nausea can be reduced by administration with water, fruit juice or meals.
- **PREGNANCY** Not known to be harmful.
- **PATIENT AND CARER ADVICE**
  - Medicines for Children leaflet: Lactulose for constipation [www.medicinesforchildren.org.uk/lactulose-for-constipation](http://www.medicinesforchildren.org.uk/lactulose-for-constipation)

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Oral solution**
    - **LACTULOSE (Non-proprietary)**
      - Lactulose 666.667 mg per 1 mL Lactulose 10g/15ml oral solution
      - 15ml sachets sugar free (sugar-free) | 10 sachet £2.50 DT price = £2.50
      - Lactulose 680 mg per 1 ml Lactulose 3.1-3.7g/5ml oral solution
      - 300 ml £6.85 | 500 ml £14.50 DT price = £3.22
    - **Brands may include Duphalac oral solution; Lactugal oral solution**
Macrogol 3350 with potassium chloride, sodium bicarbonate and sodium chloride

**INDICATIONS AND DOSE**

**Chronic constipation**

**BY MOUTH**
- Child 12-17 years: 1–3 sachets daily in divided doses usually for up to 2 weeks; maintenance 1–2 sachets daily
- Adult: 1–3 sachets daily in divided doses usually for up to 2 weeks; maintenance 1–2 sachets daily

**Faecal impaction**

**BY MOUTH**
- Child 12-17 years: 4 sachets on first day, then increased in steps of 2 sachets daily, total daily dose to be drunk within a 6 hour period, after disimpaction, switch to maintenance laxative therapy if required; maximum 8 sachets per day
- Adult: 4 sachets on first day, then increased in steps of 2 sachets daily, total daily dose to be drunk within a 6 hour period, after disimpaction, switch to maintenance laxative therapy if required; maximum 8 sachets per day

**MOVICOL® LIQUID**

**Chronic constipation**

**BY MOUTH**
- Child 12-17 years: 25 mL 1–3 times a day usually for up to 2 weeks; maintenance 25 mL 1–2 times a day
- Adult: 25 mL 1–3 times a day usually for up to 2 weeks; maintenance 25 mL 1–2 times a day

**MOVICOL-PAEDIATRIC®**

**Chronic constipation | Prevention of faecal impaction**

**BY MOUTH**
- Child 2-5 years: 1 sachet daily, adjust dose to produce regular soft stools; maximum 4 sachets per day
- Child 6-11 years: 2 sachets daily, adjust dose to produce regular soft stools; maximum 4 sachets per day

**Faecal impaction**

**BY MOUTH**
- Child 5-11 years: Initially 4 sachets daily on first day, then increased in steps of 2 sachets daily, total daily dose to be taken over a 12-hour period, after disimpaction, switch to maintenance laxative therapy; maximum 12 sachets per day

**MOVICOL® ORAL POWDER**

**Chronic constipation**

**BY MOUTH**
- Child 12-17 years: 1–3 sachets daily in divided doses usually for up to 2 weeks; maintenance 1–2 sachets daily
- Adult: 1–3 sachets daily in divided doses usually for up to 2 weeks; maintenance 1–2 sachets daily

**Faecal impaction**

**BY MOUTH**
- Child 12-17 years: Initially 4 sachets daily on first day, then increased in steps of 2 sachets daily, total daily dose to be drunk within a 6 hour period, after disimpaction, switch to maintenance laxative therapy if required; maximum 8 sachets per day
- Adult: Initially 4 sachets daily on first day, then increased in steps of 2 sachets daily, total daily dose to be drunk within a 6 hour period, after disimpaction, switch to maintenance laxative therapy if required; maximum 8 sachets per day

**MOVICOL-HALF®**

**Chronic constipation**

**BY MOUTH**
- Child 12-17 years: 2–6 sachets daily in divided doses usually for up to 2 weeks; maintenance 2–4 sachets daily
- Adult: 2–6 sachets daily in divided doses usually for up to 2 weeks; maintenance 2–4 sachets daily

**Faecal impaction**

**BY MOUTH**
- Child 12-17 years: Initially 8 sachets daily on first day, then increased in steps of 4 sachets daily, total daily dose to be drunk within 6 hours, after disimpaction, switch to maintenance laxative therapy; maximum 16 sachets per day
- Adult: Initially 8 sachets daily on first day, then increased in steps of 4 sachets daily, total daily dose to be drunk within 6 hours, after disimpaction, switch to maintenance laxative therapy; maximum 16 sachets per day

**UNLICENSED USE**

**MOVICOL-PAEDIATRIC®**

Movicol® Paediatric not licensed for use in faecal impaction in children under 5 years, or for chronic constipation in children under 2 years.

**CONTRA-INDICATIONS**
- Crohn’s disease · intestinal obstruction · intestinal perforation · paralytic ileus · severe inflammatory conditions of the intestinal tract · toxic megacolon · ulcerative colitis

**MOVICOL-PAEDIATRIC®**

Cardiovascular impairment · renal impairment.

**CAUTIONS**

Cardiovascular impairment (should not take more than 2 ‘full-strength’ sachets or 4 ‘half-strength’ sachets in any one hour) · discontinue if symptoms of fluid and electrolyte disturbance

**MOVICOL-PAEDIATRIC®**

Impaired consciousness (with high doses) · impaired gag reflex (with high doses) · reflux oesophagitis (with high doses)

**INTERACTIONS** → Appendix 1 (macrogols).

**SIDE-EFFECTS**
- Abdominal distention · flatulence · nausea

**PREGNANCY**
- Limited data, but manufacturer advises that it can be used.

**BREAST FEEDING**
- Manufacturer advises that it can be used.

**DIRECTIONS FOR ADMINISTRATION**

Contents of each ‘full strength’ sachet of oral powder to be dissolved in half a glass (approx. 125 mL) of water; after reconstitution the solution should be kept in a refrigerator and discarded if unused after 6 hours.

**MOVICOL® LIQUID**

25 mL of oral concentrate to be diluted with half a glass (approx. 100 mL) of water. After dilution the solution should be discarded if unused after 24 hours.

**MOVICOL-PAEDIATRIC®**

Contents of each sachet to be dissolved in quarter of a glass (approx. 60–65 mL) of water; after reconstitution the solution should be kept in a refrigerator and discarded if unused after 24 hours.

**MOVICOL® ORAL POWDER**

Contents of each sachet to be dissolved in half a glass (approx. 125 mL) of water; after reconstitution the solution should be kept in a refrigerator and discarded if unused after 6 hours.

**MOVICOL-HALF®**

Contents of each sachet to be dissolved in quarter of a glass (approx. 60–65 mL) of water; after reconstitution
the solution should be kept in a refrigerator and discarded if unused after 6 hours.

- **PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid paraffin formulations may include orange. Flavours of oral powder formulations may include chocolate, lime and lemon, or plain.

- **PATIENT AND CARER ADVICE**
  - Medicines for Children leaflet: **Movicol for constipation**
  - www.medicinesforchildren.org.uk/movicol-for-constipation

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Brands may include Cosmocol; Laxido; Macilax; Molaxole
  - Movicol

- **MACROGL 3350 WITH POTASSIUM CHLORIDE, SODIUM BICARBONATE AND SODIUM CHLORIDE (Non-proprietary)**
  - Liquid paraffin with magnesium hydroxide
  - The properties listed below are those particular to the combination only. For the properties of the components please consider, liquid paraffin above, magnesium hydroxide p. 46.

- **INDICATIONS AND DOSE**
  - **Constipation**
    - **By Mouth**
      - Adult: 5–20 mL as required

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Liquid paraffin and magnesium hydroxide preparations are on sale to the public. When prepared extemporaneously, the BP states Liquid Paraffin and Magnesium Hydroxide Oral Emulsion, BP consists of 25% liquid paraffin in aqueous suspension containing 6% hydrated magnesium oxide.

- **LESS SUITABLE FOR PRESCRIBING**
  - Liquid Paraffin Oral Emulsion BP is less suitable for prescribing.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops

- **Liquid paraffin with magnesium hydroxide**

- **PHOSPHATE-CONTAINING DRUGS**
  - Sodium acid phosphate with sodium phosphate

- **INDICATIONS AND DOSE**
  - **Constipation**
    - (using Phosphates Enema BP Formula B) | Bowel evacuation before abdominal radiological procedures, endoscopy, and surgery (using Phosphates Enema BP Formula B)
    - **By Rectum**
      - Child 3–6 years: 45–65 mL once daily
      - Child 7–11 years: 65–100 mL once daily
      - Child 12–17 years: 100–128 mL once daily
      - Adult: 128 mL daily
**FLEET® PHOSPHO-SODA**

**Bowel evacuation before colonic surgery** | **Bowel evacuation before colonoscopy** | **Bowel evacuation before radiological examination**
---|---|---
**BY MOUTH**
- Adult: 45 mL twice daily, each dose must be diluted with half a glass (120 mL) of cold water, followed by one full glass (240 mL) of cold water; timing of doses is dependent on the time of the procedure, for morning procedure, the first dose should be taken at 7 a.m. and second at 7 p.m. on day before the procedure; for afternoon procedure, first dose should be taken at 7 p.m. on day before and second dose at 7 a.m. on day of the procedure

**PHARMACOKINETICS**

Onset of action is within half to 6 hours of first dose.

**FLEET® READY-TO-USE ENEMA**

**Constipation** | **Bowel evacuation before abdominal radiological procedures** | **Bowel evacuation before endoscopy** | **Bowel evacuation before surgery**
---|---|---|---
**BY RECTUM**
- Adult: 118 mL

**CONTRA-INDICATIONS**

- With oral use Acute severe colitis, ascites, congestive cardiac failure, gastric retention, gastro-intestinal obstruction, gastro-intestinal perforation, toxic megacolon
- With rectal use Conditions associated with increased colonic absorption, gastro-intestinal obstruction, inflammatory bowel disease

**CAUTIONS**

- With oral use Cardiac disease (avoid in congestive cardiac failure), colitis (avoid if acute severe colitis), elderly and debilitated patients, fluid and electrolyte disturbances, hypovolaemia (should be corrected before administration), impaired gap reflex or possibility of regurgitation or aspiration
- With rectal use Ascites, congestive heart failure, elderly and debilitated patients, electrolyte disturbances, uncontrolled hypertension

**INTERACTIONS**

- With oral use Other oral drugs should not be taken one hour before or after administration of bowel cleansing preparations because absorption may be impaired. Consider withholding ACE inhibitors, angiotensin II receptor antagonists, and NSAIDs on the day that bowel cleansing preparations are given and for up to 72 hours after the procedure. Also consider withholding diuretics on the day that bowel cleansing preparations are given.

**SIDE-EFFECTS**

- Common or very common
  - With oral use Abdominal distension, abdominal pain (usually transient—reduced by taking more slowly), nausea, vomiting
  - Uncommon
  - With oral use Dehydration, dizziness, headache
  - Frequency not known
  - With oral use Arrhythmias, asthenia, chest pain, electrolyte disturbances, renal failure
  - With rectal use Electrolyte disturbances, local irritation

**PREGNANCY**

- With oral use Caution.
- With rectal use Caution.

**HEPATIC IMPAIRMENT**

Use with caution in cirrhosis.

**RENAL IMPAIRMENT**

- With oral use Avoid if eGFR less than 60 mL/minute/1.73 m²
- With rectal use Use with caution.

**MONITORING REQUIREMENTS**

- With oral use Renal function should be measured before starting treatment in patients at risk of fluid and electrolyte disturbances.

**DIRECTIONS FOR ADMINISTRATION**

**FLEET® PHOSPHO-SODA**

Copious intake of water or other clear fluids (e.g. clear soup, strained fruit juice without pulp, black tea or coffee) recommended until midnight before morning procedure and until 8 a.m. after afternoon procedure. At least one glass (approx 240 mL) of water or other clear fluid should also be taken immediately before each dose.

**PRESCRIBING AND DISPENSING INFORMATION**

- When prepared extemporaneously, the BP states Phosphates Enema BP Formula B consists of sodium dihydrogen phosphate dodecahydrate 12.8 g, disodium phosphate dodecahydrate 10.24 g, purified water, freshly boiled and cooled, to 128 mL.

**PATIENT AND CARER ADVICE**

**FLEET® PHOSPHO-SODA**

Intake of solid food should be stopped for at least 6 hours before starting treatment and until procedure completed. Patients or carers should be advised that adequate hydration should be maintained during treatment. Patients or carers should be given advice on administration of Fleet Phospho-soda® oral solution.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Oral solution**

**CAUTIONARY AND ADVISORY LABELS 10**

**ELECTROLYTES:** May contain Phosphate, sodium

- **Fleet Phospho-soda** (Laboratorios Casen-Fleet S.L.U)
  - Disodium hydrogen phosphate dodecahydrate 240 mg per 1 ml
  - Sodium dihydrogen phosphate dihydrate 542 mg per 1 ml

**Enema**

- **SODIUM ACID PHOSPHATE WITH SODIUM PHOSPHATE (Non proprietary)**
  - Disodium hydrogen phosphate dodecahydrate 80 mg per 1 ml
  - Sodium dihydrogen phosphate dihydrate 100 mg per 1 ml

- **Fleet Ready-to-use** (Laboratorios Casen-Fleet S.L.U)
  - Disodium hydrogen phosphate dodecahydrate 80 mg per 1 ml
  - Sodium dihydrogen phosphate dihydrate 181 mg per 1 ml

**SELECTIVE 5-HT4 RECEPTOR AGONISTS**

**Prucalopride**

**DRUG ACTION**

A selective serotonin 5-HT4-receptor agonist with prokinetic properties.

**INDICATIONS AND DOSE**

Chronic constipation in women when other laxatives fail to provide an adequate response

**BY MOUTH**

- Adult: 2 mg once daily, review treatment if no response after 4 weeks
- Elderly: Initially 1 mg once daily, increased if necessary to 2 mg once daily, review treatment if no response after 4 weeks

**CONTRA-INDICATIONS**

Crohn’s disease, intestinal obstruction, intestinal perforation, severe inflammatory conditions of the intestinal tract, toxic megacolon, ulcerative colitis

**CAUTIONS**

- History of arrhythmias.
- History of ischaemic heart disease, severe, unstable chronic illness
INTERACTIONS Caution with concomitant use of drugs that prolong QT interval.

SIDE-EFFECTS
- Common or very common Abdominal pain - diarrhoea - dizziness - dyspepsia - fatigue - flatulence - gastrointestinal symptoms - headache - nausea - polyuria - rectal bleeding - vomiting
- Uncommon Anorexia - fever - palpitation - tremor

SID-EFFECTS, FURTHER INFORMATION Side-effects generally occur at the start of treatment and are usually transient.

CONCEPTION AND CONTRACEPTION Manufacturer recommends effective contraception during treatment.

PREGNANCY

BREAST FEEDING Manufacturer advises avoid.

HEPATIC IMPAIRMENT In severe impairment, initially 1 mg once daily, increased if necessary to 2 mg once daily.

RENAL IMPAIRMENT Max. 1 mg daily if eGFR less than 30 ml/minute/1.73 m².

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)
- Prucalopride for the treatment of chronic constipation in women (December 2010) NICE TA211
  Prucalopride is recommended as an option for the treatment of chronic constipation in women for whom treatment with at least 2 laxatives from different classes, at the highest tolerated recommended doses for at least 6 months, has failed to provide adequate relief and invasive treatment for constipation is being considered. If treatment with prucalopride is not effective after 4 weeks, the patient should be re-examined and the benefit of continuing treatment reconsidered.
  Prucalopride should only be prescribed by a clinician with experience of treating chronic constipation, after careful review of the patient’s previous courses of laxative treatments.

Scottish Medicines Consortium (SMC) Decisions
- The Scottish Medicines Consortium (SMC) has advised (November 2010) that prucalopride (Resolor®) is not recommended for use within NHS Scotland because weaknesses in the clinical data prevent assessment of its efficacy in the target population.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
- Resolor (Shire Pharmaceuticals Ltd)
  Prucalopride (as Prucalopride succinate) 1 mg Resolor 1mg tablets 28 tablet (P) £38.69 DT price = £38.69
  Prucalopride (as Prucalopride succinate) 2 mg Resolor 2mg tablets 28 tablet (P) £59.52 DT price = £59.52

Milk.

NATIONAL FUNDING/ACCESS DECISIONS

HEPATIC IMPAIRMENT
- In severe impairment, initially 1 mg once daily, increased if necessary to 2 mg once daily.
- Max. 1 mg daily if eGFR less than 30 ml/minute/1.73 m².

NATIONAL FUNDING/ACCESS DECISIONS

Co-danthrusate

INDICATIONS AND DOSE
Constipation in terminally ill patients

BY MOUTH USING CAPSULES
- Child 6–11 years: 1 capsule once daily, to be taken at night
- Child 12–17 years: 1–3 capsules once daily, to be taken at night
- Adult: 1–3 capsules once daily, to be taken at night

BY MOUTH USING ORAL SUSPENSION
- Child 6–11 years: 5 mL once daily, to be taken at night
- Child 12–17 years: 5–15 mL once daily, to be taken at night
- Adult: 5–15 mL once daily, to be taken at night

Dose equivalence and conversion
Co-danthrusate suspension contains dantron 50 mg and docusate 60 mg per 5 mL.
Co-danthrusate capsules contain dantron 50 mg and docusate 60 mg per capsule.

CONTRA-INDICATIONS
Acute abdominal conditions (in children) - acute inflammatory bowel disease - acute surgical abdominal conditions (in adults) - intestinal obstruction - severe dehydration

CAUTIONS
- Rodent studies indicate potential carcinogenic risk - excessive use of stimulant laxatives can cause diarrhoea and related effects such as hypokalaemia - may cause local irritation

CAUTIONS, FURTHER INFORMATION
Local irritation Avoid prolonged contact with skin (as in incontinent patients or infants wearing nappies—risk of irritation and excoriation).

SIDE-EFFECTS
Abdominal cramp - urine may be coloured red

PREGNANCY
- Manufacturers advise avoid—limited information available.

BREAST FEEDING
- Manufacturer’s advise avoid—no information available.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Capsule
- CAUTIONARY AND ADVISORY LABELS 14
  - CO-DANTHRUSATE (Non-proprietary)
    - Dantron 50 mg, Docusate sodium 60 mg - Co-danthrusate 50mg/60mg capsules 63 capsule (P) £42.50 DT price = £42.50
    - Normax (Galen Ltd)
      - Dantron 50 mg, Docusate sodium 60 mg - Normax capsules 63 capsule (P) £42.50 DT price = £42.50
  - Oral suspension
    - CAUTIONARY AND ADVISORY LABELS 14
      - Normax (Focus Pharmaceuticals Ltd)
        - Dantron 10 mg per 1 mL, Docusate sodium 12 mg per 1 mL Normax oral suspension (sugar-free) 200 mL (P) £89.92 DT price = £89.92

Arachis oil

INDICATIONS AND DOSE
To soften impacted faeces

BY RECTUM
- Adult: 130 mL as required

CAUTIONS
- Hypersensitivity to soya - intestinal obstruction

ALLERGY AND CROSS-SENSITIVITY
- Contraindicated if history of hypersensitivity to arachis oil or peanuts.

DIRECTIONS FOR ADMINISTRATION
- Warm enema in warm water before use.
**52 Constipation and bowel cleansing**

**Gastro-intestinal system**

**INDICATIONS AND DOSE**

**Docusate sodium**

*(Dioctyl sodium sulphosuccinate)*

**Chronic constipation**

**BY MOUTH**

- Child 6 months–1 year: 12.5 mg 3 times a day, adjusted according to response, use paediatric oral solution
- Child 2–11 years: 12.5–25 mg 3 times a day, adjusted according to response, use paediatric oral solution
- Child 12–17 years: Up to 500 mg daily in divided doses, adjusted according to response
- Adult: Up to 500 mg daily in divided doses, adjusted according to response

**WITH RECTUM**

- Adult: 120 mg for 1 dose

**Adjunct in abdominal radiological procedures**

**BY MOUTH**

- Adult: 400 mg, to be administered with barium meal

**BY RECTUM**

- Adult: 120 mg for 1 dose

**PHARMACOKINETICS**

Oral preparations act within 1–2 days; response to rectal administration usually occurs within 20 minutes.

**SIDE-EFFECTS**

- Abdominal cramp
- Diarrhoea (excessive use) - hypokalaemia - rash
- **PREGNANCY** Not known to be harmful — manufacturer advises caution.

**CAUTIONS**

- Do not give with liquid paraffin
- Excessive use of stimulant laxatives can cause diarrhoea and related effects such as hypokalaemia - rectal preparations not indicated if haemorrhoids or anal fissure

**CONTRA-INDICATIONS**

- Acute abdominal conditions (in children)
- Acute inflammatory bowel disease
- Acute surgical abdominal conditions (in adults)
- Intestinal obstruction
- Severe dehydration

**GENERAL SIDE-EFFECTS**

- Abdominal cramp - colitis - nausea - vomiting

**SPECIFIC SIDE-EFFECTS**

- Excessive use of stimulant laxatives can cause diarrhoea and related effects such as hypokalaemia - risk of electrolyte imbalance with prolonged use (in children)

**MEDI-CAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

- Dicoaryl (UCB Pharma Ltd)
  - Docusate sodium 100 mg: Dicoaryl 100 mg capsules | 30 capsule | £2.09 DT price = £2.09 | 100 capsule | £6.98

**Oral solution**

- Docusol (Tyzharm Ltd)
  - Docusate sodium 2.5 mg per 1 ml: Docusol Paediatric 12.5 mg/5 ml oral solution (sugar-free) | 30 ml | £5.29 DT price = £5.29

**Enema**

- Norgalax (Norgine Pharmaceuticals Ltd)
  - Docusate sodium 12 mg per 1 gram: Norgalax 120 mg/10 g enema | 6 enema | £3.97

**STIMULANT LAXATIVES**

**Bisacodyl**

**INDICATIONS AND DOSE**

**Constipation**

**BY MOUTH**

- Child 4–17 years: 5–20 mg once daily, adjusted according to response, dose to be taken at night
- Adult: 5–10 mg once daily; increased if necessary up to 20 mg once daily, dose to be taken at night

**BY RECTUM**

- Adult: 10 mg once daily, dose to be taken in the morning

**Bowel clearance before radiological procedures and surgery**

**INITIALLY BY MOUTH**

- Adult: 10 mg twice daily, dose to be taken in the morning and evening on the day before procedure and (by rectum) 10 mg to be administered 1–2 hours before procedure the following day

**PHARMACOKINETICS**

Tablets act in 10–12 hours; suppositories act in 20–60 minutes.

**CONTRA-INDICATIONS**

- Acute abdominal conditions (in children)
- Acute inflammatory bowel disease
- Acute surgical abdominal conditions (in adults)
- Intestinal obstruction
- Severe dehydration

**CAUTIONS**

- Excessive use of stimulant laxatives can cause diarrhoea and related effects such as hypokalaemia
- Risk of electrolyte imbalance with prolonged use (in children)

**MEDI-CAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, enema, suppository

**Gastro-resistant tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>5, 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisacodyl 5 mg</td>
<td>Bisacodyl 5 mg gastro-resistant tablets</td>
</tr>
</tbody>
</table>

**Suppository**

- **BISACODYL (Non-proprietary)**
  - Bisacodyl 10 mg: Bisacodyl 10 mg suppositories | 12 suppository | £3.53 DT price = £3.53
  - Brands may include Dulco-Lax tablets and suppositories.

**Co-danthramer**

**INDICATIONS AND DOSE**

**Constipation in terminally ill patients (standard strength capsules)**

**BY MOUTH USING CAPSULES**

- Child 6–11 years: 1 capsule once daily, dose should be taken at night
- Child 12–17 years: 1–2 capsules once daily, dose should be taken at night
- Adult: 1–2 capsules once daily, dose should be taken at night
## Glycerol (Glycerin)

### INDICATIONS AND DOSE

#### Constipation

<table>
<thead>
<tr>
<th>Route</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>By mouth</td>
<td>By syrup</td>
</tr>
<tr>
<td>By rectum</td>
<td>By suppository</td>
</tr>
</tbody>
</table>

#### Dose

- **Child 1-11 months:** 1 g as required
- **Child 1-11 years:** 2 g as required
- **Child 12-17 years:** 4 g as required
- **Adult:** 4 g as required

#### Directions for Administration

- **Moisten suppositories with water before insertion.**

#### Prescribing and Dispensing Information

- When prepared extemporaneously, the BP states **Glycerol**
  - **Suppositories:** BP consists of gelatin 140 mg, glycerol 700 mg, purified water to 1 g.

### Medicinal Forms

There can be variation in the licensing of different medicines containing the same drug.

#### Suppository

- **GLYCEROL (Non-proprietary)**
  - Gelatin 140 mg per 1 gram, Glycerol 700 mg per 1 gram
  - Glycerol 2g suppositories | 12 suppository | GLS | £1.65 DT price = £1.53
  - Glycerol 3g suppositories | 12 suppository | GLS | £1.60 DT price = £0.88
  - Glycerol 4g suppositories | 12 suppository | GLS | £1.72 DT price = £1.94

### Senna

### INDICATIONS AND DOSE

#### Constipation

- **By mouth using tablets:**
  - Child 6-17 years: 1–4 tablets once daily, adjusted according to response
  - Adult: 2–4 tablets daily, dose usually taken at night; initial dose should be low then gradually increased

- **By mouth using syrup:**
  - Child 1 month–3 years: 2.5–10 mL once daily, adjusted according to response
  - Child 4-17 years: 2.5–20 mL once daily, adjusted according to response
  - Adult: 10–20 mL once daily, dose usually taken at bedtime

#### Pharmacokinetics

- Onset of action 8–12 hours.

### Medicinal Forms

There can be variation in the licensing of different medicines containing the same drug.

#### Capsule

- **CO-DANTHRAMER (Non-proprietary)**
  - Dantron 25 mg, Poloxamer 188 200 mg
  - 25mg/200mg capsules | 60 capsules (BDP) | £12.86 DT price = £12.86
  - Dantron 37.5 mg, Poloxamer 188 500 mg
  - 37.5mg/500mg capsules | 60 capsules (BDP) | £15.55 DT price = £15.55

#### Oral suspension

- **CO-DANTHRAMER (Non-proprietary)**
  - Dantron 5 mg per 1 mL, Poloxamer 188 40 mg per 1 mL
  - 25mg/200mg/5ml oral suspension sugar free (sugar-free) | 300 mL (BDP) | £134.99
  - Dantron 15 mg per 1 mL, Poloxamer 188 200 mg per 1 mL
  - 75mg/1000mg/5ml oral suspension sugar free (sugar-free) | 300 mL (BDP) | £274.73

### Precautions

- **Contra-indications**
  - Acute abdominal conditions (in children) - acute inflammatory bowel disease - acute surgical abdominal conditions (in adults) - intestinal obstruction - severe dehydration

- **Caution**
  - Rodent studies indicate potential carcinogenic risk - excessive use of stimulant laxatives can cause diarrhoea and related effects such as hypokalaemia - may cause local irritation

- **CAUTIONS**
  - Local irritation
    - Avoid prolonged contact with skin (as in incontinent patients or infants wearing nappies — risk of irritation and excoriation).

- **Side-effects**
  - Abdominal cramp - urine may be coloured red

- **Pregnancy**
  - Manufacturers advise avoid — limited information available.

- **Breastfeeding**
  - Manufacturer’s advise avoid — no information available.

### Unlicensed Use

- Tablets not licensed for use in children under 6 years. Syrup not licensed for use in children under 2 years.

- **Contra-indications**
  - Intestinal obstruction

- **Caution**
  - Excessive use of stimulant laxatives can cause diarrhoea and related effects such as hypokalaemia

- **Side-effects**
  - Abdominal cramp

- **Pregnancy**
  - May be suitable for constipation in pregnancy if a stimulant effect is necessary.

- **Breastfeeding**
  - Not known to be harmful.

### Patient and Carer Advice

- Medicines for Children leaflet: Senna for constipation www.medicinesforchildren.org.uk/senna-for-constipation
Gastro-intestinal system

CONTRA-INDICATIONS

▶ In adults
▶ UNLICENSED USE (Sodium picosulphate)

PATIENT AND CARER ADVICE

DIRECTIONS FOR ADMINISTRATION

EXCEPTIONS TO LEGAL CATEGORY

NATIONAL FUNDING/ACCESS DECISIONS

NHS restrictions Senokot® brand.

EXCIPIENTS: May contain Sucrose

25

Granules

Contains 0.5 mg of Loperamide hydrochloride

CAUTIONARY AND ADVISORY LABELS 25

EXCIPIENTS: May contain Sucrose

25

Ispaghula husk with senna

The properties listed below are those particular to the combination only. For the properties of the components please consider, ispaghula husk p. 45, senna p. 53.

INDICATIONS AND DOSE

Constipation

BY MOUTH

Child 12–17 years: 5–10 mL once daily, to be taken at night, 5 mL equivalent to one level teaspoonful of granules

Adult: 5–10 mL once daily, to be taken at night, 5 mL equivalent to one level teaspoonful of granules

DIRECTIONS FOR ADMINISTRATION

Take at night with at least 150 mL water, fruit juice, milk or warm drink.

PATIENT AND CARER ADVICE

Patients or carers should be given advice on how to administer ispaghula with senna granules.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Granules

CAUTIONARY AND ADVISORY LABELS 25

EXCIPIENTS: May contain Sucrose

25

Ispaghula 542 mg per 1 gram, Senna fruit 124 mg per 1 gram

Medicines for Children leaflet: Sodium picosulfate for constipation www.medicinesforchildren.org.uk/sodium-picosulfate-for-constipation

Sodium picosulfate

(Sodium picosulphate)

INDICATIONS AND DOSE

Constipation

BY MOUTH

Child 1 month–3 years: 2.5–10 mg once daily, adjusted according to response

Child 4–17 years: 2.5–20 mg once daily, adjusted according to response

Adult: 5–10 mg once daily, dose to be taken at night

PHARMACOKINETICS

Onset of action 6–12 hours.

UNLICENSED USE

▶ In children Sodium picosulfate elixir, licensed for use in children (age range not specified by manufacturer).

▶ In adults Sodium picosulfate doses in BNF may differ from those in product literature.

CONTRA-INDICATIONS

Avoid in intestinal obstruction – severe dehydration

CAUTIONS

Active inflammatory bowel disease (avoid if fulminant) – excessive use of stimulant laxatives can cause diarrhoea and related effects such as hypokalaemia

SIDE-EFFECTS

Abdominal cramp – nausea – vomiting

Medicines for Children leaflet: Sodium picosulfate for constipation www.medicinesforchildren.org.uk/sodium-picosulfate-for-constipation

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Oral solution

▶ SODIUM PICOSULFATE (Non-proprietary)

Sodium picosulfate 1 mg per 1 ml

Oral solution sugar free (sugar-free) | 500 mL [P] £2.99 DT price = £2.99

Dulco-Lax (sodium picosulfate) (Boehringer Ingelheim Self-Medication Division)

Sodium picosulfate 1 mg per 1 ml

Dulcolax Pico 5mg/5ml liquid (sugar-free) | 30 ml [G] £1.72 (sugar-free) | 100 ml [P] £1.85 (sugar-free) | 300 ml [P] £4.40 DT price = £6.75

3 Diarrhoea

Acute diarrhoea

The priority in acute diarrhoea, as in gastro-enteritis, is the prevention or reversal of fluid and electrolyte depletion. This is particularly important in infants and in frail and elderly patients. Oral rehydration preparations are used in the prevention or reversal of fluid and electrolyte depletion. Severe depletion of fluid and electrolytes requires immediate admission to hospital and urgent replacement.

Antimotility drugs

Antimotility drugs relieve symptoms of acute diarrhoea. They are used in the management of uncomplicated acute diarrhoea in adults; fluid and electrolyte replacement may be necessary in case of dehydration. However, antimotility drugs are not recommended for acute diarrhoea in young children.

Antimotility drugs prolong the duration of intestinal transit by binding to opioid receptors in the gastrointestinal tract. Loperamide hydrochloride p. 56 does not cross the blood-brain barrier readily. Antimotility drugs have a role in the management of uncomplicated acute diarrhoea in adults but not in young children. However, in severe cases, fluid and electrolyte replacement are of primary importance.

Antimotility drugs have a role in Inflammatory bowel disease p. 32 and in Stoma care p. 83.

Loperamide hydrochloride p. 56 can be used for faecal incontinence [unlicensed indication] after the underlying cause of incontinence has been addressed.

Antispasmodics

Antispasmodics are occasionally of value in treating abdominal cramp associated with diarrhoea but they should not be used for primary treatment. Antispasmodics and antiemetics should be avoided in young children with gastro-enteritis because they are rarely effective and have troublesome side-effects.

Antibacterial drugs

Antibacterial drugs are generally unnecessary in simple gastro-enteritis because the complaint usually resolves quickly without them, and infective diarrhoeas in the UK often have a viral cause. Systemic bacterial infection does, however, need appropriate systemic treatment.
Ciprofloxacin p. 490 is occasionally used for prophylaxis against travellers’ diarrhoea, but routine use is not recommended. Lactobacillus preparations have not been shown to be effective.

**Adsorbsents and bulk-forming drugs**

Adsorbsents such as kaolin p. 57 are not recommended for acute diarrhoeas. Bulk-forming drugs, such as ispaghula husk p. 45, methylcellulose p. 45, and sterculia p. 46 are useful in controlling diarrhoea associated with diverticular disease.

Colestyramine p. 173 binds unabsorbed bile salts and provides symptomatic relief of diarrhoea following ileal disease or resection.

**Enkephalinase inhibitors**

Racemadotril p. 57 is a pro-drug of thiorphan. Thiorphan is an enkephalinase inhibitor that inhibits the breakdown of endogenous opioids, thereby reducing intestinal secretions. Racemadotril is licensed, as an adjunct to rehydration, for the symptomatic treatment of uncomplicated acute diarrhoea; it should only be used in children over 3 months of age when usual supportive measures, including oral rehydration, are insufficient to control the condition. Racemadotril does not affect the duration of intestinal transit.

### Drugs used for Diarrhoea not listed below; Codeine phosphate, p. 360 - Co-phenotrope, p. 173 - Morphine, p. 367

#### Antimotility Drugs

**Co-phenotrope**

**INDICATIONS AND DOSE**

**Adjunct to rehydration in acute diarrhoea**

**BYPYOUTH**

- Adult: 10 mL every 6 hours, dose to be given in water

**CONTRA-INDICATIONS**

Acute abdomen - delayed gastric emptying - heart failure secondary to chronic lung disease - phaeochromocytoma

**CAUTIONS**

Cardiac arrhythmias - pancreatitis - severe cor pulmonale

**SIDE-EFFECTS**


**REFERENCES**

Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

**PRESCRIBING AND DISPENSING INFORMATION**

When prepared extemporaneously, the BP states Kaolin and Morphine Mixture, BP consists of light kaolin or light kaolin (natural) 20%, sodium bicarbonate 5%, and chloroform and morphine tincture 4% in a suitable vehicle. Contains anhydrous morphine 550–800 micrograms/10 mL.

**LESS SUITABLE FOR PRESCRIBING**

Kaolin and Morphine Mixture, BP (Kaolin and Morphine Oral Suspension) is less suitable for prescribing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.
Loperamide hydrochloride

**INDICATIONS AND DOSE**

**Symptomatic treatment of acute diarrhoea**

**BY MOUTH**

- **Child 4–7 years**: 1 mg 3–4 times a day for up to 3 days only
- **Child 8–11 years**: 2 mg 4 times a day for up to 5 days
- **Child 12–17 years**: Initially 4 mg, followed by 2 mg for up to 5 days, dose to be taken after each loose stool; usual dose 6–8 mg daily; maximum 16 mg per day
- **Adult**: Initially 4 mg, followed by 2 mg for up to 5 days, dose to be taken after each loose stool; usual dose 6–8 mg daily; maximum 16 mg per day

**Chronic diarrhoea**

**BY MOUTH**

- **Adult**: Initially 4–8 mg daily in divided doses, adjusted according to response; maintenance up to 16 mg daily in 2 divided doses

**Faecal incontinence**

**BY MOUTH**

- **Adult**: Initially 500 micrograms daily, adjusted according to response, maximum daily dose to be given in divided doses; maximum 16 mg per day

**Pain of bowel colic in palliative care**

**BY MOUTH**

- **Adult**: 2–4 mg 4 times a day

**UNLICENSED USE** Capsules not licensed for use in children under 8 years. Syrup not licensed for use in children under 4 years.

**CONTRA-INDICATIONS** Active ulcerative colitis - antibiotic-associated colitis - conditions where abdominal distension develops - conditions where inhibition of peristalsis should be avoided

**CAUTIONS** Not recommended for children under 12 years

**INTERACTIONS** → Appendix 1 (loperamide).

**SIDE-EFFECTS**

- **Common or very common** Dizziness - flatulence - headache - nausea
- **Uncommon** Abdominal pain - drowsiness - dry mouth - dyspepsia - rash - vomiting
- **Rare** Fatigue - hypotension - paralytic ileus - Stevens-Johnson syndrome - toxic epidermal necrolysis - urinary retention

**PREGNANCY** Manufacturers advise avoid—no information available.

**BREAST FEEDING** Amount probably too small to be harmful.

**HEPATIC IMPAIRMENT** Risk of accumulation—manufacturer advises caution.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Loperamide for diarrhoea [www.medicinesforchildren.org.uk/loperamide-for-diarrhoea](http://www.medicinesforchildren.org.uk/loperamide-for-diarrhoea)

**EXCEPTIONS TO LEGAL CATEGORY** Loperamide can be sold to the public, provided it is licensed and labelled for the treatment of acute diarrhoea associated with irritable bowel syndrome (after initial diagnosis by a doctor) in adults over 18 years of age.

Loperamide hydrochloride can be sold to the public, for use in adults and children over 12 years, provided it is licensed and labelled for the treatment of acute diarrhoea.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

- **LOPERAMIDE HYDROCHLORIDE (Non-proprietary)**
  - Loperamide hydrochloride 2 mg Loperamide 2mg tablets | 30 tablet £1.15 DT price + £2.15

**Orodispersible tablet**

- **Imodium (McNeil Products Ltd)**
  - Loperamide hydrochloride 2 mg Imodium Instant Melts 2mg orodispersible tablets (sugar-free) | 12 tablet £3.75 (sugar-free) | 18 tablet £5.02

**Capsule**

- **LOPERAMIDE HYDROCHLORIDE (Non-proprietary)**
  - Loperamide hydrochloride 2 mg Loperamide 2mg capsules | 6 capsule £3.15 | 10 capsule £4.76 | 12 capsule £1.94 | 30 capsule £3.19 DT price + £3.19
  - **Imodium (McNeil Products Ltd)**
    - Loperamide hydrochloride 2 mg Imodium IBS Relief 2mg capsules | 6 capsule £2.23 | 12 capsule £3.79
    - Imodium 2mg Soft capsules | 12 capsule £3.79
    - Imodium Classic 2mg capsules | 12 capsule £3.31 | 18 capsule £4.13

**Oral solution**

- **Imodium (Janssen-Cilag Ltd)**
  - Loperamide hydrochloride 200 microgram per 1 ml Imodium 1mg/5ml oral solution (sugar-free) | 100 ml DT price + £1.17

**Oral lyophilisate**

- **Imodium (McNeil Products Ltd)**
  - Loperamide hydrochloride 2 mg Imodium Instants 2mg oral lyophilisates (sugar-free) | 6 tablet £2.45 (sugar-free) | 12 tablet £3.76

Loperamide with simeticone

The properties listed below are those particular to the combination only. For the properties of the components please consider, loperamide hydrochloride above, simeticone p. 60.

**INDICATIONS AND DOSE**

**Acute diarrhoea with abdominal colic**

**INITIALLY BY MOUTH**

- **Child 12–17 years**: Initially 1 tablet, then (by mouth) 1 tablet, after each loose stool, for up to 2 days; maximum 4 tablets per day
- **Adult**: Initially 2 tablets, then (by mouth) 1 tablet, after each loose stool, (by mouth) for up to 2 days; maximum 4 tablets per day

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Imodium Plus (McNeil Products Ltd)**
  - Loperamide hydrochloride 2 mg, Dimeticone (as Simeticone) 125 mg Imodium Plus caplets | 12 tablet £3.66
ENKEPHALINASE INHIBITORS

Raconovidril

INDICATIONS AND DOSE
Adjunct to rehydration, for the symptomatic treatment of uncomplicated acute diarrhoea

BY MOUTH
- Child 3 months–7 years (body-weight up to 9 kg): 10 mg 3 times a day until diarrhoea stops; maximum duration of treatment 7 days
- Child 3 months–7 years (body-weight 9–13 kg): 20 mg 3 times a day until diarrhoea stops; maximum duration of treatment 7 days
- Child 3 months–7 years (body-weight 13–27 kg): 30 mg 3 times a day until diarrhoea stops; maximum duration of treatment 7 days
- Child 3 months–7 years (body-weight 28 kg and above): 60 mg 3 times a day until diarrhoea stops; maximum duration of treatment 7 days
- Adult: Initially 100 mg, then 100 mg 3 times a day until diarrhoea stops; maximum duration of treatment 7 days, dose to be taken preferably before food

SIDE-EFFECTS
- Common or very common Headache
- Common Rash
- PREGNANCY Manufacturer advises avoid—no information available.
- BREAST FEEDING Manufacturer advises avoid—no information available.
- HEPATIC IMPAIRMENT
  - In adults Manufacturer advises caution.
  - In children Manufacturer advises avoid.
- RENAL IMPAIRMENT
  - In adults Manufacturer advises caution.
  - In children Manufacturer advises avoid.
- DIRECTIONS FOR ADMINISTRATION Granules may be added to food or mixed with water or bottle feeds and then taken immediately.

PATIENT AND CARER ADVICE Patients and carers should be given advice on how to administer racecadotril granules.

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium, has advised (July 2014) that racecadotril (Hidrasec®) is not recommended for use within NHS Scotland for the treatment of acute diarrhoea in children because there is insufficient evidence that it improves the recovery rate.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Capsule
- *Hidrasec* (Lincoln Medical Ltd)
  - Racecadotril 100 mg Hidrasec 100mg capsules | 20 capsule (£4.82

Granules EXCIPIENTS: May contain Sucrose
- *Hidrasec* (Lincoln Medical Ltd)
  - Racecadotril 10 mg Hidrasec Infants 10mg granules sachets | 20 sachet (£4.82
  - Racecadotril 30 mg Hidrasec Children 30mg granules sachets | 20 sachet (£4.82

INTESTINAL ADSORBENTS

Kaolin

INDICATIONS AND DOSE
Diarrhoea (not recommended for acute diarrhoea)

BY MOUTH
- Adult: 10–20 mL every 4 hours

INTERACTIONS → Appendix 1 (kaolin).

PRESCRIBING AND DISPENSING INFORMATION Flavours of oral liquid formulations may include peppermint. When prepared extemporaneously, the BP states Kaolin Mixture, BP consists of light kaolin or light kaolin (natural) 20%, light magnesium carbonate 5%, sodium bicarbonate 5% in a suitable vehicle with a peppermint flavour.

LESS SUITABLE FOR PRESCRIBING Kaolin Mixture BP is less suitable for prescribing.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Oral suspension
- **KAOLIN (Non-proprietary)**
  - Kaolin light 200 mg per 1 ml, Magnesium carbonate light 50 mg per 1 ml, Sodium bicarbonate 50 mg per 1 ml Kaolin mixture | 200 ml (£0.86 DT price = £0.86
  - Kaolin light 200 mg per 1 gram Kaolin mixture paediatric BP 1980 | 100 ml (£0.78 DT price = £0.78

4 Disorders of gastric acid and ulceration

4.1 Dyspepsia

Dyspepsia

Dyspepsia covers upper abdominal pain, fullness, early satiety, bloating, and nausea. It can occur with gastric and duodenal ulceration and, gastric cancer, but most commonly it is of uncertain origin.

Urgent endoscopic investigation is required if dyspepsia is accompanied by ‘alarm features’ (e.g. bleeding, dysphagia, recurrent vomiting, or weight loss). Urgent investigation should also be considered for patients over 55 years with unexplained, recent-onset dyspepsia that has not responded to treatment.

Patients with dyspepsia should be advised about lifestyle changes (avoidance of excess alcohol and of aggravating foods such as fats); other measures include weight reduction, smoking cessation, and raising the head of the bed. Some medications may cause dyspepsia—these should be stopped, if possible.

Antacids may provide some symptomatic relief, however if symptoms persist in uninvestigated dyspepsia, treatment involves a proton pump inhibitor for up to 4 weeks. A proton pump inhibitor can be used intermittently to control symptoms long term. Patients with uninvestigated dyspepsia, who do not respond to an initial trial with a proton pump inhibitor, should be tested for *Helicobacter pylori* and given eradication therapy if *H. pylori* is present. Alternatively, particularly in populations where *H. pylori* infection is more likely, the ‘test and treat’ strategy for *H. pylori* can be used before a trial with a proton pump inhibitor.

If *H. pylori* is present in patients with functional (investigated, non-ulcer) dyspepsia, eradication therapy should be provided. If symptoms persist, treatment with
either a proton pump inhibitor or a histamine H$_2$-receptor antagonist can be given for 4 weeks. These antisecretory drugs can be used intermittently to control symptoms long term. However, most patients with functional dyspepsia do not benefit symptomatically from H. pylori eradication therapy or antisecretory drugs.

### Alginate

#### INDICATIONS AND DOSE

**GAVISCON INFANT® POWDER SACHETS**

Management of gastro-oesophageal reflux disease

**BY MOUTH**
- Child 1 month–2 years (body-weight up to 4.5 kg): 1 dose as required, to be mixed with feeds (or water, for breast-fed infants); maximum 6 doses per day
- Child 1 month–2 years (body-weight 4.5 kg and above): 2 doses as required, to be mixed with feeds (or water, for breast-fed infants); maximum 12 doses per day

#### PRESCRIBING AND DISPENSING INFORMATION

Each half of a dual-sachet is identified as ‘one dose’. To avoid errors prescribe with directions in terms of ‘dose’.

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Powder**
- Gaviscon Infant (Forum Health Products Ltd)
  - Magnesium alginate 87.5 mg, Sodium alginate 225 mg Gaviscon Infant oral powder sachets (sugar-free) | 15 dual dose sachet £3.99

### Calcium carbonate with sodium alginate and sodium bicarbonate

The properties listed below are those particular to the combination only. For the properties of the components please consider, alginate acid above.

#### INDICATIONS AND DOSE

**Mild symptoms of gastro-oesophageal reflux disease**

**BY MOUTH**
- Child 6–11 years: 5–10 mL, to be taken after meals and at bedtime
- Child 12–17 years: 10–20 mL, to be taken after meals and at bedtime
- Adult: 10–20 mL, to be taken after meals and at bedtime

#### PRESCRIBING AND DISPENSING INFORMATION

Flavours of oral liquid formulations may include aniseed or peppermint.

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Oral suspension**
- **ELECTROLYTES:** May contain Sodium
  - Calcium carbonate 16 mg per 1 mL, Sodium alginate 50 mg per 1 mL
  - Sodium bicarbonate 26.7 mg per 1 mL
- **Flavours of**
  - Alginic acid
  - Potassium bicarbonate
  - Sodium alginate

#### POTASSIUM BICARBONATE WITH SODIUM ALGINATE (Non-proprietary)

- Calcium carbonate 16 mg per 1 mL, Sodium alginate 50 mg per 1 mL
- Alginic acid above.

#### PRESCRIBING AND DISPENSING INFORMATION

- Flavours of oral liquid formulations may include aniseed or peppermint.

### Potassium bicarbonate with sodium alginate

The properties listed below are those particular to the combination only. For the properties of the components please consider, alginate acid above.

#### INDICATIONS AND DOSE

Management of mild symptoms of dyspepsia and gastro-oesophageal reflux disease

**BY MOUTH USING CHEWABLE TABLETS**
- **Child 6–11 years (under medical advice only):** 1 tablet, to be chewed after meals and at bedtime
- **Child 12–17 years: 1–2 tablets, to be chewed after meals and at bedtime**
- **Adult:** 1–2 tablets, to be chewed after meals and at bedtime

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Chewable tablet**
- **EXCIPIENTS:** May contain Aspartame
- **ELECTROLYTES:** May contain Potassium, sodium
  - **POTASSIUM BICARBONATE WITH SODIUM ALGINATE (Non-proprietary)**
    - Potassium bicarbonate 100 mg, Sodium alginate 500 mg / Potassium bicarbonate 100 mg chewable tablets sugar free (sugar-free) | 60 tablet | no price available
    - Brands may include Gaviscon Advance

#### Oral suspension

**ELECTROLYTES:** May contain Potassium, sodium
- **GAVISCON ADVANCE (Reckitt Benckiser Healthcare (UK) Ltd)**
  - Potassium bicarbonate 20 mg per 1 mL, Sodium alginate 100 mg per 1 mL
  - Gaviscon Advance oral suspension aniseed (sugar-free) | 30 mL [£5.82 (sugar-free)]
  - Gaviscon Advance oral suspension peppermint (sugar-free) | 30 mL [£5.82 (sugar-free)]
Calcium-containing antacids can induce rebound acid syndrome. The evidence of benefit is uncertain. Antacids are best given when symptoms occur or are expected, usually between meals and at bedtime, although additional doses may be required. Conventional doses of liquid magnesium– aluminium antacids promote ulcer healing, but less well than secretory drugs; proof of a relationship between healing and neutralising capacity is lacking. Liquid preparations are more effective than tablet preparations.

Aluminium- and magnesium-containing antacids (e.g. aluminium hydroxide p. 859, and magnesium carbonate p. 60, hydroxide and magnesium trisilicate p. 61), being relatively insoluble in water, are long-acting if retained in the stomach. They are suitable for most antacid purposes. Magnesium-containing antacids tend to be laxative whereas aluminium-containing antacids may be constipating; antacids containing both magnesium and aluminium may reduce these colonic side-effects. Aluminium accumulation does not appear to be a risk if renal function is normal. Antacids should preferably not be taken at the same time as other drugs since they may impair absorption.

The acid-neutralising capacity of preparations that contain more than one antacid may be the same as simpler preparations. Complexes such as hydrotalcite confer no special advantage. Sodium bicarbonate p. 848 should no longer be prescribed alone for the relief of dyspepsia but it is present as an ingredient in many indigestion remedies. However, it retains a place in the management of urinary-tract disorders and acidosis.

Bismuth-containing antacids (unless chelates) are not recommended because absorbed bismuth can be neurotoxic, causing encephalopathy; they tend to be constipating. Calcium-containing antacids can induce rebound acid secretion: with modest doses the clinical significance is doubtful, but prolonged high doses also cause hypercalcaemia and alkalosis, and can precipitate the milk-alkali syndrome.

Simeticone Simeticone p. 60 (activated dimeticone) is added to an antacid as an antifoaming agent to relieve flatulence. These preparations may be useful for the relief of hiccup in palliative care.

Alginates Alginates taken in combination with an antacid increases the viscosity of stomach contents and can protect the oesophageal mucosa from acid reflux. Some alginate-containing preparations form a viscous gel (‘raft’) that floats on the surface of the stomach contents, thereby reducing symptoms of reflux. The amount of additional ingredient or antacid in individual preparations varies widely, as does their sodium content, so that preparations may not be freely interchangeable.

Co-magaldrox

The properties listed below are those particular to the combination only. For the properties of the components please consider, aluminium hydroxide p. 859, magnesium hydroxide p. 46.
Magnesium carbonate

**INDICATIONS AND DOSE**

**Dyspepsia**
- **BY MOUTH USING ORAL SUSPENSION**
  - Adult: 10 mL 3 times a day, to be taken in water

**CONTRA-INDICATIONS**
- Hypophosphataemia

**INTERACTIONS**
- Avoid with antacids, as other drugs since they may impair absorption.
Antacids should preferably not be taken at the same time as aluminium-containing antacids should not be taken with children with renal impairment, because accumulation may lead to increased plasma-aluminium concentrations.

**SIDE-EFFECTS**
- Belching due to liberated carbon dioxide
- Diarrhoea

**HEPATIC IMPAIRMENT**
- In patients with fluid retention, avoid antacids containing large amounts of sodium. Avoid antacids containing magnesium salts in hepatic coma if there is a risk of renal failure.

**RENAL IMPAIRMENT**
- Avoid or use at a reduced dose; increased risk of toxicity. Magnesium carbonate mixture has a high sodium content; avoid in patients with fluid retention.

**PRESCRIBING AND DISPENSING INFORMATION**
- **Altacite Plus®** is low in Na⁺.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.
- **Oral suspension**
  - Altacite Plus (Peckforton Pharmaceuticals Ltd)
    - Hydrolatec 100 mg per 1 mL, Simeticone 25 mg per 1 mL Altacite Plus oral suspension (sugar-free) | 100 mL (£1.42) (sugar-free) | 500 mL (£3.20)
  - Infacol® oral suspension (sugar-free) (Sanofi) 40 mg per 1 mL oral suspension
  - Dentinox Infant colic drops (Dendron Ltd) 8.4 mg per 1 mL

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**DEFOAMING DRUGS**

**Simeticone (Activated dimeticone)**
- **DRUG ACTION**
  - Simeticone (activated dimeticone) is an antifoaming agent.

**INDICATIONS AND DOSE**

**INFACOL®**
- Colic | Wind pains
- **BY MOUTH**
  - Child 1 month-1 year: 0.5–1 mL, to be taken before feeds
  - DENTINOX®
  - Colic | Wind pains
  - **BY MOUTH**
  - Child 1 month-1 year: 2.5 mL, to be taken with or after each feed; may be added to bottle feed; maximum 6 doses per day

**PATIENT AND CARER ADVICE**
- Infacol®
  - Patients or carers should be given advice on use of the Infacol® dropper.

**LESS SUITABLE FOR PRESCRIBING**
- Infacol®
  - Infacol® is less suitable for prescribing (evidence of benefit in infantile colic uncertain).
  - DENTINOX®
  - Dentinox® colic drops are less suitable for prescribing (evidence of benefit in infantile colic uncertain).

**Aluminium hydroxide with magnesium hydroxide and simeticone**

The properties listed below are those particular to the combination only. For the properties of the components please consider, aluminium hydroxide p. 859, simeticone above.

**INDICATIONS AND DOSE**

**Dyspepsia**
- **BY MOUTH**
  - Child 12-17 years: 5–10 mL 4 times a day, to be taken after meals and at bedtime, or when required
  - Adult: 5–10 mL 4 times a day, to be taken after meals and at bedtime, or when required

**PRESCRIBING AND DISPENSING INFORMATION**
- **Maalox®** is low Na⁺.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.
  - **Oral suspension**
    - Maalox Plus® (Sanofi)
      - Aluminium hydroxide gel dried 44 mg per 1 mL, Magnesium hydroxide 39 mg per 1 mL, Simeticone 5 mg per 1 mL Maalox Plus oral suspension (sugar-free) | 500 mL (£3.90)

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**Magnesium Carbonate Mixture, BP**
- Magnesium carbonate, calcium carbonate, sodium bicarbonate, simeticone, hydroxide and simeticone.
- **HEPATIC IMPAIRMENT**
  - Avoid; can cause constipation which can precipitate coma. Avoid in hepatic coma; risk of renal failure.

**RENAL IMPAIRMENT**
- Antacids containing magnesium salts should be avoided or used at a reduced dose because there is an increased risk of toxicity.
  - In adults There is a risk of accumulation and aluminium toxicity with antacids containing aluminium salts. Absorption of aluminium from aluminium salts is increased by citrates, which are contained in many effervescent preparations (such as effervescent analgesics).
  - In children Aluminium-containing antacids should not be used in children with renal impairment, because accumulation may lead to increased plasma-aluminium concentrations.

**PRESCRIBING AND DISPENSING INFORMATION**
- Altacite Plus®
- Altacite
  - Magnesium Carbonate Mixture, BP consists of light Magnesium carbonate heavy (Ennogen Healthcare Ltd) 500 mg
  - Magnesite (Ennogen Healthcare Ltd)
    - Magnesium carbonate heavy 500 mg
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule
    - **Capsule**
      - Magnesite
      - Magnesium carbonate heavy 500 mg
      - Magnesite 500 mg capsules | 30 capsule £92.20
  - Also available in combination with calcium acetate, p. 61.
  - magnesium trisilicate and sodium bicarbonate, p. 61

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Magnesium trisilicate

**INDICATIONS AND DOSE**

**Dyspepsia**

- **BY MOUTH USING CHEWABLE TABLETS**
  - Adult: 1–2 tablets as required

- **CONTRA-INDICATIONS**
  - Hypophosphataemia

- **INTERACTIONS**
  - Appendix 1 (antacids).
  - Antacids should preferably not be taken at the same time as other drugs since they may impair absorption. Antacids may damage enteric coatings designed to prevent dissolution in the stomach.

- **SIDE-EFFECTS**
  - Belching due to liberated carbon dioxide - diarrhoea - silica-based renal stones (with long-term treatment)

- **HEPATIC IMPAIRMENT**
  - Avoid in hepatic coma; risk of renal failure.

- **RENAL IMPAIRMENT**
  - Avoid or used at a reduced dose (increased risk of toxicity).

- **MEDICINAL FORMS**
  - Medicines not identified.

Magnesium carbonate with magnesium trisilicate and sodium bicarbonate

The properties listed below are those particular to the combination only. For the properties of the components please consider, magnesium carbonate p. 60, magnesium trisilicate above, sodium bicarbonate p. 848.

**INDICATIONS AND DOSE**

**Dyspepsia**

- **Child 5-11 years**: 5–10 mL 3 times a day or as required, dose to be made up with water
- **Child 12-17 years**: 10–20 mL 3 times a day or as required, dose to be made up with water
- **Adult**: 10–20 mL 3 times a day or as required, dose to be made up with water

- **HEPATIC IMPAIRMENT**
  - In patients with fluid retention avoid antacids containing large amounts of sodium. Avoid antacids containing magnesium salts in hepatic coma if there is a risk of renal failure.

- **RENAL IMPAIRMENT**
  - Magnesium trisilicate mixture has a high sodium content; avoid in patients with fluid retention.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - When prepared extemporaneously, the BP states Magnesium Trisilicate Mixture, BP consists of 5% each of magnesium trisilicate, light magnesium carbonate, and sodium bicarbonate in a suitable vehicle with a peppermint flavour.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  - **Oral suspension**
    - **MAGNESIUM CARBONATE WITH MAGNESIUM TRISILICATE AND SODIUM BICARBONATE (Non-proprietary)**
      - Magnesium carbonate light 50 mg per 1 mL, Magnesium trisilicate 50 mg per 1 mL, Sodium bicarbonate 50 mg per 1 mL
      - Magnesium trisilicate oral suspension | 200 mL £1.28 DT price = £2.28

4.2 **Gastric and duodenal ulceration**

**Pepitic ulceration**

Pepitic ulceration commonly involves the stomach, duodenum, and lower oesophagus; after gastric surgery it involves the gastro-enterostomy stoma. Healing can be promoted by general measures, stopping smoking and taking antacids and by antisecretory drug treatment, but relapse is common when treatment ceases. Nearly all duodenal ulcers and most gastric ulcers not associated with NSAIDs are caused by Helicobacter pylori.

**Helicobacter pylori infection**

Eradication of Helicobacter pylori reduces recurrence of gastric and duodenal ulcers and the risk of rebleeding. It also causes regression of most localised gastric mucosa associated lymphoid-tissue (MALT) lymphomas. The presence of H. pylori should be confirmed before starting eradication treatment. Acid inhibition combined with antibacterial treatment is highly effective in the eradication of H. pylori; reinfection is rare. Antibiotic associated colitis is an uncommon risk.

For initial treatment, a one-week triple-therapy regimen that comprises a proton pump inhibitor, clarithromycin p. 470, and either amoxicillin p. 482 or metronidazole p. 475 can be used. However, if a patient has been treated with metronidazole for other infections, a regimen containing a proton pump inhibitor, amoxicillin and clarithromycin is preferred for initial therapy. If a patient has been treated with a macrolide for other infections, a regimen containing a proton pump inhibitor, amoxicillin and clarithromycin and metronidazole is preferred for initial therapy. These regimens eradicate H. pylori in about 85% of cases. There is usually no need to continue antisecretory treatment (with a proton pump inhibitor or H₂-receptor antagonist), however, if the ulcer is large, or complicated by haemorrhage or perforation, then antisecretory treatment is continued for a further 3 weeks. Treatment failure usually indicates antibacterial resistance or poor compliance. Resistance to amoxicillin is rare. However, resistance to clarithromycin and metronidazole is common and can develop during treatment.

Two-week triple-therapy regimens offer the possibility of higher eradication rates compared to one-week regimens, but adverse effects are more common and poor compliance is likely to offset any possible gain.

Two-week dual-therapy regimens using a proton pump inhibitor and a single antibacterial are licensed, but produce low rates of H. pylori eradication and are not recommended.

Tinidazole p. 476 is also used occasionally for H. pylori eradication as an alternative to metronidazole; tinidazole should be combined with antisecretory drugs and other antibacterials.

Routine retesting, to confirm eradication, is not necessary unless the patient has gastric MALT lymphoma or complicated H. pylori associated peptic ulcer.

A two-week regimen comprising a proton pump inhibitor plus tripotassium dicitratobismuthate p. 63, plus tetracycline p. 498, plus metronidazole can be used for eradication failure. Alternatively, the patient can be referred for endoscopy and treatment based on the results of culture and sensitivity testing.

See under NSAID-associated ulcers for the role of H. pylori eradication therapy in patients starting or taking a NSAID. Also see Dyspepsia p. 57 for H. pylori eradication in patients with dyspepsia.
Recommended regimens for *Helicobacter pylori* eradication

<table>
<thead>
<tr>
<th>Acid suppressant</th>
<th>Antibacterial</th>
<th>Price for 7-day course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole 20 mg twice daily</td>
<td>1 g twice daily</td>
<td>500 mg twice daily</td>
</tr>
<tr>
<td>Lansoprazole 30 mg twice daily</td>
<td>1 g twice daily</td>
<td>500 mg twice daily</td>
</tr>
<tr>
<td>Omeprazole 20 mg twice daily</td>
<td>1 g twice daily</td>
<td>500 mg twice daily</td>
</tr>
<tr>
<td>Pantoprazole 40 mg twice daily</td>
<td>1 g twice daily</td>
<td>500 mg twice daily</td>
</tr>
<tr>
<td>Rabeprozole sodium 20 mg twice daily</td>
<td>1 g twice daily</td>
<td>500 mg twice daily</td>
</tr>
</tbody>
</table>

**Test for *Helicobacter pylori***

¹³C-Urea breath test kits are available for the diagnosis of gastro-duodenal infection with *Helicobacter pylori*. The test involves collection of breath samples before and after ingestion of an oral solution of ¹³C-urea; the samples are sent for analysis by an appropriate laboratory. The test should not be performed within 4 weeks of treatment with an antibacterial or within 2 weeks of treatment with an antisecretory drug. A specific ¹⁴Curea breath test kit for children is available (*Helicobacter Test INFAI for children of the age 3–11*). However, the appropriateness of testing for *H. pylori* infection in children has not been established.

**NSAID-associated ulcers**

Gastro-intestinal bleeding and ulceration can occur with NSAID use. The risk of serious upper gastro-intestinal side-effects varies between individual NSAIDs. Whenever possible, the NSAID should be withdrawn if an ulcer occurs.

Patients at high risk of developing gastro-intestinal complications with a NSAID include those aged over 65 years, those with a history of peptic ulcer disease or serious gastro-intestinal complication, those taking other medicines that increase the risk of gastrointestinal side-effects, or those with serious co-morbidity (e.g. cardiovascular disease, diabetes, renal or hepatic impairment). In those at risk of ulceration, a proton pump inhibitor can be considered for protection against gastric and duodenal ulcers associated with non-selective NSAIDs; a H₂-receptor antagonist such as ranitidine p. 65 given at twice the usual dose or misoprostol p. 710 are alternatives. Colic and diarrhoea may limit the dose of misoprostol. Its use is most appropriate for the frail or very elderly from whom NSAIDs cannot be withdrawn. A combination of a cyclo-oxygenase-2 selective inhibitor with a proton pump inhibitor may be more appropriate for those with a history of upper gastro-intestinal bleeding or 3 or more risk factors for gastro-intestinal ulceration, but see NSAIDs and Cardiovascular Events.

NSAID use and *H. pylori* infection are independent risk factors for gastro-intestinal bleeding and ulceration. In patients already taking a NSAID, eradication of *H. pylori* is unlikely to reduce the risk of NSAID-induced bleeding or ulceration. However, in patients with dyspepsia or a history of gastric or duodenal ulcer, who are *H. pylori* positive, and who are about to start long-term treatment with a non-selective NSAID, eradication of *H. pylori* may reduce the overall risk of ulceration.

In a patient who has developed an ulcer, if the NSAID can be discontinued, a proton pump inhibitor usually produces the most rapid healing; alternatively, the ulcer can be treated with a H₂-receptor antagonist or misoprostol p. 710. On healing, patients should be tested for *H. pylori* and given eradication therapy if *H. pylori* is present (see also Test for *Helicobacter pylori*).

If treatment with a non-selective NSAID needs to continue, the following options are suitable:

- Treat ulcer with a proton pump inhibitor and on healing continue the proton pump inhibitor (dose not normally reduced because asymptomatic ulcer recurrence may occur);
- Treat ulcer with a proton pump inhibitor and on healing switch to misoprostol for maintenance therapy (colic and diarrhoea may limit the dose of misoprostol);
- Treat ulcer with a proton pump inhibitor and switch non-selective NSAID to a cyclo-oxygenase-2 selective inhibitor, but see NSAIDs and Cardiovascular Events; on healing, continuation of the proton pump inhibitor in patients with a history of upper gastro-intestinal bleeding may provide further protection against recurrence.

If treatment with a cyclo-oxygenase-2 selective inhibitor needs to continue, treat ulcer with a proton pump inhibitor; on healing continuation of the proton pump inhibitor in patients with a history of upper gastro-intestinal bleeding may provide further protection against recurrence.

**GASTROPROTECTIVE COMPLEXES AND CHELATORS**

**Chelates and complexes**

Tripotassium dicitratobismuthate p. 63 is a bismuth chelate effective in healing gastric and duodenal ulcers. See under Peptic ulceration p. 61 for the role of tripotassium dicitratobismuthate p. 63 in a *Helicobacter pylori* eradication regimen for those who have not responded to first-line regimens.

The bismuth content of tripotassium dicitratobismuthate p. 63 is low but absorption has been reported; encephalopathy (described with older high-dose bismuth preparations) has not been reported.

Sucralfate p. 63 may act by protecting the mucosa from acid-pepsin attack in gastric and duodenal ulcers. It is a complex of aluminium hydroxide and sulfated sucrose but has minimal antacid properties.
Sucralfate

**INDICATIONS AND DOSE**

**Benign gastric ulceration | Benign duodenal ulceration**

**BY MOUTH**

- Child 15-17 years: 2 g twice daily, dose to be taken on rising and at bedtime, alternatively 1 g 4 times a day for 4–6 weeks, or in resistant cases up to 12 weeks, dose to be taken 1 hour before meals and at bedtime; maximum 8 g per day
- Adult: 2 g twice daily, dose to be taken on rising and at bedtime, alternatively 1 g 4 times a day for 4–6 weeks, or in resistant cases up to 12 weeks, dose to be taken 1 hour before meals and at bedtime; maximum 8 g per day

**Chronic gastritis**

**BY MOUTH**

- Child 15-17 years: 2 g twice daily, dose to be taken on rising and at bedtime, alternatively 1 g 4 times a day for 4–6 weeks or in resistant cases up to 12 weeks, dose to be taken 1 hour before meals and at bedtime; maximum 8 g per day
- Adult: 2 g twice daily, dose to be taken on rising and at bedtime, alternatively 1 g 4 times a day for 4–6 weeks or in resistant cases up to 12 weeks, dose to be taken 1 hour before meals and at bedtime; maximum 8 g per day

**Prophylaxis of stress ulceration in child under intensive care**

**BY MOUTH**

- Child 15-17 years: 1 g 6 times a day; maximum 8 g per day

**Prophylaxis of stress ulceration**

**BY MOUTH**

- Adult: 1 g 6 times a day; maximum 8 g per day

**UNLICENSED USE**


**CAUTIONS**

Patients under intensive care (Important: reports of bezoar formation)

**CAUTIONS, FURTHER INFORMATION**

**Bezoar formation** Following reports of bezoar formation associated with sucralfate, caution is advised in seriously ill patients, especially those receiving concomitant enteral feeds or those with predisposing conditions such as delayed gastric emptying.

**INTERACTIONS** → Appendix 1 (sucralfate).

**SIDE-EFFECTS**

- Common or very common Constipation
- Uncommon Back pain, bezoar formation, diarrhoea, dizziness, dry mouth, earache, flatulence, gastric discomfort, indigestion, nausea, rash
- Pregnancy No evidence of harm; absorption from gastro-intestinal tract negligible.

**BREAST FEEDING** Amount probably too small to be harmful.

**RENAL IMPAIRMENT** Use with caution; aluminium is absorbed and may accumulate.

**DIRECTIONS FOR ADMINISTRATION** Administration of sucralfate and enteral feeds should be separated by 1 hour and for administration by mouth, sucralfate should be given 1 hour before meals. Oral suspension blocks fine-bore feeding tubes. Crushed tablets may be dispersed in water.

**PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid formulations may include aniseed and caramel.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, cream, powder, enema

**Tablet**

**CAUTIONARY AND ADVISORY LABELS**

- **Antepsin** (Chugai Pharma UK Ltd)
  - Sucralfate 1 gram Antepsin 1g tablets | 50 tablet [PO] £6.36 DT price = £6.36
  - Sucralfate 200 mg per 1 ml Antepsin 1g/5ml oral suspension (sugar-free) | 250 ml [PO] £6.36 DT price = £6.36

**Tripotassium dicitratobismuthate**

**INDICATIONS AND DOSE**

**Eradication failure of Helicobacter pylori infection (in combination with omeprazole, tetracycline and metronidazole)**

**BY MOUTH**

- Adult: 120 mg 4 times a day for 2 weeks

**Benign gastric and duodenal ulceration**

**BY MOUTH**

- Adult: 240 mg twice daily, alternatively 120 mg 4 times a day both dosage regimens taken for 28 days followed by a further 28 days if necessary, maintenance dose not indicated but course may be repeated after interval of 1 month

**INTERACTIONS** → Appendix 1 (tripotassium dicitratobismuthate).

**SIDE-EFFECTS**

- Common or very common May blacken faeces—may darken tongue
- Uncommon Constipation, diarrhoea, nausea, pruritus, rash, vomiting

**PREGNANCY** Manufacturer advises avoid on theoretical grounds.

**BREAST FEEDING** No information available.

**RENAL IMPAIRMENT** Avoid in severe impairment.

**DIRECTIONS FOR ADMINISTRATION** To be swallowed with half a glass of water. Twice-daily dosage to be taken 30 minutes before breakfast and main evening meal. Four-times-daily dosage to be taken as follows: one dose 30 minutes before breakfast, midday meal and main evening meal, and one dose 2 hours after main evening meal.

**PATIENT AND CARER ADVICE** Milk should not be drunk by itself during treatment but small quantities may be taken in tea or coffee or on cereal. Antacids, fruit, or fruit juice should not be taken half an hour before or after a dose. Patients and carers should be aware that the patient may develop darkened tongue and blackened faeces.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**ELECTROLYTES:** May contain Potassium

- **De-Noltab** (Astellas Pharma Ltd)
  - Tripotassium dicitratobismuthate 120 mg De-Noltab 120mg tablets | 112 tablet [P] £5.09
### H₂-RECEPTOR ANTAGONISTS

**H₂-receptor antagonists**

Histamine H₂-receptor antagonists heal gastric and duodenal ulcers by reducing gastric acid output as a result of histamine H₂-receptor blockade; they are also used to relieve symptoms of gastro-oesophageal reflux disease. H₂-receptor antagonists should not normally be used for Zollinger-Ellison syndrome because proton pump inhibitors are more effective.

Maintenance treatment with low doses for the prevention of peptic ulcer disease has largely been replaced in *Helicobacter pylori* positive patients by eradication regimens. In adults, H₂-receptor antagonists are used for the treatment of *functional dyspepsia* and may be used for the treatment of *uninvestigated dyspepsia* without alarm features.

H₂-receptor antagonist therapy can promote healing of NSAID-associated ulcers (particularly duodenal).

Treatment with a H₂-receptor antagonist has not been shown to be beneficial in haematemesis and melaena, but prophylactic use reduces the frequency of bleeding from *gastroduodenal erosions in hepatic coma*, and possibly in other conditions requiring intensive care. H₂-receptor antagonists also reduce the risk of *acid aspiration* in obstetric patients at delivery (Mendelson’s syndrome).

#### CAUTIONS

**Side-effects, further information**

- **Signs and symptoms of gastric cancer**
- **Caution:** Signs and symptoms of gastric cancer

- **Common or very common** Diarrhoea · dizziness · headache
- **Uncommon** Erythema multiforme · rash · toxic epidermal necrolysis
- **Rare** Arthralgia · blood disorders · bradycardia · cholestatic jaundice · confusion · depression · hallucinations · hepatitis · leucopenia · myalgia · pancytopenia · psychiatric reactions · thrombocytopenia
- **Frequency not known** Gynaecomastia · impotence

#### Side-effects, further information

- **Psychiatric reactions** Psychiatric reactions, including confusion, depression, and hallucinations occur particularly in the elderly or the very ill.

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### Cimetidine

**Indications and dose**

- **Benign duodenal ulceration**
  - Adult: 400 mg twice daily for at least 4 weeks, to be taken with breakfast and at night, alternatively 800 mg once daily for at least 4 weeks, to be taken at night; increased if necessary up to 400 mg 4 times a day; maintenance 400 mg twice daily, to be taken in the morning and at night

- **Benign gastric ulceration**
  - Adult: 400 mg twice daily for 6 weeks, to be taken with breakfast and at night, alternatively 800 mg daily for 6 weeks, to be taken at night; increased if necessary up to 400 mg 4 times daily, to be taken at night, alternatively maintenance 400 mg twice daily, to be taken in the morning at and night

- **NSAID-associated ulceration**
  - Adult: 400 mg twice daily for 8 weeks, to be taken with breakfast and at night, alternatively 800 mg daily for 8 weeks, to be taken at night; increased if necessary up to 400 mg 4 times a day; maintenance 400 mg daily, to be taken at night, alternatively maintenance 400 mg twice daily, to be taken in the morning and at night

- **Reflex oesophagitis**
  - Adult: 400 mg 4 times a day for 4–8 weeks

- **Prophylaxis of stress ulceration**
  - Adult: 200–400 mg every 4–6 hours

- **Gastric acid reduction in obstetrics**
  - Adult: Initially 400 mg, to be administered at start of labour, then increased if necessary up to 400 mg every 4 hours, do not use syrup in prophylaxis of acid aspiration; maximum 2.4 g per day

- **Gastric acid reduction during surgical procedures**
  - Adult: 400 mg, to be given 90–120 minutes before induction of general anaesthesia

- **Short-bowel syndrome**
  - Adult: 400 mg twice daily, adjusted according to response, to be taken with breakfast and at bedtime

- **To reduce degradation of pancreatic enzyme supplements**
  - Adult: 0.8–1.6 g daily in 4 divided doses, dose to be taken 1–1½ hours before meals

#### Interactions

- **Appendix 1 (histamine H₂-antagonists).**

#### Side-effects

- **Common or very common** Malaise
- **Uncommon** Tachycardia
- **Rare** Interstitial nephritis
- **Very rare** alopecia · galactorrhoea · pancreatitis · vasculitis
- **Pregnancy** Manufacturer advises avoid unless essential.
- **Breastfeeding** Significant amount present in milk—not known to be harmful but manufacturer advises avoid.
- **Hepatic Impairment** Reduce dose. Increased risk of confusion.
- **Renal Impairment** Occasional risk of confusion. Reduce dose to 200 mg 4 times daily if eGFR 30–50 mL/minute/1.73 m². Reduce dose to 200 mg 3 times daily if eGFR 15–30 mL/minute/1.73 m². Reduce dose to 200 mg twice daily if eGFR less than 15 mL/minute/1.73 m²

#### Exceptions to legal category

Cimetidine can be sold to the public for adults and children over 16 years (provided packs do not contain more than 2 weeks’ supply) for the short-term symptomatic relief of heartburn, dyspepsia, and hyperacidity (max. single dose 200 mg, max. daily dose 800 mg), and for the prophylactic management of nocturnal heartburn (single night-time dose 100 mg).

#### Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

<table>
<thead>
<tr>
<th>Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine (Non-proprietary)</td>
</tr>
<tr>
<td>Cimetidine 200 mg Cimetidine 200mg tablets</td>
</tr>
<tr>
<td>£40.00 GT price = £5.04</td>
</tr>
</tbody>
</table>
Famotidine

**INDICATIONS AND DOSE**
Treatment of benign gastric and duodenal ulceration

**BY MOUTH**
- Adult: 40 mg once daily for 4–8 weeks, dose to be taken at night

**Maintenance treatment of duodenal ulceration**

**BY MOUTH**
- Adult: 20 mg once daily, dose to be taken at night

**Reflux oesophagitis**

**BY MOUTH**
- Adult: 20–40 mg twice daily for 6–12 weeks; maintenance 20 mg twice daily

**INTERACTIONS** → Appendix 1 (histamine H₂-antagonists).

**SIDE-EFFECTS**
- Common or very common Constipation
- Uncommon Fatigue, vomiting, anorexia, dry mouth, flatulence, nausea, taste disorders
- Very rare Chest tightness, interstitial pneumonia, paraesthesia, seizures

**PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk.

**BREAST FEEDING** Present in milk—not known to be harmful but manufacturer advises avoid.

**RENAL IMPAIRMENT** Use normal dose every 36–48 hours or use half normal dose if eGFR less than 50 ml/minute/1.73 m². Seizures reported very rarely.

**EXCEPTIONS TO LEGAL CATEGORY** Famotidine can be sold to the public for the prevention and treatment of symptoms of food-related heartburn and meal-induced indigestion in adults and children over 16 years; max. single dose 75 mg, max. daily dose 150 mg for max. 14 days.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

**Capsule**
- **NIZATIDINE (Non-proprietary)**
  - Nizatidine 150 mg Nizatidine 150 mg capsules | 30 capsule £12.20 DT price = £5.40
  - Nizatidine 300 mg Nizatidine 300 mg capsules | 30 capsule £17.40 DT price = £5.43

Ranitidine

**INDICATIONS AND DOSE**
Benign gastric ulceration | Duodenal ulceration

**BY MOUTH**
- Child 1-5 years: 1 mg/kg 3 times a day (max. per dose 3 mg/kg 3 times a day)
- Child 6 months-2 years: 2–4 mg/kg twice daily
- Child 3-11 years: 2–4 mg/kg twice daily (max. per dose 150 mg) for 4–8 weeks
- Child 12-17 years: 150 mg twice daily for 4–8 weeks, alternatively 300 mg once daily for 4–8 weeks, dose to be taken at night
- Adult: 150 mg twice daily for 4–8 weeks, alternatively 300 mg once daily for 4–8 weeks, dose to be taken at night

**Chronic episodic dyspepsia**

**BY MOUTH**
- Child 12-17 years: 150 mg twice daily for 6 weeks, alternatively 300 mg once daily for 6 weeks, dose to be taken at night
- Adult: 150 mg twice daily for 6 weeks, alternatively 300 mg once daily for 6 weeks, dose to be taken at night

**INTERACTIONS** → Appendix 1 (histamine H₂-antagonists).

**SIDE-EFFECTS**
- Common or very common Sweating
- Rare Fever, hyperuricaemia, nausea, vasculitis

**PREGNANCY** Manufacturer advises avoid unless essential.

**BREAST FEEDING** Amount too small to be harmful.

**HEPATIC IMPAIRMENT** Manufacturer advises caution.

**RENAL IMPAIRMENT** Use half normal dose if eGFR 20–50 mL/minute/1.73 m². Use one-quarter normal dose if eGFR less than 20 mL/minute/1.73 m².

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

**Capsule**
- **RANITIDINE (Non-proprietary)**
  - Ranitidine 150 mg Ranitidine 150 mg capsules | 30 capsule £19.60 DT price = £5.89
  - Ranitidine 300 mg Ranitidine 300 mg capsules | 30 capsule £30.90 DT price = £5.30

Nizatidine

**INDICATIONS AND DOSE**
Benign gastric, duodenal or NSAID-associated ulceration

**BY MOUTH**
- Adult: 300 mg once daily for 4–8 weeks, dose to be taken in the evening, alternatively 150 mg twice daily for 4–8 weeks; maintenance 150 mg once daily, dose to be taken at night

**Gastro-oesophageal reflux disease**

**BY MOUTH**
- Adult: 150–300 mg twice daily for up to 12 weeks

**INTERACTIONS** → Appendix 1 (histamine H₂-antagonists).

**SIDE-EFFECTS**
- Common or very common Sweating
- Rare Fever, hyperuricaemia, nausea, vasculitis

**PREGNANCY** Manufacturer advises avoid unless essential.

**BREAST FEEDING** Amount too small to be harmful.

**HEPATIC IMPAIRMENT** Manufacturer advises caution.

**RENAL IMPAIRMENT** Use half normal dose if eGFR 20–50 mL/minute/1.73 m². Use one-quarter normal dose if eGFR less than 20 mL/minute/1.73 m².

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

**Capsule**
- **NIZATIDINE (Non-proprietary)**
  - Nizatidine 150 mg Nizatidine 150 mg capsules | 30 capsule £12.20 DT price = £5.40
  - Nizatidine 300 mg Nizatidine 300 mg capsules | 30 capsule £17.40 DT price = £5.43

**Tablet**
- **FAMOTIDINE (Non-proprietary)**
  - Famotidine 20 mg Famotidine 20 mg tablets | 28 tablet £22.00 DT price = £17.58
  - Famotidine 40 mg Famotidine 40 mg tablets | 28 tablet £39.00 DT price = £38.72

Cimetidine 400 mg Cimetidine 400 mg tablets | 60 tablet £40.00 DT price = £1.76
- Cimetidine 800 mg Cimetidine 800 mg tablets | 30 tablet £88.00 DT price = £2.90
  - Tagamet (Chemidex Pharma Ltd) Cimetidine 200 mg Tagamet 200 mg tablets | 120 tablet £24.00 DT price = £1.00
  - Cimetidine 400 mg Tagamet 400 mg tablets | 60 tablet £82.62 DT price = £1.76
  - Cimetidine 800 mg Tagamet 800 mg tablets | 30 tablet £22.62 DT price = £9.30

**Oral solution**
- **CIMETIDINE (Non-proprietary)**
  - Cimetidine 40 mg per 1 ml Cimetidine 200 mg/5 ml oral solution sugar free (sugar-free) | 300 ml £14.24 DT price = £14.25
  - Tagamet (Chemidex Pharma Ltd) Cimetidine 40 mg per 1 ml Tagamet 200 mg/5 ml syrup | 600 ml £28.49 DT price = £28.49

**SIDE-EFFECTS**
- Fever, dyspepsia, nausea, taste disorders
- Very rare Chest tightness, interstitial pneumonia, paraesthesia, seizures

**PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk.

**BREAST FEEDING** Present in milk—not known to be harmful but manufacturer advises avoid.

**RENAL IMPAIRMENT** Use normal dose every 36–48 hours or use half normal dose if eGFR less than 50 ml/minute/1.73 m². Seizures reported very rarely.

**EXCEPTIONS TO LEGAL CATEGORY** Cimetidine can be sold to the public for the prevention and treatment of symptoms of food-related heartburn and meal-induced indigestion in adults and children over 16 years; max. single dose 75 mg, max. daily dose 150 mg for max. 14 days.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

**Capsule**
- **NIZATIDINE (Non-proprietary)**
  - Nizatidine 150 mg Nizatidine 150 mg capsules | 30 capsule £12.20 DT price = £5.40
  - Nizatidine 300 mg Nizatidine 300 mg capsules | 30 capsule £17.40 DT price = £5.43

**Tablet**
- **FAMOTIDINE (Non-proprietary)**
  - Famotidine 20 mg Famotidine 20 mg tablets | 28 tablet £22.00 DT price = £17.58
  - Famotidine 40 mg Famotidine 40 mg tablets | 28 tablet £39.00 DT price = £38.72

**SIDE-EFFECTS**
- Fatigue, vomiting, anorexia, dry mouth, flatulence, nausea, taste disorders
- Very rare Chest tightness, interstitial pneumonia, paraesthesia, seizures

**PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk.

**BREAST FEEDING** Present in milk—not known to be harmful but manufacturer advises avoid.

**RENAL IMPAIRMENT** Use normal dose every 36–48 hours or use half normal dose if eGFR less than 50 ml/minute/1.73 m². Seizures reported very rarely.

**EXCEPTIONS TO LEGAL CATEGORY** Famotidine can be sold to the public for adults and children over 16 years (provided packs do not contain more than 2 weeks’ supply) for the short-term symptomatic relief of heartburn, dyspepsia, and hyperacidity, and for the prevention of these symptoms when associated with consumption of food or drink including when they cause sleep disturbance (max. single dose 10 mg, max. daily dose 20 mg).

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.
NSAID-associated gastric ulceration

**BY MOUTH**
- Child 12-17 years: 150 mg twice daily for up to 8 weeks, alternatively 300 mg once daily for up to 8 weeks, dose to be taken at night
- Adult: 150 mg twice daily for up to 8 weeks, alternatively 300 mg once daily for up to 8 weeks, dose to be taken at night

**NSAID-associated duodenal ulcer**

**BY MOUTH**
- Child 12-17 years: 300 mg twice daily for 4 weeks, to achieve a higher healing rate
- Adult: 300 mg twice daily

**Gastro-oesophageal reflux disease**

**BY MOUTH**
- Child 12-17 years: 150 mg twice daily for up to 8 weeks or if necessary 12 weeks, alternatively 300 mg once daily for up to 8 weeks or if necessary 12 weeks, dose to be taken at night
- Adult: 150 mg twice daily for up to 8 weeks or if necessary 12 weeks, alternatively 300 mg once daily for up to 8 weeks or if necessary 12 weeks, dose to be taken at night

**Moderate to severe gastro-oesophageal reflux disease**

**BY MOUTH**
- Child 12-17 years: 600 mg daily in 2–4 divided doses for up to 12 weeks
- Adult: 600 mg daily in 2–4 divided doses for up to 12 weeks

**Long-term treatment of healed gastro-oesophageal reflux disease**

**BY MOUTH**
- Child 3-11 years: 2.5–5 mg/kg twice daily (max. per dose 300 mg)
- Child 12-17 years: 150 mg twice daily
- Adult: 150 mg twice daily

**Gastric acid reduction (prophylaxis of acid aspiration) in obstetrics**

**BY MOUTH**
- Child 12-17 years: 150 mg, dose to be given at onset of labour, then 150 mg every 6 hours
- Adult: 150 mg, dose to be given at onset of labour, then 150 mg every 6 hours

**Gastric acid reduction (prophylaxis of acid aspiration) in surgical procedures**

**INITIALLY BY INTRAMUSCULAR INJECTION OR BY SLOW INTRAVENOUS INJECTION**
- Adult: 50 mg, to be given 45–60 minutes before induction of anaesthesia, intravenous injection diluted to 20 mL and given over at least 2 minutes, alternatively (by mouth) 150 mg, to be given 2 hours before induction of anaesthesia and also when possible on the preceding evening

**Prophylaxis of stress ulceration**

**INITIALLY BY SLOW INTRAVENOUS INJECTION**
- Adult: 50 mg every 8 hours, dose to be diluted to 20 mL and given over at least 2 minutes, then (by mouth) 150 mg twice daily, may be given when oral feeding commences

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**Reflex oesophagitis and other conditions where gastric acid reduction is beneficial**

**BY MOUTH**
- Child 1-5 months: 1 mg/kg 3 times a day (max. per dose 3 mg/kg 3 times a day)
- Child 6 months-2 years: 2–4 mg/kg twice daily
- Child 3-11 years: 2–4 mg/kg twice daily (max. per dose 150 mg); increased to up to 5 mg/kg twice daily (max. per dose 300 mg), dose increase for severe gastro-oesophageal disease
- Child 12-17 years: 150 mg twice daily, alternatively 300 mg once daily, dose to be taken at night, then increased if necessary to 300 mg twice daily for up to 12 weeks in moderate to severe gastro-oesophageal reflux disease, alternatively increased if necessary to 150 mg 4 times a day for up to 12 weeks in moderate to severe gastro-oesophageal reflux disease

**Conditions where reduction of gastric acidity is beneficial and oral route not available**

**BY INTRAMUSCULAR INJECTION**
- Adult: 50 mg every 6–8 hours

**BY SLOW INTRAVENOUS INJECTION**
- Adult: 50 mg, dose to be diluted to 20 mL and given over at least 2 minutes; may be repeated every 6–8 hours

**UNLICENSED USE** Oral preparations not licensed for use in children under 3 years. Injection not licensed for use in children under 6 months.

- In adults Doses given for prophylaxis of NSAID-associated gastric or duodenal ulcer, and prophylaxis of stress ulceration, are not licensed.

**INTERACTIONS** → Appendix 1 (histamine H₂-antagonists).

**SIDE-EFFECTS**

- Uncommon Blurred vision
- Frequency not known Alopecia · Interstitial nephritis · involuntary movement disorders · Pancreatitis

**PREGNANCY** Manufacturer advises avoid unless essential, but not known to be harmful.

**BREAST FEEDING** Significant amount present in milk, but not known to be harmful.

**RENAL IMPAIRMENT**

- In adults Use half normal dose if eGFR less than 50 mL/minute/1.73 m²
- In children Use half normal dose if estimated glomerular filtration rate less than 50 mL/minute/1.73 m²

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use in children For slow intravenous injection dilute to a concentration of 2.5 mg/mL with Glucose 5% or Sodium Chloride 0.9%; give over at least 3 minutes.
- With intravenous use in adults For intravenous infusion (Zantac®), give intermittently in Glucose 5% or Sodium Chloride 0.9%.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Ranitidine for acid reflux [www.medicinesforchildren.org.uk/ranitidine-for-acid-reflux](http://www.medicinesforchildren.org.uk/ranitidine-for-acid-reflux)

In fat malabsorption syndrome, give oral doses 1–2 hours before food to enhance effects of pancreatic enzyme replacement.

**EXCEPTIONS TO LEGAL CATEGORY** Ranitidine can be sold to the public for adults and children over 16 years (provided packs do not contain more than 2 weeks’ supply) for the short-term symptomatic relief of heartburn, dyspepsia, and hyperacidity, and for the prevention of these symptoms when associated with consumption of food or drink (max. single dose 75 mg, max. daily dose 300 mg).
Proton pump inhibitors

Proton pump inhibitors are effective short-term treatments for gastric and duodenal ulcers; they are also used in combination with antibiotics for the eradication of Helicobacter pylori (see specific regimens). Following endoscopic treatment of severe peptic ulcer bleeding, an intravenous, high-dose proton pump inhibitor reduces the risk of rebleeding and the need for surgery. Proton pump inhibitors can be used for the treatment of dyspepsia and gastro-oesophageal reflux disease.

Proton pump inhibitors are also used for the prevention and treatment of NSAID-associated ulcers. In patients who need to continue NSAID treatment after an ulcer has healed, the dose of proton pump inhibitor should normally not be reduced because asymptomatic ulcer deterioration may occur. A proton pump inhibitor can be used to reduce the degradation of pancreatic enzyme supplements in patients with cystic fibrosis. They can also be used to control excessive secretion of gastric acid in Zollinger–Ellison syndrome; high doses are often required.

Proton pump inhibitors

- **DRUG ACTION** Proton pump inhibitors inhibit gastric acid secretion by blocking the hydrogen-potassium adenosine triphosphatase enzyme system (the ‘proton pump’) of the gastric parietal cell.
- **CAUTIONS** Can increase the risk of fractures (particularly when used at high doses for over a year in the elderly) - may increase the risk of gastro-intestinal infections (including Clostridium difficile infection) - may mask the symptoms of gastric cancer - patients at risk of osteoporosis
- **SIDE-EFFECTS** Common or very common Abdominal pain - constipation - diarrhoea - flatulence - gastro-intestinal disturbances - headache - nausea - vomiting Uncommon Arthralgia - dizziness - dry mouth - fatigue - myalgia - paraesthesia - peripheral oedema - pruritus - rash - sleep disturbances Rare Alopecia - anaphylaxis - blood disorders - bronchospasm - confusion - depression - fever - gynaecomastia - hallucinations - hepatitis - hypersensitivity reactions - hypomagnesaemia (usually after 1 year of treatment, but sometimes after 5 months of treatment) - hypotension - intermittent nephritis - jaundice - leucocytosis - leucopenia - pancytopenia - photosensitivity - Stevens-Johnson syndrome - stomatitis - sweating - taste disturbance - thrombocytopenia - toxic epidermal necrolysis - visual disturbances
- **PRESCRIBING AND DISPENSING INFORMATION** A proton pump inhibitor should be prescribed for appropriate indications at the lowest effective dose for the shortest period; the need for long-term treatment should be reviewed periodically.

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**SIDE-EFFECTS, FURTHER INFORMATION** Risk of osteoporosis Patients at risk of osteoporosis should maintain an adequate intake of calcium and vitamin D, and if necessary, receive other preventative therapy. Gastric cancer Particular care is required in those presenting with ‘alarm features’, in such cases gastric malignancy should be ruled out before treatment.

**SIDE-EFFECTS, FURTHER INFORMATION** Risk of osteoporosis Patients at risk of osteoporosis should maintain an adequate intake of calcium and vitamin D, and if necessary, receive other preventative therapy. Gastric cancer Particular care is required in those presenting with ‘alarm features’, in such cases gastric malignancy should be ruled out before treatment.

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Gastro-intestinal system

With intravenous use in adults

**DIRECTIONS FOR ADMINISTRATION**

**RENAL IMPAIRMENT**

- Child 1-11 years: 10 mg once daily for 8 weeks
- Child 12-17 years: 20 mg once daily for up to 4 weeks

**HEPATIC IMPAIRMENT**

- Adult: 20 mg once daily for up to 4 weeks

**BREAST FEEDING**

- Adult: 20 mg once daily for up to 4 weeks

**PREGNANCY**

- Adult: 20 mg once daily for up to 4 weeks

**INTERACTIONS**

- Adult: 20 mg once daily for up to 4 weeks

**PATIENT AND CARER ADVICE**

- Oral use

**MEDICINAL FORMS**

- With intravenous use in children

- For intravenous infusion, dilute reconstituted solution to a concentration not exceeding 800 micrograms/mL with Sodium Chloride 0.9%; give over 10–30 minutes.

- With oral use

- Do not chew or crush capsules; swallow whole or mix capsule contents in water and drink within 30 minutes. Do not crush or chew tablets; swallow whole or disperse in water and drink within 30 minutes. Disperse the contents of each sachet of gastro-resistant granules in approx. 15 mL water. Stir and leave to thicken for a few minutes; stir again before administration and use within 30 minutes; rinse container with 15 mL water to obtain full dose. For administration through a gastric tube, consult product literature.

- Counselling on administration of gastro-resistant capsules, tablets, and granules advised.

- With oral use

- With intravenous use

**Gastro-resistant tablet**

- **ESOMEPRAZOLE (Non-proprietary)**

| Esomeprazole (as Esomeprazole magnesium trihydrate) | 20 mg | Esomeprazole 20 mg gastro-resistant tablets | 28 tablet | £18.50 DT price = £3.70
| Esomeprazole (as Esomeprazole magnesium trihydrate) | 40 mg | Esomeprazole 40 mg gastro-resistant tablets | 28 tablet | £25.19 DT price = £4.38

**Gastro-resistant capsule**

- **ESOMEPRAZOLE (Non-proprietary)**

| Esomeprazole (as Esomeprazole magnesium dihydrate) | 20 mg | Esomeprazole 20 mg gastro-resistant capsules | 28 capsule | £12.95 DT price = £3.40
| Esomeprazole (as Esomeprazole magnesium dihydrate) | 40 mg | Esomeprazole 40 mg gastro-resistant capsules | 28 capsule | £17.63 DT price = £3.96

**Gastro-resistant granules**

- **EMOZUL (Consilient Health Ltd)**

| Esomeprazole (as Esomeprazole magnesium dihydrate) | 20 mg | Emozul 20 mg gastro-resistant capsules | 28 capsule | £3.40 DT price = £3.40
| Esomeprazole (as Esomeprazole magnesium dihydrate) | 40 mg | Emozul 40 mg gastro-resistant capsules | 28 capsule | £3.96 DT price = £3.96

- **Nexium (AstraZeneca UK Ltd)**

| Esomeprazole (as Esomeprazole magnesium dihydrate) | 10 mg | Nexium 10 mg gastro-resistant granules sachets | 28 sachet | £25.19 DT price = £25.19
| Esomeprazole (as Esomeprazole magnesium dihydrate) | 40 mg | Nexium 40 mg solution for injection vials | 1 vial | £3.07–£3.13 (Hospital only)

- **Nexium (AstraZeneca UK Ltd)**

| Esomeprazole (as Esomeprazole sodium) | 40 mg | Nexium 40 mg powder for solution for injection vials | 1 vial | £4.25 (Hospital only)

**With intravenous use in adults**

- For intravenous infusion (Nexium®), give continuously or intermittently in Sodium Chloride 0.9%; reconstitute 40–80 mg with up to 100 mL infusion fluid; for intermittent infusion, give requisite dose over 10–30 minutes; stable for 12 hours in Sodium Chloride 0.9%.

**UNLICENSED USE** Tablets and capsules not licensed for use in children 1–12 years.

**INTERACTIONS**

- Appendix 1 (proton pump inhibitors).

**PREGNANCY**

- Manufacturer advises caution—no information available.

**BREAST FEEDING**

- Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT**

- In adults

  - Severe hepatic impairment max. 20 mg daily.

  - Severe peptic ulcer bleeding in severe hepatic impairment, initial intravenous infusion of 80 mg, then by continuous intravenous infusion, 4 mg/hour for 72 hours.

  - In children 1–11 years max. 10 mg daily in severe impairment. 12–18 years max. 20 mg daily in severe impairment.

**RENAL IMPAIRMENT**

- Manufacturer advises caution in severe renal insufficiency.

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use in adults

  - For intravenous infusion (Nexium®), give continuously or intermittently in Sodium Chloride 0.9%; reconstitute 40–80 mg with up to 100 mL infusion fluid; for intermittent infusion, give requisite dose over 10–30 minutes; stable for 12 hours in Sodium Chloride 0.9%.
Lansoprazole

**INDICATIONS AND DOSE**

*Helicobacter pylori* eradication in combination with amoxicillin and clarithromycin; or in combination with amoxicillin and metronidazole; or in combination with clarithromycin and metronidazole

**BY MOUTH**

- Adult: 30 mg twice daily

**Benign gastric ulcer**

**BY MOUTH**

- Adult: 30 mg once daily for 8 weeks, dose to be taken in the morning

**Duodenal ulcer**

**BY MOUTH**

- Adult: 30 mg once daily for 4 weeks, dose to be taken in the morning
- Maintenance: 15 mg once daily

**NSAID-associated duodenal ulcer | NSAID-associated gastric ulcer**

**BY MOUTH**

- Adult: 30 mg once daily for 4 weeks, continued for further 4 weeks if not fully healed

**Prophylaxis of NSAID-associated duodenal ulcer | Prophylaxis of NSAID-associated gastric ulcer**

**BY MOUTH**

- Adult: 15–30 mg once daily

**Zollinger-Ellison syndrome (and other hypersecretory conditions)**

**BY MOUTH**

- Adult: Initially 60 mg once daily, adjusted according to response, daily doses of 120 mg or more given in two divided doses

**Gastro-oesophageal reflux disease**

**BY MOUTH**

- Adult: 30 mg once daily for 4 weeks, continued for further 4 weeks if not fully healed; maintenance 15–30 mg once daily, doses to be taken in the morning

**Acid-related dyspepsia**

**BY MOUTH**

- Adult: 15–30 mg once daily for 2-4 weeks, doses to be taken in the morning

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, powder

**Orodispersible tablet**

**CAUTIONARY AND ADVISORY LABELS**

- Lansoprazole 15 mg Lansoprazole 15mg orodispersible tablets | 28 tablet (Pfizer) £3.99 DT price = £3.35
- Lansoprazole 30 mg Lansoprazole 30mg orodispersible tablets | 28 tablet (Pfizer) £6.99 DT price = £6.01
- Zoton FasTab (Pfizer Ltd) Lansoprazole 15 mg Zoton FasTab 15mg | 28 tablet (Pfizer) £2.99 DT price = £1.35
- Lansoprazole 30 mg Zoton FasTab 30mg | 28 tablet (Pfizer) £5.50 DT price = £4.80

**Gastro-resistant capsule**

**CAUTIONARY AND ADVISORY LABELS**

- Lansoprazole 15 mg Lansoprazole 15mg gastro-resistant capsules | 28 capsule (Pfizer) £12.92 DT price = £11.17
- Lansoprazole 30 mg Lansoprazole 30mg gastro-resistant capsules | 28 capsule (Pfizer) £23.63 DT price = £13.52

Omeprazole

**INDICATIONS AND DOSE**

*Helicobacter pylori* eradication in combination with amoxicillin and clarithromycin; or in combination with amoxicillin and metronidazole; or in combination with clarithromycin and metronidazole

**BY MOUTH**

- Adult: 20 mg twice daily

**Eradication failure of Helicobacter pylori infection in combination with tripotassium dicitratobismuthate, tetracycline and metronidazole**

**BY MOUTH**

- Adult: 20 mg twice daily

**Benign gastric ulceration**

**BY MOUTH**

- Adult: 20 mg once daily for 8 weeks, increased if necessary to 40 mg once daily, in severe or recurrent cases

**Duodenal ulceration**

**BY MOUTH**

- Adult: 20 mg once daily for 4 weeks, increased if necessary to 40 mg once daily, in severe or recurrent cases

**Prevention of relapse in gastric ulcer**

**BY MOUTH**

- Adult: 20 mg once daily, increased if necessary to 40 mg once daily

**Prevention of relapse in duodenal ulcer**

**BY MOUTH**

- Adult: 20 mg once daily, dose may range between 10–40 mg daily

**NSAID-associated duodenal ulcer | NSAID-associated gastric ulcer | NSAID-associated gastroduodenal erosions**

**BY MOUTH**

- Adult: 20 mg once daily for 4 weeks, continued for a further 4 weeks if not fully healed
Prophylaxis in patients with a history of NSAID-associated duodenal ulcer who require continued NSAID treatment
Prophylaxis in patients with a history of NSAID-associated gastric ulcer who require continued NSAID treatment
Prophylaxis in patients with a history of NSAID-associated gastroduodenal lesions who require continued NSAID treatment
Prophylaxis in patients with a history of NSAID-associated dyspeptic symptoms who require continued NSAID treatment

**DIRECTIONS FOR ADMINISTRATION**

**BREAST FEEDING**

**INTERACTIONS**

**UNLICENSED USE** Treatment of major peptic ulcer bleeding (following endoscopic treatment) is an unlicensed indication.

**INTERACTIONS** → Appendix 1 (proton pump inhibitors).

**SIDE-EFFECTS** Agitation - impotence

**PREGNANCY** Not known to be harmful.

**BREAST FEEDING** Present in milk but not known to be harmful.

**HEPATIC IMPAIRMENT** Not more than 20 mg daily should be needed.

**DIRECTIONS FOR ADMINISTRATION** For administration by mouth, swallow whole, or disperse Losec MUPS tablets in water, or mix capsule contents or Losec MUPS tablets with fruit juice or yoghurt. Preparations consisting of an e/c tablet within a capsule should not be opened.

With intravenous use For intravenous infusion (Losec®), give intermittently or continuously in Glucose 5% or Sodium chloride 0.9%; reconstitute each 40 mg vial with infusion fluid and dilute to 100 mL; for intermittent infusion give 40 mg over 20–30 minutes; stable for 3 hours in glucose 5% or 12 hours in sodium chloride 0.9%

**PATIENT AND CARER ADVICE**

**With oral use** Counselling on administration advised.

**PROFESSION SPECIFIC INFORMATION**

Dental practitioners’ formulary
Gastro-resistant omeprazole capsules may be prescribed.

**EXCEPTIONS TO LEGAL CATEGORY** Omeprazole 10 mg tablets can be sold to the public for the short-term relief of reflux-like symptoms (e.g. heartburn) in adults over 18 years, max. daily dose 20 mg for max. 4 weeks, and a pack size of 28 tablets.

**MEDITICAL FORMS**

There may be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Gastro-resistant tablet**

**CAUTIONARY AND ADVISORY LABELS** 25

**OMEPRAZOLE (Non-proprietary)**

Omeprazole 10 mg Omeprazole 10mg gastro-resistant tablets | 28 tablet (Pent) £18.91 DT price = £7.90

Omeprazole (as Omeprazole magnesium) 10 mg Omeprazole 10mg dispersible gastro-resistant tablets | 28 tablet (Pent) £7.75 DT price = £7.75

Omeprazole (as Omeprazole magnesium) 20 mg Omeprazole 20mg dispersible gastro-resistant tablets | 28 tablet (Pent) £11.60 DT price = £11.60

Omeprazole 20 mg Omeprazole 20mg gastro-resistant tablets | 28 tablet (Pent) £8.56 DT price = £6.11

Omeprazole 40 mg Omeprazole 40mg gastro-resistant tablets | 7 tablet (Pent) £15.00 DT price = £5.20

Omeprazole (as Omeprazole magnesium) 40 mg Omeprazole 40mg dispersible gastro-resistant tablets | 7 tablet (Pent) £5.80 DT price = £5.80

Brands may include Mezipram tablets;

Losec (AstraZeneca UK Ltd)

Omeprazole (as Omeprazole magnesium) 10 mg Losec MUPS 10mg gastro-resistant tablets | 28 tablet (Pent) £7.75 DT price = £7.75

Omeprazole (as Omeprazole magnesium) 20 mg Losec MUPS 20mg gastro-resistant tablets | 28 tablet (Pent) £11.60 DT price = £11.60

Omeprazole (as Omeprazole magnesium) 40 mg Losec MUPS 40mg gastro-resistant tablets | 7 tablet (Pent) £5.80 DT price = £5.80

Brands may include Mezprader capsules

**Gastro-resistant capsule**

**OMEPRAZOLE (Non-proprietary)**

Omeprazole 10 mg Omeprazole 10mg gastro-resistant capsules | 28 capsule (Pent) £18.91 DT price = £1.25

Omeprazole 20 mg Omeprazole 20mg gastro-resistant capsules | 28 capsule (Pent) £13.92 DT price = £1.23

Omeprazole 40 mg Omeprazole 40mg gastro-resistant capsules | 7 capsule (Pent) £4.93 DT price = £1.09 | 28 capsule (Pent) £21.65

**Losec (AstraZeneca UK Ltd)**

Omeprazole 10 mg Losec 10mg gastro-resistant capsules | 28 capsule (Pent) £9.30 DT price = £1.25

Omeprazole 20 mg Losec 20mg gastro-resistant capsules | 28 capsule (Pent) £13.92 DT price = £1.23

Omeprazole 40 mg Losec 40mg gastro-resistant capsules | 7 capsule (Pent) £6.96 DT price = £1.09

**Powder and solvent for solution for injection**

Losec (AstraZeneca UK Ltd)

Omeprazole (as Omeprazole sodium) 40 mg Losec IV. 40mg powder and solvent for solution for injection vials | 1 vial (Pent) £6.49

**Powder for solution for infusion**

**OMEPRAZOLE (Non-proprietary)**

Omeprazole (as Omeprazole sodium) 40 mg Omeprazole 40mg powder for solution for infusion vials | 5 vial (Pent) £6.47
Pantoprazole

INDICATIONS AND DOSE

*Helicobacter pylori* eradication in combination with amoxicillin and clarithromycin; or in combination with clarithromycin and metronidazole

**BY MOUTH**
- Adult: 40 mg twice daily

Benign gastric ulcer

**BY MOUTH**
- Adult: 40 mg daily for 8 weeks; increased if necessary up to 80 mg daily, dose increased in severe cases

Gastric ulcer

**BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION**
- Adult: 40 mg daily until oral administration can be resumed, injection to be given over at least 2 minutes

Duodenal ulcer

**BY MOUTH**
- Adult: 40 mg daily for 4 weeks; increased if necessary up to 80 mg daily, dose increased in severe cases

**BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION**
- Adult: 40 mg daily until oral administration can be resumed, injection to be given over at least 2 minutes

Prophylaxis of NSAID-associated gastric ulcer in patients with an increased risk of gastroduodenal complications who require continued NSAID treatment

**BY MOUTH**
- Adult: 20 mg daily

Gastro-oesophageal reflux disease

**BY MOUTH**
- Adult: 20–80 mg daily for 4 weeks, continued for further 4 weeks if not fully healed, dose to be taken in the morning; maintenance 20 mg daily and increased to 40 mg daily, increased only if symptoms return

**BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION**
- Adult: 40 mg daily until oral administration can be resumed, injection to be given over at least 2 minutes

Zollinger-Ellison syndrome (and other hypersecretory conditions)

**BY MOUTH**
- Adult: Initially 80 mg daily (max. per dose 80 mg), adjusted according to response
- Elderly: 40 mg daily

**BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION**
- Adult: Initially 80 mg, alternatively 160 mg in 2 divided doses, if rapid acid control required, then 80 mg once daily (max. per dose 80 mg), adjusted according to response

DIRECTIONS FOR ADMINISTRATION

For *intravenous infusion* (*Protium®*), give intermittently in Glucose 5% or Sodium chloride 0.9%; reconstitute 40 mg with 10 mL sodium chloride 0.9% and dilute with 100 mL of infusion fluid; give 40 mg over 15 minutes.

EXCEPTIONS TO LEGAL CATEGORY

Pantoprazole 20 mg tablets can be sold to the public for the short-term treatment of reflux symptoms (e.g. heartburn) in adults over 18 years, max. daily dose 20 mg for max. 4 weeks.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Gastro-resistant tablet**

CAUTIONARY AND ADVISORY LABELS 25

**PANTOPRAZOLE (Non-proprietary)**

Pantoprazole (as Pantoprazole sodium sesquihydrate)

- 20 mg Pantoprazole 20mg gastro-resistant tablets | 28 tablet [PoC] £11.83 DT price = £1.22
- Pantoprazole (as Pantoprazole sodium sesquihydrate)
- 40 mg Pantoprazole 40mg gastro-resistant tablets | 28 tablet [PoC] £20.57 DT price = £1.59

**Pantoloc Control (Novartis Consumer Health UK Ltd)**

Pantoprazole (as Pantoprazole sodium sesquihydrate)

- 20 mg Pantoloc Control 20mg gastro-resistant tablets | 7 tablet [P] £4.11 | 14 tablet [P] £7.09

**Powder for solution for injection**

**PANTOPRAZOLE (Non-proprietary)**

Pantoprazole (as Pantoprazole sodium sesquihydrate)

- 40 mg Pantoprazole 40mg powder for solution for injection vials | 1 vial [PoC] £4.65–5.00
- Pantoloc (Nycomed UK Ltd)

Pantoprazole (as Pantoprazole sodium sesquihydrate)

- 40 mg Protium IV. 40mg powder for solution for injection vials | 5 vial [PoC] £25.53

Rabeprazole sodium

INDICATIONS AND DOSE

Benign gastric ulcer

**BY MOUTH**
- Adult: 20 mg daily for 8 weeks, dose to be taken in the morning

Duodenal ulcer

**BY MOUTH**
- Adult: 20 mg daily for 4 weeks, dose to be taken in the morning

Gastro-oesophageal reflux disease

**BY MOUTH**
- Adult: 20 mg once daily for 4-8 weeks; maintenance 10–20 mg daily

Gastro-oesophageal reflux disease (symptomatic treatment in the absence of oesophagitis)

**BY MOUTH**
- Adult: 10 mg daily for up to 4 weeks, then 10 mg daily if required

Zollinger-Ellison syndrome

**BY MOUTH**
- Adult: Initially 60 mg once daily, adjusted according to response, doses above 100 mg daily given in 2 divided doses; maximum 120 mg per day

*Helicobacter pylori* eradication in combination with amoxicillin or metronidazole and clarithromycin

**BY MOUTH**
- Adult: 20 mg twice daily

INTERACTIONS

Appendix 1 (proton pump inhibitors).

SIDE-EFFECTS

- Hyperlipidaemia - weight changes
- *Pregnancy* Manufacturer advises avoid unless potential benefit outweighs risk – fetotoxic in animals.
- *Breast Feeding* Manufacturer advises avoid unless potential benefit outweighs risk – small amount present in milk.
- *Hepatic Impairment* Max. 20 mg daily in severe impairment and cirrhosis. Monitor liver function in hepatic impairment (discontinue if deterioration).
- *Renal Impairment* Max. oral dose 40 mg daily.
Gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease is common in infancy but most symptoms resolve without treatment between 12 and 18 months of age. In infants, mild or moderate reflux without complications can be managed initially by changing the frequency and volume of feed; a feed thickener or thickened formula feed can be used (with advice of a dietitian). If necessary, a suitable alginate-containing preparation can be used instead of thickened feeds. For older children, life-style changes similar to those for adults may be helpful followed if necessary by treatment with an alginate-containing preparation. Children who do not respond to these measures or who have problems such as respiratory disorders or suspected oesophagitis need to be referred to hospital; an H2-receptor antagonist may be needed to reduce acid secretion. If the oesophagitis is resistant to H2-receptor blockade, the proton pump inhibitor omeprazole p. 69 can be tried.

4.4 Helicobacter pylori diagnosis

DIAGNOSTICS

Urea (13c)

INDICATIONS AND DOSE
Diagnosis of gastro-duodenal Helicobacter pylori infection

BY MOUTH

Adult: (consult product literature)

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

- diabact UBT (Seahorse Laboratories Ltd)
  - Urea [13-C] 50 mg diabact UBT 50mg tablets | 1 tablet PON £21.25 | 10 tablet PON no price available (Hospital only)

Soluble tablet

- Pylobactell (Torbet Laboratories Ltd)
  - Urea [13-C] 100 mg Pylobactell breath test kit | 1 kit PON £20.75

Powder

- UREA (13C) (Non-proprietary)
  - Urea [13-C] 45 mg Helicobacter Test INFAI for children breath test kit (sugar-free) | 1 kit PON £12.20
  - Urea [13-C] 75 mg Helicobacter Test INFAI breath test kit (sugar-free) | 1 kit PON £19.20

5 Food allergy

Food allergy

Allergy with classical symptoms of vomiting, colic and diarrhoea caused by specific foods such as cow’s milk or shellfish should be managed by strict avoidance. The
condition should be distinguished from symptoms of occasional food intolerance in those with irritable bowel syndrome. Sodium cromoglicate p. 234 may be helpful as an adjunct to dietary avoidance.

6 Gastro-intestinal smooth muscle spasm

ANTIMUSCARINICS

Dicycloverine hydrochloride

(Dicyclomine hydrochloride)

The properties listed below are those particular to the drug only. For properties common to the class, see antimuscarinics (systemic), p. 668.

INDICATIONS AND DOSE

Symptomatic relief of gastro-intestinal disorders characterised by smooth muscle spasm

BY MOUTH

- Child 6 months–1 year: 5–10 mg 3–4 times a day, dose to be taken 15 minutes before feeds
- Child 2–11 years: 10 mg 3 times a day
- Child 12–17 years: 10–20 mg 3 times a day
- Adult: 10–20 mg 3 times a day

- CONTRA-INDICATIONS Child under 6 months
- PREGNANCY Not known to be harmful; manufacturer advises use only if essential.
- BREAST FEEDING Avoid—present in milk; apnoea reported in infant.
- EXCEPTIONS TO LEGAL CATEGORY Dicycloverine hydrochloride can be sold to the public provided that max. single dose is 10 mg and max. daily dose is 60 mg.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

- DICYCLOVERINE HYDROCHLORIDE (Non-proprietary) Dicycloverine hydrochloride 10 mg Dicycloverine 10 mg tablets | 100 tablet | £141.68 DT price = £117.22
- Dicycloverine hydrochloride 20 mg Dicycloverine 20 mg tablets | 84 tablet | £149.66 DT price = £123.91

Oral solution

- DICYCLOVERINE HYDROCHLORIDE (Non-proprietary) Dicycloverine hydrochloride 2 mg per 1 ml Dicycloverine 10 mg | 120 ml no price available | 100 ml (sugar-free) no price available | £138.30 DT price = £115.41 | 300 ml (sugar-free) no price available

Aluminium hydroxide with dicycloverine hydrochloride, magnesium oxide and simeticone

The properties listed below are those particular to the combination only. For the properties of the components please consider, aluminium hydroxide p. 859, dicycloverine hydrochloride above, simeticone p. 60.

INDICATIONS AND DOSE

Symptomatic relief of gastro-intestinal disorders characterised by smooth muscle spasm

BY MOUTH

- Child 12–17 years: 10–20 mL every 4 hours as required
- Adult: 10–20 mL every 4 hours as required

Hyoscine butylbromide

The properties listed below are those particular to the drug only. For properties common to the class, see antimuscarinics (systemic), p. 668.

INDICATIONS AND DOSE

Symptomatic relief of gastro-intestinal or genito-urinary disorders characterised by smooth muscle spasm

BY MOUTH

- Child 6–11 years: 10 mg 3 times a day
- Child 12–17 years: 20 mg 4 times a day
- Adult: 20 mg 4 times a day

Irritable bowel syndrome

BY MOUTH

- Adult: 10 mg 3 times a day; increased if necessary up to 20 mg 4 times a day

Acute spasm | Spasm in diagnostic procedures

INITIALLY BY INTRAMUSCULAR INJECTION OR BY SLOW INTRAVENOUS INJECTION

- Adult: 20 mg, then (by intramuscular injection or by slow intravenous injection) 20 mg after 30 minutes if required, dose may be repeated more frequently in endoscopy; maximum 100 mg per day

Excessive respiratory secretions (in palliative care)

BY MOUTH

- Child 1 month–1 year: 300–500 micrograms/kg 3–4 times a day (max. per dose 5 mg)
- Child 2–4 years: 5 mg 3–4 times a day
- Child 5–11 years: 10 mg 3–4 times a day
- Child 12–17 years: 10–20 mg 3–4 times a day

BY INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INJECTION

- Child 1 month–3 years: 300–500 micrograms/kg 3–4 times a day (max. per dose 5 mg)
- Child 5–11 years: 5–10 mg 3–4 times a day
- Child 12–17 years: 10–20 mg 3–4 times a day

BY SUBCUTANEOUS INJECTION

- Adult: 20 mg every 4 hours if required, increased according to response, up to 20 mg every hour

BY SUBCUTANEOUS INFUSION

- Adult: 20–120 mg/24 hours

Bowel colic (in palliative care)

BY MOUTH

- Child 1 month–1 year: 300–500 micrograms/kg 3–4 times a day (max. per dose 5 mg)
- Child 2–4 years: 5 mg 3–4 times a day
- Child 5–11 years: 10 mg 3–4 times a day
- Child 12–17 years: 10–20 mg 3–4 times a day

BY INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INJECTION

- Child 1 month–3 years: 300–500 micrograms/kg 3–4 times a day (max. per dose 5 mg)
- Child 5–11 years: 5–10 mg 3–4 times a day
- Child 12–17 years: 10–20 mg 3–4 times a day

BY SUBCUTANEOUS INJECTION

- Adult: 20 mg every 4 hours if required, increased according to response, up to 20 mg every hour

BY SUBCUTANEOUS INFUSION

- Adult: 20–300 mg/24 hours

PHARMACOKINETICS

Administration by mouth is associated with poor absorption.
Gastro-intestinal smooth muscle spasm

INDICATIONS AND DOSE
Symptomatic relief of gastro-intestinal disorders characterised by smooth muscle spasm

BY MOUTH
- Child 12-17 years: 15 mg 3 times a day, dose to be taken at least one hour before food and 30 mg, dose to be taken at night; maximum 120 mg per day
- Adult: 15 mg 3 times a day, dose to be taken at least one hour before food and 30 mg, dose to be taken at night; maximum 120 mg per day

Propantheline bromide

INDICATIONS AND DOSE
Adjunct in gastro-intestinal disorders characterised by smooth muscle spasm | Dysmenorrhoea

BY MOUTH
- Child 12-17 years: 60–120 mg 1–3 times a day
- Adult: 60–120 mg 1–3 times a day

Alverine citrate

INDICATIONS AND DOSE
Adjunct in gastro-intestinal disorders characterised by smooth muscle spasm

BY MOUTH
- Child 12-17 years: 60–120 mg 1–3 times a day
- Adult: 60–120 mg 1–3 times a day

Antispasmodics

Antimuscarinics
The intestinal smooth muscle relaxant properties of antimuscarinic and other antispasmodic drugs may be useful in irritable bowel syndrome and in diverticular disease. Antimuscarinics (formerly termed 'anticholinergics') reduce intestinal motility. They can be used for the management of irritable bowel syndrome and diverticular disease. However, their value has not been established and response varies.

Antimuscarinics that are used for gastro-intestinal smooth muscle spasm include the tertiary amines atropine sulfate p. 1099 and dicycloverine hydrochloride p. 73 and the quaternary ammonium compounds propantheline bromide above and hyoscine butylbromide p. 73. The quaternary ammonium compounds are less lipid soluble than atropine sulfate and are less likely to cross the blood–brain barrier; they are also less well absorbed from the gastro-intestinal tract.

Dicycloverine hydrochloride has a much less marked antimuscarinic action than atropine sulfate and may also have some direct action on smooth muscle. Hyoscine butylbromide is advocated as a gastro-intestinal antispasmodic, but it is poorly absorbed; the injection is useful in endoscopy and radiology. Atropine sulfate and the belladonna alkaloids are outmoded treatments, any clinical virtues being outweighed by atropinic side-effects.

Other indications for antimuscarinic drugs include arrhythmias, asthma and airways disease, motion sickness, parkinsonism, urinary incontinence, mydriasis and cycloplegia, premedication, and as an antidote to organophosphorus poisoning.

Other antispasmodics
Alverine citrate below, mebeverine hydrochloride p. 75, and peppermint oil p. 40 are believed to be direct relaxants of intestinal smooth muscle and may relieve pain in irritable bowel syndrome and diverticular disease. They have no serious adverse effects but, like all antispasmodics, should be avoided in paralytic ileus.
Mebeverine hydrochloride

INDICATIONS AND DOSE

Adjunct in gastro-intestinal disorders characterised by smooth muscle spasm

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

▷ Child 10-17 years: 135–150 mg 3 times a day, dose preferably taken 20 minutes before meals

▷ Adult: 135–150 mg 3 times a day, dose preferably taken 20 minutes before meals

Irritable bowel syndrome

BY MOUTH USING MODIFIED-RELEASE MEDICINES

▷ Child 12-17 years: 200 mg twice daily

▷ Adult: 200 mg twice daily

UNLICENSED USE

Granules not licensed for use in children under 12 years. Modified-release capsules not licensed for use in children under 18 years.

CONTRA-INDICATIONS

Paralytic ileus

SIDE-EFFECTS

Allergic reactions • angioedema • rash • urticaria

PREGNANCY

Not known to be harmful—manufacturers advise avoid.

BREAST FEEDING

Manufacturers advise avoid—no information available.

PATIENT AND CARER ADVICE

Patients or carers should be given advice on the timing of administration of mebeverine hydrochloride tablets and oral suspension.

Medicines for Children leaflet: Mebeverine for intestinal spasm www.medicinesforchildren.org.uk/mebeverine-for-intestinal-spasms

EXCEPTIONS TO LEGAL CATEGORY

Mebeverine hydrochloride can be sold to the public for symptomatic relief of irritable bowel syndrome provided that max. single dose is 135 mg and max. daily dose is 405 mg; for uses other than symptomatic relief of irritable bowel syndrome provided that max. single dose is 100 mg and max. daily dose is 300 mg.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: powder

Tablet

▷ MEBEVERINE HYDROCHLORIDE (Non-proprietary)

Mebeverine hydrochloride 135 mg Boots IBS Relief 135mg tablets | 15 tablet [P] no price available

Mebeverine 135 mg tablets | 15 tablet [P] no price available

15 tablet [P] £4.50 | 100 tablet [P] £33.67 DT price = £8.44

Colofac (BGP Products Ltd)

Mebeverine hydrochloride 135 mg Colofac 135mg tablets | 100 tablet [P] £9.02 DT price = £8.44

Colofac IBS 135mg tablets | 15 tablet [P] £2.83

Modified-release capsule

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Colofac MR (BGP Products Ltd)

Mebeverine hydrochloride 200 mg Colofac MR 200mg capsules | 60 capsule [P] £6.92 DT price = £6.92

Oral suspension

▷ MEBEVERINE HYDROCHLORIDE (Non-proprietary)

Mebeverine hydrochloride (as Mebeverine pamoate) 10 mg per 1 ml Mebeverine 50mg/5ml oral suspension sugar free (sugar-free) | 300 ml [P] DT price = £14.43

7 Liver disorders and related conditions

7.1 Biliary disorders

Biliary disorders

Drugs affecting biliary composition and flow

The use of laparoscopic cholecystectomy and of endoscopic biliary techniques has limited the place of the bile acid ursodeoxycholic acid p. 76 in gallstone disease. Ursodeoxycholic acid is suitable for patients with unimpaired gall bladder function, small or medium-sized radiolucent stones, and whose mild symptoms are not amenable to other treatment. Long-term prophylaxis may be needed after complete dissolution of the gallstones has been confirmed because they may recur in up to 25% of patients within one year of stopping treatment. Ursodeoxycholic acid is also used in primary biliary cirrhosis; liver tests improve in most patients but the effect on overall survival is uncertain.

A terpene mixture (Rowachol®) raises biliary cholesterol solubility. It is not considered to be a useful adjunct.
Bile acid sequestrants
Colestyramine p. 173 is an anion-exchange resin that is not absorbed from the gastro-intestinal tract. It relieves diarrhoea and pruritus by forming an insoluble complex with bile acids in the intestine.

Pancreatin
Supplements of pancreatin are given by mouth to compensate for reduced or absent exocrine secretion in cystic fibrosis, and following pancreatectomy, gastrectomy, or chronic pancreatitis. Pancreatin may also be necessary if a tumour (e.g. pancreatic cancer) obstructs outflow from the pancreas.

**Pancreatin preparations**

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Protease units</th>
<th>Amylase units</th>
<th>Lipase units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creon® 10 000 capsule, e/c granules</td>
<td>600</td>
<td>8000</td>
<td>10 000</td>
</tr>
<tr>
<td>Creon® Micro e/c granules (per 100 mg)</td>
<td>200</td>
<td>3600</td>
<td>5000</td>
</tr>
<tr>
<td>Pancrex® granules (per gram)</td>
<td>300</td>
<td>4000</td>
<td>5000</td>
</tr>
<tr>
<td>Pancrex V® capsule, powder</td>
<td>430</td>
<td>9000</td>
<td>8000</td>
</tr>
<tr>
<td>Pancrex V® '125®' capsule, powder</td>
<td>160</td>
<td>3300</td>
<td>2950</td>
</tr>
<tr>
<td>Pancrex V® e/c tablet</td>
<td>110</td>
<td>1700</td>
<td>1900</td>
</tr>
<tr>
<td>Pancrex V® Forte e/c tablet</td>
<td>330</td>
<td>5000</td>
<td>5600</td>
</tr>
<tr>
<td>Pancrex V® powder (per gram)</td>
<td>1400</td>
<td>30000</td>
<td>25000</td>
</tr>
</tbody>
</table>

**Higher-strength pancreatin preparations**

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Protease units</th>
<th>Amylase units</th>
<th>Lipase units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creon® 25 000 capsule, e/c pellets</td>
<td>1000</td>
<td>18 000</td>
<td>25 000</td>
</tr>
<tr>
<td>Creon® 40 000 capsule, e/c granules</td>
<td>1600</td>
<td>25 000</td>
<td>40 000</td>
</tr>
<tr>
<td>Nutrizym 22® capsule, e/c minitablets</td>
<td>1100</td>
<td>19 800</td>
<td>22 000</td>
</tr>
<tr>
<td>Pancrease HL® capsule, e/c minitablets</td>
<td>1250</td>
<td>22 500</td>
<td>25 000</td>
</tr>
</tbody>
</table>

**BILE ACIDS**

**Ursodeoxycholic acid**

**INDICATIONS AND DOSE**

**Dissolution of gallstones**

**BY MOUTH**

- Adult: 8–12 mg/kg once daily, dose to be taken at bedtime, alternatively 8–12 mg/kg daily in 2 divided doses for up to 2 years; treatment is continued for 3–4 months after stones dissolve

**Primary biliary cirrhosis**

**BY MOUTH**

- Adult: 12–16 mg/kg daily in 3 divided doses for 3 months, then 12–16 mg/kg once daily, dose to be taken at bedtime

**SIDE-EFFECTS**

- Common or very common Diarrhoea
- Very rare Abdominal pain, gallstone calcification, pruritus
- Frequency not known Nausea, pruritus, vomiting
- **PREGNANCY** No evidence of harm but manufacturer advises avoid.
- **BREAST FEEDING** Not known to be harmful but manufacturer advises avoid.
- **HEPATIC IMPAIRMENT** Avoid in chronic liver disease (but used in primary biliary cirrhosis).
- **MONITORING REQUIREMENTS** In primary biliary cirrhosis, monitor liver function every 4 weeks for 3 months, then every 3 months.

**PATIENT AND CARER ADVICE**

- Patients should be given dietary advice (including avoidance of excessive cholesterol and calories).

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

**Tablet CAUTIONARY AND ADVISORY LABELS 21**

- **URSOODEOXYCHOLIC ACID (Non-proprietary)**
  - Ursodeoxycholic acid 150 mg Ursodeoxycholic acid 150mg tablets | 60 tablet (Ref) £19.02 DT price = £13.91
  - Ursodeoxycholic acid 300 mg Ursodeoxycholic acid 300mg tablets | 60 tablet (Ref) £38.86 DT price = £38.86
  - Destolt (Norgine Pharmaceuticals Ltd)
  - Ursodeoxycholic acid 150 mg Destolt 150mg tablets | 60 tablet (Ref) £18.39 DT price = £19.01
  - Ursolfak (Dr. Falk Pharma UK Ltd)
  - Ursodeoxycholic acid 500 mg Ursolfak 500mg tablets | 100 tablet (Ref) £8.00
  - Ursogal (Galen Ltd)
  - Ursodeoxycholic acid 150 mg Ursogal 150mg tablets | 60 tablet (Ref) £14.49 DT price = £19.01

**Capsule CAUTIONARY AND ADVISORY LABELS 21**

- **URSOODEOXYCHOLIC ACID (Non-proprietary)**
  - Ursodeoxycholic acid 250 mg Ursodeoxycholic acid 250mg capsules | 60 capsule (Ref) £25.29 DT price = £25.29
  - Ursolfak (Dr. Falk Pharma UK Ltd)
  - Ursodeoxycholic acid 250 mg Ursolfak 250mg capsules | 60 capsule (Ref) £30.17 DT price = £25.29
  - 100 capsule (Ref) £31.88
  - Ursogal (Galen Ltd)
  - Ursodeoxycholic acid 250 mg Ursogal 250mg capsules | 60 capsule (Ref) £25.93 DT price = £25.29

**Oral suspension**

- **URSOODEOXYCHOLIC ACID (Non-proprietary)**
  - Ursodeoxycholic acid 50 mg per 1 ml Ursolfak 250mg/5ml oral suspension (sugar-free) | 250 ml (Ref) £26.98 DT price = £26.98

**TERPENES**

**Borneol with camphene, cineole, menthol, menthone and pinene**

**INDICATIONS AND DOSE**

**Biliary disorders**

**BY MOUTH**

- Adult: 1–2 capsules 3 times a day, to be taken before food

**LESS SUITABLE FOR PRESCRIBING**

- Rowachol® is less suitable for prescribing.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.
7.2 Oesophageal varices

**VASOPRESSIN AND ANALOGUES**

Drugs used for Oesophageal varices not listed below; Vasopressin, p. 576

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Terlipressin acetate

**INDICATIONS AND DOSE**

**Glypressin® INJECTION**

**Bleeding from oesophageal varices**

**BY INTRAVENOUS INJECTION**

- Adult (body-weight up to 50 kg): Initially 2 mg every 4 hours until bleeding controlled, then reduced to 1 mg every 4 hours if required, maximum duration 48 hours
- Adult (body-weight 50 kg and above): Initially 2 mg every 4 hours until bleeding controlled, reduced if not tolerated to 1 mg every 4 hours, maximum duration 48 hours

**Variquel® INJECTION**

**Bleeding from oesophageal varices**

**BY INTRAVENOUS INJECTION**

- Adult (body-weight up to 49 kg): Initially 1 mg, then 1 mg every 4–6 hours for up to 72 hours, to be administered over 1 minute
- Adult (body-weight 50–69 kg): Initially 1.5 mg, then 1 mg every 4–6 hours for up to 72 hours, to be administered over 1 minute
- Adult (body-weight 70 kg and above): Initially 2 mg, then 1 mg every 4–6 hours for up to 72 hours, to be administered over 1 minute

**CAUTIONS** Arrhythmia - elderly - electrolyte and fluid disturbances - heart disease - history of QT-interval prolongation - respiratory disease - septic shock - uncontrolled hypertension - vascular disease

**INTERACTIONS** Caution with concomitant use of drugs that prolong the QT-interval.

**SIDE-EFFECTS**

- Common or very common: Abdominal cramps - arrhythmia - bradycardia - diarrhoea - headache - hypertension - hypotension - pallor - peripheral ischaemia
- Rare: Dyspnoea
- Very rare: Hyperglycaemia - stroke
- Frequency not known: Heart failure - skin necrosis

**PREGNANCY** Avoid unless benefits outweigh risk—uterine contractions and increased intra-uterine pressure in early pregnancy, and decreased uterine blood flow reported.

**BREAST FEEDING** Avoid unless benefits outweigh risk—no information available.

**RENAL IMPAIRMENT** Use with caution in chronic renal failure.

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8 Obesity

**Obesity**

Obesity is associated with many health problems including cardiovascular disease, diabetes mellitus, gallstones and osteoarthritis. Factors that aggravate obesity may include depression, other psychosocial problems, and some drugs.

The main treatment of the obese individual is a suitable diet, carefully explained to the individual, with appropriate support and encouragement; the individual should also be advised to increase physical activity. Smoking cessation (while maintaining body weight) may be worthwhile before attempting supervised weight loss since cigarette smoking may be more harmful than obesity. Attendance at weight loss groups helps some individuals. Obesity should be managed in an appropriate setting by staff who have been trained in the management of obesity; the individual should receive advice on diet and lifestyle modification and be monitored for changes in weight as well as in blood pressure, blood lipids and other associated conditions.

An anti-obesity drug should be considered only for those with a body mass index (BMI, individual’s bodyweight divided by the square of the individual’s height) of 30 kg/m² or greater in whom at least 3 months of managed care involving supervised diet, exercise and behaviour modification fails to achieve a realistic reduction in weight. In the presence of associated risk factors, it may be appropriate to prescribe an anti-obesity drug to individuals with a BMI of 28 kg/m² or greater. Drugs should never be used as the sole element of treatment. The individual should be monitored on a regular basis; drug treatment should be discontinued if the individual regains weight at any time whilst receiving drug treatment.

Combination therapy involving more than one anti-obesity drug is contra-indicated by the manufacturers; there is no evidence-base to support such treatment.

Thyroid hormones have no place in the treatment of obesity except in biochemically proven hypothyroid patients. The use of diuretics, choriionic gonadotrophin, or amphetamines is not appropriate for weight reduction.

**Anti-obesity drugs acting on the gastro-intestinal tract**

Orlistat p. 78 should be used in conjunction with other lifestyle measures to manage obesity; treatment should only be continued beyond 12 months after discussing potential benefits and risks with the patient. On stopping orlistat, there may be a gradual reversal of weight loss.
Some of the weight loss in those taking orlistat below probably results from individuals reducing their fat intake to avoid severe gastro-intestinal effects including steatorrhoea.

Methylcellulose p. 45 is claimed to reduce food intake by producing a feeling of satiety, but there is little evidence to support its use in the management of obesity.

**Centrally acting appetite suppressants**

Phentermine and diethylpropion are central stimulants; they are not recommended for the treatment of obesity. Phentermine has been associated with a risk of pulmonary hypertension.

Sibutramine, dexfenfluramine, and fenfluramine have been withdrawn because the benefit of treatment does not outweigh the risk of serious adverse effects.

**LIPASE INHIBITORS**

**Orlistat**

- **DRUG ACTION** Orlistat, a lipase inhibitor, reduces the absorption of dietary fat.

**INDICATIONS AND DOSE**

Adjuvant in obesity (in conjunction with a mildly hypocaloric diet in individuals with a body mass index (BMI) of 30 kg/m² or more or in individuals with a BMI of 28 kg/m² or more in the presence of other risk factors such as type 2 diabetes, hypertension, or hypercholesterolaemia)

**BY MOUTH**

- **Adult:** 120 mg up to 3 times a day, dose to be taken immediately before, during, or up to 1 hour after each main meal, continue treatment beyond 12 weeks only if weight loss since start of treatment exceeds 5% (target for initial weight loss may be lower in patients with type 2 diabetes), if a meal is missed or contains no fat, the dose of orlistat should be omitted

- **CONTRA-INDICATIONS** Cholestasis - chronic malabsorption syndrome

- **CAUTIONS** Chronic kidney disease - may impair absorption of fat-soluble vitamins - volume depletion

**CAUTIONS, FURTHER INFORMATION**

Vitamin supplementation (especially of vitamin D) may be considered if there is concern about deficiency of fat-soluble vitamins.

- **INTERACTIONS** → Appendix 1 (orlistat).

- **Interactive effects**
  - **Multivitamins** If a multivitamin supplement is required, it should be taken at least 2 hours after orlistat dose or at bedtime.

- **SIDE-EFFECTS**
  - **Common or very common** Abdominal distension (gastro-intestinal effects minimised by reduced fat intake) - abdominal pain (gastro-intestinal effects minimised by reduced fat intake) - anxiety - faecal incontinence - faecal urgency - flatulence - gingival disorders - headache - hypoglycaemia - liquid stools - malaise - menstrual disturbances - oily leakage from rectum - oily stools - respiratory infections - tooth disorders - urinary tract infection
  - **Frequency not known** Bullous eruptions - cholelithiasis - diverticulitis - hepatitis - hypothyroidism - oxalate nephropathy - rectal bleeding

- **PREGNANCY** Use with caution.

- **BREAST FEEDING** Avoid—no information available.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

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**9 Rectal and anal disorders**

**Rectal and anal disorders**

Anal and perianal pruritus, soreness, and excoriation are best treated by application of bland ointments and suppositories. These conditions occur commonly in patients suffering from haemorrhoids, fistulas, and proctitis. Cleansing with attention to any minor faecal soilings, adjustment of the diet to avoid hard stools, the use of bulk-forming materials such as bran and a high residue diet are helpful. In proctitis these measures may supplement treatment with corticosteroids or sulphasalazine p. 37.

When necessary, topical preparations containing local anaesthetics or corticosteroids are used, provided perianal thrush has been excluded. Perianal thrush is treated with a topical antifungal preparation.

**Soothing haemorrhoidal preparations**

Soothing preparations containing mild astringents such as bismuth subgallate, zinc oxide, and hamamelis may give symptomatic relief in haemorrhoids. Many proprietary preparations also contain lubricants, vasoconstrictors, or mild antiseptics.

**Local anaesthetics** are used to relieve pain associated with haemorrhoids and pruritus ani but good evidence is lacking. Lidocaine hydrochloride ointment is used before emptying the bowel to relieve pain associated with anal fissure. Alternative local anaesthetics include tetracaine, cinchocaine (dibucaine), and pramocaine (pramoxine), but they are more irritant. Local anaesthetic ointments can be absorbed through the rectal mucosa therefore excessive application should be avoided, particularly in infants and children. Preparations containing local anaesthetics should be used for short periods only (no longer than a few days) since they may cause sensitisation of the anal skin.

**Compound haemorrhoidal preparations with corticosteroids**

Corticosteroids are often combined with local anaesthetics and soothing agents in preparations for haemorrhoids. They are suitable for occasional short-term use after exclusion of infections, such as herpes simplex; prolonged use can cause atrophy of the anal skin.

**Rectal sclerosants**

**Oily phenol injection** is used to inject haemorrhoids particularly when unprolapsed.

**Anal fissures**

The management of anal fissures requires stool softening by increasing dietary fibre in the form of bran or by using a bulk-forming laxative. Short-term use of local anaesthetic preparations may help. If these measures are inadequate, the patient should be referred for specialist treatment in hospital. The use of a topical nitrate (e.g. glyceryl trinitrate 0.4% ointment p. 190) may be considered. Before considering surgery, topical diltiazem hydrochloride 2%
may be used twice daily [unlicensed indication] in patients with chronic anal fissures unresponsive to topical nitrates.

Rectal and anal disorders in children
Haemorrhoids in children are rare. Treatment is usually symptomatic and the use of a locally applied cream is appropriate for short periods; however, local anaesthetics can cause stinging initially and this may aggravate the child’s fear of defaecation.

9.1 Haemorrhoids

CORTICOSTEROIDS

Benzyl benzoate with bismuth oxide, bismuth subgallate, hydrocortisone acetate, peru balsam and zinc oxide

**INDICATIONS AND DOSE**

**Haemorrhoids** | **Pruritus ani**
---|---
**BY RECTUM USING SUPPOSITORIES**
- Adult: Apply twice daily for no longer than 7 days, to be applied morning and night, an additional dose should be applied after a bowel movement

**BY RECTUM USING CREAM**
- Adult: 1 suppository twice daily for no longer than 7 days, to be inserted night and morning, additional dose after a bowel movement

**CAUTIONS** Local anaesthetic component may be absorbed through the rectal mucosa (avoid excessive application, particularly in children and infants) • local anaesthetic component may cause sensitisation (use for short periods only—no longer than a few days)

**PRESCRIBING AND DISPENSING INFORMATION**

A proprietary brand Anusol Plus HC® (ointment and suppositories) is on sale to the public.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Cream**

- BENZYL BENZOATE WITH BISMUTH OXIDE, HYDROCORTISONE ACETATE, PERU BALSAM, PRAMOCAINE HYDROCHLORIDE AND ZINC OXIDE (Non-proprietary)
  Benzyl benzoate 12 mg per 1 gram, Bismuth oxide 8.75 mg per 1 gram, Hydrocortisone acetate 5 mg per 1 gram, Peru Balsam 18.5 mg per 1 gram, Pramocaine hydrochloride 10 mg per 1 gram, Zinc oxide 123.5 mg per 1 gram Anugesic-HC cream | 30 gram | £3.71

**Benzyl benzoate with bismuth oxide, hydrocortisone acetate, peru balsam, pramocaine hydrochloride and zinc oxide**

**INDICATIONS AND DOSE**

**Haemorrhoids** | **Pruritus ani**
---|---
**BY RECTUM USING SUPPOSITORIES**
- Adult: Apply twice daily for no longer than 7 days, to be applied morning and night and after a bowel movement

**CAUTIONS** Local anaesthetic component can be absorbed through the rectal mucosa (avoid excessive application, particularly in children and infants) • local anaesthetic component may cause sensitisation (use for short periods only—no longer than a few days)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Suppository**

- BENZYL BENZOATE WITH BISMUTH OXIDE, BISMUTH SUBGALLATE, HYDROCORTISONE ACETATE, PERU BALSAM AND ZINC OXIDE (Non-proprietary)
  Benzyl benzoate 33 mg, Bismuth oxide 24 mg, Bismuth subgallate 59 mg, Hydrocortisone acetate 10 mg, Peru Balsam 49 mg, Zinc oxide 296 mg Anusol HC suppositories | 12 suppository | £1.74
  Anusol Plus HC suppositories | 12 suppository | £3.03

**Ointment**

- BENZYL BENZOATE WITH BISMUTH OXIDE, BISMUTH SUBGALLATE, HYDROCORTISONE ACETATE, PERU BALSAM AND ZINC OXIDE (Non-proprietary)
  Benzyl benzoate 12.5 mg per 1 gram, Bismuth oxide 8.75 mg per 1 gram, Bismuth subgallate 22.5 mg per 1 gram, Hydrocortisone acetate 2.5 mg per 1 gram, Peru Balsam 18.75 mg per 1 gram, Zinc oxide 107.5 mg per 1 gram Anusol Plus HC ointment | 15 gram | £3.03

**Cinchoacaine hydrochloride with fluocortolone caproate and fluocortolone pivalate**

**INDICATIONS AND DOSE**

**Haemorrhoids** | **Pruritus ani**
---|---
**BY RECTUM USING OINTMENT**
- Adult: Apply twice daily for 5–7 days, apply 3–4 times a day if required, on the first day of treatment, then apply once daily for a few days after symptoms have cleared

**BY RECTUM USING SUPPOSITORIES**
- Adult: Initially 1 suppository daily for 5–7 days, to be inserted after a bowel movement, then 1 suppository once daily on alternate days for 1 week

**Haemorrhoids (severe cases)** | **Pruritus ani (severe cases)**
---|---
**BY RECTUM USING SUPPOSITORIES**
- Adult: Initially 1 suppository 2–3 times a day for 5–7 days, then 1 suppository once daily on alternate days for 1 week

**CAUTIONS** Local anaesthetic component can be absorbed through the rectal mucosa (avoid excessive application, particularly in children and infants) • local anaesthetic component may cause sensitisation (use for short periods only—no longer than a few days)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Suppository**

- Ultraproct (Meadow Laboratories Ltd)
  Cinchoacaine hydrochloride 1 mg, Fluocortolone caproate 630 microgram, Fluocortolone pivalate 610 microgram Ultraproct suppositories | 12 suppository | £2.15

**Cinchoacaine hydrochloride with fluocortolone caproate and fluocortolone pivalate**

**INDICATIONS AND DOSE**

**Haemorrhoids** | **Pruritus ani**
---|---
**BY RECTUM USING OINTMENT**
- Adult: Apply twice daily for 5–7 days, apply 3–4 times a day if required, on the first day of treatment, then apply once daily for a few days after symptoms have cleared

**BY RECTUM USING SUPPOSITORIES**
- Adult: Initially 1 suppository daily for 5–7 days, to be inserted after a bowel movement, then 1 suppository once daily on alternate days for 1 week

**CAUTIONS** Local anaesthetic component can be absorbed through the rectal mucosa (avoid excessive application, particularly in children and infants) • local anaesthetic component may cause sensitisation (use for short periods only—no longer than a few days)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Suppository**

- Ultraproct (Meadow Laboratories Ltd)
  Cinchoacaine hydrochloride 1 mg, Fluocortolone caproate 630 microgram, Fluocortolone pivalate 610 microgram Ultraproct suppositories | 12 suppository | £2.15
Ointment
- **Ultraproct** (Meadow Laboratories Ltd)
  Cinchocaine hydrochloride 5 mg per 1 gram, Fluocortolone caproate 950 microgram per 1 gram, Fluocortolone pivalate 920 microgram per 1 gram
  Ultraproct ointment | 30 gram [PDR] £4.57

**Cinchocaine with hydrocortisone**

**INDICATIONS AND DOSE**

**UNIROID-HC**® **SUPPOSITORIES**

- **Haemorrhoids** | **Pruritus ani**
  BY RECTUM
  - Child 12-17 years: 1 suppository, insert twice daily and after a bowel movement, do not use for longer than 7 days
  - Adult: 1 suppository, insert twice daily and after a bowel movement, do not use for longer than 7 days

**PROCTOSEDYL**® **SUPPOSITORIES**

- **Haemorrhoids** | **Pruritus ani**
  BY RECTUM
  - Child 12-17 years: 1 suppository, insert suppository night and morning and after a bowel movement, do not use for longer than 7 days
  - Adult: 1 suppository, insert suppository night and morning and after a bowel movement, do not use for longer than 7 days

**UNIROID-HC**® **OINTMENT**

- **Haemorrhoids** | **Pruritus ani**
  TO THE SKIN OR BY RECTUM
  - Child 12-17 years: Apply twice daily, and apply after a bowel movement, apply externally or by rectum, do not use for longer than 7 days
  - Adult: Apply twice daily, and apply after a bowel movement, apply externally or by rectum, do not use for longer than 7 days

**PROCTOSEDYL**® **OINTMENT**

- **Haemorrhoids** | **Pruritus ani**
  TO THE SKIN OR BY RECTUM
  - Child: Apply twice daily, to be administered morning and night and after a bowel movement, apply externally or by rectum, do not use for longer than 7 days
  - Adult: Apply twice daily, to be administered morning and night and after a bowel movement, apply externally or by rectum, do not use for longer than 7 days

**CAUTIONS**
- Local anaesthetic component may cause sensitisation (use for short periods only—no longer than a few days)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Suppository**
  - **Cinchocaine with Hydrocortisone** (Non-proprietary)
    Cinchocaine hydrochloride 5 mg, Hydrocortisone 5 mg | 12 suppository [PDR] no price available
  - **Proctosedyl** (Sanofi)
    Cinchocaine hydrochloride 5 mg, Hydrocortisone 5 mg | 12 suppository [PDM] £5.08
  - **Uniroid HC** (Chemidex Pharma Ltd)
    Cinchocaine hydrochloride 5 mg, Hydrocortisone 5 mg | 12 suppository [PDR] £1.91

**Ointment**
- **CINCHOCAINS WITH HYDROCORTISONE** (Non-proprietary)
  Cinchocaine hydrochloride 5 mg per 1 gram, Hydrocortisone 5 mg per 1 gram
  Cinchocaine 0.5% / Hydrocortisone 0.5% ointment | 30 gram [PDR] no price available
  - **Proctosedyl** (Sanofi)
    Cinchocaine hydrochloride 5 mg per 1 gram, Hydrocortisone 5 mg per 1 gram
    Proctosedyl ointment | 30 gram [PDR] £10.34
  - **Uniroid HC** (Chemidex Pharma Ltd)
    Cinchocaine hydrochloride 5 mg per 1 gram, Hydrocortisone 5 mg per 1 gram
    Uniroid HC ointment | 30 gram [PDR] £4.23

**Hydrocortisone with lidocaine**

**INDICATIONS AND DOSE**

- **Haemorrhoids** | **Pruritus ani**
  ▶ **BY RECTUM USING SUPPOSITORIES**
  - Adult: Initially 1 suppository daily for 5–7 days, to be inserted after a bowel movement
  - Haemorrhoids (severe cases) | **Pruritus ani (severe cases)**
    **INITIALLY BY RECTUM USING SUPPOSITORIES**
    - Adult: Initially 1 suppository 2–3 times a day, then (by rectum) 1 suppository daily for a total of 5–7 days, to be inserted after a bowel movement

**CAUTIONS**
- Local anaesthetic component may be absorbed through the rectal mucosa (avoid excessive application - local anaesthetic component may cause sensitisation (use for short periods only—no longer than a few days)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Suppository**
  - **Schepiroc** (Bayer Plc)
    Cinchocaine hydrochloride 1 mg, Prednisolone hexanoate 1.3 mg | 12 suppository [PDR] £1.38
  - **Ointment**
    - **Schepiroc** (Bayer Plc)
      Cinchocaine hydrochloride 5 mg per 1 gram, Prednisolone hexanoate 1.9 mg per 1 gram | 30 gram [PDR] £2.94

**INDICATIONS AND DOSE**

- **Haemorrhoids** | **Pruritus ani**
  ▶ **BY RECTUM USING AEROSOL SPRAY**
  - Adult: 1 spray up to 3 times a day for no longer than 7 days without medical advice, spray once over the affected area
  - ▶ **BY RECTUM USING OINTMENT**
  - Adult: Apply several times daily, for short term use only

**CAUTIONS**
- Local anaesthetic component may be absorbed through the rectal mucosa (avoid excessive application - local anaesthetic component may cause sensitisation (use for short periods only—no longer than a few days)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: mouthwash.
10 Reduced exocrine secretions

PANCREATIC ENZYMES

Pancreatin

● **DRUG ACTION** Supplements of pancreatin are given to compensate for reduced or absent exocrine secretion. They assist the digestion of starch, fat, and protein.

### INDICATIONS AND DOSE

**PANCREX® V TABLETS**

Pancreatic insufficiency

**BY MOUTH**

- Child: 2–17 years: 5–15 capsules, to be taken 30 minutes before meals
- Adult: 5–15 capsules, to be taken 30 minutes before meals

**PANCREX® V TABLETS FORTE**

Pancreatic insufficiency

**BY MOUTH**

- Child: 2–17 years: 6–10 capsules, to be taken before meals
- Adult: 6–10 capsules, to be taken before meals

**PANCREX® V**

Pancreatic insufficiency

**BY MOUTH**

- Child: 1–11 months: 1–2 capsules, contents of capsule to be mixed with feeds
- Child: 1–7 years: 2–6 capsules, dose to be taken with each meal
- Child: 8–11 years: 2–6 capsules, dose to be taken with each meal
- Adult: 2–6 capsules, dose to be taken with each meal

**CREON® 10000**

Pancreatic insufficiency

**BY MOUTH**

- Child: Initially 1–2 capsules, dose to be taken with each meal
- Adult: Initially 1–2 capsules, dose to be taken with each meal

**CREON® 40000**

Pancreatic insufficiency

**BY MOUTH**

- Child: 2–17 years: 1–2 capsules, dose to be taken with each meal
- Adult: 1–2 capsules, dose to be taken with each meal

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**INDICATIONS AND DOSE**

**HYDROCORTISONE WITH LIDOCAINE (Non-proprietary)**

Hydrocortisone acetate 2.75 mg per 1 gram, Lidocaine 50 mg per 1 gram

**BY RECTUM**

- Adult: 1 applicable 2–3 times a day and 1 applicable, after a bowel movement, do not use for longer than 7 days; maximum 4 applicatorfuls per day

- **CAUTIONS** Local anaesthetic component can be absorbed through the rectal mucosa (avoid excessive application) - local anaesthetic component may cause sensitisation (use for short periods only—no longer than a few days)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Foam**
  - Proctofoam HC (Meda Pharmaceuticals Ltd)
    - Hydrocortisone acetate 10 mg per 1 gram, Pramocaine hydrochloride 10 mg per 1 gram

- **Ointment**
  - Hydrocortisone with pramocaine

**INDICATIONS AND DOSE**

**INDICATIONS AND DOSE**

**Haemorrhoids | Proctitis**

**BY RECTUM**

- Adult: 1 applicable 2–3 times a day and 1 applicable, after a bowel movement, do not use for longer than 7 days; maximum 4 applicatorfuls per day

- **CAUTIONS** Local anaesthetic component can be absorbed through the rectal mucosa (avoid excessive application) - local anaesthetic component may cause sensitisation (use for short periods only—no longer than a few days)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Oily phenol**
  - Phenol 50 mg per 1 ml

- **Solution for injection**
  - Phenol 50 mg per 1 ml
  - Oily phenol 5% solution for injection 5ml

- **Spray**
  - Perinal (Dermal Systems Ltd)
  - Hydrocortisone 2 mg per 1 gram, Lidocaine hydrochloride 10 mg per 1 gram

**RECED SCLEORSANTS**

Phenol

**INDICATIONS AND DOSE**

**Haemorrhoids (particularly when unprolapsed)**

**BY SUBMUCOSAL INJECTION**

- Adult: 2–3 ml, dose (using phenol 5%) to be injected into the submucosal layer at the base of the pile; several injections may be given at different sites, max. total injected 10 ml at any one time

- **SIDE-EFFECTS** Irritation • tissue necrosis

- **PRESCRIBING AND DISPENSING INFORMATION** When prepared extemporaneously, the BP states Oily Phenol Injection, BP consists of phenol 5% in a suitable fixed oil.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, cutaneous solution, liquid

**Solution for injection**

- Phenol 50 mg per 1 ml
  - Oily phenol 5% solution for injection 5ml
  - Oily phenol 5% solution for injection 2ml

- **Spray**
  - Perinal (Dermal Systems Ltd)
  - Hydrocortisone 2 mg per 1 gram, Lidocaine hydrochloride 10 mg per 1 gram
NUTRIZYM 22® GASTRO-RESISTANT CAPSULES

Pancreatic insufficiency

BY MOUTH

- Child: Initially 100 mg, to be taken before each feed or meal; granules can be mixed with a small amount of milk or soft food and administered immediately (manufacturer recommends mixing with acidic liquid or pureed fruit before administration), granules should not be chewed before swallowing

- Adult: Initially 100 mg, to be taken before each feed or meal; granules can be mixed with a small amount of milk or soft food and administered immediately (manufacturer recommends mixing with acidic liquid or pureed fruit before administration), granules should not be chewed before swallowing

Dose equivalence and conversion

100 mg granules = one measured scoopful (scoop supplied with product).

PANCREASE HL

Pancreatic insufficiency

BY MOUTH

- Child: 2–17 years: 5–10 g, to be taken just before meals, washed down or mixed with milk or water

- Adult: 5–10 g, to be taken just before meals, washed down or mixed with milk or water

PANCREASE HL gastro-resistant capsules

Pancreatic insufficiency

BY MOUTH

- Child 2-17 years: Initially 1–2 capsules, dose to be taken with each meal either taken whole or contents mixed with acidic fluid or soft food (then swallowed immediately without chewing)

- Adult: Initially 1–2 capsules, dose to be taken with each meal either taken whole or contents mixed with acidic fluid or soft food (then swallowed immediately without chewing)

CREON® 25000

Pancreatic insufficiency

BY MOUTH

- Child 2–17 years: Initially 1–2 capsules, dose to be taken with each meal either taken whole or contents mixed with acidic fluid or soft food (then swallowed immediately without chewing)

- Adult: Initially 1–2 capsules, dose to be taken with each meal either taken whole or contents mixed with acidic fluid or soft food (then swallowed immediately without chewing)

CREON® MICRO

Pancreatic insufficiency

BY MOUTH

<table>
<thead>
<tr>
<th>Medicinal forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creon (BGP Products Ltd)</td>
</tr>
<tr>
<td>Amylase 8000 unit, Lipase 10000 unit, Protease 600 unit</td>
</tr>
<tr>
<td>£58.00</td>
</tr>
<tr>
<td>Creon 10000 gastro-resistant capsules</td>
</tr>
<tr>
<td>100 capsule Unit pack</td>
</tr>
<tr>
<td>Amylase 18000 unit, Lipase 25000 unit, Protease 1000 unit</td>
</tr>
<tr>
<td>Creon 25000 gastro-resistant capsules</td>
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<tr>
<td>100 capsule Unit pack</td>
</tr>
<tr>
<td>Amylase 25000 unit, Lipase 40000 unit, Protease 1600 unit</td>
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<tr>
<td>Creon 40000 gastro-resistant capsules</td>
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<tr>
<td>100 capsule Unit pack</td>
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<tr>
<td>Nutrizym (Merck Serono Ltd)</td>
</tr>
<tr>
<td>Amylase 19800 unit, Lipase 22000 unit, Protease 1100 unit</td>
</tr>
<tr>
<td>Nutrizym 22 gastro-resistant capsules</td>
</tr>
<tr>
<td>100 capsule Unit pack</td>
</tr>
<tr>
<td>Creon (BGP Products Ltd)</td>
</tr>
<tr>
<td>Amylase 36000 unit, Lipase 50000 unit, Protease 200 unit</td>
</tr>
<tr>
<td>Creon Micro Pancrease 60.12mg gastro-resistant granules</td>
</tr>
<tr>
<td>40 gram Unit pack</td>
</tr>
<tr>
<td>Creon (Essential Pharmaceuticals Ltd)</td>
</tr>
<tr>
<td>Amylase 40000 unit, Lipase 50000 unit, Protease 300 unit</td>
</tr>
<tr>
<td>Creon gastro-resistant granules</td>
</tr>
<tr>
<td>300 gram Unit pack</td>
</tr>
</tbody>
</table>

Gastro-resistant granules

CAUTIONARY AND ADVISORY LABELS 25

- Creon (BGP Products Ltd) |
| Amylase 36000 unit, Lipase 50000 unit, Protease 200 unit |
| Creon Micro Pancrease 60.12mg gastro-resistant granules |
| 40 gram Unit pack | £31.50 |
| Creon (Essential Pharmaceuticals Ltd) |
| Amylase 40000 unit, Lipase 50000 unit, Protease 300 unit |
| Creon gastro-resistant granules |
| 300 gram Unit pack | £57.00 |

Powder

- Creon (Essential Pharmaceuticals Ltd) |
| Amylase 30000 unit, Lipase 25000 unit, Protease 1400 unit |
| Creon V oral powder (sugar-free) |
| 300 gram Unit pack | £58.88 |
11 Stoma care

Stoma care
Prescribing for patients with stoma calls for special care. The following is a brief account of some of the main points to be borne in mind.

Enteric-coated and modified-release preparations are unsuitable, particularly in patients with an ileostomy, as there may not be sufficient release of the active ingredient.

Laxatives
Enemas and washouts should not be prescribed for patients with an ileostomy as they may cause rapid and severe loss of water and electrolytes. Colostomy patients may suffer from constipation and whenever possible should be treated by increasing fluid intake or dietary fibre. Bulk-forming drugs should be tried. If they are insufficient, as small a dose as possible of senna p. 53 should be used.

Antidiarrhoeals
Drugs such as loperamide hydrochloride p. 56, codeine phosphate p. 360, or co-phenotrope p. 55 (diphenoxylate with atropine) are effective. Bulk-forming drugs may be tried but it is often difficult to adjust the dose appropriately. Antibacterials should not be given for an episode of acute diarrhoea.

Antacids
The tendency to diarrhoea from magnesium salts or constipation from aluminium salts may be increased in these patients.

Diuretics
Diuretics should be used with caution in patients with an ileostomy as they may become excessively dehydrated and potassium depletion may easily occur. It is usually advisable to use a potassium-sparing diuretic.

Digoxin
Patients with a stoma are particularly susceptible to hypokalaemia if on digoxin p. 94 therapy and potassium supplements or a potassium-sparing diuretic may be advisable.

Potassium supplements
Liquid formulations are preferred to modified-release formulations.

Analgesics
Opioid analgesics may cause troublesome constipation in colostomy patients. When a non-opioid analgesic is required paracetamol p. 354 is usually suitable but anti-inflammatory analgesics may cause gastric irritation and bleeding.

Iron preparations
Iron preparations may cause loose stools and sore skin in these patients. If this is troublesome and if iron is definitely indicated an intramuscular iron preparation should be used. Modified-release preparations should be avoided for the reasons given above.

Care of stoma
Patients are usually given advice about the use of cleansing agents, protective creams, lotions, deodorants, or sealants whilst in hospital, either by the surgeon or by stoma care nurses. Voluntary organisations offer help and support to patients with stoma.
1 Arrhythmias

Arrhythmias

Management of an arrhythmia requires precise diagnosis of the type of arrhythmia, and electrocardiography is essential; underlying causes such as heart failure require appropriate treatment.

Ectopic beats

If ectopic beats are spontaneous and the patient has a normal heart, treatment is rarely required and reassurance to the patient will often suffice. If they are particularly troublesome, beta-blockers are sometimes effective and may be safer than other suppressant drugs.

Atrial fibrillation

Treatment of patients with atrial fibrillation aims to reduce symptoms and prevent complications, especially stroke. All patients with atrial fibrillation should be assessed for their risk of stroke and thromboembolism. Atrial fibrillation can be managed by either controlling the ventricular rate (‘rate control’) or by attempting to restore and maintain sinus rhythm (‘rhythm control’). At any stage if treatment fails to control symptoms, or, if symptoms reoccur after cardioversion and specialised management is required, referral should be made within 4 weeks. If drug treatment fails to control the symptoms of atrial fibrillation or is unsuitable, ablation strategies can be considered. Review anticoagulation, stroke, and bleeding risk at least annually in all patients with atrial fibrillation.

Acute presentation

All patients with life-threatening haemodynamic instability caused by new-onset atrial fibrillation should undergo emergency electrical cardioversion without delaying to achieve anticoagulation. In patients presenting acutely but without life-threatening haemodynamic instability, rate or rhythm control can be offered if the onset of arrhythmia is less than 48 hours; rate control is preferred if onset is more than 48 hours or uncertain. Consideration of pharmacological or electrical cardioversion should be based on clinical circumstances. If pharmacological cardioversion has been agreed, intravenous amiodarone hydrochloride p. 88, or alternatively flecainide acetate p. 91, can be used (amiodarone hydrochloride is preferred if there is structural heart disease). If urgent rate control is required, a beta-blocker or verapamil hydrochloride p. 156 can be given intravenously.

Cardioversion

Sinus rhythm can be restored by electrical cardioversion, or pharmacological cardioversion with an oral or intravenous antiarrhythmic drug e.g. flecainide acetate or amiodarone hydrochloride. If atrial fibrillation has been present for more than 48 hours, electrical cardioversion is preferred and should not be attempted until the patient has been fully anticoagulated for at least 3 weeks; if this is not possible, parenteral anticoagulation should be commenced, and a left atrial thrombus ruled out immediately before cardioversion; oral anticoagulation should be given after cardioversion and continued for at least 4 weeks; prior to cardioversion, offer rate control as appropriate.

Drug treatment

Rate control is the preferred first-line drug treatment strategy for atrial fibrillation except in patients with new-onset atrial fibrillation, heart failure secondary to atrial fibrillation, atrial flutter suitable for an ablation strategy, atrial fibrillation with a reversible cause, or if rhythm control is more suitable based on clinical judgement. Ventricular rate can be controlled with a standard beta-blocker (not sotalol hydrochloride p. 93) or a rate-limiting calcium channel blocker such as diltiazem hydrochloride p. 149 [unlicensed indication], or verapamil hydrochloride p. 156 as monotherapy. Choice of drug should be based on individual symptoms, heart rate, comorbidities, and patient preference. Digoxin p. 94 is usually only effective for controlling the ventricular rate at rest, and should therefore only be used as monotherapy in predominantly sedentary patients with non-paroxysmal atrial fibrillation. When a single drug fails to adequately control the ventricular rate, a combination of two drugs including a beta-blocker, digoxin, or diltiazem hydrochloride can be used. If symptoms are not controlled with a combination of two drugs, a rhythm-control strategy should be considered. If ventricular function is diminished, the combination of a beta-blocker (that is licensed for use in heart failure) and digoxin is preferred. Digoxin is also used when atrial fibrillation is accompanied by congestive heart failure.

If drug treatment is required to maintain sinus rhythm (‘rhythm control’) post-cardioversion, a standard beta-
blocker is used. If a standard beta-blocker is not appropriate or is ineffective, consider an oral anti-arrhythmic drug such as sotalol hydrochloride p. 93, flecainide acetate p. 91, propafenone hydrochloride p. 92, or amiodarone hydrochloride p. 88; dronedarone p. 90 may be considered in paroxysmal or persistent atrial fibrillation (see NICE guidance). If necessary, amiodarone hydrochloride can be started 4 weeks before and continuing for up to 12 months after electrical cardioversion to increase success of the procedure, and to maintain sinus rhythm. Flecainide acetate or propafenone hydrochloride should not be given when there is known ischaemic or structural heart disease. Control of heart rate; the management of patients with left ventricular impairment or heart failure.

Paroxysmal atrial fibrillation
In symptomatic paroxysmal atrial fibrillation, ventricular rhythm is controlled with a standard beta-blocker. Alternatively, if symptoms persist or a standard beta-blocker is not appropriate, an oral anti-arrhythmic drug such as sotalol hydrochloride p. 93, flecainide acetate p. 91, propafenone hydrochloride p. 92, or amiodarone hydrochloride p. 88 can be given (see also Paroxysmal supraventricular tachycardia and Supraventricular arrhythmias). In selected patients with infrequent episodes of symptomatic paroxysmal atrial fibrillation, sinus rhythm can be restored using the ‘pill-in-the-pocket’ approach; this involves the patient taking oral flecainide acetate or propafenone hydrochloride to self-treat an episode of atrial fibrillation when it occurs. 

Stroke prevention
All patients with atrial fibrillation should be assessed for their risk of stroke and the need for thromboprophylaxis; this needs to be balanced with the patient’s risk of bleeding; a NICE guideline (NICE clinical guideline 180 (June 2014). Atrial fibrillation: The management of atrial fibrillation) recommends using the CHA2DS2-VASc assessment tool for stroke risk and the HAS-BLED tool for bleeding risk prior to and during anticoagulation. Risk factors for stroke taken into account by CHA2DS2-VASc include prior ischaemic stroke, transient ischaemic attacks, or thromboembolic events, heart failure, left ventricular systolic dysfunction, vascular disease, diabetes, hypertension, females, and patients over 65 years. Patients with a very low risk of stroke (CHA2DS2-VASc score of 0 for men or 1 for women) do not require an antithrombotic for stroke prevention. Parenteral anticoagulation should be offered to patients with new-onset atrial fibrillation who are receiving subtherapeutic or no anticoagulation therapy until assessment is made, and appropriate anticoagulation is started. Oral anticoagulation should be offered to patients with confirmed diagnosis of atrial fibrillation in whom sinus rhythm has not been successfully restored within 48 hours of onset, patients who have had, or are at high risk of recurrence of atrial fibrillation such as those with structural heart disease, prolonged history of atrial fibrillation (more than 12 months), a history of failed attempts at cardioversion, and patients whom the risk of stroke outweighs the risk of bleeding. Anticoagulant treatment should not be withheld solely because of the risk of falls, and choice of treatment should be based on clinical features and patient preferences. Oral anticoagulation may be with a vitamin K antagonist (e.g warfarin sodium p. 121, or in non-valvular atrial fibrillation with apixaban p. 108, dabigatran etexilate p. 117, or rivaroxaban p. 109. Anticoagulants are also indicated during cardioversion procedures. Aspirin p. 104 is less effective than warfarin sodium at preventing emboli; the modest benefit is offset by the risk of bleeding, and aspirin should not be offered as monotherapy solely for stroke prevention in atrial fibrillation. If anticoagulant treatment is contraindicated or not tolerated, left atrial appendage occlusion can be considered.

Atrial flutter
Like atrial fibrillation, treatment options for atrial flutter involve either controlling the ventricular rate or attempting to restore and maintain sinus rhythm. However, atrial flutter generally responds less well to drug treatment than atrial fibrillation. 

Control of the ventricular rate is usually an interim measure pending restoration of sinus rhythm. Ventricular rate can be controlled by administration of a beta-blocker, diltiazem hydrochloride p. 149 [unlicensed indication], or verapamil hydrochloride p. 156; an intravenous beta-blocker or verapamil hydrochloride is preferred for rapid control. Digoxin p. 94 can be added if rate control remains inadequate, and may be particularly useful in those with heart failure.

Conversion to sinus rhythm can be achieved by electrical cardioversion (by cardiac pacing or direct current), pharmacological cardioversion, or catheter ablation. If the duration of atrial flutter is unknown, or it has lasted for over 48 hours, cardioversion should not be attempted until the patient has been fully anticoagulated for at least 3 weeks; if this is not possible, parenteral anticoagulation should be commenced and a left atrial thrombus ruled out immediately before cardioversion; oral anticoagulation should be given after cardioversion and continued for at least 4 weeks.

Direct current cardioversion is usually the treatment of choice when rapid conversion to sinus rhythm is necessary (e.g. when atrial flutter is associated with haemodynamic compromise); catheter ablation is preferred for the treatment of recurrent atrial flutter. There is a limited role for anti-arrhythmic drugs as their use is not always successful. Flecainide acetate p. 91 or propafenone hydrochloride p. 92 can slow atrial flutter, resulting in 1:1 conduction to the ventricles, and should therefore be prescribed in conjunction with a ventricular rate controlling drug such as a beta-blocker, diltiazem hydrochloride p. 149 [unlicensed indication], or verapamil hydrochloride p. 156. Amiodarone hydrochloride p. 88 can be used when other drug treatments are contra-indicated or ineffective.

All patients should be assessed for their risk of stroke and the need for thromboprophylaxis; the choice of anticoagulant is based on the same criteria as for atrial fibrillation.

Paroxysmal supraventricular tachycardia
This will often terminate spontaneously or with reflex vagal stimulation such as a Valsalva manoeuvre, immersing the face in ice-cold water, or carotid sinus massage; such manoeuvres should be performed with ECG monitoring. If the effects of reflex vagal stimulation are transient or ineffective, or if the arrhythmia is causing severe symptoms, intravenous adenosine p. 87 should be given. If adenosine is ineffective or contra-indicated, intravenous verapamil hydrochloride p. 156 is an alternative, but it should be avoided in patients recently treated with beta-blockers.

Failure to terminate paroxysmal supraventricular tachycardia with reflex vagal stimulation or drug treatment may suggest an arrhythmia of atrial origin, such as focal atrial tachycardia or atrial flutter.

Treatment with direct current cardioversion is needed in haemodynamically unstable patients or when the above measures have failed to restore sinus rhythm (and an alternative diagnosis has not been found). Recurrent episodes of paroxysmal supraventricular tachycardia can be treated by catheter ablation, or prevented with drugs such as diltiazem hydrochloride p. 149, verapamil hydrochloride p. 156, beta-blockers including sotalol hydrochloride p. 93, flecainide acetate p. 91 or propafenone hydrochloride p. 92.
Arrhythmias after myocardial infarction

In patients with a paroxysmal tachycardia or rapid irregularity of the pulse it is best not to administer an anti-arrhythmic until an ECG record has been obtained. Bradycardia, particularly if complicated by hypotension, should be treated with an intravenous dose of atropine sulfate p. 949 the dose may be repeated if necessary. If there is a risk of asystole, or if the patient is unstable and has failed to respond to atropine sulfate, adrenaline/epinephrine p. 196 should be given by intravenous infusion, and the dose adjusted according to response.

For further advice, refer to the most recent recommendations of the Resuscitation Council (UK) available at www.resus.org.uk.

Ventricular tachycardia

Pulseless ventricular tachycardia or ventricular fibrillation should be treated with immediate defibrillation (see Cardiopulmonary resuscitation).

Patients with unstable sustained ventricular tachycardia, who continue to deteriorate with signs of hypotension or reduced cardiac output, should receive direct current cardioversion to restore sinus rhythm. If this fails, intravenous amiodarone hydrochloride p. 88 should be administered and direct current cardioversion repeated.

For episodes of sustained ventricular tachycardia who are haemodynamically stable can be treated with intravenous anti-arrhythmic drugs. Amiodarone hydrochloride is the preferred drug. Flecainide acetate p. 91, propafenone hydrochloride p. 92, and, although less effective, lidocaine hydrochloride p. 91 have all been used. If sinus rhythm is not restored, direct current cardioversion or pacing should be considered. Catheter ablation is an alternative if cessation of the arrhythmia is not urgent. Non-sustained ventricular tachycardia can be treated with a beta-blocker.

All patients presenting with ventricular tachycardia should be referred to a specialist. Following restoration of sinus rhythm, patients who remain at high risk of cardiac arrest will require maintenance therapy. Most patients will be treated with an implantable cardioverter defibrillator. Beta-blockers or sotalol hydrochloride p. 93 (in place of a standard beta-blocker), or amiodarone hydrochloride (in combination with a standard beta-blocker), can be used in addition to the device in some patients; alternatively, they can be used alone when use of an implantable cardioverter defibrillator is not appropriate.

Torsade de points

*Torsade de points* is a form of ventricular tachycardia associated with a long QT syndrome (usually drug-induced, but other factors including hypokalaemia, severe bradycardia, and genetic predisposition are also implicated). Episodes are usually self-limiting, but are frequently recurrent and can cause impairment or loss of consciousness. If not controlled, the arrhythmia can progress to ventricular fibrillation and sometimes death. Intravenous infusion of magnesium sulfate p. 858 is usually effective. A beta-blocker (but not sotalol hydrochloride p. 93) and atrial (or ventricular) pacing can be considered. Anti-arrhythmics can further prolong the QT interval, thus worsening the condition.

Drugs for arrhythmias

Anti-arrhythmic drugs can be classified clinically into those that act on supraventricular arrhythmias (e.g. verapamil hydrochloride p. 156), those that act on both supraventricular and ventricular arrhythmias (e.g. amiodarone hydrochloride p. 88), and those that act on ventricular arrhythmias (e.g. lidocaine hydrochloride p. 91).

Anti-arrhythmic drugs can also be classified according to their effects on the electrical behaviour of myocardial cells during activity (the Vaughan Williams classification) although this classification is of less clinical significance:

- **Class I**: membrane stabilising drugs (e.g. lidocaine, flecainide)
- **Class II**: beta-blockers
- **Class III**: amiodarone, sotalol (also Class II)
- **Class IV**: calcium-channel blockers (includes verapamil but not dicypropiridines)

The negative inotropic effects of anti-arrhythmic drugs tend to be additive. Therefore special care should be taken if two or more are used, especially if myocardial function is impaired. Most drugs that are effective in countering arrhythmias can also provoke them in some circumstances; moreover, hypokalaemia enhances the arrhythmogenic (pro-arrhythmic) effect of many drugs.

Supraventricular arrhythmias

Adenosine p. 87 is usually the treatment of choice for terminating paroxysmal supraventricular tachycardia. As it has a very short duration of action (half-life only about 8 to 10 seconds, but prolonged in those taking dipyridamole p. 107), most side-effects are short lived. Unlike verapamil hydrochloride p. 156, adenosine can be used after a beta-blocker. Verapamil hydrochloride may be preferable to adenosine in asthma.

Oral administration of a *cardiac glycoside* (such as digoxin p. 94) slows the ventricular response in cases of atrial fibrillation and atrial flutter. However, intravenous infusion of digoxin is rarely effective for rapid control of ventricular rate. Cardiac glycosides are contra-indicated in supraventricular arrhythmias associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome).

Verapamil hydrochloride is usually effective for supraventricular tachycardias. An initial intravenous dose (important: serious beta-blocker interaction hazard) may be followed by oral treatment; hypotension may occur with large doses. It should not be used for tachyarrhythmias where the QRS complex is wide (i.e. broad complex) unless a supraventricular origin has been established beyond reasonable doubt. It is also contra-indicated in atrial fibrillation or atrial flutter associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome). It should not be used in children with arrhythmias without specialist advice; some supraventricular arrhythmias in childhood can be accelerated by verapamil hydrochloride with dangerous consequences.

Intravenous administration of a *beta-blocker* such as esmolol hydrochloride p. 143 or propranolol hydrochloride p. 146, can achieve rapid control of the ventricular rate.

Drugs for both supraventricular and ventricular arrhythmias include amiodarone hydrochloride p. 88, *beta-blockers*, disopyramide p. 89, flecainide acetate p. 91, *procainamide* (available from ‘special-order’ manufacturers or specialist importing companies), and propafenone hydrochloride p. 92.

Supraventricular and ventricular arrhythmias

Amiodarone hydrochloride is used in the treatment of arrhythmias, particularly when other drugs are ineffective or contra-indicated. It can be used for paroxysmal supraventricular, nodal and ventricular tachycardias, atrial fibrillation and flutter, and ventricular fibrillation. It can also be used for tachyarrhythmias associated with Wolff-Parkinson-White syndrome. It should be initiated only under hospital or specialist supervision. Amiodarone hydrochloride may be given by intravenous infusion as well as by mouth, and has the advantage of causing little or no myocardial depression. Unlike oral amiodarone hydrochloride, intravenous amiodarone hydrochloride acts relatively rapidly.

Intravenous injection of amiodarone hydrochloride can be used in cardiopulmonary resuscitation for ventricular
fibrillation or pulseless tachycardia unresponsive to other interventions.

Amiodarone hydrochloride has a very long half-life (extending to several weeks) and only needs to be given once daily (but high doses can cause nausea unless divided). Many weeks or months may be required to achieve steady-state plasma-amiodarone concentration; this is particularly important when drug interactions are likely. **Beta-blockers** act as anti-arrhythmic drugs principally by attenuating the effects of the sympathetic system on automaticity and conductivity within the heart. Sotalol hydrochloride p. 93 has a role in the management of ventricular arrhythmias.

Disopyramide p. 89 can be given by intravenous injection to control arrhythmias after myocardial infarction (including those not responding to lidocaine hydrochloride p. 91), but it impairs cardiac contractility. Oral administration of disopyramide is useful, but it has an antimuscarinic effect which limits its use in patients susceptible to angle-closure glaucoma or with prostatic hyperplasia.

Flecainide acetate p. 91 belongs to the same general class as lidocaine hydrochloride p. 91 and may be of value for serious symptomatic ventricular arrhythmias. It may also be indicated for junctional re-entry tachycardias and for paroxysmal atrial fibrillation. However, it can precipitate serious arrhythmias in a small minority of patients (including those with otherwise normal hearts).

Propafenone hydrochloride p. 92 is used for the prophylaxis and treatment of ventricular arrhythmias and also for some supraventricular arrhythmias. It has complex mechanisms of action, including weak beta-blocking activity (therefore caution is needed in obstructive airways disease—contra-indicated if severe).

Drugs for supraventricular arrhythmias include adenosine below, **cardiac glycosides**, and verapamil hydrochloride p. 156. Drugs for ventricular arrhythmias include lidocaine hydrochloride.

Mexiteline and procainamide are both available from ‘special-order’ manufacturers or specialist importing companies. Mexiteline can be used for life-threatening ventricular arrhythmias; procainamide is given by intravenous injection to control ventricular arrhythmias.

**Ventricular arrhythmias**

Intravenous lidocaine hydrochloride can be used for the treatment of ventricular tachycardia in haemodynamically stable patients, and ventricular fibrillation and pulseless ventricular tachycardia in cardiac arrest refractory to defibrillation, however it is no longer the anti-arrhythmic drug of first choice.

Drugs for both supraventricular and ventricular arrhythmias include amiodarone hydrochloride, **beta-blockers**, disopyramide, flecainide acetate, **procainamide** (available from ‘special-order’ manufacturers or specialist importing companies), and propafenone hydrochloride.

**Mexiteline** is available from ‘special-order’ manufacturers or specialist importing companies for treatment of life-threatening ventricular arrhythmias.  

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**ANTIARRHYTHMICS**

**Adenosine**

**INDICATIONS AND DOSE**

**Rapid reversion to sinus rhythm of paroxysmal supraventricular tachycardias, including those associated with accessory conducting pathways (e.g. Wolf-Parkinson-White syndrome)** | **Used to aid to diagnosis of broad or narrow complex supraventricular tachycardias**

**BY RAPID INTRAVENOUS INJECTION**

- Adult: Initially 6 mg, administer into central or large peripheral vein and give over 2 seconds, cardiac monitoring required, followed by 12 mg after 1–2 minutes if required, then 12 mg after 1–2 minutes if required, increments should not be given if high level AV block develops at any particular dose.

**Rapid reversion to sinus rhythm of paroxysmal supraventricular tachycardias, including those associated with accessory conducting pathways (e.g. Wolf-Parkinson-White syndrome) in patients with a heart transplant** | **Aid to diagnosis of broad or narrow complex supraventricular tachycardias in patients with a heart transplant**

**BY RAPID INTRAVENOUS INJECTION**

- Adult: Initially 3 mg, administer into a central or large peripheral vein and give over 2 seconds, followed by 6 mg after 1–2 minutes if required, then 12 mg after 1–2 minutes if required, patients with a heart transplant are very sensitive to the effects of adenosine

**Used in conjunction with radionuclide myocardial perfusion imaging in patients who cannot exercise adequately or for whom exercise is inappropriate**

**BY INTRAVENOUS INFUSION**

- Adult: (consult product literature)

**Dose adjustments due to interactions**

If essential to give with dipyridamole reduce adenosine dose to a quarter of the usual dose.

**UNLICENSED USE** Adenosine doses in the BNF may differ from those in the product literature.

**CONTRA-INDICATIONS** Asthma; chronic obstructive lung disease; decompenated heart failure; long QT syndrome; second- or third-degree AV block and sick sinus syndrome (unless pacemaker fitted); severe hypertension.

**CAUTIONS** Atrial fibrillation with accessory pathway (conduction down anomalous pathway may increase) - atrial flutter with accessory pathway (conduction down anomalous pathway may increase) - autonomic dysfunction - bundle branch block - first-degree AV block - heart transplant - left main coronary artery stenosis - left to right shunt - pericardial effusion - pericarditis - QT-interval prolongation - recent myocardial infarction - severe heart failure - stenotic carotid artery disease with cerebrovascular insufficiency - stenotic valvar heart disease - uncorrected hypovolaemia

**INTERACTIONS**

- Appendix 1 (adenosine); also possibility of interaction with drugs tending to impair myocardial conduction.

**SIDE-EFFECTS**

- **Common or very common** Angina (discontinue) - apprehension - arrhythmia (discontinue if asystole or severe bradycardia occur) - AV block - dizziness - dyspnoea - flushing - headache - nausea - sinus pause.

- **Uncommon** Blurred vision - hyperventilation - metallic taste - palpitation - sweating - weakness.

- **Very rare** Bronchospasm - injection-site reactions - transient worsening of intracranial hypertension.

- **Frequency not known** Cardiac arrest - convulsions - hypotension (discontinue if severe) - respiratory failure (discontinue) - syncope - vomiting.
CARDIOVASCULAR SYSTEM

CONTRA-INDICATIONS

MONITORING REQUIREMENTS

BREAST FEEDING

PREGNANCY

SPECIFIC CONTRA-INDICATIONS

With intravenous use Avoid bolus injection in cardiomyopathy - avoid bolus injection in congestive heart failure - avoid in circulatory collapse - avoid in severe arterial hypotension - avoid in severe respiratory failure

CAUTIONS

GENERAL CAUTIONS

Acute porphyrias p. 864 - conduction disturbances (in excessive dosage) - elderly - heart failure - hypokalaemia - severe bradycardia (in excessive dosage)

SPECIAL CAUTIONS

With intravenous use Moderate and transient fall in blood pressure (circulatory collapse precipitated by rapid administration or overdosage) - severe hepatocellular toxicity

INTERACTIONS ➔ Appendix 1 (amiodarone). Amiodarone has a long half-life; there is a potential for drug interactions to occur for several weeks (or even months) after treatment with it has been stopped. Use extreme caution or avoid concomitant use of drugs that prolong QT interval. Risk of severe bradycardia or heart block when amiodarone is used in combination with sofosbuvir and daclatasvir for hepatitis C.

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

Common or very common Bradycardia - hyperthyroidism - hypothyroidism - jaundice - nausea - persistent slate grey skin discoloration - phototoxicity - pulmonary toxicity (including pneumonitis and fibrosis) - raised serum transaminases (may require dose reduction or withdrawal if accompanied by acute liver disorders) - reversible corneal microdeposits (sometimes with night glare) - sleep disorders - taste disturbances - tremor - vomiting

Uncommon Conduction disturbances - onset or worsening of arrhythmia - peripheral myopathy (usually reversible on withdrawal) - peripheral neuropathy (usually reversible on withdrawal)

Very rare Alopecia - aplastic anaemia - ataxia - benign intracranial hypertension - bronchospasm (in patients with severe respiratory failure) - chronic liver disease - cirrhosis - epididymo-orchitis - exfoliative dermatitis - haemolytic anaemia - headache - hypersensitivity - impaired vision due to optic neuritis or optic neuropathy (including blindness) - impotence - rash - sinus arrest - thrombocytopenia - vasculitis - vertigo

Frequency not known Hot flushes - hypotension - respiratory distress syndrome - sweating

SPECIFIC SIDE-EFFECTS

Common or very common With intravenous use injection-site reactions

Very rare

With intravenous use anaphylaxis on rapid injection

SIDE-EFFECTS, FURTHER INFORMATION

Corneal microdeposits Most patients taking amiodarone develop corneal microdeposits (reversible on withdrawal of treatment); these rarely interfere with vision, but drivers may be dazzled by headlights at night. However, if vision is impaired or if optic neuritis or optic neuropathy occur, amiodarone must be stopped to prevent blindness and expert advice sought.

Thyroid function Amiodarone contains iodine and can cause disorders of thyroid function; both hypothyroidism and hyperthyroidism can occur. Thyrotoxicosis may be very refractory, and amiodarone should usually be withdrawn at least temporarily to help achieve control; treatment with carbimazole may be required. Hypothyroidism can be treated with replacement therapy without withdrawing amiodarone if it is essential; careful supervision is required.

Hepatotoxicity Amiodarone is also associated with hepatotoxicity and treatment should be discontinued if

88 Arrhythmias

BNF 70

Medicinal Forms

There can be variation in the licensing of different medicines containing the same drug. Foremost available from special-order manufacturers include: solution for injection, solution for infusion, infusion

Solution for injection

ELECTROLYTES: May contain Sodium

> ADENOSINE (Non-proprietary)

Adenosine 3 mg per 1 ml Adenosine 6mg/2ml solution for injection vials | 6 vial | £22.00–£29.24 (Hospital only)

Adenoscan (Sanofi)

Adenosine 3 mg per 1 ml Adenoscan 6mg/ml solution for injection vials | 6 vial | £29.94 (Hospital only)

Solution for infusion

ELECTROLYTES: May contain Sodium

> ADENOSINE (Non-proprietary)

Adenosine 3 mg per 1 ml Adenosine 30mg/10ml solution for infusion vials | 6 vial | £65.00–£85.57 (Hospital only)

> Adenoscan (Sanofi)

Adenoscan 3mg/1ml solution for infusion vials | 6 vial | £65.57

Amiodarone hydrochloride

INDICATIONS AND DOSE

Treatment of arrhythmias, particularly when other drugs are ineffective or contra-indicated (including paroxysmal supraventricular, nodal and ventricular tachycardias, atrial fibrillation and flutter, ventricular fibrillation, and tachyarrhythmias associated with Wolff-Parkinson-White syndrome) (initiated in hospital or under specialist supervision)

BY MOUTH

Adult: 200 mg 3 times a day for 1 week, then reduced to 200 mg twice daily for a further week, following by maintenance dose, usually 200 mg daily or the minimum dose required to control arrhythmia

BY INTRAVENOUS INFUSION

Adult: Initially 5 mg/kg, to be given over 20–120 minutes with ECG monitoring, subsequent infusions given if necessary according to response; maximum 1.2 g per day

Ventricular fibrillation or pulseless ventricular tachycardia refractory to defibrillation initially by intravenous injection

Adult: Initially 300 mg, dose to be considered after administration of adrenaline, dose should be given from a pre-filled syringe or diluted in 20 ml Glucose 5%, then (by intravenous injection) 150 mg if required, followed by (by intravenous infusion) 900 mg/24 hours

CONTRA-INDICATIONS

GENERAL CONTRA-INDICATIONS

Avoid in severe conduction disturbances (unless pacemaker fitted) - avoid in sinus node disease (unless pacemaker fitted) - iodine sensitivity - sino-atrial heart block (except in cardiac arrest) - sinus bradycardia (except in cardiac arrest) - thyroid dysfunction

SPECIFIC CONTRA-INDICATIONS

With intravenous use Avoid bolus injection in cardiomyopathy - avoid bolus injection in congestive heart failure - avoid in circulatory collapse - avoid in severe arterial hypotension - avoid in severe respiratory failure

CAUTIONS

GENERAL CAUTIONS

Acute porphyrias p. 864 - conduction disturbances (in excessive dosage) - elderly - heart failure - hypokalaemia - severe bradycardia (in excessive dosage)

SPECIAL CAUTIONS

With intravenous use Moderate and transient fall in blood pressure (circulatory collapse precipitated by rapid administration or overdosage) - severe hepatocellular toxicity

INTERACTIONS ➔ Appendix 1 (amiodarone). Amiodarone has a long half-life; there is a potential for drug interactions to occur for several weeks (or even months) after treatment with it has been stopped. Use extreme caution or avoid concomitant use of drugs that prolong QT interval. Risk of severe bradycardia or heart block when amiodarone is used in combination with sofosbuvir and daclatasvir for hepatitis C.

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

Common or very common Bradycardia - hyperthyroidism - hypothyroidism - jaundice - nausea - persistent slate grey skin discoloration - phototoxicity - pulmonary toxicity (including pneumonitis and fibrosis) - raised serum transaminases (may require dose reduction or withdrawal if accompanied by acute liver disorders) - reversible corneal microdeposits (sometimes with night glare) - sleep disorders - taste disturbances - tremor - vomiting

Uncommon Conduction disturbances - onset or worsening of arrhythmia - peripheral myopathy (usually reversible on withdrawal) - peripheral neuropathy (usually reversible on withdrawal)

Very rare Alopecia - aplastic anaemia - ataxia - benign intracranial hypertension - bronchospasm (in patients with severe respiratory failure) - chronic liver disease - cirrhosis - epididymo-orchitis - exfoliative dermatitis - haemolytic anaemia - headache - hypersensitivity - impaired vision due to optic neuritis or optic neuropathy (including blindness) - impotence - rash - sinus arrest - thrombocytopenia - vasculitis - vertigo

Frequency not known Hot flushes - hypotension - respiratory distress syndrome - sweating

SPECIFIC SIDE-EFFECTS

Common or very common With intravenous use injection-site reactions

Very rare

With intravenous use anaphylaxis on rapid injection

SIDE-EFFECTS, FURTHER INFORMATION

Corneal microdeposits Most patients taking amiodarone develop corneal microdeposits (reversible on withdrawal of treatment); these rarely interfere with vision, but drivers may be dazzled by headlights at night. However, if vision is impaired or if optic neuritis or optic neuropathy occur, amiodarone must be stopped to prevent blindness and expert advice sought.

Thyroid function Amiodarone contains iodine and can cause disorders of thyroid function; both hypothyroidism and hyperthyroidism can occur. Thyrotoxicosis may be very refractory, and amiodarone should usually be withdrawn at least temporarily to help achieve control; treatment with carbimazole may be required. Hypothyroidism can be treated with replacement therapy without withdrawing amiodarone if it is essential; careful supervision is required.

Hepatotoxicity Amiodarone is also associated with hepatotoxicity and treatment should be discontinued if
severe liver function abnormalities or clinical signs of liver disease develop.

**Pulmonary toxicity** Pneumonitis should always be suspected if new or progressive shortness of breath or cough develops in a patient taking amiodarone.

**Peripheral neuropathy** Fresh neurological symptoms should raise the possibility of peripheral neuropathy.

- **PREGNANCY** Possible risk of neonatal goitre; use only if no alternative.

- **BREAST FEEDING** Avoid; present in milk in significant amounts; theoretical risk of neonatal hypothyroidism from release of iodine.

- **MONITORING REQUIREMENTS**
  - Thyroid function tests should be performed before treatment and then every 6 months. Clinical assessment of thyroid function alone is unreliable. Thyroxine (T<sub>4</sub>) may be raised in the absence of hyperthyroidism; therefore tri-iodothyronine (T<sub>3</sub>), T<sub>4</sub>, and thyroid-stimulating hormone (thyrotrophin, TSH) should all be measured. A raised T<sub>3</sub> and T<sub>4</sub> with a very low or undetectable TSH concentration suggests the development of thyrotoxicosis.
  - Liver function tests required before treatment and then every 6 months.
  - Serum potassium concentration should be measured before treatment.
  - Chest x-ray required before treatment.
  - If concomitant use of amiodarone with sofosbuvir and daclatasvir cannot be avoided because other anti-arrhythmics are not tolerated or contraindicated, patients should be closely monitored, particularly during the first weeks of treatment.
  - Patients at high risk of bradycardia should be monitored continuously for 48 hours in an appropriate clinical setting after starting concomitant treatment.
  - Patients who have stopped amiodarone within the last few months and need to start sofosbuvir and daclatasvir should be monitored.
  - With intravenous use ECG monitoring and resuscitation facilities must be available. Monitor liver transaminases closely.

- **DIRECTIONS FOR ADMINISTRATION**
  - With intravenous use For *intravenous infusion (Cordarone X®)*, give continuously or intermittently in Glucose 5%. Suggested initial infusion volume 250 ml given over 20~120 minutes; for repeat infusions up to 1.2 g in max. 500 ml; should not be diluted to less than 600 micrograms/mL. See cardio-pulmonary resuscitation for details of infusion in extreme emergency. Incompatible with Sodium Chloride infusion fluids; avoid equipment containing the plasticizer di-2-ethylhexylphthalate (DEHP).
  - With oral use For administration by *mouth*, tablets may be crushed and dispersed in water; injection solution should not be given orally (irritant).

- **PATIENT AND CARER ADVICE** Because of the possibility of phototoxic reactions, patients should be advised to shield the skin from light during treatment and for several months after discontinuing amiodarone; a wide-spectrum sunscreen to protect against both long-wave ultraviolet and visible light should be used. If taking amiodarone with sofosbuvir and daclatasvir, patients and their carers should be told how to recognise signs and symptoms of bradycardia and heart block and advised to seek immediate medical attention if symptoms such as shortness of breath, light-headedness, palpitations, fainting, unusual tiredness or chest pain develop.

### Disopyramide

**INDICATIONS AND DOSE**

Prevention and treatment of ventricular and supraventricular arrhythmias, including after myocardial infarction | Maintenance of sinus rhythm after cardioversion

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

- Adult: 300–800 mg daily in divided doses

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

- Adult: 250–375 mg every 12 hours

**CONTRA-INDICATIONS** Bundle-branch block associated with first-degree AV block - second- and third-degree AV block or bifascicular block (unless pacemaker fitted) - severe heart failure (unless secondary to arrhythmia) - severe sinus node dysfunction

**CAUTIONS** Atrial flutter or atrial tachycardia with partial block - avoid in Acute porphyrias p. 864 - elderly - heart failure (avoid if severe) - myasthenia gravis - prostatic enlargement - structural heart disease - susceptibility to angle-closure glaucoma

**INTERACTIONS** → Appendix 1 (disopyramide).

**SIDE-EFFECTS** Angle-closure glaucoma - antimuscarinic effects - AV block - blurred vision - cholestatic jaundice - dry mouth - gastro-intestinal irritation - hypoglycaemia - hypotension - myocardial depression - psychosis - urinary retention - ventricular tachycardia, ventricular fibrillation or torsade de pointes (usually associated with prolongation of QRS complex or QT interval)

**PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk; may induce labour if used in third trimester.

**BREAST FEEDING** Present in milk—use only if essential. Monitor infant for antimuscarinic effects.

**HEPATIC IMPAIRMENT** Half-life prolonged—may need dose reduction. Avoid modified-release preparation.

**RENAL IMPAIRMENT** Reduce dose by increasing dose interval; adjust according to response. Avoid modified-release preparation.
Dronedarone

**DRUG ACTION** Dronedarone is a multi-channel blocking anti-arrhythmic drug.

**INDICATIONS AND DOSE**

Maintenance of sinus rhythm after cardioversion in clinically stable patients with paroxysmal or persistent atrial fibrillation, when alternative treatments are unsuitable (initiated under specialist supervision)

**BY MOUTH**
- Adult: 400 mg twice daily

**CONTRA-INDICATIONS** Atrial conduction defects - bradycardia - complete bundle branch block - distal block - existing or previous heart failure or left ventricular systolic dysfunction - haemodynamically unstable patients - liver toxicity associated with previous amiodarone use - permanent atrial fibrillation - prolonged QT interval - second- or third-degree AV block - sick sinus syndrome (unless pacemaker fitted) - sinus node dysfunction

**CAUTIONS** Coronary artery disease - correct hypokalaemia and hypomagnesaemia before starting and during treatment

**INTERACTIONS** → Appendix 1 (dronedarone).

**SIDE-EFFECTS**
- Common or very common: Bradycardia - gastro-intestinal disturbances - heart failure - malaise - pruritus - QT-interval prolongation - raised serum creatinine - rash
- Uncommon: Dermatitis - eczema - erythema - interstitial lung disease (investigate if symptoms such as dyspnoea or dry cough develop and discontinue treatment if confirmed) - photosensitivity - pneumonitis (investigate if symptoms such as dyspnoea or dry cough develop and discontinue treatment if confirmed) - pulmonary fibrosis (investigate if symptoms such as dyspnoea or dry cough develop and discontinue treatment if confirmed) - taste disturbance
- Rare: Liver injury (including life-threatening acute liver failure)

**SIDE-EFFECTS, FURTHER INFORMATION**

**Liver injury** Liver injury, including life-threatening acute liver failure reported rarely; discontinue treatment if 2 consecutive alanine aminotransferase concentrations exceed 3 times upper limit of normal.

**MONITORING REQUIREMENTS**
- Monitor for hypotension, hypoglycaemia, ventricular tachycardia, ventricular fibrillation or torsade de pointes (discontinue if occur).
- Monitor serum potassium.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension, tablet containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension, tablet containing the same drug.

- **Modified-release tablet**
  - CAUTIONARY AND ADVISORY LABELS 25
    - Rythmodan Retard (Sanofi)
      - Disopyramide (as Disopyramide phosphate) 250 mg Rythmodan Retard 250mg tablets | 60 tablet [PBR] £32.08 DT price = £32.08
    - DISOPYRAMIDE (Non-proprietary)
      - Disopyramide 100 mg Disopyramide 100mg capsules | 84 capsule [PBR] £25.00 DT price = £22.09
      - Disopyramide 150 mg Disopyramide 150mg capsules | 84 capsule [PBR] £33.40 DT price = £27.58
    - Rythmodan (Sanofi)
      - Disopyramide 100 mg Rythmodan 100mg capsules | 84 capsule [PBR] £14.14 DT price = £22.09

**DISOPYRAMIDE (Non-proprietary)**

- **Rythmodan**
- **Rythmodan Retard**
  - 25

**HEPATIC IMPAIRMENT** Avoid in severe impairment.

**RENAL IMPAIRMENT** Avoid if eGFR less than 30 mL/minute/1.73 m².

**MONITORING REQUIREMENTS**
- Ongoing monitoring should occur under specialist supervision.
- Monitor for heart failure.
- Perform ECG at least every 6 months—consider discontinuation if atrial fibrillation reoccurs.
- Measure serum creatinine before treatment and 7 days after initiation—if raised, measure again after a further 7 days and consider discontinuation if creatinine continues to rise.
- Monitor liver function before treatment, 1 week and 1 month after initiation of treatment, then monthly for 6 months, then every 3 months for 6 months and periodically thereafter.

**PATIENT AND CARER ADVICE**

Heart failure Patients or their carers should be told how to recognise signs of heart failure and advised to seek prompt medical attention if symptoms such as weight gain, dependent oedema, or dyspnoea develop or worsen.

Hepatic disorders Patients or their carers should be told how to recognise signs of liver disorder and advised to seek prompt medical attention if symptoms such as abdominal pain, anorexia, nausea, vomiting, fever, malaise, itching, dark urine, or jaundice develop.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- **Dronedarone for the treatment of non-permanent atrial fibrillation (December 2012) NICE TA197**
  - Dronedarone is an option for the maintenance of sinus rhythm after successful cardioversion in paroxysmal or persistent atrial fibrillation which is not controlled by first-line therapy (usually including beta-blockers), and after alternative options have been considered in patients:
  - who have at least 1 of the following cardiovascular risk factors: hypertension requiring drugs of at least 2 different classes, diabetes mellitus, previous transient ischaemic attack, stroke or systemic embolism, left atrial diameter of 50 mm or greater, or age 70 years or older and
  - who do not have left ventricular systolic dysfunction nor a history of, or current, heart failure
  - Patients who do not meet the above criteria who are currently receiving dronedarone should have the option to continue treatment until they and their clinicians consider it appropriate to stop. www.nice.org.uk/TA197

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS 21**
  - DRONEDARONE (Non-proprietary)
    - Dronedarone (as Dronedarone hydrochloride) 400 mg Dronedarone 400mg tablets | 60 tablet [PBR] no price available
    - Multaq (Sanofi)
      - Dronedarone (as Dronedarone hydrochloride) 400 mg Multaq 400mg tablets | 20 tablet [PBR] £22.50 | 60 tablet [PBR] £67.50

**Arrhythmias**
Flecainide acetate

**INDICATIONS AND DOSE**

AV nodal reciprocating tachycardia, arrhythmias associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome), disabling symptoms of paroxysmal atrial fibrillation in patients without left ventricular dysfunction (arrhythmias of recent onset will respond more readily) (specialist supervision in hospital) | Ventricular tachyarrhythmias resistant to other treatment (specialist supervision in hospital)

**INITIALLY BY SLOW INTRAVENOUS INJECTION**
- **Adult:** Initially 2 mg/kg (max. per dose 150 mg), to be given over 10–30 minutes with ECG monitoring, followed by (by intravenous infusion) 1.5 mg/kg/hour if required for 1 hour, then (by intravenous infusion) reduced to 100–250 micrograms/kg/hour for up to 24 hours, maximum cumulative dose of 600 mg in first 24 hours, then transfer to oral treatment

**Supraventricular arrhythmias**

**INITIALLY BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
- **Adult:** Initially 50 mg twice daily, (by mouth) increased if necessary up to 300 mg daily
- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
- **Adult:** 200 mg daily

**Ventricular arrhythmias (initiated under direction of hospital consultant)**
- **Adult:** Initially 100 mg twice daily for 3–5 days, maximum 400 mg daily reserved for rapid control or in heavily built patients, then (by mouth) maintenance, reduce to the lowest dose that controls the arrhythmia

**Dose equivalence and conversion**

Patients stabilised on 200 mg daily immediate-release flecainide may be transferred to modified-release medicines.

**UNLICENSED USE**

Capsules, tablets and injections: AV nodal reciprocating tachycardia, arrhythmias associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome), disabling symptoms of paroxysmal atrial fibrillation in patients without left ventricular dysfunction (arrhythmias of recent onset will respond more readily). Immediate-release tablets only: symptomatic sustained ventricular tachycardia, disabling symptoms of pre- mature ventricular contractions or non-sustained ventricular tachycardia in patients resistant to or intolerant of other therapy. Injection only: ventricular tachyarrhythmias resistant to other treatment.

**CONTRA-INDICATIONS**

Abnormal left ventricular function - atrial conduction defects (unless pacing rescue available) - bundle branch block (unless pacing rescue available) - control of arrhythmias in acute situations (for modified-release forms only) - distal block (unless pacing rescue available) - haemodynamically significant valvular heart disease - heart failure - history of myocardial infarction and either asymptomatic ventricular ectopics or asymptomatic non-sustained ventricular tachycardia - long-standing atrial fibrillation where conversion to sinus rhythm not attempted - second-degree or greater AV block (unless pacing rescue available) - sinus node dysfunction (unless pacing rescue available)

**CAUTIONS**

Atrial fibrillation following heart surgery - elderly (accumulation may occur) - patients with pacemakers (especially those who may be pacemaker dependent because stimulation threshold may rise appreciably)

**INTERACTIONS**

> Appendix 1 (flecainide).

**SIDE-EFFECTS**

- **Common or very common** Asthenia - dizziness - dyspnoea - fatigue - fever - oedema - pro-arrhythmic effects - visual disturbances
- **Rare** Amnesia - confusion - convulsions - depression - dyskinesia - hallucinations - peripheral neuropathy - pneumonitis
- **Frequency not known** Anaemia - anorexia - anxiety - ataxia - corneal deposits - drowsiness - flushing - gastrointestinal disturbances - headache - hepatic dysfunction - hypersensitivity reactions - increased antinuclear antibodies - increased sweating - insomnia - leucopenia - paraesthesia - photosensitivity - rash - syncope - thrombocytopenia - tinnitus - tremor - urticaria - vertigo

**PREGNANCY**

Used in pregnancy to treat maternal and fetal arrhythmias in specialist centres; toxicity reported in animal studies; infant hyperbilirubinaemia also reported.

**BREAST FEEDING**

Significant amount present in milk but not known to be harmful.

**HEPATIC IMPAIRMENT**

Avoid or reduce dose in severe impairment.

**RENAL IMPAIRMENT**

Reduce initial oral dose to max. 100 mg daily or reduce intravenous dose by 50%, if eGFR less than 35 mL/minute/1.73 m².

**MONITORING REQUIREMENTS**

With intravenous use ECG monitoring and resuscitation facilities must be available.

**DIRECTIONS FOR ADMINISTRATION**

For intravenous infusion (Tambocor®), give continuously or intermittently in Glucose 5% or Sodium Chloride 0.9%. Minimum volume in infusion fluids containing chlorides 500 mL.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

- **FLECAINIDE ACETATE (Non-proprietary)**
  - Flecainide acetate 50 mg Flecainide 50mg tablets | 60 tablet [PDR] £19.50 DT price = £3.25
  - Flecainide acetate 100 mg Flecainide 100mg tablets | 60 tablet [PDR] £20.00 DT price = £4.96
  - Tambocor (Meda Pharmaceuticals Ltd)
  - Flecainide acetate 50 mg Tambocor 50mg tablets | 60 tablet [PDR] £11.57 DT price = £3.52
  - Flecainide acetate 100 mg Tambocor 100mg tablets | 60 tablet [PDR] £16.53 DT price = £4.96
  - Modified-release capsule

**CAUTIONARY AND ADVISORY LABELS**

25
- Tambocor XL (Meda Pharmaceuticals Ltd)
  - Flecainide acetate 200 mg Tambocor XL 200mg capsules | 30 capsule [PDR] £14.77

**Solution for injection**

- Tambocor (Meda Pharmaceuticals Ltd)
  - Flecainide acetate 10 mg per 1 ml Tambocor 150mg/15ml solution for injection ampoules | 3 ampoule [PDR] £21.99

Lidocaine hydrochloride

(Lignocaine hydrochloride)

**INDICATIONS AND DOSE**

Cardiopulmonary resuscitation (as an alternative if amiodarone is not available)

**BY INTRAVENOUS INJECTION**
- **Adult:** 1 mg/kg, do not exceed 3 mg/kg over the first hour

continued
Ventricular arrhythmias, especially after myocardial infarction in patients without gross circulatory impairment

INITIALLY BY INTRAVENOUS INJECTION
- Adult: 100 mg, to be given as a bolus dose over a few minutes, followed immediately by (by intravenous infusion) 4 mg/minute for 30 minutes, then (by intravenous infusion) 2 mg/minute for 2 hours, then (by intravenous infusion) 1 mg/minute, reduce concentration further if infusion continued beyond 24 hours (ECG monitoring and specialist advice for infusion), following intravenous injection lidocaine has a short duration of action (lasting for 15–20 minutes). If an intravenous infusion is not immediately available the initial intravenous injection of 100 mg can be repeated if necessary once or twice at intervals of not less than 10 minutes

Ventricular arrhythmias, especially after myocardial infarction in lighter patients or those whose circulation is severely impaired

INITIALLY BY INTRAVENOUS INJECTION
- Adult: Initially 50 mg, to be given as a bolus dose over a few minutes, followed immediately by (by intravenous infusion) 4 mg/minute for 30 minutes, then (by intravenous infusion) 2 mg/minute for 2 hours, then (by intravenous infusion) 1 mg/minute, reduce concentration further if infusion continued beyond 24 hours (ECG monitoring and specialist advice for infusion), following intravenous injection lidocaine has a short duration of action (lasting for 15–20 minutes). If an intravenous infusion is not immediately available the initial intravenous injection of 50 mg can be repeated if necessary once or twice at intervals of not less than 10 minutes

Doses at extremes of body-weight
To avoid excessive dosage in obese patients, dose may need to be calculated on the basis of ideal body-weight.

- CONTRA-INDICATIONS All grades of atioventricular block - severe myocardial depression - sino-attrial disorders
- CAUTIONS Acute prophyria (consider infusion with glucose for its anti-porphyrinogetic effects) - congestive cardiac failure (consider lower dose) - post cardiac surgery (consider lower dose)
- INTERACTIONS → Appendix 1 (lidocaine).
- SIDE-EFFECTS
  - Common or very common Bradycardia (may lead to cardiac arrest) - confusion - convulsions - dizziness (particularly if injection too rapid) - hypotension (may lead to cardiac arrest) - paraesthesia (particularly if injection too rapid) - respiratory depression
  - Rare Anaphylaxis
- PREGNANCY Crosses the placenta but not known to be harmful in animal studies—use if benefit outweighs risk.
- BREAST FEEDING Present in milk but amount too small to be harmful.
- HEPATIC IMPAIRMENT Caution—increased risk of side-effects.
- RENAL IMPAIRMENT Possible accumulation of lidocaine and active metabolite; caution in severe impairment.
- MONITORING REQUIREMENTS Monitor ECG and have resuscitation facilities available.
- MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

Solution for injection

- LIDOCAINE HYDROCHLORIDE (Non-proprietary)
  - Lidocaine hydrochloride 5 mg per 1 ml Lidocaine 50mg/10ml (0.5%) solution for injection ampoules | 10 ampoule £0.70
  - Lidocaine hydrochloride 10 mg per 1 ml Lidocaine 100mg/10ml (1%) solution for injection Mini-Plasco ampoules | 20 ampoule £10.89
  - Lidocaine 100mg/10ml (1%) solution for injection ampoules | 10 ampoule £4.50 DT price = £4.01
  - Lidocaine 100mg/10ml (1%) solution for injection Sure-Amp ampoules | 20 ampoule £8.80
  - Lidocaine 200mg/20ml (1%) solution for injection ampoules | 10 vial £18.00–19.00
  - Lidocaine 200mg/20ml (1%) solution for injection ampoules | 10 ampoule £2.35–3.10 DT price = £2.38
  - Lidocaine 20mg/2ml (1%) solution for injection ampoules | 10 ampoule £3.50 DT price = £2.00
  - Lidocaine 50mg/5ml (1%) solution for injection Sure-Amp ampoules | 20 ampoule £6.00
  - Lidocaine hydrochloride 20 mg per 1 ml Lidocaine 100mg/5ml (2%) solution for injection ampoules | 10 ampoule £2.40–3.80 DT price = £2.43
  - Lidocaine 400mg/20ml (2%) solution for injection vials | 10 vial (P) £18.50–19.50
  - Lidocaine 200mg/10ml (2%) solution for injection Mini-Plasco ampoules | 20 ampoule (P) £14.52
  - Lidocaine 400mg/2ml (2%) solution for injection ampoules | 10 ampoule (P) £4.00 DT price = £2.13
  - Lidocaine 100mg/5ml (2%) solution for injection Sure-Amp ampoules | 20 ampoule (P) £6.00
  - Lidocaine 400mg/20ml (2%) solution for injection ampoules | 10 ampoule (P) £18.00–19.00 DT price = £9.07

Propafenone hydrochloride

INDICATIONS AND DOSE

Ventricular arrhythmias (specialist supervision in hospital) | Paroxysmal supraventricular tachyarrhythmias which include paroxysmal atrial flutter or fibrillation and paroxysmal re-entrant tachycardias involving the AV node or accessory pathway, where standard therapy ineffective or contra-indicated (specialist supervision in hospital) BY MOUTH

- Adult: Initially 150 mg 3 times a day, dose to be taken after food, monitor ECG and blood pressure, if QRS interval prolonged by more than 20%, reduce dose or discontinue until ECG returns to normal limits; increased if necessary to 300 mg twice daily (max. per dose 300 mg 3 times a day), dose to be increased at intervals of at least 3 days, reduce total daily dose for patients under 70 kg
- Elderly: Initially 150 mg 3 times a day, dose to be taken after food, monitor ECG and blood pressure, if QRS interval prolonged by more than 20%, reduce dose or discontinue until ECG returns to normal limits; increased if necessary to 300 mg twice daily (max. per dose 300 mg 3 times a day), dose to be increased at intervals of at least 5 days, reduce total daily dose for patients under 70 kg

- CONTRA-INDICATIONS Atrial conduction defects (unless adequately paced) - Brugada syndrome - bundle branch block (unless adequately paced) - cardiogenic shock (except arrhythmia induced) - distal block (unless adequately paced) - electrolyte disturbances - marked hypotension - myasthenia gravis - myocardial infarction within last 3 months - second degree or greater AV block (unless adequately paced) - severe bradycardia - severe obstructive pulmonary disease (due to weak beta-blocking activity) - sinus node dysfunction (unless adequately paced) - uncontrolled congestive heart failure with left ventricular ejection fraction less than 35%
Arrhythmias

Sotalol hydrochloride

The properties listed below are those particular to the drug only. For properties common to the class, see Beta-blockers, p. 139.

INDICATIONS AND DOSE

Symptomatic non-sustained ventricular tachyarrhythmias | Prophylaxis of paroxysmal atrial tachycardia or fibrillation, paroxysmal AV re-entrant tachycardias (both nodal and involving accessory pathways), and paroxysmal supraventricular tachycardia after cardiac surgery | Maintenance of sinus rhythm following cardioversion of atrial fibrillation or flutter

BY MOUTH

Adult: Initially 80 mg daily in 1–2 divided doses, then increased to 160–320 mg daily in 2 divided doses, dose to be increased gradually at intervals of 2–3 days

Life-threatening arrhythmias including ventricular tachyarrhythmias (under expert supervision)

BY MOUTH

Adult: Initially 80 mg daily in 1–2 divided doses, then increased to 480–640 mg daily in 2 divided doses, dose to be increased gradually at intervals of 2–3 days

Important safety information

Sotalol may prolong the QT interval, and it occasionally causes life threatening ventricular arrhythmias (important: particular care is required to avoid hypokalaemia in patients taking sotalol—electrolyte disturbances, particularly hypokalaemia and hypomagnesaemia should be corrected before sotalol started and during use).

CONTRA-INDICATIONS

Long QT syndrome (congenital or acquired) | torsade de points

CAUTIONS

Diarrhoea (severe or prolonged)

INTERACTIONS

Extreme caution or avoid concomitant use of drugs that prolong QT interval.

SIDE-EFFECTS

Arrhythmogenic (pro-arrhythmic) effect (torsade de points—increased risk in females)

BREAST FEEDING

Water soluble beta-blockers such as sotalol are present in breast milk in greater amounts than other beta blockers.

RENAL IMPAIRMENT

Use half normal dose if eGFR 30–60 mL/minute/1.73 m²; use one-quarter normal dose if eGFR 10–30 mL/minute/1.73 m². Avoid if eGFR less than 10 mL/minute/1.73 m².

MONITORING REQUIREMENTS

Measurement of corrected QT interval, and monitoring of ECG and electrolytes required; correct hypokalaemia, hypomagnesaemia, or other electrolyte disturbances.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

Tablet

CAUTIONARY AND ADVISORY LABELS 21, 25

> PROPafenone hydrochloride (Non-proprietary)

| Propafenone hydrochloride 150 mg | Propafenone 150mg tablets | 90 tablet (£7.00 DT price + £1.37) |
| Propafenone hydrochloride 300 mg | Propafenone 300mg tablets | 60 tablet (£9.34 DT price) |
| Arythmol (BGP Products Ltd) |
| Propafenone hydrochloride 150 mg | Propafenone 150mg tablets | 90 tablet (£7.37 DT price + £1.37) |
| Propafenone hydrochloride 300 mg | Propafenone 300mg tablets | 60 tablet (£9.34 DT price + £1.37) |

BETA-ADRENOCEPTOR BLOCKERS

Sotalol hydrochloride

The properties listed below are those particular to the drug only. For properties common to the class, see Beta-blockers, p. 139.
arrhythmias or bradycardias unresponsive to atropine
sulfate p. 949 and when measures beyond the withdrawal of
digoxin and correction of any electrolyte abnormalities are
considered necessary.

Digoxin is most useful for controlling ventricular response
in persistent and permanent atrial fibrillation and atrial
flutter. Digoxin also has a role in heart failure.

For management of atrial fibrillation the maintenance
dose of digoxin can usually be determined by the ventricular
rate at rest, which should not usually be allowed to fall
persistently below 60 beats per minute.

Digoxin is now rarely used for rapid control of heart rate
(seen management of supraventricular arrhythmias). Even
with intravenous administration, response may take many
hours; persistence of tachycardia is therefore not an
indication for exceeding the recommended dose. The
intravenous route is not recommended.

In patients with heart failure who are in sinus rhythm a
loading dose is not required, and a satisfactory plasma-
digoxin concentration can be achieved over a period of
about a week.

Digoxin has a long half-life and maintenance doses need
to be given only once daily (although higher doses may
divided to avoid nausea); renal function is the most
important determinant of digoxin dosage.

Unwanted effects depend both on the concentration of
digoxin in the plasma and on the sensitivity of the
conducting system or of the myocardium, which is often
increased in heart disease. It can sometimes be difficult to
distinguish between toxic effects and clinical deterioration
because symptoms of both are similar. The plasma
concentration alone cannot indicate toxicity reliably, but
the likelihood of toxicity increases progressively through
the range 1.5 to 3 micrograms/litre for digoxin. Digoxin
should be used with special care in the elderly, who may be
particularly susceptible to digitalis toxicity.

Regular monitoring of plasma-digoxin concentration
during maintenance treatment is not necessary unless
problems are suspected. Hypokalaemia predisposes the
patient to digitalis toxicity; it is managed by giving a
potassium-sparing diuretic or, if necessary, potassium
supplementation.

If toxicity occurs, digoxin should be withdrawn; serious
manifestations require urgent specialist management.
Digoxin-specific antibody fragments are available for
reversal of life-threatening overdosage.

Digoxin

***DRUG ACTION*** Digoxin is a cardiac glycoside that increases
the force of myocardial contraction and reduces
conductivity within the atrioventricular (AV) node.

**INDICATIONS AND DOSE**

<table>
<thead>
<tr>
<th>Rapid digitalisation, for atrial fibrillation or flutter</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BY MOUTH</strong></td>
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<tr>
<td>▶ Adult: 0.75–1.5 mg in divided doses, dose to be given</td>
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<tr>
<td>over 24 hours, reduce dose in the elderly</td>
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<tr>
<td><strong>Maintenance, for atrial fibrillation or flutter</strong></td>
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<tr>
<td><strong>BY MOUTH</strong></td>
</tr>
<tr>
<td>▶ Adult: Maintenance 125–250 micrograms daily, dose</td>
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<tr>
<td>according to renal function and initial loading dose,</td>
</tr>
<tr>
<td>reduce dose in the elderly</td>
</tr>
<tr>
<td><strong>Heart failure (for patients in sinus rhythm)</strong></td>
</tr>
<tr>
<td><strong>BY MOUTH</strong></td>
</tr>
<tr>
<td>▶ Adult: 62.5–125 micrograms once daily, reduce dose</td>
</tr>
<tr>
<td>in the elderly</td>
</tr>
</tbody>
</table>

Emergency loading dose, for atrial fibrillation or flutter
INITIALLY BY INTRAVENOUS INFUSION
▶ Adult: Loading dose 0.75–1 mg, to be given over at
least 2 hours, then (by mouth) maintenance, start on
the following day, reduce dose in the elderly

**Dose equivalence and conversion**
Dose may need to be reduced if digoxin (or another
cardiac glycoside) has been given in the preceding 2
weeks. When switching from intravenous to oral route may
need to increase dose by 20–33% to maintain the same
plasma-digoxin concentration.

**SIDE-EFFECTS**

- Hypercalcaemia (risk of digitalis toxicity)
- Hypokalaemia (risk of digitalis toxicity)
- Hypomagnesaemia (risk of digitalis toxicity)
- Hypoxia (risk of digitalis toxicity)
- Recent myocardial infarction
- Severe respiratory disease
- Sick sinus syndrome
- Thyroid disease
- Wolff-Parkinson-White syndrome

**INTERACTIONS** → Appendix 1 (cardiac glycosides).

**CONTRA-INDICATIONS**
- Constrictive pericarditis (unless to control atrial fibrillation or improve systolic dysfunction—
  but use with caution)
- Hypertrophic cardiomyopathy (unless concomitant atrial fibrillation and heart failure—
  but use with caution)
- Intermittent complete heart block
- Myocarditis
- Second degree AV block
- Supraventricular arrhythmias associated with accessory conducting pathways e.g. Wolff-Parkinson-White syndrome (although can be used in infancy)
- Ventricular tachycardia or fibrillation

**CAUTIONS**
- Hypercalcaemia
- Hypokalaemia
- Hypomagnesaemia
- Hypoxia
- Recent myocardial infarction
- Severe respiratory disease
- Sick sinus syndrome
- Thyroid disease

**OVERDOSE**
- If toxicity occurs, digoxin should be withdrawn; serious
  manifestations require urgent specialist management.

- PREGNANCY
  - May need dosage adjustment.

- BREAST FEEDING
  - Amount too small to be harmful.

- RENAL IMPAIRMENT
  - Reduce dose. Monitor plasma-digoxin concentration in renal impairment.

- MONITORING REQUIREMENTS
  - For plasma-digoxin concentration assay, blood should be
    taken at least 6 hours after a dose.
  - Monitor serum electrolytes and renal function. Toxicity increased by electrolyte disturbances.

- DIRECTIONS FOR ADMINISTRATION
  - With intravenous use Avoid rapid intravenous
    administration (risk of hypertension and reduced
    coronary flow). For intravenous infusion (Lanoxin®), give
    intermittently in Glucose 5% or Sodium chloride 0.9%;
    dilute to a concentration of not more than
    62.5 micrograms/mL. To be given over at least 2 hours.
  - With oral use For oral administration, oral solution must
    not be diluted.

- PATIENT AND CARER ADVICE
  - Patient counselling is advised for digoxin elixir (use pipette).

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines
containing the same drug. Forms available from special-order
manufacturers include: solution for injection, oral suspension,
oral solution.
**2 Bleeding disorders**

### Antifibrinolytic drugs and haemostatics

Fibrin dissolution can be impaired by the administration of tranexamic acid, which inhibits fibrinolysis. It can be used to prevent bleeding or to treat bleeding associated with excessive fibrinolysis (e.g. in surgery, dental extraction, obstetric disorders, and traumatic haemorrhage) and in the management of menorrhagia. Tranexamic acid below may also be used in hereditary angioedema, epistaxis, and in thrombolytic overdose.

Desmopressin p. 574 is used in the management of mild to moderate haemophilia and von Willebrand’s disease. It is also used for fibrinolytic response testing.

Etamsylate p. 96 reduces capillary bleeding in the presence of a normal number of platelets; it does not act by fibrin stabilisation, but probably by correcting abnormal adhesion. Etamsylate is less effective than other treatments in the management of heavy menstrual bleeding and its use is no longer recommended.

### ANTIFIBRINOLYTICS

#### Tranexamic acid

**INDICATIONS AND DOSE**

**Inhibition of fibrinolysis (local)**

**BY MOUTH**

- Adult: 1–1.5 g 2–3 times a day, alternatively 15–25 mg/kg 2–3 times a day

**INITIALLY BY SLOW INTRAVENOUS INJECTION**

- Adult: 0.5–1 g 2–3 times a day, to be administered at a rate not exceeding 100 mg/minute, dose may be followed by continuous infusion; (by continuous intravenous infusion) 25–50 mg/kg, dose to be given over 24 hours

#### Menorrhagia

**BY MOUTH**

- Adult: 1 g 3 times a day for up to 4 days, to be initiated when menstruation has started; maximum 4 g per day

#### Hereditary angioedema

**BY MOUTH**

- Adult: 1–1.5 g 2–3 times a day, for short-term prophylaxis of hereditary angioedema, tranexamic acid is started several days before planned procedures which may trigger an acute attack of hereditary angioedema (e.g. dental work) and continued for 2–5 days afterwards

#### Epistaxis

**BY MOUTH**

- Adult: 1 g 3 times a day for 7 days

#### General fibrinolysis

**BY SLOW INTRAVENOUS INJECTION**

- Adult: 1 g every 6–8 hours, alternatively 15 mg/kg every 6–8 hours, dose to be given at a rate not exceeding 100 mg/minute

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**UNLICENSED USE** Use of tranexamic acid by continuous intravenous infusion for treatment of local fibrinolysis is an unlicensed route of administration.

**CONTRA-INDICATIONS** Fibrinolytic conditions following disseminated intravascular coagulation (unless predominant activation of fibrinolytic system with severe bleeding) - history of convulsions - thromboembolic disease

**CAUTIONS** Irregular menstrual bleeding (establish cause before initiating therapy) - massive haematuria (avoid if risk of ureteric obstruction) - patients receiving oral contraceptives (increased risk of thrombosis)

**CAUTIONS, FURTHER INFORMATION**

**Menorrhagia** Before initiating treatment for menorrhagia, exclude structural or histological causes or fibroids causing distortion of uterine cavity.

**SIDE-EFFECTS**

- **Common or very common** Diarrhoea (reduce dose) - nausea - vomiting
- **Uncommon** Dermatitis
- **Rare** Impairment of colour vision (discontinue) - thromboembolic events - visual disturbances (discontinue)
- **Frequency not known** Convulsions (usually with high doses) - hypotension (on rapid intravenous injection) - malaise (on rapid intravenous injection)

**PREGNANCY** No evidence of teratogenicity in animal studies; manufacturer advises use only if potential benefit outweighs risk—crosses the placenta.

**BREAST FEEDING** Small amount present in milk—antifibrinolytic effect in infant unlikely.

**RENAL IMPAIRMENT** Reduce dose—consult product literature for details.

**MONITORING REQUIREMENTS** Regular liver function tests in long-term treatment of hereditary angioedema.

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Cyklokapron\textsuperscript{®}), give continuously in Glucose 5% or Sodium chloride 0.9%.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, mouthwash

**Tablet**

- **DIOXIN (Non-proprietary)**
  - **Digoxin 62.5 microgram** Digoxin 62.5 microgram tablets | 28 tablet (PPh £5.68 DT price = £1.49 | 500 tablet (PPh) no price available
  - **Digoxin 125 microgram** Digoxin 125 microgram tablets | 28 tablet (PPh £5.67 DT price = £1.04
  - **Digoxin 250 microgram** Digoxin 250 microgram tablets | 28 tablet (PPh £5.68 DT price = £1.02 | 500 tablet (PPh) no price available
  - **Lanoxin (Aspen Pharma Trading Ltd)**
    - **Digoxin 62.5 microgram** Lanoxin PG 62.5 microgram tablets | 500 tablet (PPh £8.09
    - **Digoxin 125 microgram** Lanoxin 125 tablets | 500 tablet (PPh £8.09
  - **Digoxin 250 microgram** Lanoxin 250 microgram tablets | 500 tablet (PPh £8.09

**Oral solution**

- **Lanoxin (Aspen Pharma Trading Ltd)**
  - **Digoxin 50 microgram per 1 ml** Lanoxin PG 50 micrograms/ml elixir | 60 ml (PPh £5.35 DT price = £5.35

**Solution for infusion**

- **DIOXIN (Non-proprietary)**
  - **Digoxin 250 microgram per 1 ml** Digoxin 50 micrograms/2ml solution for infusion ampoules | 10 ampoule (PPh £7.00
  - **Lanoxin (Aspen Pharma Trading Ltd)**
    - **Digoxin 250 microgram per 1 ml** Lanoxin 500 micrograms/2ml solution for infusion ampoules | 5 ampoule (PPh £3.30

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**REFERENCES**

- [Tranexamic acid](https://www.medicines.org.uk/medicines/095476/summary)
- [Hereditary angioedema](https://www.medicines.org.uk/medicines/095476/summary)
- [Menorrhagia](https://www.medicines.org.uk/medicines/095476/summary)
Solution for injection

- Tranexamic acid (Non-proprietary)
  Tranexamic acid 100 mg per 1 ml
  Tranexamic acid 500mg/5ml solution for injection ampoules | 5 ampoules (Pfizer) £7.50 (Hospital only) | 10 ampoules (Pfizer) £14.90–£15.47 (Hospital only)

- Cyklokapron (Pfizer Ltd)
  Tranexamic acid 100 mg per 1 ml
  Cyklokapron 500mg/5ml solution for injection ampoules | 10 ampoule (Pfizer) £15.47

HAEMOSTATICS

Etamsylate
(Ethamsylate)

INDICATIONS AND DOSE
Short-term blood loss in menorrhagia
BY MOUTH
- Adult: 500 mg 4 times a day during menstruration

- CONTRA-INDICATIONS: Acute porphyrias p. 864
- CAUTIONS: Exclude structural or histological causes of menorrhagia, or fibroids causing distortion of the uterine cavity, before initiating treatment
- SIDE-EFFECTS: Diarrhoea - fever (discontinue treatment), headache - nausea - rashes - vomiting
- BREAST FEEDING: Present in milk - manufacturer advises avoid.
- LESS SUITABLE FOR PRESCRIBING: Less suitable for prescribing.
- MEDICINAL FORMS: There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

2.1 Coagulation factor deficiencies

BLOOD COAGULATION FACTORS

Dried prothrombin complex
(Human prothrombin complex)

INDICATIONS AND DOSE
Treatment and peri-operative prophylaxis of haemorrhage in patients with congenital deficiency of factors II, VII, IX, or X if purified specific coagulation factors not available.
Treatment and peri-operative prophylaxis of haemorrhage in patients with acquired deficiency of factors II, VII, IX, or X (e.g. during warfarin treatment)
BY INTRAVENOUS INJECTION
- Adult: (consult haematologist)
Major bleeding in patients on warfarin following phymenadione
BY INTRAVENOUS INJECTION
- Adult: 25–50 units/kg

- CONTRA-INDICATIONS: Angina - history of heparin induced thrombocytopenia - recent myocardial infarction (except in life-threatening haemorrhage following overdose of oral anticoagulants, and before induction of fibrinolytic therapy)
- CAUTIONS: Disseminated intravascular coagulation - history of myocardial infarction or coronary heart disease - postoperative use - risk of thrombosis
- SIDE-EFFECTS
  - Rare: Headache

- FREQUENCY not known: Disseminated intravascular coagulation - nephrotic syndrome - thrombotic events
- HEPATIC IMPAIRMENT: Monitor closely in hepatic impairment (risk of thromboembolic complications).
- PRESCRIBING AND DISPENSING INFORMATION: Dried prothrombin complex is prepared from human plasma by a suitable fractionation technique, and contains factor IX, together with variable amounts of factors II, VII, and X.
  Available from CSL Behring (Beriplex®P/N) Octapharma (Octaplex®)

Factor IX fraction, dried

INDICATIONS AND DOSE
Treatment and prophylaxis of haemorrhage in congenital factor IX deficiency (haemophilia B)
BY INTRAVENOUS INJECTION OR BY CONTINUOUS INTRAVENOUS INFUSION
- Adult: (consult haematologist)

- CONTRA-INDICATIONS: Disseminated intravascular coagulation
- CAUTIONS: Risk of thrombosis - principally with former low purity products
- SIDE-EFFECTS: Allergic reactions - chills - dizziness - fever - gastro-intestinal disturbances - headache
- PRESCRIBING AND DISPENSING INFORMATION: Dried factor IX fraction is prepared from human plasma by a suitable fractionation technique; it may also contain clotting factors II, VII, and X.

- MEDICINAL FORMS: There can be variation in the licensing of different medicines containing the same drug.

Powder and solvent for solution for injection
- AlphaNine (Grifols UK Ltd)
  Factor IX high purity 500 unit AlphaNine 500 unit powder and solvent for solution for injection vials | 1 vial (Grifols) no price available
  Factor IX high purity 1000 unit AlphaNine 1000 unit powder and solvent for solution for injection vials | 1 vial (Grifols) £390.00
  Factor IX high purity 1500 unit AlphaNine 1500 unit powder and solvent for solution for injection vials | 1 vial (Grifols) no price available

- Mononine (CSL Behring UK Ltd)
  Factor IX high purity 1000 unit Mononine 1000 unit powder and solvent for solution for injection vials | 1 vial (Grifols) £478.43

- Repleni-VF (Bio Products Laboratory Ltd)
  Factor IX high purity 500 unit Repleni-VF 500 unit powder and solvent for solution for injection vials | 1 vial (Pfizer) £180.00 | 10 vial (Pfizer) no price available
  Factor IX high purity 1000 unit Repleni-VF 1000 unit powder and solvent for solution for injection vials | 1 vial (Pfizer) £360.00 | 10 vial (Pfizer) no price available

Powder and solvent for solution for infusion
- BeneFIX (Pfizer Ltd)
  Nonacog alfa 250 unit BeneFIX 250 unit powder and solvent for solution for infusion vials | 1 vial (Pfizer) £151.80
  Nonacog alfa 500 unit BeneFIX 500 unit powder and solvent for solution for infusion vials | 1 vial (Pfizer) £363.60

- BeneFIX (Pfizer Ltd)
  Nonacog alfa 1000 unit BeneFIX 1000 unit powder and solvent for solution for infusion vials | 1 vial (Pfizer) £607.70

- BeneFIX (Pfizer Ltd)
  Nonacog alfa 2000 unit BeneFIX 2000 unit powder and solvent for solution for infusion vials | 1 vial (Pfizer) £1,214.40

- BeneFIX (Pfizer Ltd)
  Nonacog alfa 3000 unit BeneFIX 3000 unit powder and solvent for solution for infusion vials | 1 vial (Pfizer) £1,821.60
Coagulation factor deficiencies

Factor VIIa (recombinant)
(Eptacog alfa (activated))

INDICATIONS AND DOSE
Treatment and prophylaxis of haemorrhage in patients with haemophilia A or B with inhibitors to factors VIII or IX, acquired haemophilia, factor VII deficiency, or Glanzmann's thrombasthenia

BY INTRAVENOUS INJECTION OR BY CONTINUOUS INTRAVENOUS INFUSION
> Adult: (consult haematologist)

● CAUTIONS Disseminated intravascular coagulation - risk of thrombosis
● SIDE-EFFECTS
  ▶ Uncommon Deep vein thrombosis - fever - pulmonary embolism - rash - venous thromboembolic events
  ▶ Rare Angina - arterial thrombotic events - cerebrovascular accident - coagulation disorders - headache - myocardial infarction - nausea
  ▶ Frequency not known Anaphylaxis - angioedema - flushing

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Powder and solvent for solution for injection

> NovoSeven (Novo Nordisk Ltd)
  Eptacog alfa activated 50000 unit NovoSeven 1mg (50,000units)
  powder and solvent for solution for injection pre-filled syringes
  1 pre-filled disposable injection (PFS) £525.20 (Hospital only)
  NovoSeven 1mg (50,000units) powder and solvent for solution for injection vials | 1 vial (PFS) £525.20 (Hospital only)
  Eptacog alfa activated 100000 unit NovoSeven 2mg (100,000units) powder and solvent for solution for injection vials | 1 vial (PFS) £1,050.40 (Hospital only)
  NovoSeven 2mg (100,000units) powder and solvent for solution for injection pre-filled syringes | 1 pre-filled disposable injection (PFS) £1,050.40 (Hospital only)
  Eptacog alfa activated 250000 unit NovoSeven 5mg (250,000units) powder and solvent for solution for injection pre-filled syringes | 1 pre-filled disposable injection (PFS) £2,626.00 (Hospital only)
  NovoSeven 5mg (250,000units) powder and solvent for solution for injection vials | 1 vial (PFS) £2,626.00 (Hospital only)
  Eptacog alfa activated 400000 unit NovoSeven 8mg (400,000units) powder and solvent for solution for injection vials | 1 vial (PFS) £4,201.60 (Hospital only)
  NovoSeven 8mg (400,000units) powder and solvent for solution for injection pre-filled syringes | 1 pre-filled disposable injection (PFS) £4,201.60 (Hospital only)

Factor VIII fraction, dried
(Human coagulation factor VIII, dried)

INDICATIONS AND DOSE
Treatment and prophylaxis of haemorrhage in patients with congenital factor VIII deficiency (haemophilia A), acquired factor VIII deficiency | Von Willebrand's disease

BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION OR BY CONTINUOUS INTRAVENOUS INFUSION
> Adult: (consult haematologist)

● CAUTIONS Intravascular haemolysis after large or frequently repeated doses in patients with blood groups A, B, or AB—less likely with high potency concentrates

● SIDE-EFFECTS

● MONITORING REQUIREMENTS Monitor for development of factor VIII inhibitors.

● PRESCRIBING AND DISPENSING INFORMATION
Dried factor VIII fraction is prepared from human plasma by a suitable fractionation technique; it may also contain varying amounts of von Willebrand factor.

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Powder and solvent for solution for injection

> Advate (Baxter Healthcare Ltd)
  Octocog alfa 250 unit Advate 250unit powder and solvent for solution for injection vials | 1 vial (PFS) no price available
  Octocog alfa 500 unit Advate 500unit powder and solvent for solution for injection vials | 1 vial (PFS) no price available

> Fanhdi (Griifols Uk Ltd)
  Factor VII high purity 500 unit Fanhdi 500unit powder and solvent for solution for injection vials | 1 vial (PFS) £165.00 (Hospital only)
  Factor VII high purity 1000 unit Fanhdi 1,000unit powder and solvent for solution for injection vials | 1 vial (PFS) £330.00 (Hospital only)

> Helixate NexGen (CSL Behring Uk Ltd)
  Octocog alfa 250 unit Helixate NexGen 250unit powder and solvent for solution for injection vials | 1 vial (PFS) £118.57
  Octocog alfa 500 unit Helixate NexGen 500unit powder and solvent for solution for injection vials | 1 vial (PFS) £237.15
  Octocog alfa 1000 unit Helixate NexGen 1000unit powder and solvent for solution for injection vials | 1 vial (PFS) £474.30
  Octocog alfa 2000 unit Helixate NexGen 2,000unit powder and solvent for solution for injection vials | 1 vial (PFS) £948.60

> Kogenate (Bayer Plc)
  Octocog alfa 250 unit Kogenate Bayer 250unit powder and solvent for solution for injection vials | 1 vial (PFS) £157.50
  Octocog alfa 500 unit Kogenate Bayer 500unit powder and solvent for solution for injection vials | 1 vial (PFS) £315.00
  Octocog alfa 1000 unit Kogenate Bayer 1,000unit powder and solvent for solution for injection vials | 1 vial (PFS) £630.00
  Octocog alfa 2000 unit Kogenate Bayer 2,000unit powder and solvent for solution for injection vials | 1 vial (PFS) £1,260.00

Powder and solvent for solution for infusion

> Advate (Baxter Healthcare Ltd)
  Octocog alfa 1500 unit Advate 1,500unit powder and solvent for solution for infusion vials | 1 vial (PFS) no price available
  Octocog alfa 3000 unit Advate 3,000unit powder and solvent for solution for infusion vials | 1 vial (PFS) no price available

> Kogenate (Bayer Plc)
  Octocog alfa 3000 unit Kogenate Bayer 3,000unit powder and solvent for solution for injection vials | 1 vial (PFS) £1,890.00

Factor VIII inhibitor bypassing fraction

INDICATIONS AND DOSE
Treatment and prophylaxis of haemorrhage in patients with congenital factor VIII deficiency (haemophilia A) and factor VIII inhibitors | Treatment of haemorrhage in non-haemophilic patients with acquired factor VIII inhibitors

BY INTRAVENOUS INFUSION OR BY INTRAVENOUS INJECTION
> Adult: (consult haematologist)

● CONTRA-INDICATIONS
Disseminated intravascular coagulation

● SIDE-EFFECTS
Anaphylaxis - disseminated intravascular coagulation - flushing - hypersensitivity - hypotension - myocardial infarction - paraesthesia - pyrexia - rash - thrombosis - urticaria

● PRESCRIBING AND DISPENSING INFORMATION
Preparations with factor VIII inhibitor bypassing activity are prepared from human plasma.
Factor XIII fraction, dried
(Human fibrin-stabilising factor, dried)

**INDICATIONS AND DOSE**
Congenital factor XIII deficiency
BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION
Adult: (consult haematologist)

**SIDE-EFFECTS**
Rare Allergic reactions · fever

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for solution for injection**
- FEIBA Immuno (Baxter Healthcare Ltd)
  Factor VIII inhibitor bypassing fraction 500 unit FEIBA 500unit powder and solvent for solution for injection vials | 1 vial £90.59 no price available

**Powder and solvent for solution for infusion**
- FEIBA Immuno (Baxter Healthcare Ltd)
  Factor VIII inhibitor bypassing fraction 1000 unit FEIBA 1,000unit powder and solvent for solution for infusion vials | 1 vial £90.59 no price available

**Fibrinogen, dried (Human fibrinogen)**

**INDICATIONS AND DOSE**
Treatment of haemorrhage in congenital hypofibrinogenenaemia or afibrinogenenaemia
BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION
Adult: (consult haematologist)

**CAUTIONS** Risk of thrombosis

**SIDE-EFFECTS**
- Rare Allergic reactions · fever
  - Very rare Myocardial infarction · pulmonary embolism · thromboembolic events

**PREGNANCY**
Manufacturer advises not known to be harmful—no information available.

**BREAST FEEDING**
Manufacturer advises avoid—no information available.

**PREScribing AND DISPensing INFORMATION**
Fibrinogen is prepared from human plasma.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**
- Riastap (CSL Behring UK Ltd) Fibrinogen 1 gram Riastap 1g powder for solution for infusion vials | 1 vial £340.00

**Solution for sealant**
- FIBRINOGEN, DRIED (Non-proprietary) Fibrinogen 91 mg Fibrinogen 91mg powder for solution for sealant vials | 1 vial £90.59 no price available
- Fibrinogen 182 mg Fibrinogen 182mg powder for solution for sealant vials | 1 vial £90.59 no price available
- Fibrinogen 70 mg per 1 ml Fibrinogen 350mg/5ml solution for sealant vials | 1 vial £90.59 no price available (Hospital only)
  - Fibrinogen 140mg/2ml solution for sealant vials | 1 vial £90.59 no price available (Hospital only)

**BLOOD PRODUCTS**

**Fresh frozen plasma**

**INDICATIONS AND DOSE**
Replacement of coagulation factors or other plasma proteins where their concentration or functional activity is critically reduced
BY INTRAVENOUS INFUSION
Adult: (consult haematologist)
- Major bleeding in patients on warfarin following phytomenadione
  - Adult: 15 mL/kilogram

**Dose equivalence and conversion**
Fresh frozen plasma is prepared from the supernatant liquid obtained by centrifugation of one donation of whole blood.

**CONTRA-INDICATIONS** Avoid use as a volume expander · IgA deficiency with confirmed antibodies to IgA

**CAUTIONS**
Cardiac decompensation · need for compatibility · pulmonary oedema · severe protein S deficiency (avoid products with low protein S activity e.g. OctaplasLG®)

**SIDE-EFFECTS**
- Common or very common Nausea · pruritus · rash
- Uncommon Oedema · vomiting
- Rare Agitation · allergic reactions · bronchospasm · cardiorespiratory collapse · chills · fever · tachycardia
  - Very rare Arrhythmia · hypertension · thromboembolism

**PREScribing AND DISPensing INFORMATION**
Fresh frozen plasma is prepared from the supernatant liquid obtained by centrifugation of one donation of whole blood. A preparation of solvent/detergent treated human plasma (frozen) from pooled donors is available from Octapharma (OctaplasLG®)

**Protein C concentrate**

**INDICATIONS AND DOSE**
Congenital protein C deficiency
BY INTRAVENOUS INJECTION
Adult: (consult haematologist)

**CAUTIONS**
Hypersensitivity to heparins

**SIDE-EFFECTS**
- Very rare Bleeding · dizziness · fever · hypersensitivity reactions

**PREScribing AND DISPensing INFORMATION**
Protein C is prepared from human plasma.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for solution for injection**
- Ceprotin (Baxter Healthcare Ltd) Protein C 500 unit Ceprotin 500unit powder and solvent for solution for injection vials | 1 vial £90.59 no price available

- Ceprotin 1000 unit Ceprotin 1000unit powder and solvent for solution for injection vials | 1 vial £90.59 no price available

**Fibrinogen 455 mg** Fibrinogen 455mg powder for solution for sealant vials | 1 vial £90.59 no price available
2.2 Subarachnoid haemorrhage

CALCIUM-CHANNEL BLOCKERS

Nimodipine

The properties listed below are those particular to the drug. For properties common to the class, see Calcium-channel blockers, p. 147.

» DRUG ACTION Nimodipine is a dihydropyridine calcium-channel blocker.

INDICATIONS AND DOSE

Prevention of ischaemic neurological defects following aneurysmal subarachnoid haemorrhage

BY MOUTH

Adult: 60 mg every 4 hours, to be started within 4 days of aneurysmal subarachnoid haemorrhage and continued for 21 days

Treatment of ischaemic neurological defects following aneurysmal subarachnoid haemorrhage

BY INTRAVENOUS INFUSION

Adult (body-weight up to 70 kg): Initially 0.5 mg/hour, increased after 2 hours if no severe fall in blood pressure; increased to 2 mg/hour and continue for at least 5 days (max. 14 days); if surgical intervention during treatment, continue for at least 5 days after surgery; max. total duration of nimodipine use 21 days, to be given via central catheter

Adult (body-weight 70 kg and above): Initially 1 mg/hour, increased after 2 hours if no severe fall in blood pressure; increased to 2 mg/hour and continue for at least 5 days (max. 14 days); if surgical intervention during treatment, continue for at least 5 days after surgery; max. total duration of nimodipine use 21 days, to be given via central catheter

Treatment of ischaemic neurological defects following aneurysmal subarachnoid haemorrhage in patients with unstable blood pressure

BY INTRAVENOUS INFUSION

Adult: Initially up to 0.5 mg/hour, increased after 2 hours if no severe fall in blood pressure; increased to 2 mg/hour and continue for at least 5 days (max. 14 days); if surgical intervention during treatment, continue for at least 5 days after surgery; max. total duration of nimodipine use 21 days, to be given via central catheter

» CONTRA-INDICATIONS Acute porphyrias p. 864 · unstable angina · within 1 month of myocardial infarction

» CAUTIONS Cerebral oedema · hypotension · severely raised intracranial pressure

» INTERACTIONS ➔ Appendix 1 (calcium-channel blockers, alcohol (infusion only)). Avoid concomitant administration with other calcium-channel blockers, beta-blocker and nephrotoxic drugs.

» SIDE-EFFECTS Flushing · gastro-intestinal disorders · headache · hypotension · ileus · nausea · sweating and feeling of warmth · thrombocytopenia · variation in heart-rate

» PREGNANCY Manufacturer advises use only if potential benefit outweighs risk.

» BREAST FEEDING Manufacturer advises avoid—present in milk.

» HEPATIC IMPAIRMENT Elimination reduced in cirrhosis—monitor blood pressure.

» RENAL IMPAIRMENT

» With intravenous use Manufacturer advises monitor renal function closely in renal impairment.

» DIRECTIONS FOR ADMINISTRATION Avoid concomitant administration of nimodipine infusion and tablets.

» With oral use For administration by mouth, tablets may be crushed or halved but are light sensitive—administer immediately.

» With intravenous use For intravenous infusion, give via drip tubing in Glucose 5% or Sodium chloride 0.9%. Not to be added to infusion container; administer via an infusion pump through a Y-piece into a central catheter; incompatible with polyvinyl chloride giving sets or containers; protect infusion from light. Polyethylene, polypropylene, or glass apparatus should be used. PVC should be avoided.

» MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Tablet

» Nimotop (Bayer Plc) Nimodipine 30 mg Nimotop 30mg tablets | 100 tablet PFR £40.00

Solution for infusion

» Nimotop (Bayer Plc) Nimodipine 200 microgram per 1 ml Nimotop 0.02% solution for infusion 50ml vials | 5 vial PFR £68.00 (Hospital only)

3 Blood clots

3.1 Blocked catheters and lines

Drugs used for Blocked catheters and lines not listed below; Heparin (unfractionated), p. 114 · Urokinase, p. 119

PROSTAGLANDINS (CARDIOVASCULAR)

Epoprostenol

(Prostacyclin)

» DRUG ACTION Epoprostenol is a prostaglandin and a potent vasodilator. It is also a powerful inhibitor of platelet aggregation.

INDICATIONS AND DOSE

Inhibition of platelet aggregation during renal dialysis when heparins are unsuitable or contra-indicated | Treatment of primary pulmonary hypertension resistant to other treatments, usually with oral anti-coagulation (initiated by a specialist)

BY CONTINUOUS INTRAVENOUS INFUSION

» Adult: (consult product literature)

PHARMACOKINETICS

Short half-life of approximately 3 minutes, therefore it must be administered by continuous intravenous infusion.

» CONTRA-INDICATIONS Severe left ventricular dysfunction

» CAUTIONS Avoid abrupt withdrawal when used for primary pulmonary hypertension (risk of rebound pulmonary hypertension) · extreme caution in coronary artery disease · haemorrhagic diathesis · pulmonary veno-occlusive disease · reconstituted solution highly alkaline—avoid extravasation (irritant to tissues) · risk of pulmonary oedema (dose titration for pulmonary hypertension should be in hospital)

» INTERACTIONS Caution with concomitant use of drugs that increase risk of bleeding.
Prophylaxis of venous thromboembolism

All patients admitted to hospital should undergo a risk assessment for venous thromboembolism on admission. Patients considered to be at high risk include those anticipated to have a substantial reduction in mobility, those with obesity, malignant disease, history of venous thromboembolism, thrombophilic disorder, or patients over 60 years. Patients with risk factors for bleeding (e.g. acute stroke, thrombocytopenia, acquired or untreated inherited bleeding disorders) should only receive pharmaceutical prophylaxis when the risk of bleeding does not outweigh the risk of venous thromboembolism. NICE clinical guideline 92 (January 2010) provides a full list of risk factors, and gives recommendations for prophylaxis. A venous thromboembolism risk assessment checklist is also available from the Department of Health (www.gov.uk/dh).

Patients scheduled for surgery should be offered mechanical prophylaxis (e.g. anti-embolism stockings) on admission if appropriate; prophylaxis should continue until the patient is sufficiently mobile. Choice of mechanical prophylaxis will depend on factors such as the type of surgery, suitability for the patient, and their condition.

Patients undergoing general or orthopaedic surgery, who are considered to be at high risk of venous thromboembolism, should be offered pharmacological prophylaxis. Choice of prophylaxis will depend on the type of surgery, suitability for the patient, and local policy. A low molecular weight heparin is suitable in all types of general and orthopaedic surgery; heparin (unfractionated) p. 114 is preferred for patients in renal failure. Fondaparinux sodium p. 109 is an option for patients undergoing hip or knee replacement surgery, hip fracture surgery, gastro-intestinal, bariatric, or day surgery procedures. The oral anticoagulants apixaban p. 108, dabigatran etexilate p. 117, and rivaroxaban p. 109 are indicated for thromboprophylaxis following hip or knee replacement surgery.

Pharmacological prophylaxis in general surgery should usually continue for 5–7 days, or until sufficient mobility has been re-established. Pharmacological prophylaxis should be extended to 28 days after major cancer surgery in the abdomen or pelvis. Hip or knee replacement surgery, and hip fracture surgery, require an extended duration of pharmacological prophylaxis, depending on the preparation used (consult product literature).

General medical patients who are considered to be at high risk of venous thromboembolism should be offered pharmacological prophylaxis on admission. Choice of prophylaxis will depend on the medical condition, suitability for the patient, and local policy. Patients should receive either a low molecular weight heparin, heparin (unfractionated) (if patient in renal failure), or fondaparinux sodium prophylaxis should continue until the patient is no longer considered to be at significant risk of venous thromboembolism. Mechanical prophylaxis (e.g. anti-embolism stockings) can be offered to medical patients in whom pharmacological prophylaxis is contra-indicated, and continued until the patient is sufficiently mobile.

Treatment of venous thromboembolism

For the initial treatment of deep-vein thrombosis and pulmonary embolism a low molecular weight heparin is used; alternatively, heparin (unfractionated) is given as an intravenous loading dose, followed by continuous intravenous infusion (using an infusion pump) or (for deep-vein thrombosis only) by intermittent subcutaneous injection. Intermittent intravenous injection of heparin (unfractionated) is no longer recommended. An oral anticoagulant (usually warfarin sodium p. 121 is started at the same time as unfractionated or low molecular weight heparin (the heparin needs to be continued for at least 5 days and until the INR is ≥2 for at least 24 hours). Laboratory monitoring for heparin (unfractionated),

3.2 Thromboembolism

Venous thromboembolism

Venous thromboembolism includes deep-vein thrombosis and pulmonary embolism, and occurs as a result of thrombus formation in a vein.
preferably on a daily basis, is essential; determination of the activated partial thromboplastin time (APTT) is the most widely used measure (for heparin (unfractionated). A low molecular weight heparin or, in some circumstances, heparin (unfractionated) is also used in regimens for the management of myocardial infarction and unstable angina.

Management of venous thromboembolism in pregnancy

Heparins are used for the management of venous thromboembolism in pregnancy because they do not cross the placenta. Low molecular weight heparins are preferred because they have a lower risk of osteoporosis and of heparin-induced thrombocytopenia. Low molecular weight heparins are eliminated more rapidly in pregnancy, requiring alteration of the dosage regimen for drugs such as dalteparin sodium p. 112, enoxaparin sodium p. 113, and tinzaparin sodium p. 115. Treatment should be stopped at the onset of labour and advice sought from a specialist on continuing therapy after birth.

Extracorporeal circuits

Heparin (unfractionated) is also used in the maintenance of extracorporeal circuits in cardiopulmonary bypass and haemodialysis.

Haemorrhage

If haemorrhage occurs it is usually sufficient to withdraw unfractionated or low molecular weight heparin, but if rapid reversal of the effects of the heparin is required, protamine sulfate p. 1133 is a specific antidote (but only partially reverses the effects of low molecular weight heparins).

Management of stroke

Stroke is associated with a significant risk of morbidity and mortality. Patients presenting with acute symptoms should be immediately transferred to hospital for accurate diagnosis of stroke type, and urgent initiation of appropriate treatment; patients should be managed by a specialist multidisciplinary stroke team.

The following notes give an overview of the initial and long-term management of transient ischaemic attack, ischaemic stroke, and intracerebral haemorrhage.

Transient ischaemic attack

Patients suspected of having a transient ischaemic attack should immediately receive aspirin p. 104 (patients with aspirin hypersensitivity, or those intolerant of aspirin despite the addition of a proton pump inhibitor, should receive clopidogrel p. 106 [unlicensed use] as an alternative). Following a confirmed diagnosis, patients should receive treatment for secondary prevention (see Long-term Management, under Ischaemic Stroke).

Ischaemic stroke

Initial management

Alteplase p. 194 is recommended in the treatment of acute ischaemic stroke if it can be administered within 4.5 hours of symptom onset; it should be given by medical staff experienced in the administration of thrombolytics and the treatment of acute stroke, preferably within a specialist stroke centre. Treatment with aspirin should be initiated 24 hours after thrombolysis (or as soon as possible within 48 hours of symptom onset in patients not receiving thrombolysis); patients with aspirin hypersensitivity, or those intolerant of aspirin despite the addition of a proton pump inhibitor, should receive clopidogrel [unlicensed use] as an alternative.

Anticoagulants are not recommended as an alternative to antiplatelet drugs in acute ischaemic stroke in patients who are in sinus rhythm. However, parenteral anticoagulants may be indicated in patients who are symptomatic of, or at high risk of developing, deep vein thrombosis or pulmonary embolism; warfarin sodium p. 121 should not be commenced in the acute phase of ischaemic stroke.

Anticoagulants should be considered after cardio-embolic ischaemic stroke in patients with atrial fibrillation, however patients presenting with atrial fibrillation following a disabling ischaemic stroke should receive aspirin before being considered for anticoagulant treatment. Patients already receiving anticoagulation for a prosthetic heart valve who experience a disabling ischaemic stroke and are at significant risk of haemorrhagic transformation, should have their anticoagulant treatment stopped for 7 days and substituted with aspirin.

Treatment of hypertension in the acute phase of ischaemic stroke can result in reduced cerebral perfusion, and should therefore only be instituted in the event of a hypertensive emergency, or in those patients considered for thrombolysis.

Long-term management

Patients should receive long-term treatment following a transient ischaemic attack or an ischaemic stroke to reduce the risk of further cardiovascular events.

Following a transient ischaemic attack, long-term treatment with modified-release dipyridamole in combination with aspirin is recommended. If patients are intolerant of aspirin, or it is contra-indicated, then modified-release dipyridamole p. 107 alone is recommended; if patients are intolerant of dipyridamole, or it is contra-indicated, then aspirin alone is recommended.

Patients who are intolerant of both aspirin and dipyridamole should receive clopidogrel alone [unlicensed use].

Following an ischaemic stroke (not associated with atrial fibrillation), clopidogrel is recommended as long-term treatment. If clopidogrel is contra-indicated or not tolerated, patients should receive modified-release dipyridamole in combination with aspirin; if both aspirin and clopidogrel are contra-indicated or not tolerated, then modified-release dipyridamole alone is recommended; if both dipyridamole and clopidogrel are contra-indicated or not tolerated, then aspirin alone is recommended.

Patients with stroke associated with atrial fibrillation should be reviewed for long-term treatment with warfarin sodium or an alternative anticoagulant (see Initial Management under Ischaemic Stroke).

Anticoagulants are not routinely recommended in the long-term prevention of recurrent stroke, except in patients with atrial fibrillation.

A statin should be initiated 48 hours after stroke symptom onset, irrespective of the patient’s serum-cholesterol concentration.

Following the acute phase of ischaemic stroke, blood pressure should be measured and treatment initiated to achieve a target blood pressure of < 130/80 mmHg. Beta-blockers should not be used in the management of hypertension following a stroke, unless they are indicated for a co-existing condition.

All patients should be advised to make lifestyle modifications that include beneficial changes to diet, exercise, weight, alcohol intake, and smoking.

Intracerebral haemorrhage

Initial Management

Surgical intervention may be required following intracerebral haemorrhage to remove the haematoma and relieve intracranial pressure. Patients taking anticoagulants should have this treatment stopped and reversed; anticoagulant therapy has, however, been used in patients with intracerebral haemorrhage who are symptomatic of
deep vein thrombosis or pulmonary embolism; placement of a caval filter is an alternative in this situation.

Long-term management
Aspirin therapy should only be given to patients at a high risk of a cardiac ischaemic event. Anticoagulant therapy is not recommended following an intracerebral haemorrhage, even in those with atrial fibrillation, unless the patient is at very high risk of an ischaemic stroke or cardiac ischaemic events; advice from a specialist should be sought in this situation. Blood pressure should be measured and treatment initiated where appropriate, taking care to avoid hypoperfusion. Statins should be avoided following intracerebral haemorrhage, however they can be used with caution when the risk of a vascular event outweighs the risk of further haemorrhage.

Oral anticoagulants
The main use of anticoagulants is to prevent thrombus formation or extension of an existing thrombus in the slower-moving venous side of the circulation, where the thrombus consists of a fibrin web enmeshed with platelets and red cells.

Anticoagulants are of less use in preventing thrombus formation in arteries, for in faster-flowing vessels thrombi are composed mainly of platelets with little fibrin.

Coumarins and phenindione
The oral anticoagulants warfarin sodium p. 121, acenocoumarol p. 120 and phenindione p. 120, antagonise the effects of vitamin K, and take at least 48 to 72 hours for the anticoagulant effect to develop fully; warfarin sodium is the drug of choice. If an immediate effect is required, unfractionated or low molecular weight heparin must be given concomitantly.

These oral anticoagulants should not be used in cerebral artery thrombosis or peripheral artery occlusion as first-line therapy; aspirin p. 104 is more appropriate for reduction of risk in transient ischaemic attacks. Unfractionated or a low molecular weight heparin (see under Parenteral anticoagulants p. 104) is usually preferred for the prophylaxis of venous thromboembolism in patients undergoing surgery; alternatively, warfarin sodium can be continued in selected patients currently taking long-term warfarin sodium and who are at high risk of thromboembolism (seek expert advice).

Dose
The base-line prothrombin time should be determined but the initial dose should not be delayed whilst awaiting the result.

Target INR
The following indications and target INRs for adults for warfarin take into account recommendations of the British Society for Haematology guidelines on oral anticoagulation with warfarin—fourth edition. Br J Haematol 2011; 154: 311–324:

An INR which is within 0.5 units of the target value is generally satisfactory; larger deviations require dosage adjustment. Target values (rather than ranges) are now recommended.

INR 2.5 for:
• treatment of deep-vein thrombosis or pulmonary embolism (including those associated with antiphospholipid syndrome or for recurrence in patients no longer receiving warfarin sodium p. 121)
• atrial fibrillation
• cardioversion—target INR should be achieved at least 3 weeks before cardioversion and anticoagulation should continue for at least 4 weeks after the procedure (higher target values, such as an INR of 3, can be used for up to 4 weeks before the procedure to avoid cancellations due to low INR)
• dilated cardiomyopathy
• mitral stenosis or regurgitation in patients with either atrial fibrillation, a history of systemic embolism, a left atrial thrombus, or an enlarged left atrium
• bioprosthetic heart valves in the mitral position (treat for 3 months), or in patients with a history of systemic embolism (treat for at least 3 months), or with a left atrial thrombus at surgery (treat until clot resolves), or with other risk factors (e.g. atrial fibrillation or a low ventricular ejection fraction)
• acute arterial embolism requiring embolectomy (consider long-term treatment)
• myocardial infarction
INR 3.5 for:
• recurrent deep-vein thrombosis or pulmonary embolism in patients currently receiving anticoagulation and with an INR above 2:
  • Mechanical prosthetic heart valves:
    • the recommended target INR depends on the type and location of the valve, and patient-related risk factors
    • consider increasing the INR target or adding an antiplatelet drug, if an embolic event occurs whilst anticoagulated at the target INR.

Duration

- 6 weeks for isolated calf-vein deep-vein thrombosis
- 3 months for venous thromboembolism provoked by surgery or other transient risk factor (e.g. combined oral contraceptive use, pregnancy, plaster cast)
- at least 3 months for unprovoked proximal deep-vein thrombosis or pulmonary embolism; long-term anticoagulation may be required.

Haemorrhage
The main adverse effect of all oral anticoagulants is haemorrhage. Checking the INR and omitting doses when appropriate is essential; if the anticoagulant is stopped but not reversed, the INR should be measured 2–3 days later to ensure that it is falling. The cause of an elevated INR should be investigated. The following recommendations (which take into account the recommendations of the British Society for Haematology Guidelines on Oral Anticoagulation with Warfarin—fourth edition. Br J Haematol 2011; 154: 311–324) are based on the result of the INR and whether there is major or minor bleeding; the recommendations apply to adults taking warfarin:

- Major bleeding—stop warfarin sodium; give phytomenadione p. 889 (vitamin K₁) by slow intravenous injection; give dried prothrombin complex p. 96 (factors II, VII, IX, and X); if dried prothrombin complex unavailable, fresh frozen plasma can be given but is less effective; recombinant factor VIIa is not recommended for emergency anticoagulation reversal
- INR >8.0, minor bleeding—stop warfarin sodium p. 121; give phytomenadione p. 889 (vitamin K₁) by slow intravenous injection; repeat dose of phytomenadione p. 889 if INR still too high after 24 hours; restart warfarin sodium when INR <5.0
- INR >8.0, no bleeding—stop warfarin sodium; give phytomenadione (vitamin K₁) by mouth using the intravenous preparation orally (funs of the use); repeat dose of phytomenadione if INR still too high after 24 hours; restart warfarin when INR <5.0
● INR 5.0–8.0, minor bleeding—stop warfarin sodium; give phenytoin mononitrone (vitamin K₃) by slow intravenous injection; restart warfarin sodium when INR <5.0
● INR 5.0–8.0, no bleeding— withhold 1 or 2 doses of warfarin sodium and reduce subsequent maintenance dose
● Unexpected bleeding at therapeutic levels—always investigate possibility of underlying cause e.g. unsuspected renal or gastro-intestinal tract pathology

**Peri-operative anticoagulation**
Warfarin sodium should usually be stopped 5 days before elective surgery; phenytoin mononitrone (vitamin K₃) by mouth (using the intravenous preparation orally [unlicensed use]) should be given the day before surgery if the INR is >1.5. If haemostasis is adequate, warfarin sodium can be resumed at the normal maintenance dose on the evening of surgery or the next day.

Patients stopping warfarin sodium prior to surgery who are considered to be at high risk of thromboembolism (e.g. those with a venous thromboembolic event within the last 3 months, atrial fibrillation with previous stroke or transient ischaemic attack, or mitral mechanical heart valve) may require interim therapy ('bridging') with a low molecular weight heparin (using treatment dose). The low molecular weight heparin should be stopped at least 24 hours before surgery; if the surgery carries a high risk of bleeding, the low molecular weight heparin should not be restarted until at least 48 hours after surgery.

Patients on warfarin sodium who require emergency surgery that can be delayed for 6–12 hours can be given intravenous phenytoin mononitrone (vitamin K₃) to reverse the anticoagulant effect. If surgery cannot be delayed, dried prothrombin complex p. 96 can be given in addition to intravenous phenytoin mononitrone (vitamin K₃) and the INR checked before surgery.

**Combined anticoagulant and antiplatelet therapy**
Existing antiplatelet therapy following an acute coronary syndrome or percutaneous coronary intervention should be continued for the necessary duration according to the indication being treated. The addition of warfarin sodium, when indicated (e.g. for venous thromboembolism or atrial fibrillation) should be considered following an assessment of the patient’s risk of bleeding and discussion with a cardiologist. The duration of treatment with dual therapy (e.g. aspirin p. 104 and warfarin sodium) or triple therapy (e.g. aspirin with clopidogrel p. 106 and warfarin sodium) should be kept to a minimum where possible. The risk of bleeding with aspirin and warfarin sodium dual therapy is lower than with clopidogrel and warfarin sodium. Depending on the indications being treated and the patient’s risk of thromboembolism, it may be possible to withhold antiplatelet therapy until warfarin sodium therapy is complete, or vice versa (on specialist advice) in order to reduce the length of time on dual or triple therapy.

**Antiplatelet drugs**
Antiplatelet drugs decrease platelet aggregation and inhibit thrombus formation in the arterial circulation, because in faster-flowing vessels, thrombi are composed mainly of platelets with little fibrin.

Use of aspirin p. 104 in primary prevention of cardiovascular events, in patients with or without diabetes, is of unproven benefit. Long-term use of aspirin is of benefit in established cardiovascular disease (secondary prevention); unduly high blood pressure must be controlled before aspirin is given. If the patient is at a high risk of gastro-intestinal bleeding, a proton pump inhibitor can be added.

Aspirin is given following coronary bypass surgery. It is also used in atrial fibrillation, for intermittent claudication, for stable angina and acute coronary syndromes, for use following placement of coronary stents and for use in stroke.

Clopidogrel p. 106 is licensed for the prevention of atherothrombotic events in patients with a history of symptomatic ischaemic disease. Clopidogrel, in combination with low-dose aspirin, is also licensed for acute coronary syndrome without ST-segment elevation; in these circumstances the combination is given for up to 12 months (most benefit occurs during the first 3 months; there is no evidence of benefit beyond 12 months). Clopidogrel, in combination with low-dose aspirin, is also licensed for acute myocardial infarction with ST-segment elevation; the combination is licensed for at least 4 weeks, but the optimum treatment duration has not been established. In patients undergoing percutaneous coronary intervention, clopidogrel is used as an adjunct with aspirin. Patients who are not already taking clopidogrel should receive a loading dose prior to procedure.

Clopidogrel is also licensed, in combination with low-dose aspirin, for the prevention of atherothrombotic and thromboembolic events in patients with atrial fibrillation (and at least one risk factor for a vascular event), and for whom warfarin sodium is unsuitable.

Use of clopidogrel with aspirin increases the risk of bleeding. Clopidogrel monotherapy may be an alternative when aspirin is contra-indicated, for example in those with aspirin hypersensitivity, or when aspirin is not tolerated despite the addition of a proton pump inhibitor (see also NICE guidance). Clopidogrel also has uses in stroke.

Dipyridamole is used by mouth as an adjunct to oral anticoagulation for prophylaxis of thromboembolism associated with prosthetic heart valves. Modified-release preparations are licensed for secondary prevention of ischaemic stroke and transient ischaemic attacks.

Prasugrel p. 188, in combination with aspirin, is licensed for the prevention of atherothrombotic events in patients with acute coronary syndrome undergoing percutaneous coronary intervention; the combination is usually given for up to 12 months.

Ticagrelor p. 188, in combination with aspirin, is licensed for the prevention of atherothrombotic events in patients with acute coronary syndrome; the combination is usually given for up to 12 months.

**Antiplatelet drugs and coronary stents**
Patients selected for percutaneous coronary intervention, with the placement of a coronary stent, will require dual antiplatelet therapy with aspirin and either clopidogrel, prasugrel, or ticagrelor. Aspirin therapy should continue indefinitely. Clopidogrel is recommended for 1 month following elective percutaneous coronary intervention with placement of a bare-metal stent, and for 12 months if percutaneous coronary intervention with placement of a bare-metal stent was for an acute coronary syndrome; clopidogrel should be given for 12 months following placement of a drug-eluting stent. Clopidogrel should not be discontinued prematurely in patients with a drug-eluting stent—there is an increased risk of stent thrombosis as a result of the eluted drug slowing the re-endothelialisation process. Patients considered to be at high risk of developing late stent thrombosis with a drug-eluting stent may require a longer duration of treatment with clopidogrel. Prasugrel or ticagrelor are alternatives to clopidogrel in certain patients undergoing percutaneous coronary intervention.

**Glycoprotein IIb/IIIa inhibitors**
Glycoprotein IIb/IIIa inhibitors prevent platelet aggregation by blocking the binding of fibrinogen to receptors on platelets. Abciximab p. 183 is a monoclonal antibody which binds to glycoprotein IIb/IIIa receptors and to other related sites; it is licensed as an adjunct to heparin
Cardiovascular system

Venous thromboembolism.

Healthcare professionals experienced in the treatment of and for the prevention of clotting in extracorporeal circuits.

A duration of patients with solid tumours; treatment is recommended for treatment and prophylaxis of venous thromboembolism in patients with ST-segment elevation myocardial infarction. Tirofiban is also licensed for the extended use in combination with heparin (unfractionated), aspirin, and clopidogrel, for the reduction of major cardiovascular events in patients with ST-segment elevation myocardial infarction intended for primary percutaneous coronary intervention. Abciximab, eptifibatide p. 183 and tirofiban should be used by specialists only.

Epoprostenol p. 99 is also used to inhibit platelet aggregation during renal dialysis when heparins are unsuitable or contra-indicated.

Parenteral anticoagulants

The main use of anticoagulants is to prevent thrombus formation or extension of an existing thrombus in the slower-moving venous side of the circulation, where the thrombus consists of a fibrin web enmeshed with platelets and red cells.

Anticoagulants are of less use in preventing thrombus formation in arteries, for in faster-flowing vessels thrombi are composed mainly of platelets with little fibrin.

Heparin

Heparin initiates anticoagulation rapidly but has a short duration of action. It is often referred to as ‘standard’ or heparin (unfractionated) p. 114 to distinguish it from the low molecular weight heparins, which have a longer duration of action. Although a low molecular weight heparin is generally preferred for routine use, heparin (unfractionated) can be used in those at high risk of bleeding because its effect can be terminated rapidly by stopping the infusion.

Low molecular weight heparins

Low molecular weight heparins (dalteparin sodium p. 112, enoxaparin sodium p. 113, and tinzaparin sodium p. 115) are usually preferred over heparin (unfractionated) in the prevention of Venous thromboembolism because they are as effective and they have a lower risk of heparin-induced thrombocytopenia. The standard prophylactic regimen does not require anticoagulant monitoring. The duration of action of low molecular weight heparins is longer than that of heparin (unfractionated) and once-daily subcutaneous administration is possible for some indications, making them convenient to use.

Low molecular weight heparins are generally preferred over heparin (unfractionated) in the treatment of deep vein thrombosis and pulmonary embolism, and are also used in the treatment of myocardial infarction, unstable coronary artery disease (see under Acute coronary syndromes p. 186) and for the prevention of clotting in extracorporeal circuits.

Dalteparin sodium and tinzaparin sodium (only 20 000 unit/mL syringe) are also licensed for the extended treatment and prophylaxis of venous thromboembolism in patients with solid tumours; treatment is recommended for a duration of 6 months. Treatment should be initiated by healthcare professionals experienced in the treatment of venous thromboembolism.

Heparinoids

Danaparoid sodium p. 111 is a heparinoid used for prophylaxis of deep-vein thrombosis in patients undergoing general or orthopaedic surgery. Providing there is no evidence of cross-reactivity, it also has a role in patients who develop heparin-induced thrombocytopenia.

Argatroban

An oral anticoagulant can be given with argatroban monohydrate p. 116, but it should only be started once thrombocytopenia has substantially resolved.

Hirudins

Bivalirudin, a hirudin analogue, is a thrombin inhibitor which is licensed for unstable angina or non-ST-segment elevation myocardial infarction in patients planned for urgent or early intervention, and as an anticoagulant for patients undergoing percutaneous coronary intervention (including patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention—see also Myocardial infarction: ST-segment elevation p. 186).

Heparin flushes

The role of heparin flushes in maintaining patency of arterial and central venous catheters is unclear.

Epoprostenol

Epoprostenol (prostacyclin) p. 99 can be given to inhibit platelet aggregation during renal dialysis when heparins are unsuitable or contra-indicated. It is also licensed for the treatment of primary pulmonary hypertension resistant to other treatment, usually with oral anticoagulation; it should be initiated by specialists in pulmonary hypertension. Epoprostenol is a potent vasodilator. It has a short half-life of approximately 3 minutes and therefore it must be administered by continuous intravenous infusion.

Fondaparinux

Fondaparinux sodium p. 109 is a synthetic pentasaccharide that inhibits activated factor X.

Aspirin

(Acetylsalicylic Acid)

<table>
<thead>
<tr>
<th>INDICATIONS AND DOSE</th>
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<tbody>
<tr>
<td>Cardiovascular disease (secondary prevention)</td>
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<tr>
<td><strong>BY MOUTH</strong></td>
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<tr>
<td>▷ Adult: 75 mg daily</td>
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<tr>
<td>Management of unstable angina and non-ST-segment elevation myocardial infarction (NSTE MI) Management of ST-segment elevation myocardial infarction (STEMI)</td>
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<tr>
<td><strong>BY MOUTH</strong></td>
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<tr>
<td>▷ Adult: 300 mg</td>
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<td>Suspected transient ischaemic attack</td>
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<tr>
<td><strong>BY MOUTH</strong></td>
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<tr>
<td>▷ Adult: 300 mg daily until diagnosis established</td>
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<tr>
<td>Transient ischaemic attack (long-term treatment following in combination with dipyridamole) Ischaemic stroke not associated with atrial fibrillation (in combination with dipyridamole if clopidogrel contraindicated or not tolerated)</td>
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<tr>
<td><strong>BY MOUTH</strong></td>
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<tr>
<td>▷ Adult: 75 mg daily</td>
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Acute ischaemic stroke
BY MOUTH
▶ Adult: 300 mg daily for 14 days, to be initiated 24 hours after thrombolysis or as soon as possible within 48 hours of symptom onset in patients not receiving thrombolysis

Atrial fibrillation following a disabling ischaemic stroke
BY MOUTH
▶ Adult: 300 mg daily for 14 days
Following disabling ischaemic stroke in patients receiving anticoagulation for a prosthetic heart valve
BY MOUTH
▶ Adult: 300 mg daily, anticoagulant treatment stopped for 7 days and to be substituted with aspirin

Following coronary by-pass surgery
BY MOUTH
▶ Adult: 75–300 mg daily
Mild to moderate pain
BY MOUTH
▶ Adult: 300–900 mg every 4–6 hours as required; maximum 4 g per day
BY RECTUM
▶ Adult: 450–900 mg every 4 hours; maximum 3.6 g per day

CONTRA-INDICATIONS Active peptic ulceration - bleeding disorders (antiplatelet dose) - children under 16 years (risk of Reye’s syndrome) - haemophilia - previous peptic ulceration (analgesic dose) - severe cardiac failure (analgesic dose)

CONTRA-INDICATIONS, FURTHER INFORMATION
Reye’s syndrome Owing to an association with Reye’s syndrome, aspirin-containing preparations should not be given to children under 16 years, unless specifically indicated, e.g. for Kawasaki disease.

CAUTIONS Allergic disease - anaemia - asthma - dehydration - elderly - G6PD deficiency - preferably avoid during fever or viral infection in children (risk of Reye’s syndrome) - previous peptic ulceration (but manufacturers may advise avoidance of low-dose aspirin in history of peptic ulceration) - thyrotoxicosis - uncontrolled hypertension

INTERACTIONS → Appendix 1 (aspirin).
Caution with concomitant use of drugs that increase risk of bleeding.

SIDE-EFFECTS Blood disorders (with analgesic doses) - bronchospasm - confusion (with analgesic doses) - gastrointestinal haemorrhage (occasionally major) - gastrointestinal irritation (with slight asymptomatic blood loss at higher doses) - haemorrhage including subconjunctival haemorrhage (reported with antiplatelet doses) - increased bleeding time - skin reactions in hypersensitive patients - tinnitus (with analgesic doses)

Overdose The main features of salicylate poisoning are hyperventilation, tinnitus, deafness, vasodilatation, and sweating. Coma is uncommon but indicates very severe poisoning.
For specific details on the management of poisoning, see Aspirin, under Emergency treatment of poisoning p. 1123.

ALLERGY AND CROSS-SENSITIVITY Aspirin is contra-indicated in history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria, or rhinitis have been precipitated by aspirin or any other NSAID.

PREGNANCY Use antiplatelet doses with caution during third trimester; impaired platelet function and risk of haemorrhage; delayed onset and increased duration of labour with increased blood loss; avoid analgesic doses if possible in last few weeks (low doses probably not harmful); high doses may be related to intra-uterine growth restriction, teratogenic effects, closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of newborn; kernicterus may occur in jaundiced neonates.

BREAST FEEDING Avoid—possible risk of Reye’s syndrome; regular use of high doses could impair platelet function and produce hypoprothrombinemia in infant if neonatal vitamin K stores low.

HEPATIC IMPAIRMENT Avoid in severe impairment—increased risk of gastro-intestinal bleeding.

RENAL IMPAIRMENT Use with caution; avoid in severe impairment; sodium and water retention; deterioration in renal function; increased risk of gastro-intestinal bleeding.

PRESCRIBING AND DISPENSING INFORMATION BP directs that when no strength is stated the 300 mg strength should be dispensed, and that when soluble aspirin tablets are prescribed, dispersible aspirin tablets shall be dispensed.

PROFESSION SPECIFIC INFORMATION
Dental practitioners’ formulary Aspirin Dispersible Tablets 300 mg may be prescribed.

EXCEPTIONS TO LEGAL CATEGORY Can be sold to the public provided packs contain no more than 32 capsules or tablets; pharmacists can sell multiple packs up to a total quantity of 100 capsules or tablets in justifiable circumstances.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, powder, capsules, liquid

Tablet
CAUTIONARY AND ADVISORY LABELS 21, 32
▶ ASPIRIN (Non-proprietary)
Aspirin 75 mg Aspirin 75mg tablets | 28 tablet £0.82 DT price = £0.82
Aspirin 300 mg Aspirin 300mg tablets | 16 tablet GSS no price available | 28 tablet GSS £2.93 | 32 tablet GSS £0.31–0.33 DT price = £3.35 | 32 tablet P £3.35 DT price = £3.35 | 100 tablet P £10.47
Dispersible tablet
CAUTIONARY AND ADVISORY LABELS 13, 21, 32
▶ ASPIRIN (Non-proprietary)
Aspirin 75 mg Aspirin 75mg dispersible tablets | 28 tablet P £0.90 DT price = £0.87 | 28 tablet GSS £0.87 DT price = £0.87 | 100 tablet P £3.12 DT price = £3.11 | 100 tablet GSS £3.11 DT price = £3.11 | 1000 tablet Boot P £31.28
Pure Health Aspirin 75mg dispersible tablets | 28 tablet P £0.23 DT price = £0.87 | 100 tablet P £0.89 DT price = £3.11
Aspirin 300 mg Aspirin 300mg dispersible tablets | 32 tablet P £1.37 DT price = £1.06 | 32 tablet P no price available DT price = £1.06 | 100 tablet P £0.94–4.28 DT price = £3.31 | 1000 tablet P £33.10
Gastro-resistant tablet
CAUTIONARY AND ADVISORY LABELS 5, 25, 32
▶ ASPIRIN (Non-proprietary)
Aspirin 75 mg Aspirin 75mg gastro-resistant tablets | 28 tablet P £0.93–0.94 DT price = £0.94 | 28 tablet GSS £0.93 DT price = £0.94 | 56 tablet P £1.93 | 56 tablet P no price available Boots Aspirin 75mg gastro-resistant tablets | 56 tablet P no price available
Aspirin 300 mg Aspirin 300mg gastro-resistant tablets | 100 tablet P £20.34 DT price = £20.24
Microplan (Dexcel-Pharma Ltd)
Aspirin 75 mg Microplan 75mg gastro-resistant tablets | 28 tablet P £1.45 DT price = £0.94 | 56 tablet P £2.87
Nu-Seals (Alliance Pharmaceuticals Ltd)
Aspirin 75 mg Nu-Seals 75 gastro-resistant tablets | 56 tablet P £3.12
Suppository

CAUTIONARY AND ADVISORY LABELS 32

▶ ASPIRIN (Non-proprietary)

Aspirin 150 mg Aspirin 150mg suppositories | 10 suppository £16.37–£21.95
Aspirin 300 mg Aspirin 300mg suppositories | 10 suppository £32.63

Also available in combination with dipyramidole, p. 107

Clopidogrel

INDICATIONS AND DOSE

Prevention of atherothrombotic events in percutaneous coronary intervention (adjunct with aspirin) in patients not already on clopidogrel

BY MOUTH

▶ Adult: Loading dose 300 mg, to be taken prior to the procedure, alternatively loading dose 600 mg, higher dose may produce a greater and more rapid inhibition of platelet aggregation

Transient ischaemic attack for patients with aspirin hypersensitivity, or those intolerant of aspirin / Acute ischaemic stroke for patients with aspirin hypersensitivity, or those intolerant of aspirin

BY MOUTH

▶ Adult: 75 mg once daily

Prevention of atherothrombotic events in peripheral arterial disease or within 35 days of myocardial infarction, or within 6 months of ischaemic stroke

BY MOUTH

▶ Adult: 75 mg once daily

Prevention of atherothrombotic events in acute coronary syndrome without ST-segment elevation (given with aspirin)

BY MOUTH

▶ Adult: Initially 300 mg, then 75 mg daily for up to 12 months

Prevention of atherothrombotic events in acute myocardial infarction with ST-segment elevation (given with aspirin)

BY MOUTH

▶ Adult 18-75 years: Initially 300 mg, then 75 mg for at least 4 weeks
▶ Adult 76 years and over: 75 mg daily

Prevention of atherothrombotic and thromboembolic events in patients with atrial fibrillation (with aspirin) and for whom warfarin is unsuitable

BY MOUTH

▶ Adult: 75 mg once daily

UNLICENSED USE 600 mg loading dose prior to percutaneous coronary intervention is an unlicensed dose. Use in transient ischaemic attack or acute ischaemic stroke, in patients with aspirin hypersensitivity or intolerant of aspirin, is unlicensed.

CONTRA-INDICATIONS Active bleeding

CAUTIONS Discontinue 7 days before elective surgery if antiplatelet effect not desirable - patients at risk of increased bleeding from trauma, surgery, or other pathological conditions

INTERACTIONS → Appendix 1 (clopidogrel).

Caution with concomitant use of drugs that increase risk of bleeding.

SIDE-EFFECTS

▶ Abdominal pain - bleeding disorders (including gastro-intestinal and intracranial) - diarrhoea - dyspepsia

▶ Constipation - decreased platelets - dizziness - duodenal ulcers - eosinophilia - flatulence - gastric ulcer - gastritis - headache - leucopenia - nausea - paraesthesia - pruritus - rash - vomiting

Rare Vertigo


ALLERGY AND CROSS-SENSITIVITY Caution with history of hypersensitivity reactions to thienopyridines (e.g. prasugrel).

PREGNANCY Manufacturer advises avoid — no information available.

HEPATIC IMPAIRMENT Manufacturer advises caution (risk of bleeding). Avoid in severe impairment.

RENAL IMPAIRMENT Manufacturer advises caution.

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

Clopidogrel and modified-release dipyramidole in the prevention of occlusive vascular events (December 2010) NICE TA210

The guidance applies to patients who have had an occlusive vascular event, or who have established peripheral arterial disease. The guidance does not apply to patients who have had, or are at risk of, stroke associated with atrial fibrillation, or who need prophylaxis for occlusive events following coronary revascularisation or carotid artery procedures. Clopidogrel monotherapy is recommended as an option to prevent occlusive vascular events in patients who have had:

▶ an ischaemic stroke, or who have peripheral arterial disease or multivascular disease, or
▶ a myocardial infarction, only if aspirin is contraindicated or not tolerated. www.nice.org.uk/TA210

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (February 2004) that clopidogrel be accepted for restricted use for the treatment of confirmed acute coronary syndrome (without ST-segment elevation), in combination with aspirin. Clopidogrel should be initiated in hospital inpatients only.

The Scottish Medicines Consortium has also advised (July 2007) that clopidogrel be accepted for restricted use for patients at ST-segment elevation acute myocardial infarction in combination with aspirin; treatment with clopidogrel is restricted to 4 weeks only.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension, powder for suspension.

Tablet

▶ CLOPIDOGREL (Non-proprietary)

Clopidogrel 75 mg Plavix 75mg tablets | 28 tablet £30.54 DT price = £1.82 | 30 tablet £32.71

Grepid (Beacon Pharmaceuticals Ltd)

Clopidogrel 75 mg Grepid 75mg tablets | 30 tablet £32.28

Plavix (Sanofi)

Clopidogrel 75 mg Plavix 75mg tablets | 30 tablet £35.64

Clopidogrel (as Clopidogrel hydrogen sulfate) 300 mg Plavix 300mg tablets | 30 tablet £142.54 DT price = £142.54
Dipyridamole

INDICATIONS AND DOSE
Secondary prevention of ischaemic stroke (not associated with atrial fibrillation) and transient ischaemic attacks (used alone or with aspirin) | Adjunct to oral anticoagulation for prophylaxis of thromboembolism associated with prosthetic heart valves

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
Adult: 200 mg twice daily, to be taken preferably with food

BY MOUTH USING MODIFIED-RELEASE MEDICINES
Adult: 300–600 mg daily in 3–4 divided doses

Myocardial imaging—diagnostic use only
Adult: (consult product literature)

CAUTIONS
Aortic stenosis · coagulation disorders · heart failure · hypotension · left ventricular outflow obstruction · may exacerbate migraine · myasthenia gravis (risk of exacerbation) · rapidly worsening angina · recent myocardial infarction

INTERACTIONS Appendix 1 (dipyridamole). Caution with concomitant use of drugs that increase risk of bleeding.

SIDE-EFFECTS
Angioedema · dizziness · gastro-intestinal effects · hot flushes · hypersensitivity reactions · hypotension · increased bleeding after surgery · increased bleeding during surgery · myalgia · rash · severe bronchospasm · tachycardia · throbbing headache · thrombocytopnea · urticaria · worsening symptoms of coronary heart disease

PREGNANCY
Not known to be harmful.

BREAST FEEDING
Manufacturers advise use only if essential—small amount present in milk.

PRESCRIBING AND DISPENSING INFORMATION
Modified-release capsules should be dispensed in original container (pack contains a desiccant) and any capsules remaining should be discarded 6 weeks after opening.

NATIONAL FUNDING/ACCESS DECISIONS
NICE technology appraisals (TAs)
Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events (December 2010) NICE TA210

The guidance applies to patients who have had an occlusive vascular event, or who have established peripheral arterial disease. The guidance does not apply to patients who have had, or are at risk of, stroke associated with atrial fibrillation, or who need prophylaxis for occlusive events following coronary revascularisation or carotid artery procedures.

Modified-release dipyridamole, in combination with aspirin, is recommended as an option to prevent occlusive vascular events in patients who have had:
- a transient ischaemic attack, or
- an ischaemic stroke, only if clopidogrel is contraindicated or not tolerated.

Modified-release dipyridamole monotherapy is recommended as an option to prevent occlusive vascular events in patients who have had:
- an ischaemic stroke, only if aspirin and clopidogrel are contra-indicated or not tolerated, or
- a transient ischaemic attack, only if aspirin is contraindicated or not tolerated. www.nice.org.uk/TA210

Aspirin with dipyridamole

The properties listed below are those particular to the combination only. For the properties of the components please consider, aspirin p. 104, dipyridamole above.

INDICATIONS AND DOSE
Secondary prevention of ischaemic stroke and transient ischaemic attacks

BY MOUTH USING MODIFIED-RELEASE MEDICINES
Adult: 25/200 mg twice daily

PRESCRIBING AND DISPENSING INFORMATION
Dispense in original container (pack contains a desiccant) and discard any capsules remaining 6 weeks after opening.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Modified-release capsule
CAUTIONARY AND ADVISORY LABELS
Aspirin 25 mg, Dipyridamole 200 mg

Aspirin 25 mg, Dipyridamole 200 mg
Aspirin 25 mg, Dipyridamole 200 mg
Aspirin 25 mg, Dipyridamole 200 mg
Aspirin 25 mg, Dipyridamole 200 mg
Aspirin 25 mg, Dipyridamole 200 mg

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.


**Cardiovascular system**

When used for prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation and/or pulmonary embolism in adults following knee or hip replacement surgery, prophylaxis of recurrent deep-vein thrombosis or pulmonary embolism, and treatment of deep-vein thrombosis or pulmonary embolism. Use with caution if creatinine clearance < 30 mL/minute—no information available.

**INDICATIONS AND DOSE**

**Prophylaxis of venous thromboembolism following knee replacement surgery**

**BY MOUTH**

- Adult: 2.5 mg twice daily for 10–14 days, to be started 12–24 hours after surgery.

**Prophylaxis of venous thromboembolism following hip replacement surgery**

**BY MOUTH**

- Adult: 2.5 mg twice daily for 32–38 days, to be started 12–24 hours after surgery.

**Treatment of deep-vein thrombosis | Treatment of pulmonary embolism**

**BY MOUTH**

- Adult: Initially 10 mg twice daily for 7 days, then maintenance 5 mg twice daily.

**Prophylaxis of recurrent deep-vein thrombosis | Prophylaxis of recurrent pulmonary embolism**

**BY MOUTH**

- Adult: 2.5 mg twice daily, following completion of 6 months anticoagulant treatment.

**Prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation and at least one risk factor such as previous stroke or transient ischaemic attack, symptomatic heart failure, diabetes mellitus, hypertension, or age ≥ 75 years**

**BY MOUTH**

- Adult: 2.5 mg twice daily.
- Adult 18-79 years: 5 mg twice daily.
- Adult 80 years and over (body-weight up to 61 kg): 2.5 mg twice daily.

**Dose equivalence and conversion**

For information on changing from, or to, other anticoagulants, consult product literature.

**CONTRA-INDICATIONS**

Active bleeding, malignant neoplasms, oesophageal varices, recent brain surgery, recent gastro-intestinal ulcer, recent intracranial haemorrhage, recent ophthalmic surgery, recent spine surgery, significant risk of major bleeding, vascular aneurysm.

**CAUTIONS**

Anaesthesia with postoperative indwelling epidural catheter (risk of paralysis—monitor neurological signs and wait 20–30 hours after apixaban dose before removing catheter and do not give next dose until at least 5 hours after catheter removal), prosthetic heart valve (efficacy not established)—risk of bleeding.

**INTERACTIONS**

Appendix 1 (apixaban). Caution in concomitant use of drugs that increase risk of bleeding.

**SIDE-EFFECTS**

- Common or very common: Anaemia, bruising, haemorrhage, nausea.
- Uncommon: Hypotension, rash, thrombocytopenia.
- PREGNANCY: Manufacturer advises avoid—no information available.
- BREAST FEEDING: Manufacturer advises avoid—present in milk in animal studies.
- HEPATIC IMPAIRMENT: Avoid in severe impairment and in hepatic disease associated with coagulopathy.
- RENAL IMPAIRMENT:

  - When used for prophylaxis of stroke and systemic embolism in atrial fibrillation: Reduce dose to 2.5 mg twice daily if creatinine clearance 15–29 mL/minute, or if serum-creatinine ≥ 133 micromol/ litre and age ≥ 80 years or body-weight < 60 kg.

  - When used for prophylaxis of venous thromboembolism following knee or hip replacement surgery, prophylaxis of recurrent deep-vein thrombosis or pulmonary embolism, and treatment of deep-vein thrombosis or pulmonary embolism: Use with caution if creatinine clearance 15–29 mL/minute. Manufacturer advises avoid if creatinine clearance less than 15 mL/minute—no information available.

**MONITORING REQUIREMENTS**

- Patients should be monitored for signs of bleeding or anaemia; treatment should be stopped if severe bleeding occurs.
- No routine anticoagulant monitoring required (INR tests are unreliable).

**PRESCRIBING AND DISPENSING INFORMATION**

Duration of treatment should be determined by balancing the benefit of treatment with the bleeding risk; shorter duration of treatment (at least 3 months) should be based on transient risk factors i.e. recent surgery, trauma, immobilisation. Apixaban should not be used as an alternative to unfractionated heparin in pulmonary embolism in patients with haemodynamic instability, or who may receive thrombolysis or pulmonary embolectomy.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults (January 2012) NICE TA245

Apixaban is an option for the prevention of venous thromboembolism in adults following elective hip or knee replacement surgery. www.nice.org.uk/TA245

- Apixaban for the prevention of stroke and systemic embolism in non-valvular atrial fibrillation (February 2013) NICE TA275

Apixaban is an option for the prevention of stroke and systemic embolism in non-valvular atrial fibrillation in accordance with its licensed indication; with one or more of the following risk factors:

- previous stroke or transient ischaemic attack
- symptomatic heart failure
- age ≥ 75 years
- diabetes mellitus
- hypertension

The risks and benefits of apixaban compared to warfarin, dabigatran etexilate, and rivaroxaban should be discussed with the patient. www.nice.org.uk/TA275

- Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism (June 2015) NICE TA341

Apixaban is an option for the treatment and prevention of recurrent deep-vein thrombosis and pulmonary embolism in adults. www.nice.org.uk/TA341

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Eliquis** (Bristol-Myers Squibb Pharmaceuticals Ltd) ▼
  - Apixaban 5 mg: Eliquis 5 mg tablets | 28 tablet [P] £30.75 | 56 tablet [P] £61.50 DT price = £61.50
Fondaparinux sodium

**DRUG ACTION** Fondaparinux sodium is a synthetic pentasaccharide that inhibits activated factor X.

**INDICATIONS AND DOSE**

**Prophylaxis of venous thromboembolism in patients after undergoing major orthopaedic surgery of the hip or leg, or abdominal surgery**

**BY SUBCUTANEOUS INJECTION**
- Adult: Initially 2.5 mg, dose to be given 6 hours after surgery, then 2.5 mg once daily.

**Prophylaxis of venous thromboembolism in medical patients immobilised because of acute illness**

**BY SUBCUTANEOUS INJECTION**
- Adult: 2.5 mg once daily.

**Treatment of superficial-vein thrombosis**

**BY SUBCUTANEOUS INJECTION**
- Adult (body-weight 50 kg and above): 2.5 mg once daily for at least 30 days (max. 45 days if high risk of thromboembolic complications), treatment should be stopped 24 hours before surgery and restarted at least 6 hours post operatively.

**Treatment of unstable angina and non-ST-segment elevation myocardial infarction**

**BY SUBCUTANEOUS INJECTION**
- Adult: 2.5 mg once daily for up to 8 days (or until hospital discharge if sooner), treatment should be stopped 24 hours before coronary artery bypass graft surgery (where possible) and restarted 48 hours post operatively.

**Treatment of ST-segment elevation myocardial infarction initially by intravenous injection or by intravenous infusion**

- Adult: Initially 2.5 mg daily for the first day, then (by subcutaneous injection) 2.5 mg once daily for up to 8 days (or until hospital discharge if sooner), treatment should be stopped 24 hours before coronary artery bypass graft surgery (where possible) and restarted 48 hours post operatively.

**Treatment of deep-vein thrombosis and pulmonary embolism**

**BY SUBCUTANEOUS INJECTION**
- Adult (body-weight up to 50 kg): 5 mg every 24 hours, an oral anticoagulant (usually warfarin) is started at the same time as fondaparinux (fondaparinux should be continued for at least 5 days and until INR ≥ 2 for at least 24 hours).
- Adult (body-weight 50-100 kg): 7.5 mg every 24 hours, an oral anticoagulant (usually warfarin) is started at the same time as fondaparinux (fondaparinux should be continued for at least 5 days and until INR ≥ 2 for at least 24 hours).
- Adult (body-weight 101 kg and above): 10 mg every 24 hours, an oral anticoagulant (usually warfarin) is started at the same time as fondaparinux (fondaparinux should be continued for at least 5 days and until INR ≥ 2 for at least 24 hours).

**CONTRA-INDICATIONS** Active bleeding - bacterial endocarditis

**CAUTIONS** Active gastro-intestinal ulcer disease - bleeding disorders - brain surgery - elderly patients - low body-weight - ophthalmic surgery - recent intracranial haemorrhage - risk of catheter thrombus during percutaneous coronary intervention - spinal or epidural anaesthesia (risk of spinal haematoma—avoid if using treatment doses) - spinal surgery

**INTERACTIONS** → Appendix 1 (fondaparinux).

Caution with concomitant use of drugs that increase risk of bleeding.

**SIDE-EFFECTS**
- **Common or very common** Anaemia - bleeding - purpura
- **Uncommon** Chest pain - dyspnoea - gastro-intestinal disturbances - hepatic impairment - oedema - pruritus - rash - thrombocytopenia - thrombocytopenia
- **Rare** Anxiety - confusion - cough - dizziness - drowsiness - flushing - headache - hyperbilirubinaemia - hypokalaemia - hypotension - injection-site reactions - vertigo
- **Frequency not known** Atrial fibrillation - pyrexia - tachycardia

**PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs possible risk—no information available.

**BREAST FEEDING** Present in milk in animal studies—manufacturer advises avoid.

**HEPATIC IMPAIRMENT** Caution in severe impairment (increased risk of bleeding).

**RENAL IMPAIRMENT** Increased risk of bleeding in renal impairment.

- When used for prophylaxis of venous thromboembolism and treatment of superficial-vein thrombosis Reduce dose to 1.5 mg daily if eGFR 20–50 mL/minute/1.73 m².
- When used for treatment of acute coronary syndromes or prophylaxis of venous thromboembolism and treatment of superficial-vein thrombosis Avoid if eGFR less than 20 mL/minute/1.73 m².
- When used for treatment of venous thromboembolism Use with caution if eGFR 30–50 mL/minute/1.73 m², avoid if eGFR less than 30 mL/minute/1.73 m².

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Arixtra®), give intermittently in Sodium chloride 0.9%. For ST-segment elevation myocardial infarction, add requisite dose to 25–50 mL infusion fluid and give over 1–2 minutes.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Arixtra (Aspen Pharma Trading Ltd)

  **Fondaparinux sodium 5 mg per 1 ml** Arixtra 2.5mg/0.5ml solution for injection pre-filled syringes | 10 pre-filled disposable injection (£62.79)
  Arixtra 1.5mg/0.3ml solution for injection pre-filled syringes | 10 pre-filled disposable injection (£62.79, Hospital only)
  Fondaparinux sodium 12.5 mg per 1 ml Arixtra 7.5mg/0.6ml solution for injection pre-filled syringes | 10 pre-filled disposable injection (£116.53)
  Arixtra 5mg/0.4ml solution for injection pre-filled syringes | 10 pre-filled disposable injection (£116.53)
  Arixtra 10mg/0.8ml solution for injection pre-filled syringes | 10 pre-filled disposable injection (£116.53)

**Rivaroxaban**

**DRUG ACTION** Rivaroxaban is a direct inhibitor of activated factor X (factor Xa).

**INDICATIONS AND DOSE**

**Prophylaxis of venous thromboembolism following knee replacement surgery**

**BY MOUTH**
- Adult: 10 mg once daily for 2 weeks, to be started 6–10 hours after surgery.

**Prophylaxis of venous thromboembolism following hip replacement surgery**

**BY MOUTH**
- Adult: 10 mg once daily for 5 days, to be started 6–10 hours after surgery (continued).
Initial treatment of deep-vein thrombosis | Initial treatment of pulmonary embolism
BY MOUTH
- Adult: Initially 15 mg twice daily for 21 days, to be taken with food

Continued treatment of deep-vein thrombosis (following initial treatment) | Continued treatment of pulmonary embolism (following initial treatment)
Prophylaxis of recurrent deep-vein thrombosis | Prophylaxis of recurrent pulmonary embolism
BY MOUTH
- Adult: 20 mg once daily, to be taken with food

Prophylaxis of stroke and systemic embolism in patients with non-valvular atrial fibrillation and with at least one of the following risk factors: congestive heart failure, hypertension, previous stroke or transient ischaemic attack, age ≥75 years, or diabetes mellitus
BY MOUTH
- Adult: 2.5 mg twice daily usual duration 12 months

Dose equivalence and conversion
For information on changing from, or to, other anticoagulants—consult product literature.


- CAUTIONS Anaesthesia with postoperative indwelling epidural catheter (risk of paralysis—monitor neurological signs and wait at least 18 hours after rivaroxaban dose before removing catheter and do not give next dose until at least 6 hours after catheter removal) - bronchiectasis - prostatic heart valve (efficacy not established) - risk of bleeding - rivaroxaban should not be used as an alternative to unfractionated heparin in pulmonary embolism in patients with haemodynamic instability, or who may receive thrombolysis or pulmonary embolectomy - severe hypertension - vascular retinopathy

- INTERACTIONS Appendix 1 (rivaroxaban).

Caution in concomitant use of drugs that increase risk of bleeding.

- SIDE-EFFECTS
  - Common or very common Abdominal pain - constipation - diarrhoea - dizziness - dyspepsia - haemorrhage - headache - hypotenion - nausea - pain in extremities - pruritus - rash - renal impairment - vomiting
  - Uncommon Angioedema - dry mouth - malaise - syncope - tachycardia - thrombocytopenia
  - Rare Jaundice - oedema

- PREGNANCY Manufacturer advises avoid—toxicity in animal studies.

- BREAST FEEDING Manufacturer advises avoid—present in milk in animal studies.

- HEPATIC IMPAIRMENT Avoid in liver disease with coagulopathy.

- RENAL IMPAIRMENT When used for treatment of deep-vein thrombosis or pulmonary embolism and prophylaxis of recurrent deep-vein thrombosis and pulmonary embolism Initially 15 mg twice daily for 21 days, then 20 mg once daily (but consider reducing to 15 mg once daily if risk of bleeding outweighs risk of recurrent deep-vein thrombosis or pulmonary embolism) if creatinine clearance 15–49 mL/minute.

- When used for prophylaxis of stroke and systemic embolism in atrial fibrillation Reduce dose to 15 mg once daily if creatinine clearance 15–49 mL/minute.

- When used for prophylaxis of venous thromboembolism following knee or hip replacement surgery and prophylaxis of atherothrombotic events in acute coronary syndrome Use with caution if creatinine clearance 15–29 mL/minute. Use with caution if concomitant use of drugs that increase plasma-rivaroxaban concentration (consult product literature).

Avoid if creatinine clearance less than 15 mL/minute; manufacturer recommends Cockcroft and Gault formula to calculate creatinine clearance.

- MONITORING REQUIREMENTS
  - Patients should be monitored for signs of bleeding or anaemia; treatment should be stopped if severe bleeding occurs.
  - No routine anticoagulant monitoring required (INR tests are unreliable).

- DIRECTIONS FOR ADMINISTRATION Tablets may be crushed and mixed with water or apple puree just before administration.

- PRESCRIBING AND DISPENSING INFORMATION Low-dose rivaroxaban, in combination with aspirin alone or aspirin and clopidogrel, is licensed for the prevention of atherothrombotic events following an acute coronary syndrome with elevated cardiac biomarkers. Treatment should be started as soon as possible after the patient has been stabilised following the acute coronary event, at the earliest 24 hours after admission to hospital, and at the time when parenteral anticoagulation therapy would normally be discontinued; the usual duration of treatment is 12 months.

- NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)
- Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults (April 2009) NICE TA170 Rivaroxaban is an option for the prophylaxis of venous thromboembolism in adults after total hip replacement or total knee replacement surgery. www.nice.org.uk/TA170

- Rivaroxaban for the prevention of stroke and systemic embolism in atrial fibrillation (May 2012) NICE TA256 Rivaroxaban is an option for the prevention of stroke and systemic embolism (in accordance with its licensed indication) in patients with non-valvular atrial fibrillation and with at least one of the following risk factors: previous stroke or transient ischaemic attack - congestive heart failure - age ≥75 years - diabetes mellitus - hypertension

The risks and benefits of rivaroxaban compared with warfarin should be discussed with the patient. www.nice.org.uk/TA256


- Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism (June 2013) NICE TA287 Rivaroxaban is an option for treating pulmonary embolism and preventing recurrent deep-vein thrombosis and pulmonary embolism in adults. www.nice.org.uk/TA287
Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome (March 2015)

NICE TA335

Rivaroxaban is an option within its marketing authorisation, in combination with aspirin plus clopidogrel or aspirin alone, for preventing atherothrombotic events in patients who have had an acute coronary syndrome with elevated cardiac biomarkers. The patient’s risk of bleeding should be carefully assessed before treatment is initiated and the risks and benefits of rivaroxaban in combination with aspirin plus clopidogrel or with aspirin alone, compared with aspirin plus clopidogrel or aspirin alone should be discussed with the patient. A decision on continuation of treatment should be taken no later than 12 months after starting treatment.

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (January 2012) that rivaroxaban (Xarelto®) is accepted for restricted use within NHS Scotland for the prevention of stroke and systemic embolism in accordance with the licensed indication; use is restricted to patients with poor INR control despite compliance with coumarin anticoagulant therapy, or to patients who are allergic to, or unable to tolerate, a coumarin anticoagulant.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Xarelto (Bayer Plc) ▼
  - Rivaroxaban 2.5 mg: Xarelto 2.5mg tablets | 56 tablet £58.80
  - Rivaroxaban 10 mg: Xarelto 10mg tablets | 10 tablet £21.00 | 30 tablet £63.00
  - Rivaroxaban 15 mg: Xarelto 15mg tablets | 14 tablet £29.40 | 28 tablet £58.80 | 42 tablet £88.20 | 100 tablet £210.00
  - Rivaroxaban 20 mg: Xarelto 20mg tablets | 28 tablet £58.80 | 100 tablet £210.00

**HEPARINOIDs**

**Danaparoid sodium**

**INDICATIONS AND DOSE**

Prevention of deep-vein thrombosis in general or orthopaedic surgery

**BY SUBCUTANEOUS INJECTION**

- Adult: 750 units twice daily for 7–10 days, initiate treatment before operation, with last pre-operative dose 1–4 hours before surgery

Thromboembolic disease in patients with history of heparin-induced thrombocytopenia

**INITIALLY BY INTRAVENOUS INJECTION**

- Adult (body-weight up to 55 kg): Initially 1250 units, then (by continuous intravenous infusion) 400 units/hour for 2 hours, then (by continuous intravenous infusion) 300 units/hour for 2 hours, then (by continuous intravenous infusion) 200 units/hour for 5 days
- Adult (body-weight 55–89 kg): Initially 2500 units, then (by continuous intravenous infusion) 400 units/hour for 2 hours, then (by continuous intravenous infusion) 300 units/hour for 2 hours, then (by continuous intravenous infusion) 200 units/hour for 5 days
- Adult (body-weight 90 kg and above): Initially 3750 units, then (by continuous intravenous infusion) 400 units/hour for 2 hours, then (by continuous intravenous infusion) 300 units/hour for 2 hours, then (by continuous intravenous infusion) 200 units/hour for 5 days

**CONTRA-INDICATIONS**

Active peptic ulcer (unless this is the reason for operation) • acute bacterial endocarditis • diabetic retinopathy • epidural anaesthesia (with treatment doses) • haemophilia and other haemorrhagic disorders • recent cerebral haemorrhage • severe hypertension • spinal anaesthesia (with treatment doses) • thrombocytopenia (unless patient has heparin-induced thrombocytopenia)

**CAUTIONS**

Antibodies to heparins (risk of antibody-induced thrombocytopenia) • body-weight over 90 kg • recent bleeding • risk of bleeding

**INTERACTIONS**

Appendix 1 (danaparoid).

Caution with concomitant use of drugs that increase risk of bleeding.

**SIDE-EFFECTS**

Bleeding • hypersensitivity reactions • rash

**PREGNANCY**

Manufacturer advises avoid—limited information available but not known to be harmful.

**BREAST FEEDING**

Amount probably too small to be harmful but manufacturer advises avoid.

**HEPATIC IMPAIRMENT**

Caution in moderate impairment (increased risk of bleeding). Avoid in severe impairment unless patient has heparin-induced thrombocytopenia and no alternative available.

**RENAL IMPAIRMENT**

Use with caution in moderate impairment. Avoid in severe impairment unless patient has heparin-induced thrombocytopenia and no alternative available.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Orgaran (Aspen Pharma Trading Ltd)
  - Danaparoid sodium 1250 unit per 1 ml
  - Orgaran 750units/0.6ml solution for injection ampoules | 10 ampoule £266.73

**Heparins**

**CONTRA-INDICATIONS**

Acute bacterial endocarditis • after major trauma • epidural anaesthesia with treatment doses • haemophilia and other haemorrhagic disorders • peptic ulcer • recent cerebral haemorrhage • recent surgery to eye • recent surgery to nervous system • severe hypertension • spinal anaesthesia with treatment doses • thrombocytopenia (including history of heparin-induced thrombocytopenia)

**CAUTIONS**

Elderly

**INTERACTIONS**

Appendix 1 (heparins).

Caution with concomitant use of drugs that increase risk of bleeding.

**SIDE-EFFECTS**

- Rare Alopecia (on prolonged use) • anaphylaxis • angioedema • hyperkalaemia • hypersensitivity reactions • injection-site reactions • osteoporosis (risk lower with low molecular weight heparins) • priapism • rebound hyperlipidaemia (following unfractonated heparin withdrawal) • skin necrosis • urticaria
- Frequency not known Haemorrhage • thrombocytopenia
SIDE-EFFECTS, FURTHER INFORMATION

Haemorrhage If haemorrhage occurs it is usually sufficient to withdraw unfracti"oned or low molecular weight heparin, but if rapid reversal of the effects of the heparin is required, protamine sulfate is a specific antidote (but only partially reverses the effects of low molecular weight heparins).

Heparin-induced thrombocytopenia Clinically important heparin-induced thrombocytopenia is immune-mediated and does not usually develop until after 5–10 days; it can be complicated by thrombosis. Signs of heparin-induced thrombocytopenia include a 30% reduction of platelet count, thrombosis, or skin allergy. If heparin-induced thrombocytopenia is strongly suspected or confirmed, the heparin should be stopped and an alternative anticoagulant, such as danaparoid, should be given. Ensure platelet counts return to normal range in those who require warfarin.

Hyperkalaemia Inhibition of aldosterone secretion by unfracti"oned or low molecular weight heparin can result in hyperkalaemia; patients with diabetes mellitus, chronic renal failure, acidosis, raised plasma potassium or those taking potassium-sparing drugs seem to be more susceptible. The risk appears to increase with duration of therapy.

- Allergy and cross-sensitivity Hypersensitivity to unfracti"oned or low molecular weight heparin.

• Monitoring requirements
  - Heparin-induced thrombocytopenia Platelet counts should be measured just before treatment with unfracti"oned or low molecular weight heparin, and regular monitoring of platelet counts may be required if given for longer than 4 days. See the British Society for Haematology’s Guidelines on the diagnosis and management of heparin-induced thrombocytopenia: second edition. Br J Haematol 2012; 159: 528–540.
  - Hyperkalaemia Plasma-potassium concentration should be measured in patients at risk of hyperkalaemia before starting the heparin and monitored regularly thereafter, particularly if treatment is to be continued for longer than 7 days.

Dalteparin sodium

Indications and dose Fragmin® graduated syringes

Unstable coronary artery disease (including non-ST-segment-elevation myocardial infarction) BY SUBCUTANEOUS INJECTION
- Adult: 120 units/kg every 12 hours (max. per dose 10 000 units twice daily) for up to 8 days

Patients with unstable coronary artery disease (including non-ST-segment-elevation myocardial infarction) awaiting angiography or revascularisation and having already had 8 days treatment with dalteparin BY SUBCUTANEOUS INJECTION
- Adult (body-weight up to 69 kg and male): 5000 units every 12 hours until the day of the procedure (max. 45 days)
- Adult: (body-weight up to 79 kg and female): 5000 units every 12 hours until the day of the procedure (max. 45 days)
- Adult (body-weight 70 kg and above and male): 7500 units every 12 hours until the day of the procedure (max. 45 days)
- Adult (body-weight 80 kg and above and female): 7500 units every 12 hours until the day of the procedure (max. 45 days)

Fragmin® single-dose syringes

Prophylaxis of deep-vein thrombosis in surgical patients—moderate risk BY SUBCUTANEOUS INJECTION
- Adult: Initially 2500 units for 1 dose, dose to be given 1–2 hours before surgery, then 2500 units every 24 hours

Prophylaxis of deep-vein thrombosis in surgical patients—high risk BY SUBCUTANEOUS INJECTION
- Adult: Initially 2500 units for 1 dose, dose to be administered 1–2 hours before surgery, followed by 2500 units after 8–12 hours, then 5000 units every 24 hours, alternatively initially 5000 units for 1 dose, dose to be given on the evening before surgery, followed by 5000 units after 24 hours, then 5000 units every 24 hours

Prophylaxis of deep-vein thrombosis in medical patients BY SUBCUTANEOUS INJECTION
- Adult: 5000 units every 24 hours

Treatment of deep-vein thrombosis, with oral anticoagulant treatment / Treatment of pulmonary embolism, with oral anticoagulant treatment BY SUBCUTANEOUS INJECTION
- Adult (body-weight up to 45 kg): 7500 units daily until adequate oral anticoagulation established
- Adult (body-weight 46–56 kg): 10 000 units daily until adequate oral anticoagulation established
- Adult (body-weight 57–68 kg): 12 500 units daily until adequate oral anticoagulation established
- Adult (body-weight 69–82 kg): 15 000 units daily until adequate oral anticoagulation established
- Adult (body-weight 83 kg and above): 18 000 units daily until adequate oral anticoagulation established

Extended treatment and prophylaxis of venous thromboembolism in patients with solid tumours
- Adult (body-weight 40–45 kg): 7500 units once daily for 30 days, then 7500 units once daily for a further 5 months, interrupt treatment or reduce dose in chemotherapy-induced thrombocytopenia—consult product literature
- Adult (body-weight 46–56 kg): 10 000 units once daily for 30 days, then 7500 units once daily for a further 5 months, interrupt treatment or reduce dose in chemotherapy-induced thrombocytopenia—consult product literature
- Adult: (body-weight 57–68 kg): 12 500 units once daily for 30 days, then 7500 units once daily for a further 5 months, interrupt treatment or reduce dose in chemotherapy-induced thrombocytopenia—consult product literature
- Adult (body-weight 69–82 kg): 15 000 units once daily for 30 days, then 12 500 units once daily for a further 5 months, interrupt treatment or reduce dose in chemotherapy-induced thrombocytopenia—consult product literature
- Adult (body-weight 83 kg and above): 18 000 units once daily for 30 days, then 18 000 units once daily for a further 5 months, interrupt treatment or reduce dose in chemotherapy-induced thrombocytopenia—consult product literature
Treatment of venous thromboembolism in pregnancy

**BY SUBCUTANEOUS INJECTION**
- Adult (body-weight up to 49 kg): 5000 units twice daily, use body-weight in early pregnancy to calculate the dose
- Adult (body-weight 50–69 kg): 6000 units twice daily, use body-weight in early pregnancy to calculate the dose
- Adult (body-weight 70–89 kg): 8000 units twice daily, use body-weight in early pregnancy to calculate the dose
- Adult (body-weight 90 kg and above): 10 000 units twice daily, use body-weight in early pregnancy to calculate the dose

**FRAGMIN®**

Treatment of deep-vein thrombosis, with oral anticoagulant treatment

**BY SUBCUTANEOUS INJECTION**
- Adult: 200 units/kg daily (max. per dose 18 000 units) until adequate oral anticoagulation established

Treatment of deep-vein thrombosis, with oral anticoagulant treatment (in patients at increased risk of haemorrhage)

**BY SUBCUTANEOUS INJECTION**
- Adult: 100 units/kg twice daily until adequate oral anticoagulation established

**UNLICENSED USE**

Not licensed for treatment of venous thromboembolism in pregnancy.

**PREGNANCY**

Not known to be harmful, low molecular weight heparins do not cross the placenta. Multidose vial contains benzyl alcohol—manufacturer advises avoid.

**BREAST FEEDING**

Due to the relatively high molecular weight and inactivation in the gastro-intestinal tract, passage into breast-milk and absorption by the nursing infant are likely to be negligible, however manufacturers advise avoid.

**HEPATIC IMPAIRMENT**

Dose reduction may be required in severe impairment—risk of bleeding may be increased.

**RENAL IMPAIRMENT**

Risk of bleeding may be increased—dose reduction may be required. Use of unfractionated heparin may be preferable.

**MONITORING REQUIREMENTS**

- For monitoring during treatment of deep-vein thrombosis and of pulmonary embolism, blood should be taken 3–4 hours after a dose (recommended plasma concentration of anti-Factor Xa 0.5–1 unit/mL); monitoring not required for once-daily treatment regimen and not generally necessary for twice-daily regimen.
- Routine monitoring of anti-Factor Xa activity is not usually required during treatment with dalteparin, but may be necessary in patients at increased risk of bleeding (e.g. in renal impairment and those who are underweight or overweight).

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium (SMC) has advised (February 2011) that dalteparin (Fragmin®) is accepted for restricted use within NHS Scotland as extended treatment of symptomatic venous thromboembolism and prevention of its recurrence in patients with solid tumours.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

**EXCIPIENTS:** May contain Benzyl alcohol

- Fragmin (Pfizer Ltd)
  - Dalteparin sodium 2500 unit per 1 ml Fragmin 10,000 units/4ml solution for injection ampoules | 10 ampoule (PFS) £51.22
  - Dalteparin sodium 10000 unit per 1 ml Fragmin 10,000 units/1ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (PFS) £28.23
  - Fragmin 10,000units/1ml solution for injection ampoules | 10 ampoule (PFS) £51.22
  - Dalteparin sodium 12500 unit per 1 ml Fragmin 2,500units/0.2ml solution for injection pre-filled syringes | 10 pre-filled disposable injection (PFS) £18.58
  - Dalteparin sodium 25000 unit per 1 ml Fragmin 18,000units/0.72ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (PFS) £50.82
  - Fragmin 15,000units/0.6ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (PFS) £42.34
  - Fragmin 5,000units/0.2ml solution for injection pre-filled syringes | 10 pre-filled disposable injection (PFS) £28.23
  - Fragmin 12,500units/0.5ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (PFS) £35.25
  - Fragmin 7,500units/0.3ml solution for injection pre-filled syringes | 10 pre-filled disposable injection (PFS) £42.34
  - Fragmin 100,000units/4ml solution for injection vials | 1 vial (PFS) £48.66
  - Fragmin 10,000units/0.4ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (PFS) £28.23

**Enoxaparin sodium**

**INDICATIONS AND DOSE**

Treatment of venous thromboembolism in pregnancy

**BY SUBCUTANEOUS INJECTION**
- Adult (body-weight up to 50 kg): 40 mg twice daily, dose based on early pregnancy body-weight
- Adult (body-weight 50–69 kg): 60 mg twice daily, dose based on early pregnancy body-weight
- Adult (body-weight 70–89 kg): 80 mg twice daily, dose based on early pregnancy body-weight
- Adult (body-weight 90 kg and above): 100 mg twice daily, dose based on early pregnancy body-weight

**Prophylaxis of deep-vein thrombosis, especially in surgical patients—moderate risk**

**BY SUBCUTANEOUS INJECTION**
- Adult: 20 mg for 1 dose, dose to be given approximately 2 hours before surgery, then 20 mg every 24 hours

**Prophylaxis of deep-vein thrombosis, especially surgical patients—high risk (e.g. orthopaedic surgery)**

**BY SUBCUTANEOUS INJECTION**
- Adult: 40 mg for 1 dose, dose to be given 12 hours before surgery, then 40 mg every 24 hours

**Prophylaxis of deep-vein thrombosis in medical patients**

**BY SUBCUTANEOUS INJECTION**
- Adult: 40 mg every 24 hours

**Treatment of deep-vein thrombosis | Treatment of pulmonary embolism**

**BY SUBCUTANEOUS INJECTION**
- Adult: 1.5 mg/kg every 24 hours until adequate oral anticoagulation established

**Treatment of acute ST-segment elevation myocardial infarction (patients not undergoing percutaneous coronary intervention)**

**INITIALLY BY INTRAVENOUS INJECTION**
- Adult 18–74 years: Initially 30 mg, followed by (by subcutaneous injection) 1 mg/kg for 1 dose, then (by subcutaneous injection) 1 mg/kg every 12 hours...
(max. per dose 100 mg) for up to 8 days, maximum dose applies for the first two subcutaneous doses only

- **BY SUBCUTANEOUS INJECTION**
  - Adult 75 years and over: 750 micrograms/kg every 12 hours (max. per dose 75 mg), maximum dose applies for the first two doses only

**Treatment of acute ST-segment elevation myocardial infarction (patients undergoing percutaneous coronary intervention)**

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult 18–74 years: Initially 30 mg, followed by (by subcutaneous injection) 1 mg/kg for 1 dose, then (by subcutaneous injection) 1 mg/kg every 12 hours (max. per dose 100 mg) for up to 8 days, maximum dose applies for the first two subcutaneous doses only, then (by intravenous injection) 300 micrograms/kg for 1 dose, dose to be given at the time of procedure if the last subcutaneous dose was given more than 8 hours previously

- **INITIALLY BY SUBCUTANEOUS INJECTION**
  - Adult 75 years and over: 750 micrograms/kg every 12 hours (max. per dose 75 mg), maximum dose applies for the first two doses only, then (by intravenous injection) 300 micrograms/kg for 1 dose, dose to be given at the time of procedure if the last subcutaneous dose was given more than 8 hours previously

**Unstable angina | Non-ST-segment-elevation myocardial infarction**

- **BY SUBCUTANEOUS INJECTION**
  - Adult: 1 mg/kg every 12 hours usually for 2–8 days (minimum 2 days)

**Prevention of clotting in extracorporeal circuits**

- **TO THE DEVICE AS A FLUSH**
  - Adult: (consult product literature)

**Dose equivalence and conversion**

1 mg equivalent to 100 units.

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**Solution for injection**

**EXCIPIENTS:** May contain Benzyl alcohol

- **Clexane (Sanofi)**
  - Enoxaparin sodium 100 mg per 1 ml Clexane 60mg/0.6ml solution for injection pre-filled syringes | 10 pre-filled disposable injection | £45.65 DT price = £45.65
  - Clexane 300mg/3ml solution for injection multidose vials | 1 vial | £21.33
  - Clexane 80mg/0.8ml solution for injection pre-filled syringes | 10 pre-filled disposable injection | £64.86 DT price = £64.86
  - Clexane 40mg/0.4ml solution for injection pre-filled syringes | 10 pre-filled disposable injection | £30.27 DT price = £30.27
  - Clexane 100mg/1ml solution for injection pre-filled syringes | 10 pre-filled disposable injection | £80.33 DT price = £80.33
  - Clexane 20mg/0.2ml solution for injection pre-filled syringes | 10 pre-filled disposable injection | £22.72 DT price = £22.72

- **Enoxaparin sodium 150 mg per 1 ml**
  - Clexane Forte 120mg/0.8ml solution for injection pre-filled syringes | £97.70 DT price = £97.70
  - Clexane Forte 150mg/1ml solution for injection pre-filled syringes | 10 pre-filled disposable injection | £111.01 DT price = £111.01

**Heparin (unfractionated)**

**INDICATIONS AND DOSE**

- **Treatment of mild to moderate pulmonary embolism**
  - **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Loading dose 5000 units, alternatively (by intravenous injection) loading dose 75 units/kg, followed by (by continuous intravenous infusion) 18 units/kg/hour, laboratory monitoring essential—preferably on a daily basis, and dose adjusted accordingly

- **Treatment of unstable angina | Treatment of acute peripheral arterial occlusion**
  - **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Loading dose 10 000 units, followed by (by continuous intravenous infusion) 18 units/kg/hour, laboratory monitoring essential—preferably on a daily basis, and dose adjusted accordingly

- **Treatment of deep-vein thrombosis**
  - **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Loading dose 5000 units, alternatively (by intravenous injection) loading dose 75 units/kg, followed by (by continuous intravenous infusion) 18 units/kg/hour, alternatively (by subcutaneous injection) 15 000 units every 12 hours, laboratory monitoring essential—preferably on a daily basis, and dose adjusted accordingly

**Thromboprophylaxis in medical patients**

- **BY SUBCUTANEOUS INJECTION**
  - Adult: 5000 units every 8–12 hours

**Thromboprophylaxis in surgical patients**

- **BY SUBCUTANEOUS INJECTION**
  - Adult: 5000 units for 1 dose, to be taken 2 hours before surgery, then 5000 units every 8–12 hours

**Thromboprophylaxis during pregnancy**

- **BY SUBCUTANEOUS INJECTION**
  - Adult: 5000–10 000 units every 12 hours, to be administered with monitoring. **Important:** prevention of prosthetic heart-valve thrombosis in pregnancy calls for specialist management

**Haemodialysis**

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 1000–5000 units, followed by (by continuous intravenous infusion) 250–1000 units/hour

**Prevention of clotting in extracorporeal circuits**

- **TO THE DEVICE AS A FLUSH**
  - Adult: (consult product literature)
Thromboembolism

**Tinzaparin sodium**

**INDICATIONS AND DOSE**

**INNOHEP® 10,000 UNITS/ML**

Prophylaxis of deep-vein thrombosis (general surgery)
- Adult: 3500 units for 1 dose, dose to be given 2 hours before surgery, then 3500 units every 24 hours

Prophylaxis of deep-vein thrombosis (orthopaedic surgery)
- Adult: Initially 50 units/kg for 1 dose, dose to be given 2 hours before surgery, then 50 units/kg every 24 hours, alternatively initially 4500 units for 1 dose, dose to be given 12 hours before surgery, then 4500 units every 24 hours

Treatment of deep-vein thrombosis | Treatment of pulmonary embolism
- **BY SUBCUTANEOUS INJECTION**
  - Adult: 175 units/kg once daily for up to 6 months

Treatment of venous thromboembolism in patients with solid tumours | Prophylaxis of venous thromboembolism in patients with solid tumours
- **BY SUBCUTANEOUS INJECTION**
  - Adult: 175 units/kg once daily, dose based on early pregnancy body-weight, treatment regimens do not require anticoagulation monitoring

**SIDE-EFFECTS**
- Uncommon: Headache

**UNLICENSED USE**
- Not licensed for the treatment of venous thromboembolism in pregnancy.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops, solution for injection, solution for infusion

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**Sniff**

To maintain patency of catheters, cannulas, other indwelling intravenous infusion devices

- **TO THE DEVICE AS A FLUSH**
  - Adult: 10–200 units, to be flushed through every 4–8 hours, not for therapeutic use

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#### PREGNANCY
- Does not cross the placenta; maternal osteoporosis reported after prolonged use; multidose vials may contain benzyl alcohol—some manufacturers advise avoid.

#### BREAST FEEDING
- Not excreted into milk due to high molecular weight.

#### HEPATIC IMPAIRMENT
- Risk of bleeding increased—reduce dose or avoid in severe impairment (including oesophageal varices).

#### RENAL IMPAIRMENT
- Risk of bleeding increased in severe impairment—dose may need to be reduced.

#### DIRECTIONS FOR ADMINISTRATION
- For intravenous infusion, give continuously in Glucose 5% or Sodium chloride 0.9%; administration with a motorised pump is advisable.

#### PRESCRIBING AND DISPENSING INFORMATION
- Doses listed take into account the guidelines of the British Society for Haematology.

#### MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops, solution for injection, solution for infusion

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**Solution for injection**

**EXCIPIENTS:** May contain Benzy alcohol

- **HEPARIN (UNFRACTIONATED) (Non-proprietary)**
  - Heparin sodium 1000 unit per 1 ml: Heparin sodium 1000 units/1ml solution for injection ampoules | 10 ampoule (POM) £14.85
  - Heparin sodium 5000 units/5ml solution for injection vials | 10 vial (P03) £16.50–£37.41
  - Heparin sodium 20,000 units/20ml solution for injection ampoules | 10 ampoule (P03) £70.80–£70.88
  - Heparin sodium 5000 units/5ml solution for injection ampoules | 10 ampoule (POM) £37.45–£37.47
  - Heparin sodium 10,000 units/10ml solution for injection ampoules | 10 ampoule (P03) £64.50–£64.59
  - Heparin sodium 5000 units/1ml solution for injection ampoules | 10 vial (P03) £45.00–£84.60
  - Heparin sodium 5000 units/1ml solution for injection ampoules | 10 ampoule (P03) £29.04
  - Heparin sodium 25,000 units/5ml solution for injection ampoules | 10 ampoule (P03) £75.78
  - Heparin calcium 25000 unit per 1 ml: Heparin calcium 5000 units/0.2ml solution for injection ampoules | 10 ampoule (P03) £33.12
  - Heparin sodium 25000 unit per 1 ml: Heparin sodium 25000 units/lml solution for injection ampoules | 10 ampoule (P03) £76.95
  - Heparin sodium 5000 units/0.2ml solution for injection ampoules | 10 ampoule (P03) £37.35

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**Infusion**

- **HEPARIN (UNFRACTIONATED) (Non-proprietary)**
  - Heparin sodium 1000 unit per 1 ml: Heparin sodium 1000 units/500ml infusion Viaflex bags | 1 bag (P03) no price available
  - Heparin sodium 2000 units/1000ml infusion Viaflex bags | 1 bag (P03) no price available
  - Heparin sodium 5000 units/litre infusion Viaflex bags | 1 bag (P03) no price available

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**Intravenous Flush**

**EXCIPIENTS:** May contain Benzy alcohol

- **HEPARIN (UNFRACTIONATED) (Non-proprietary)**
  - Heparin sodium 50 units/5ml patency solution ampoules | 10 ampoule (P03) £14.96
  - Heparin sodium 50 units/5ml IV. flush solution ampoules | 10 ampoule (P03) £14.96
  - Heparin sodium 200 units/2ml IV. flush solution ampoules | 10 ampoule (P03) £15.68

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**BNF 70**

To maintain patency of catheters, cannulas, other indwelling intravenous infusion devices

- **TO THE DEVICE AS A FLUSH**
  - Adult: 10–200 units, to be flushed through every 4–8 hours, not for therapeutic use

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**RENAL IMPAIRMENT**
- Risk of bleeding increased in severe impairment—dose may need to be reduced.

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**DIRECTIONS FOR ADMINISTRATION**
- For intravenous infusion, give continuously in Glucose 5% or Sodium chloride 0.9%; administration with a motorised pump is advisable.

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**PRESCRIBING AND DISPENSING INFORMATION**
- Doses listed take into account the guidelines of the British Society for Haematology.

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**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.
Argatroban monohydrate

INDICATIONS AND DOSE
Anticoagulation in patients with heparin-induced thrombocytopenia type II who require parenteral antithrombotic treatment

INITIALLY BY CONTINUOUS INTRAVENOUS INFUSION
- Adult: Initially 2 micrograms/kg/minute, dose to be adjusted according to activated partial thromboplastin time, (by intravenous infusion) increased up to 10 micrograms/kg/minute maximum duration of treatment 14 days

Anticoagulation in patients with heparin-induced thrombocytopenia type II who require parenteral antithrombotic treatment (for dose in cardiac surgery, percutaneous coronary intervention, or critically ill patients)

BY CONTINUOUS INTRAVENOUS INFUSION
- Adult: (consult product literature)

Anticoagulation in patients with heparin-induced thrombocytopenia type II who require parenteral antithrombotic treatment (when initiating concomitant warfarin treatment)

BY CONTINUOUS INTRAVENOUS INFUSION
- Adult: Dose should be temporarily reduced to 2 micrograms/kg/minute, and INR measured after 4–6 hours; warfarin should be initiated at intended maintenance dose (do not give loading dose of warfarin); consult product literature for further details

CAUTIONS
- Bleeding disorders - diabetic retinopathy - gastro-intestinal ulceration - immediately after lumbar puncture - major surgery (especially of brain, spinal cord, or eye) - risk of bleeding - severe hypertension - spinal anaesthesia

INTERACTIONS
- Appendix 1 (argatroban). Caution with concomitant use of drugs that increase risk of bleeding.

SIDE-EFFECTS
- Common or very common Haemorrhage - nausea - purpura

PREGNANCY
- Manufacturer advises avoid unless essential—limited information available.

BREAST FEEDING
- Avoid—no information available.

HEPATIC IMPAIRMENT
- Reduce initial dose to 500 nanograms/kg/minute in moderate impairment. Avoid in severe impairment or in patients with hepatic impairment undergoing percutaneous coronary intervention.

MONITORING REQUIREMENTS
- Determine activated partial thromboplastin time 2 hours after start of treatment, then 2 or 4 hours after infusion rate altered (consult product literature), and at least once daily thereafter.

DIRECTIONS FOR ADMINISTRATION
- For intravenous infusion (Exembol®) give continuously in Glucose 5% or Sodium chloride 0.9%. Dilute each 2.5–mL vial with 250 mL infusion fluid.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.

Solution for infusion
- EXCEPT FOR: May contain Ethanol
- Exembol (Mitsubishi Pharma Europe Ltd)
- Argatroban monohydrate 100 mg per 1 ml Exembol 250mg/2.5ml concentrate for solution for infusion vials | 1 vial (Post) no price available

Bivalirudin

DRUG ACTION
- Bivalirudin, a hirudin analogue, is a thrombin inhibitor.

INDICATIONS AND DOSE
Unstable angina or non-ST-segment elevation myocardial infarction in patients planned for urgent or early intervention (in addition to aspirin and clopidogrel) INITIALLY BY INTRAVENOUS INJECTION
- Adult: Initially 100 micrograms/kg, then (by intravenous infusion) 250 micrograms/kg/hour (for up to 72 hours in medically managed patients)

Unstable angina or non-ST-segment elevation myocardial infarction (in addition to aspirin and clopidogrel) in patients proceeding to percutaneous coronary intervention or coronary artery bypass surgery without cardiopulmonary bypass INITIALLY BY INTRAVENOUS INJECTION
- Adult: Initially 100 micrograms/kg for 1 dose, then (by intravenous injection) 500 micrograms/kg for 1 dose, then (by intravenous infusion) 1.75 mg/kg/hour for duration of procedure; (by intravenous infusion) reduced to 250 micrograms/kg/hour for 4–12 hours as necessary following percutaneous coronary intervention, for patients proceeding to coronary artery bypass surgery with cardiopulmonary bypass, discontinue intravenous infusion 1 hour before procedure and treat with unfractionated heparin
Anticoagulation in patients undergoing percutaneous coronary intervention including patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention (in addition to aspirin and clopidogrel)

INITIALLY BY INTRAVENOUS INJECTION
- Adult: Initially 750 micrograms/kg, followed immediately by (by intravenous infusion) 1.75 mg/kg/hour during procedure and for up to 4 hours after procedure, then (by intravenous infusion) reduced to 250 micrograms/kg/hour may be continued for a further 4–12 hours if necessary

CONTRA-INDICATIONS Active bleeding - bleeding disorders - severe hypertension - subacute bacterial endocarditis

CAUTIONS Brachytherapy procedures - previous exposure to lepirudin (theoretical risk from lepirudin antibodies)

INTERACTIONS → Appendix 1 (bivalirudin).
Caution with concomitant use of drugs that increase risk of bleeding.

SIDE-EFFECTS
- Common or very common Bleeding (discontinue) - ecchymosis
- Uncommon Allergic reactions - anemia - headache - hypotension - isolated reports of anaphylaxis - nausea - thrombocytopenia
- Rare Back pain - bradycardia - dyspnoea - tachycardia - thrombosis - vomiting

PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk—no information available.

BREAST FEEDING Manufacturer advises caution—no information available.

RENAL IMPAIRMENT Avoid if eGFR less than 30 mL/minute/1.73 m².
- When used for percutaneous coronary intervention Reduce rate of infusion to 1.4 mg/kg/hour and monitor blood clotting parameters if eGFR 30–60 mL/minute/1.73 m².

DIRECTIONS FOR ADMINISTRATION For intravenous infusion (Angiox®), give continuously in Glucose 5% or Sodium chloride 0.9%. Reconstitute each 250-mg vial with 5 mL water for injections then withdraw 5 mL and dilute to 50 mL with infusion fluid.

NATIONAL FUNDING/ACCESS DECISIONS
- NICE technology appraisals (TAs)
  - Bivalirudin for the treatment of ST-segment elevation myocardial infarction (July 2011) NICE TA230

Bivalirudin in combination with aspirin and clopidogrel is recommended for the treatment of adults with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. www.nice.org.uk/TA230

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (November 2008) that bivalirudin (Angiox®) is accepted for restricted use within NHS Scotland for patients with acute coronary syndromes planned for urgent or early intervention who would have been considered for treatment with unfractionated heparin in combination with a glycoprotein IIb/IIIa inhibitor; it should not be used as an alternative to heparin alone.

The Scottish Medicines Consortium has advised (August 2010) that bivalirudin (Angiox®) is accepted for restricted use within NHS Scotland as an anticoagulant in patients undergoing percutaneous coronary intervention who would have been considered for treatment with unfractionated heparin in combination with a glycoprotein IIb/IIIa inhibitor; it should not be used as an alternative to heparin alone.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Powder for solution for injection
- Angiox (The Medicines Company UK Ltd)
  - Bivalirudin 250 mg Angiox 250mg powder for solution for injection vials 10 vial (£39) no price available

Dabigatran etexilate
- DRUG ACTION Dabigatran etexilate is a direct thrombin inhibitor with a rapid onset of action.

INDICATIONS AND DOSE
Prophylaxis of venous thromboembolism following total knee replacement surgery
BY MOUTH
- Adult 18–74 years: 110 mg, to be taken 1–4 hours after surgery, followed by 220 mg once daily for 9 days, to be followed 12–24 hours after initial dose
- Adult 75 years and over: 75 mg, to be taken 1–4 hours after surgery, followed by 150 mg once daily for 9 days, to be followed 12–24 hours after initial dose

Prophylaxis of venous thromboembolism following total knee replacement surgery in patients receiving concomitant treatment with amiodarone or verapamil
BY MOUTH
- Adult: 110 mg, to be taken 1–4 hours after surgery, followed by 150 mg once daily for 9 days, to be followed 12–24 hours after initial dose

Prophylaxis of venous thromboembolism following total hip replacement surgery
BY MOUTH
- Adult 18–74 years: 110 mg, to be taken 1–4 hours after surgery, followed by 220 mg once daily for 27–34 days, to be followed 12–24 hours after initial dose
- Adult 75 years and over: 75 mg, to be taken 1–4 hours after surgery, followed by 150 mg once daily for 27–34 days, to be followed 12–24 hours after initial dose

Prophylaxis of venous thromboembolism following total hip replacement surgery in patients receiving concomitant treatment with amiodarone or verapamil
BY MOUTH
- Adult: 110 mg, to be taken 1–4 hours after surgery, followed by 150 mg daily for 27–34 days, to be followed 12–24 hours after initial dose

TREATMENT OF DEEP-VEIN THROMBOSIS | TREATMENT OF PULMONARY EMBOLISM | PROPHYLAXIS OF RECURRENT DEEP-VEIN THROMBOSIS | PROPHYLAXIS OF RECURRENT PULMONARY EMBOLISM
BY MOUTH
- Adult 18–74 years: 150 mg twice daily, following at least 5 days treatment with a parenteral anticoagulant
- Adult 75–79 years: 110–150 mg twice daily, following at least 5 days treatment with a parenteral anticoagulant
- Adult 80 years and over: 110 mg twice daily, following at least 5 days treatment with a parenteral anticoagulant

continued
Treatment of deep-vein thrombosis in patients with moderate renal impairment | Treatment of deep-vein thrombosis in patients at increased risk of bleeding | Treatment of pulmonary embolism in patients with moderate renal impairment | Treatment of pulmonary embolism in patients at increased risk of bleeding | Prophylaxis of recurrent deep-vein thrombosis in patients with moderate renal impairment | Prophylaxis of recurrent deep-vein thrombosis in patients at increased risk of bleeding | Prophylaxis of recurrent pulmonary embolism in patients with moderate renal impairment | Prophylaxis of recurrent pulmonary embolism in patients at increased risk of bleeding

**BY MOUTH**
- Adult: 110–150 mg twice daily, following at least 5 days treatment with a parenteral anticoagulant
- Treatment of deep-vein thrombosis in patients receiving concomitant treatment with verapamil | Treatment of pulmonary embolism in patients receiving concomitant treatment with verapamil | Prophylaxis of recurrent deep-vein thrombosis in patients receiving concomitant treatment with verapamil | Prophylaxis of recurrent pulmonary embolism in patients receiving concomitant treatment with verapamil

**Prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation**
- with and one or more risk factors such as previous stroke or transient ischaemic attack, symptomatic heart failure, age ≥ 75 years, diabetes mellitus, or hypertension

**BY MOUTH**
- Adult 18–74 years: 150 mg twice daily
- Adult 75–79 years: 110–150 mg twice daily
- Adult 80 years and over: 110 mg twice daily

**Prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation**
- with and one or more risk factors such as previous stroke or transient ischaemic attack, symptomatic heart failure, age ≥ 75 years, diabetes mellitus, or hypertension in patients at increased risk of bleeding | Prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation

**Dose equivalence and conversion**
For information on changing from, or to, other anticoagulants, consult product literature.

**CONTRA-INDICATIONS**
- Active bleeding | do not use as anticoagulant for prosthetic heart valve | malignant neoplasms | oesophageal varices | recent brain surgery | recent gastro-intestinal ulcer | recent intracranial haemorrhage | recent ophthalmic surgery | recent spine surgery | significant risk of major bleeding | vascular aneurysm

**CAUTIONS**
- Anaesthesia with postoperative indwelling epidural catheter (risk of paralysis—give initial dose at least 2 hours after catheter removal and monitor neurological signs) | bacterial endocarditis | bleeding disorders | body-weight less than 50 kg | elderly | gastritis | gastro-oesophageal reflux | oesophagitis | recent biopsy | recent major trauma | thrombocytopenia

**INTERACTIONS**
- Appendix 1 (dabigatran)
- Caution in concomitant use of drugs that increase risk of bleeding.

**SIDE-EFFECTS**
- Common or very common Abdominal pain | anaemia | diarrhoea | dyspepsia | haemorrhage | nausea
- Uncommon Dysphagia | gastro-intestinal ulcer | gastro-oesophageal reflux | hepatobiliary disorders | oesophagitis | thrombocytopenia | vomiting

**PREGNANCY**
- Manufacturer advises avoid unless essential—toxicity in animal studies.

**BREAST FEEDING**
- Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT**
- Avoid in severe liver disease, especially if prothrombin time already prolonged.

**RENAL IMPAIRMENT**
- When used for prophylaxis of venous thromboembolism following knee or hip replacement surgery Reduce initial dose to 75 mg and subsequent doses to 150 mg once daily if creatinine clearance 30–50 mL/minute; reduce dose to 75 mg once daily if creatinine clearance 30–50 mL/minute and patient receiving concomitant treatment with verapamil.
- When used for treatment of deep-vein thrombosis and pulmonary embolism, prophylaxis of recurrent deep-vein thrombosis and pulmonary embolism, prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation. Consider reduced dose of 110 mg twice daily if creatinine clearance 30–50 mL/minute, based on individual assessment of thromboembolic risk and risk of bleeding. Avoid if creatinine clearance less than 30 mL/minute. In renal impairment monitor renal function at least annually (manufacturer recommends Cockcroft and Gault formula to calculate creatinine clearance).

**MONITORING REQUIREMENTS**
- Patients should be monitored for signs of bleeding or anaemia; treatment should be stopped if severe bleeding occurs.
- No routine anticoagulant monitoring required (INR tests are unreliable).
- Assess renal function (manufacturer recommends Cockcroft and Gault formula to calculate creatinine clearance) before treatment in all patients and at least annually in elderly.

**DIRECTIONS FOR ADMINISTRATION**
- When given concomitantly with amiodarone or verapamil, doses should be taken at the same time.

**PRESCRIBING AND DISPENSING INFORMATION**
- Dabigatran etexilate is given orally for prophylaxis of venous thromboembolism in adults after total hip replacement or total knee replacement surgery; it is also licensed for the treatment of deep-vein thrombosis and pulmonary embolism, and prophylaxis of recurrent deep-vein thrombosis and pulmonary embolism in adults. Duration of treatment should be determined by balancing the benefit of treatment with the bleeding risk; shorter duration of treatment (at least 3 months) should be based on transient risk factors i.e recent surgery, trauma, immobilisation, and longer duration of treatment should be based on permanent risk factors, or idiopathic deep-vein thrombosis or pulmonary embolism.

**NATIONAL FUNDING/ACCESS DECISIONS**
- **NICE technology appraisals (TAs)**
  - Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults (September 2008) NICE TAs?
  - Dabigatran etexilate is an option for the prophylaxis of venous thromboembolism in adults after total hip surgery.
replacement or total knee replacement surgery. www.nice.org.uk/TA157

- Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation (March 2012) NICE TA249

Dabigatran etexilate is an option for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and with one or more of the following risk factors:

- previous stroke, transient ischaemic attack, or systemic embolism
- left ventricular ejection fraction <40%
- symptomatic heart failure
- age ≥75 years
- age ≥65 years in patients with diabetes mellitus, coronary artery disease, or hypertension

The risks and benefits of dabigatran compared to warfarin should be discussed with the patient. www.nice.org.uk/TA249

- Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism (December 2014) NICE TA327

Dabigatran etexilate is recommended, within its marketing authorisation, as an option for treating and for preventing recurrent deep vein thrombosis and pulmonary embolism in adults. www.nice.org.uk/TA327

- MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

CAUTIONARY AND ADVISORY LABELS 25

- Pradaxa (Boehringer Ingelheim Ltd)
- Dabigatran etexilate (as Dabigatran etexilate mesilate)

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<th>Dosage</th>
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**Tissue Plasminogen Activators**

**Urokinase**

The properties listed below are those particular to the drug only. For properties common to the class, see fibrinolytics, p. 154.

**INDICATIONS AND DOSE**

**Deep-vein thrombosis (thromboembolic occlusive vascular disease)**

**BY INTRAVENOUS INFUSION**

- Adult: Initially 4400 units/kg, to be given over 10–20 minutes, followed by 100 000 units/hour for 2–3 days

**Pulmonary embolism (thromboembolic occlusive vascular disease)**

**BY INTRAVENOUS INFUSION**

- Adult: Initially 4400 units/kg, to be given over 10–20 minutes, followed by 4400 units/kg/hour for 12 hours

**Occlusive peripheral arterial disease (thromboembolic occlusive vascular disease)**

**BY INTRA-ARTERIAL INFUSION**

- Adult: (consult product literature)

**Occluded central venous catheters**

**BY INTRA-ARTERIAL INJECTION**

- Adult: Inject directly into occluded catheter, to be dissolved in sodium chloride 0.9% to a concentration of 5000 units/ml; use a volume sufficient to fill the catheter lumen; leave for 20–60 minutes then aspirate the lysate; repeat if necessary

**Occluded arteriovenous haemodialysis shunts**

**BY INTRAVENOUS INFUSION OR BY INTRA-ARTERIAL INFUSION**

- Adult: (consult product literature)

**SYNER-KINASE®**

**Deep-vein thrombosis (thromboembolic occlusive vascular disease)**

**BY INTRAVENOUS INFUSION**

- Adult: Initially 4400 units/kg, to be given over 10 minutes, dose to be made up in 15 ml sodium chloride 0.9%, followed by 4400 units/kg/hour for 12–24 hours

**Pulmonary embolism (thromboembolic occlusive vascular disease)**

**INITIALLY BY INTRAVENOUS INFUSION**

- Adult: Initially 4400 units/kg, to be given over 10 minutes, dose to be made up in 15 ml sodium chloride 0.9%, followed by (by intravenous infusion) 4400 micrograms/kg/hour for 12 hours, alternatively (by intra-arterial injection) initially 15 000 units/kg, to be injected into pulmonary artery, subsequent doses adjusted according to response; maximum 3 doses per day

**Occlusive peripheral arterial disease**

**BY INTRA-ARTERIAL INFUSION**

- Adult: (consult product literature)

**Occluded catheters and cannulas**

**BY INTRA-ARTERIAL INJECTION OR BY INTRAVENOUS INJECTION**

- Adult: 5000–25 000 units, to be injected directly into catheter or cannula, dose dissolved in suitable volume of sodium chloride 0.9% to fill the catheter or cannula lumen; leave for 20–60 minutes then aspirate the lysate; repeat if necessary

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT** Dose reduction may be required.

- **RENAL IMPAIRMENT** Dose reduction may be required.

- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Syner-KINASE®), give continuously or intermittently in Sodium chloride 0.9%.

**VITAMIN K ANTAGONISTS**

**Vitamin K antagonists**

- **CONTRA-INDICATIONS** Avoid use within 48 hours postpartum - haemorrhagic stroke - significant bleeding

- **CAUTIONS** Bacterial endocarditis (use only if warfarin otherwise indicated) - conditions in which risk of bleeding
is increased · history of gastrointestinal bleeding · peptic ulcer · postpartum (delay warfarin until risk of haemorrhage is low—usually 5–7 days after delivery) · recent ischaemic stroke · recent surgery · uncontrolled hypertension

**INTERACTIONS** → Appendix 1 (coumarins, phenindione). Major changes in diet (especially involving salads and vegetables) and in alcohol consumption may affect warfarin control. Caution if concomitant use of drugs that increase risk of bleeding. Avoid cranberry juice.

**SIDE-EFFECTS** Alopecia · diarrhoea · haemorrhage · hepatic dysfunction · jaundice · nausea · pancreatitis · purpura · pyrexia · rash · skin necrosis (increased risk in patients with protein C or protein S deficiency) · vomiting · ‘purple toes’

**CONCEPTION AND CONTRACEPTION** Women of childbearing age should be warned of the danger of teratogenicity.

**PREGNANCY** Should not be given in the first trimester of pregnancy. Warfarin, acenocoumarol, and phenindione cross the placenta with risk of congenital malformations, and placental, fetal, or neonatal haemorrhage, especially during the last few weeks of pregnancy and at delivery. Therefore, if at all possible, they should be avoided in pregnancy, especially in the first and third trimesters (difficult decisions may have to be made, particularly in women with prosthetic heart valves, atrial fibrillation, or with a history of recurrent venous thrombosis or pulmonary embolism). Stopping these drugs before the sixth week of gestation may largely avoid the risk of fetal abnormality.

**MONITORING REQUIREMENTS**
- The base-line prothrombin time should be determined but the initial dose should not be delayed whilst awaiting the result.
- It is essential that the INR be determined daily or on alternate days in early days of treatment, then at longer intervals (depending on response), then up to every 12 weeks.
- Change in patient’s clinical condition, particularly associated with liver disease, intercurrent illness, or drug administration, necessitates more frequent testing.

**PATIENT AND CARER ADVICE** Anticoagulant treatment booklets should be issued to all patients or their carers; these booklets include advice for patients on anticoagulant treatment, an alert card to be carried by the patient at all times, and a section for recording of INR results and dosage information. In England, Wales, and Northern Ireland, they are available for purchase from: 3M Security Print and Systems Limited Gorse Street, Chaddington Oldham OL9 9QH
Tel: 0845 610 1112
GP practices can obtain supplies through their Local Area Team stores. NHS Trusts can order supplies from www.nhsforms.co.uk or by emailing nhsforms@mmm.com.

In Scotland, treatment booklets and starter information packs can be obtained by emailing stockholders: dppas@theapsgroup.com or by fax on (0131) 6299 967
Electronic copies of the booklets and further advice are also available at www.npsa.nhs.uk/nrls/alerts-and-directives/alerts/anticoagulant.

## Acenocoumarol
(Nicoumalone)

**INDICATIONS AND DOSE**

Prophylaxis of embolisation in rheumatic heart disease and atrial fibrillation | Prophylaxis after insertion of prosthetic heart valve | Prophylaxis and treatment of venous thrombosis and pulmonary embolism | Transient ischaemic attacks

**BY MOUTH**
- Adult: Initially 2–4 mg once daily for 2 days, alternatively initially 5 mg on day 1, then 4 mg on day 2; maintenance 1–8 mg daily, adjusted according to response, dose to be taken at the same time each day, lower doses may be required in patients over 65 years, liver disease, severe heart failure with hepatic congestion, and malnutrition

**CAUTIONS**
- Patients over 65 years

**SIDE-EFFECTS**
- Rare Anorexia
- Very rare Vasculitis

**BREAST FEEDING** Risk of haemorrhage; increased by vitamin K deficiency—manufacturer recommends prophylactic vitamin K for the infant (consult product literature).

**HEPATIC IMPAIRMENT** Use with caution in mild to moderate impairment. Avoid in severe impairment, especially if prothrombin time is already prolonged.

**RENAL IMPAIRMENT** Caution in mild to moderate impairment. Avoid in severe impairment.

**PATIENT AND CARER ADVICE** Anticoagulant card to be provided.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

CAUTIONARY AND ADVISORY LABELS

- ACENOCOUMAROL (Non-proprietary)
- Acenocoumarol 1 mg Acenocoumarol 1mg tablets | 100 tablet (P)M no price available DT price = £4.62
- Sinthrome (Novartis Pharmaceuticals UK Ltd) Acenocoumarol 1 mg Sinthrome 1mg tablets | 100 tablet (P)M £4.62 DT price = £4.62

**Phenindione**

**INDICATIONS AND DOSE**

Prophylaxis of embolisation in rheumatic heart disease and atrial fibrillation | Prophylaxis after insertion of prosthetic heart valve | Prophylaxis and treatment of venous thrombosis and pulmonary embolism

**BY MOUTH**
- Adult: Initially 200 mg on day 1, then 100 mg on day 2, then, adjusted according to response; maintenance 50–150 mg daily

**SIDE-EFFECTS**
- Agranulocytosis · eosinophilia · exanthema · exfoliative dermatitis · fever · hypersensitivity reactions · leucopenia · micro-adenopathy · renal damage · urine coloured pink or orange

**BREAST FEEDING** Avoid. Risk of haemorrhage; increased by vitamin K deficiency.

**HEPATIC IMPAIRMENT** Avoid in severe impairment, especially if prothrombin time is already prolonged.

**RENAL IMPAIRMENT** Caution in mild to moderate impairment. Avoid in severe impairment.
● **PATIENT AND CARER ADVICE** Anticoagulant card to be provided. Patient counselling is advised for phenindione tablets (may turn urine pink or orange).

● **MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

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**PATIENT AND CARER ADVICE**

Anticoagulant card to be provided.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Warfarin sodium**

**INDICATIONS AND DOSE**

Prophylaxis of embolisation in rheumatic heart disease and atrial fibrillation | Prophylaxis after insertion of prosthetic heart valve | Prophylaxis and treatment of venous thrombosis and pulmonary embolism | Transient ischaemic attacks

BY MOUTH

- Adult: Initially 5–10 mg, to be taken on day 1; subsequent doses dependent on the prothrombin time, reported as INR (international normalised ratio), a lower induction dose can be given over 3–4 weeks in patients who do not require rapid anticoagulation, elderly patients to be given a lower induction dose; maintenance 3–9 mg daily, to be taken at the same time each day

- **PREGNANCY** Babies of mothers taking warfarin at the time of delivery need to be offered immediate prophylaxis with intramuscular phytonadione (vitamin K).

- **BREAST FEEDING** Not present in milk in significant amounts and appears safe. Risk of haemorrhage which is increased by vitamin K deficiency.

- **HEPATIC IMPAIRMENT** Avoid in severe impairment, especially if prothrombin time is already prolonged.

- **RENAL IMPAIRMENT** Use with caution in mild to moderate impairment. In severe renal impairment, monitor INR more frequently.

- **PATIENT AND CARER ADVICE** Anticoagulant card to be provided.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

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**Hypertension**

Lowering raised blood pressure decreases the risk of stroke, coronary events, heart failure, and renal impairment. Advice on antihypertensive therapy in this section takes into account the recommendations of NICE clinical guidance 127 (August 2011), Hypertension—Clinical management of primary hypertension in adults.

Possible causes of hypertension (e.g. renal disease, endocrine causes), contributory factors, risk factors, and the presence of any complications of hypertension, such as left ventricular hypertrophy, should be established. Patients should be given advice on lifestyle changes to reduce blood pressure or cardiovascular risk; these include smoking cessation, weight reduction, reduction of excessive intake of alcohol and caffeine, reduction of dietary salt, reduction of total and saturated fat, increasing exercise, and increasing fruit and vegetable intake.

**Thresholds and targets for treatment**

Patients presenting with a blood pressure of 140/90 mmHg or higher when measured in a clinic setting, should be offered ambulatory blood pressure monitoring (or home blood pressure monitoring if ambulatory blood pressure monitoring is unsuitable) to confirm the diagnosis and stage of hypertension.

Stage 1 hypertension:

- Clinic blood pressure 140/90 mmHg or higher, and ambulatory daytime average or home blood pressure average 135/85 mmHg or higher
- Treat patients under 80 years who have stage 1 hypertension and target-organ damage (e.g. left ventricular hypertrophy, chronic kidney disease, hypertensive retinopathy), cardiovascular disease, renal disease, diabetes, or a 10 year cardiovascular risk >20%; in the absence of these conditions, advise lifestyle changes and review annually. For patients under 40 years with stage 1 hypertension but no overt target-organ damage, cardiovascular disease, renal disease, or diabetes, consider seeking specialist advice for evaluation of secondary causes of hypertension

Stage 2 hypertension:

- Clinic blood pressure 160/100 mmHg or higher, and ambulatory daytime average or home blood pressure average 150/95 mmHg or higher
- Treat all patients who have stage 2 hypertension, regardless of age

Severe hypertension:

- Clinic systolic blood pressure >180 mmHg or clinic diastolic blood pressure >110 mmHg; treat promptly—see Hypertensive Crises p. 123.

A target clinic blood pressure below 140/90 mmHg is suggested for patients under 80 years; a target ambulatory or home blood pressure average (during the patient’s waking hours) of below 135/85 mmHg is suggested for patients under 80 years; see also Hypertension in the Elderly p. 122. A target clinic blood pressure below...
130/80 mmHg should be considered for those with established atherosclerotic cardiovascular disease, or diabetes in the presence of kidney, eye, or cerebrovascular disease. In some individuals it may not be possible to reduce blood pressure below the suggested targets despite the use of appropriate therapy.

Drug treatment of hypertension

A single antihypertensive drug is often inadequate in the management of hypertension, and additional antihypertensive drugs are usually added in a step-wise manner until control is achieved. Unless it is necessary to lower the blood pressure urgently (see Hypertensive Crises), an interval of at least 4 weeks should be allowed to determine response; clinicians should ensure antihypertensive drugs are titrated to the optimum or maximum tolerated dose at each step of treatment. Response to drug treatment may be affected by age and ethnicity.

**Patients under 55 years:**

1. **Step 1**
   - ACE inhibitor; if not tolerated, offer an angiotensin-II receptor antagonist. If both ACE inhibitors and angiotensin-II receptor antagonists are contra-indicated or not tolerated, consider a beta-blocker; beta-blockers, especially when combined with a thiazide diuretic, should be avoided for the routine treatment of uncomplicated hypertension in patients with diabetes or at high risk of developing diabetes.

2. **Step 2**
   - ACE inhibitor or angiotensin-II receptor antagonist in combination with a calcium-channel blocker. If a calcium-channel blocker is not tolerated or if there is evidence of, or a high risk of, heart failure, give a thiazide-related diuretic (e.g. chlortalidone or indapamide). If a beta-blocker was given at Step 1, add a calcium channel blocker in preference to a thiazide-related diuretic (see Step 1).

3. **Step 3**
   - ACE inhibitor or angiotensin-II receptor antagonist in combination with a calcium-channel blocker and a thiazide-related diuretic.

4. **Step 4 (resistant hypertension)**
   - Consider seeking specialist advice
   - Add low-dose spironolactone [unlicensed indication], or use high-dose thiazide related diuretic if plasma-potassium concentration above 4.5 mmol/litre
   - Monitor renal function and electrolytes
   - If additional diuretic therapy is contra-indicated, ineffective, or not tolerated, consider an alpha-blocker or a beta-blocker

**Patients over 55 years, and patients of any age who are of African or Caribbean family origin:**

1. **Step 1**
   - Calcium-channel blocker; if not tolerated or if there is evidence of, or a high risk of, heart failure, give a thiazide-related diuretic (e.g. chlortalidone or indapamide)

2. **Step 2**
   - Calcium-channel blocker or thiazide-related diuretic in combination with an ACE inhibitor or angiotensin-II receptor antagonist (an angiotensin-II receptor antagonist in combination with a calcium-channel blocker is preferred in patients of African or Caribbean family origin)

3. **Steps 3 and 4**
   - Treat as for patients under 55 years

**Other measures to reduce cardiovascular risk**

Aspirin p. 104 reduces the risk of cardiovascular events and myocardial infarction. Unduly high blood pressure must be controlled before aspirin is given. Unless contra-indicated, aspirin is recommended for all patients with established cardiovascular disease. Use of aspirin in primary prevention, in those with or without diabetes, is of unproven benefit. Aspirin also has a role in the prevention of stroke in patients with atrial fibrillation.

Statins are also of benefit in cardiovascular disease or in those who are at high risk of developing cardiovascular disease.

**Hypertension in the elderly**

Benefit from antihypertensive therapy is evident up to at least 80 years of age, but it is probably inappropriate to apply a strict age limit when deciding on drug therapy. Patients who reach 80 years of age while taking antihypertensive drugs should continue treatment, provided that it continues to be of benefit and does not cause significant side-effects. If patients are aged over 80 years when diagnosed with stage 1 hypertension, the decision to treat should be based on the presence of other comorbidities; patients with stage 2 hypertension should be treated as for patients over 55 years. A target clinic blood pressure below 150/90 mmHg is suggested for patients over 80 years; the suggested target ambulatory or home blood pressure average (during the patient’s waking hours) is below 145/85 mmHg.

**Isolated systolic hypertension**

Isolated systolic hypertension (systolic pressure ≥160 mmHg, diastolic pressure < 90 mmHg) is common in patients over 60 years, and is associated with an increased cardiovascular disease risk; it should be treated as for patients with both a raised systolic and diastolic blood pressure. Patients with severe postural hypotension should be referred to a specialist.

**Hypertension in diabetes**

For patients with diabetes, a target clinic blood pressure below 140/80 mmHg is suggested (below 130/80 mmHg is advised if kidney, eye, or cerebrovascular disease are also present). However, in some individuals, it may not be possible to achieve this level of control despite appropriate therapy. Most patients require a combination of antihypertensive drugs.

Hypertension is common in type 2 diabetes, and antihypertensive treatment prevents macrovascular and microvascular complications. In type 1 diabetes, hypertension usually indicates the presence of diabetic nephropathy. An ACE inhibitor (or an angiotensin-II receptor antagonist) may have a specific role in the management of diabetic nephropathy; in patients with type 2 diabetes, an ACE inhibitor (or an angiotensin-II receptor antagonist) can delay progression of microalbuminuria to nephropathy.

**Hypertension in renal disease**

A target clinic blood pressure below 140/90 mmHg is suggested (below 130/80 mmHg is advised in patients with chronic kidney disease and diabetes, or if proteinuria exceeds 1 g in 24 hours). An ACE inhibitor (or an angiotensin-II receptor antagonist) should be considered for patients with proteinuria; however, ACE inhibitors should be used with caution in renal impairment. Thiazide diuretics may be ineffective and high doses of loop diuretics may be required.

**Hypertension in pregnancy**

Hypertensive complications in pregnancy can be hazardous for both the mother and the fetus, and are associated with a significant risk of morbidity and mortality; complications can occur in pregnant women with pre-existing chronic hypertension, or in those who develop hypertension in the latter half of pregnancy.
Hypertension

Labetalol hydrochloride p. 143 is widely used for treating hypertension in pregnancy. Methyldopa p. 138 is considered safe for use in pregnancy. Modified-release preparations of nifedipine p. 154 [unlicensed] are also used.

The following advice takes into account the recommendations of NICE Clinical Guideline 107 (August 2010), Hypertension in Pregnancy.

Pregnant women with chronic hypertension who are already receiving antihypertensive treatment should have their drug therapy reviewed. In uncomplicated chronic hypertension, a target blood pressure of <150/100 mmHg is recommended; women with target-organ damage as a result of chronic hypertension, and in women with chronic hypertension who have given birth, a target blood pressure of <140/90 mmHg is advised. Long-term antihypertensive treatment should be reviewed 2 weeks following the birth. Women managed with methyldopa during pregnancy should discontinue treatment and restart their original antihypertensive medication within 2 days of the birth.

Pregnant women are at high risk of developing pre-eclampsia if they have chronic kidney disease, diabetes mellitus, autoimmune disease, chronic hypertension, or if they have had hypertension during a previous pregnancy; these women are advised to take aspirin p. 104 once daily [unlicensed indication] from week 12 of pregnancy until the baby is born. Women with more than one moderate risk factor (first pregnancy, aged >35 years, BMI ≥ 35 kg/m² at first visit, multiple pregnancy, or family history of pre-eclampsia) for developing pre-eclampsia should receive critical care during pregnancy or after birth. Women with a blood pressure of <150/100 mmHg, or oral modified-release nifedipine to achieve a target blood pressure of <150 mmHg systolic, and diastolic 80–100 mmHg. If labetalol hydrochloride is unsuitable, methyldopa or modified-release nifedipine may be considered. Women already receiving antihypertensive treatment should have their treatment options include sodium nitroprusside p. 143, a powerful alpha-blocker, is effective in the management of pheochromocytoma but it has many side-effects. Phentolamine mesilate p. 161 is a short-acting alpha-blocker used mainly during surgery of pheochromocytoma; its use for the diagnosis of pheochromocytoma has been superseded by measurement of catecholamines in blood and urine.

Metyrosine (available from ‘special-order’ manufacturers or specialist importing companies) inhibits the enzyme tyrosine hydroxylase, and hence the synthesis of catecholamines. It is rarely used in the pre-operative management of pheochromocytoma, and long term in patients unsuitable for surgery; an alpha-adrenoceptor blocking drug may also be required. Metyrosine should not be used to treat essential hypertension.

Antihypertensive drugs

Vasodilator antihypertensive drugs

Vasodilators have a potent hypertensive effect, especially when used in combination with a beta-blocker and a thiazide. Important: see Hypertension (hypertensive crises) for a warning on the hazards of a very rapid fall in blood pressure.

Hydralazine hydrochloride p. 157 is given by mouth as an adjunct to other antihypertensives for the treatment of resistant hypertension but is rarely used; when used alone it causes tachycardia and fluid retention.

Sodium nitroprusside p. 161 [unlicensed] is given by intravenous infusion to control severe hypertensive emergencies when parenteral treatment is necessary.

Minoxidil p. 158 should be reserved for the treatment of severe hypertension resistant to other drugs. Vasodilatation is accompanied by increased cardiac output and tachycardia and the patients develop fluid retention. For this reason the addition of a beta-blocker and a diuretic (usually furosemide p. 201, in high dosage) are mandatory. Hypertrichosis is troublesome and renders this drug unsuitable for females.

Prazosin p. 674, doxazosin p. 673, and terazosin p. 675 have alpha-blocking and vasodilator properties.

Ambisentan p. 162, bosentan p. 163, iloprost p. 164, macitentan p. 163, sildenafil p. 699, and tadalafil p. 700 are licensed for the treatment of pulmonary arterial hypertension and should be used under specialist supervision. Epoprostenol p. 99 can be used in patients with primary pulmonary hypertension resistant to other

Pregnant women with pre-eclampsia or gestational hypertension who present with a blood pressure over 150/100 mmHg should receive immediate treatment with oral labetalol hydrochloride to achieve a target blood pressure of <150 mmHg systolic, and diastolic 80–100 mmHg. Labetalol hydrochloride is unsuitable, methyldopa or modified-release nifedipine may be considered. Women with pre-eclampsia or gestational hypertension who have been managed with methyldopa during pregnancy should discontinue treatment within 2 days of the birth. Women with a blood pressure of ≥160/110 mmHg who require critical care during pregnancy or after birth should receive immediate treatment with either oral or intravenous labetalol hydrochloride, intravenous hydralazine hydrochloride p. 157, or oral modified-release nifedipine to achieve a target blood pressure of <150 mmHg systolic, and diastolic 80–100 mmHg. Also see use of magnesium sulfate in preeclampsia and eclampsia p. 858.

Hypertensive crises

If blood pressure is reduced too quickly in the management of hypertensive crises, there is a risk of reduced organ perfusion leading to cerebral infarction, blindness, deterioration in renal function, and myocardial ischaemia.

A hypertensive emergency is defined as severe hypertension with acute damage to the target organs (e.g. signs of papilloedema or retinal haemorrhage, or the presence of clinical conditions such as acute coronary syndromes, acute aortic dissection, acute pulmonary oedema, hypertensive encephalopathy, acute cerebral infarction, intracerebral or subarachnoid haemorrhage, eclampsia, or rapidly progressing renal failure); prompt treatment with intravenous antihypertensive therapy is generally required. Over the first few minutes or within 2 hours, blood pressure should be reduced by 20–25%. When intravenous therapy is indicated, treatment options include sodium nitroprusside p. 161 [unlicensed], nicardipine hydrochloride p. 153, labetalol hydrochloride p. 143, glyceryl trinitrate p. 190, phentolamine mesilate p. 161, hydralazine hydrochloride p. 157, or esmolol hydrochloride p. 143; choice of drug is dependent on concomitant conditions and clinical status of the patient.

Severe hypertension (blood pressure ≥ 180/110 mmHg) without acute target-organ damage is defined as a hypertensive urgency; blood pressure should be reduced gradually over 24–48 hours with oral antihypertensive therapy, such as labetalol hydrochloride, or the calcium-channel blockers amlopidine p. 148 or felodipine p. 151. Use of sublingual nifedipine is not recommended. Also see advice on short-term management of hypertensive episodes in pheochromocytoma.

Phaeochromocytoma

Long-term management of phaeochromocytoma involves surgery. However, surgery should not take place until there is adequate blockade of both alpha- and beta-adrenoceptors; the optimal choice of drug therapy remains unclear. Alpha-blockers are used in the short-term management of hypertensive episodes in pheochromocytoma.

Metirosine (available from ‘special-order’ manufacturers or specialist importing companies) inhibits the enzyme tyrosine hydroxylase, and hence the synthesis of catecholamines. It is rarely used in the pre-operative management of pheochromocytoma, and long term in patients unsuitable for surgery; an alpha-adrenoceptor blocking drug may also be required. Metyrosine should not be used to treat essential hypertension.
treatments. Bosentan p. 163 is also licensed to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease. Riociguat p. 163 is licensed for the treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension; it should be used under specialist supervision.

**Sitaxsentan** has been withdrawn from the market because the benefit of treatment does not outweigh the risk of severe hepatotoxicity.

**Centrally acting antihypertensive drugs**

Methyldopa p. 138 is a centrally acting antihypertensive; it may be used for the management of hypertension in pregnancy.

Clonidine hydrochloride p. 137 has the disadvantage that sudden withdrawal of treatment may cause severe rebound hypertension.

Moxonidine p. 138, a centrally acting drug, is licensed for mild to moderate essential hypertension. It may have a role when thiazides, calcium-channel blockers, ACE inhibitors, and beta-blockers are not appropriate or have failed to control blood pressure.

**Alpha-adrenoceptor blocking drugs**

Prazosin has post-synaptic alpha-blocking and vasodilator properties and rarely causes tachycardia. It may, however, reduce blood pressure rapidly after the first dose and should be introduced with caution. Doxazosin, indoramin p. 673, and terazosin have properties similar to those of prazosin. Alpha-blockers can be used with other antihypertensive drugs in the treatment of resistant hypertension.

**Prostatic hyperplasia**

Alfuzosin hydrochloride p. 672, doxazosin, indoramin, prazosin, tamsulosin hydrochloride p. 674, and terazosin are indicated for benign prostatic hyperplasia.

**Angiotensin-converting enzyme inhibitors**

Angiotensin-converting enzyme inhibitors (ACE inhibitors) inhibit the conversion of angiotensin I to angiotensin II. They have many uses and are generally well tolerated. The main indications of ACE inhibitors are shown below.

**Heart Failure**

ACE inhibitors are used in all grades of heart failure, usually combined with a beta-blocker. Potassium supplements and potassium-sparing diuretics should be discontinued before introducing an ACE inhibitor because of the risk of hyperkalaemia. However, a low dose of spironolactone p. 168 may be beneficial in severe heart failure and can be used with an ACE inhibitor provided serum potassium is monitored carefully. Prolonged first-dose hypotension may occur when ACE inhibitors are introduced to patients with heart failure who are already taking a high dose of a loop diuretic (e.g. furosemide p. 201 80 mg daily or more).

Temporary withdrawal of the loop diuretic reduces the risk, but may cause severe rebound pulmonary oedema. Therefore, for patients on high doses of loop diuretics, the ACE inhibitor may need to be initiated under specialist supervision. An ACE inhibitor can be initiated in the community in patients who are receiving a low dose of a diuretic or who are not otherwise at risk of serious hypotension; nevertheless, care is required and a very low dose of the ACE inhibitor is given initially.

**Hypertension**

An ACE inhibitor may be the most appropriate initial drug for hypertension in younger Caucasian patients; Afro-Caribbean patients, those aged over 55 years, and those with primary aldosteronism respond less well. ACE inhibitors are particularly indicated for hypertension in patients with type 1 diabetes with nephropathy. They may reduce blood pressure very rapidly in some patients particularly in those receiving diuretic therapy.

**Diabetic nephropathy**

ACE inhibitors have a role in the management of diabetic nephropathy.

**Prophylaxis of cardiovascular events**

ACE inhibitors are used in the early and long-term management of patients who have had a myocardial infarction. ACE inhibitors may also have a role in preventing cardiovascular events.

**Initiation under specialist supervision**

ACE inhibitors should be initiated under specialist supervision and with careful clinical monitoring in those with severe heart failure or in those:

- receiving multiple or high-dose diuretic therapy (e.g. more than 80 mg of furosemide daily or its equivalent);
- receiving concomitant angiotensin-II receptor antagonist or aliskiren;
- with hypovolaemia;
- with hypotension (systolic blood pressure below 90 mmHg);
- with unstable heart failure;
- receiving high-dose vasodilator therapy;
- known renovascular disease.

**Renal effects**

Renal function and electrolytes should be checked before starting ACE inhibitors (or increasing the dose) and monitored during treatment (more frequently if features mentioned below present); hyperkalaemia and other side-effects of ACE inhibitors are more common in those with impaired renal function and the dose may need to be reduced. Although ACE inhibitors now have a specialised role in some forms of renal disease, including chronic kidney disease, they also occasionally cause impairment of renal function which may progress and become severe in other circumstances (at particular risk are the elderly). A specialist should be involved if renal function is significantly reduced as a result of treatment with an ACE inhibitor.

Concomitant treatment with NSAIDs increases the risk of renal damage, and potassium-sparing diuretics (or potassium-containing salt substitutes) increase the risk of hyperkalaemia. In patients with severe bilateral renal artery stenosis (or severe stenosis of the artery supplying a single functioning kidney), ACE inhibitors reduce or abolish glomerular filtration and are likely to cause severe and progressive renal failure. They are therefore not recommended in patients known to have these forms of critical renovascular disease.

ACE inhibitor treatment is unlikely to have an adverse effect on overall renal function in patients with severe
unilateral renal artery stenosis and a normal contralateral kidney, but glomerular filtration is likely to be reduced (or even abolished) in the affected kidney and the long-term consequences are unknown.

ACE inhibitors are therefore best avoided in patients with known or suspected renovascular disease, unless the blood pressure cannot be controlled by other drugs. If ACE inhibitors are used, they should be initiated only under specialist supervision and renal function should be monitored regularly.

ACE inhibitors should also be used with particular caution in patients who may have undiagnosed and clinically silent renovascular disease. This includes patients with peripheral vascular disease or those with severe generalised atherosclerosis.

Cautions
ACE inhibitors need to be initiated with care in patients receiving diuretics.

Concomitant diuretics
ACE inhibitors can cause a very rapid fall in blood pressure in volume-depleted patients; treatment should therefore be initiated with very low doses. If the dose of diuretic is greater than 80 mg furosemide p. 201 or equivalent, the ACE inhibitor should be initiated under close supervision and in some patients the diuretic dose may need to be reduced or the diuretic discontinued at least 24 hours beforehand (may not be possible in heart failure—risk of pulmonary oedema). If high-dose diuretic therapy cannot be stopped, close observation is recommended after administration of the first dose of ACE inhibitor, for at least 2 hours or until the blood pressure has stabilised.

Combination products
Products incorporating an ACE inhibitor with a thiazide diuretic or a calcium-channel blocker are available for the management of hypertension. Use of these combination products should be reserved for patients whose blood pressure has not responded adequately to a single antihypertensive drug and who have been stabilised on the individual components of the combination in the same proportions.

Angiotensin-II receptor antagonists
Azilsartan medoxomil p. 132, candesartan cilexetil p. 133, eprosartan p. 133, irbesartan p. 133, losartan potassium p. 134, olmesartan medoxomil p. 135, telmisartan p. 136, and valsartan p. 136 are angiotensin-II receptor antagonists with many properties similar to those of the ACE inhibitors. However, unlike ACE inhibitors, they do not inhibit the breakdown of bradykinin and other kinins, and thus are less likely to cause the persistent dry cough which can complicate ACE inhibitor therapy. They are therefore a useful alternative for patients who have to discontinue an ACE inhibitor because of persistent cough.

An angiotensin-II receptor antagonist may be used as an alternative to an ACE inhibitor in the management of heart failure or diabetic nephropathy. Candesartan cilexetil and valsartan are also licensed as adjuncts to ACE inhibitors under specialist supervision, in the management of heart failure when other treatments are unsuitable.

Renal effects
Angiotensin-II receptor antagonists should be used with caution in renal artery stenosis (see also Renal effects under ACE Inhibitors, above).

Renin inhibitor
Aliskiren is a renin inhibitor that is licensed for the treatment of hypertension.

Concomitant use of drugs affecting the renin-angiotensin system
Combination therapy with two drugs affecting the renin-angiotensin system (ACE inhibitors, angiotensin-II receptor antagonists, and aliskiren p. 158 is not recommended due to an increased risk of hyperkalaemia, hypotension, and renal impairment, compared to use of a single drug. Patients with diabetic nephropathy are particularly susceptible to developing hyperkalaemia and should not be given an ACE inhibitor with an angiotensin-II receptor antagonist. There is some evidence that the benefits of combination use of an ACE inhibitor with candesartan or valsartan may outweigh the risks in selected patients with heart failure for whom other treatments are unsuitable, however, the concomitant use of this combination, together with an aldosterone antagonist or a potassium-sparing diuretic is not recommended.

For patients currently taking combination therapy, the need for continued combined therapy should be reviewed. If combination therapy is considered essential, it should be carried out under specialist supervision, with close monitoring of blood pressure, renal function, and electrolytes (particularly potassium); monitoring should be considered at the start of treatment, then monthly, and also after any change in dose or during intercurrent illness.

Drugs used for Hypertension not listed below;
Chlortalidone, p. 204 · Cyclopenthiazide, p. 204 · Doxazosin, p. 673 · Furosemide, p. 201 · Indoramin, p. 673 · Metolazone, p. 205 · Prazosin, p. 674 · Spirinolactone, p. 168 · Terazosin, p. 765 · Torasemide, p. 202 · Xipamide, p. 205

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme inhibitors

CONTRA-INDICATIONS

The combination of an ACE inhibitor with aliskiren is contra-indicated in patients with an eGFR less than 60 mL/minute/1.73 m² - the combination of an ACE inhibitor with aliskiren is contra-indicated in patients with diabetes mellitus

CAUTIONS

Afro-Caribbean patients (may respond less well to ACE inhibitors) · concomitant diuretics - (first dose hypotension (especially in patients taking high doses of diuretics, on a low-sodium diet, on dialysis, dehydrated, or with heart failure) · peripheral vascular disease or generalised atherosclerosis (risk of clinically silent renovascular disease) · primary aldosteronism (patients may respond less well to ACE inhibitors) · the risk of agranulocytosis is possibly increased in collagen vascular disease (blood counts recommended) · use-with care (or avoid) in those with a history of idiopathic or hereditary angioedema · use with care in patients with hypertrophic cardiomyopathy · use with care in patients with severe or symptomatic aortic stenosis (risk of hypotension)

CAUTIONS, FURTHER INFORMATION

Anaphylactoid reactions
To prevent anaphylactoid reactions, ACE inhibitors should be avoided during dialysis with high-flux polyacrylonitrile membranes and during low-density lipoprotein apheresis with dextran sulfate; they should also be withheld before desensitisation with wasp or bee venom.

INTERACTIONS

Appendix 1 (ACE inhibitors).

SIDE-EFFECTS

Pruritus · abdominal pain · altered liver function tests · angioedema (onset may be delayed; higher incidence reported in Afro-Caribbean patients) · arthralgia · blood disorders · bronchospasm · cholestatic jaundice ·
constipation · diarrhea · dizziness · dyspepsia ·
onephrophiha · fatigue · fever · fulminant hepatic necrosis ·
haemolytic anaemia · headache · hepatic failure · hepatitis ·
hyperkaemia · hypoglycaemia · leucocytosis ·
leucopenia · malaise · myalgia · nausea · neutropenia ·
pancreatitis · paraesthesia · persistent dry cough ·
photosensitivity · positive antinuclear antibody · profound
hypotension · raised erythrocyte sedimentation rate · rash ·
renal impairment · rhinitis · serositis · sinuses · sore
throat · taste disturbance · thrombocytopenia · urticaria ·
vasculitis · vomiting

SIDE-EFFECTS, FURTHER INFORMATION

Hepatic effects In light of reports of cholestatic jaundice, hepatic, fulminant hepatic necrosis, and hepatic failure, ACE inhibitors should be discontinued if marked elevation of hepatic enzymes or jaundice occur.

ALLERGY AND CROSS-SENSITIVITY ACE inhibitors are contra-indicated in patients with hypersensitivity to ACE inhibitors (including angioedema).

PREGNANCY ACE inhibitors should be avoided in pregnancy unless essential. They may adversely affect the fetus and neonatal blood pressure control and renal function; skull defects and oligohydramnios have also been reported.

BREAST FEEDING Information on the use of ACE inhibitors in breast-feeding is limited.

RENAL IMPAIRMENT Use with caution, starting with low dose, and adjust according to response. Hyperkalaemia and other side-effects of ACE inhibitors are more common in those with impaired renal function and the dose may need to be reduced.

MONITORING REQUIREMENTS Renal function and electrolytes should be checked before starting ACE inhibitors (or increasing the dose) and monitored during treatment (more frequently if side effects mentioned are present).

DIRECTIONS FOR ADMINISTRATION For hypertension the first dose should preferably be given at bedtime.

Captopril

INDICATIONS AND DOSE

Hypertension BY MOUTH

Adult: Initially 12.5–25 mg twice daily, then increased if necessary up to 150 mg daily in 2 divided doses, once-daily dosing may be appropriate if other concomitant antihypertensive drugs taken

Essential hypertension if used in volume depletion, cardiac decompensation, or renovascular hypertension BY MOUTH

Adult: Initially 6.25–12.5 mg for 1 dose (under close medical supervision), then 6.25–12.5 mg twice daily; increased if necessary up to 100 mg daily in 1–2 divided doses, dosed to be increased at intervals of at least 2 weeks, once-daily dosing may be appropriate if other concomitant antihypertensive drugs taken

Heart failure BY MOUTH

Adult (under close medical supervision): Initially 6.25–12.5 mg 2–3 times a day, then increased if tolerated to up to 150 mg daily in divided doses, dose to be increased gradually at intervals of at least 2 weeks

Short-term treatment within 24 hours of onset of myocardial infarction in clinically stable patients BY MOUTH

Adult: Initially 6.25 mg, then increased to 12.5 mg after 2 hours, followed by 25 mg after 12 hours, increased if tolerated to 50 mg twice daily for 4 weeks

Prophylaxis of symptomatic heart failure after myocardial infarction in clinically stable patients with asymptomatic left ventricular dysfunction (starting 3–16 days after infarction) (under close medical supervision) BY MOUTH

Adult: Initially 6.25 mg daily, then increased to 12.5 mg 3 times a day for 2 days, then increased if tolerated to 25 mg 3 times a day, then increased if tolerated to 75–150 mg daily in 2–3 divided doses, doses to be increased gradually

Diabetic nephropathy BY MOUTH

Adult: 75–100 mg daily in divided doses

SIDE-EFFECTS

Common or very common Alopecia · dry mouth · dyspnoea · sleep disorder

Uncommon Angina · arthralgia · flushing · pallor · palpitation · Raynaud’s syndrome · tachycardia

Rare Anorexia · stomatitis

Very rare Allergic alveolitis · blurred vision · cardiac arrest · cardiogenic shock · cerebrovascular events · confusion · depression · eosinophilic pneumonia · glossitis · gynaecomastia · hyponatraemia · impotence · peptic ulcer · photosensitivity · Stevens-Johnson syndrome · syncope

BREAST FEEDING Avoid in first few weeks after delivery, particularly in preterm infants—risk of profound neonatal hypotension; can be used in mothers breast-feeding older infants if essential but monitor infant’s blood pressure.

RENAL IMPAIRMENT Reduce dose; max. initial dose 50 mg if eGFR above 40 mL/minute/1.73 m²; max. initial dose 25 mg daily (do not exceed 100 mg daily) if eGFR 20–40 mL/minute/1.73 m²; max. initial dose 12.5 mg daily (do not exceed 75 mg daily) if eGFR 10–20 mL/minute/1.73 m²; max. initial dose 6.25 mg daily (do not exceed 37.5 mg daily) if eGFR less than 10 mL/minute/1.73 m².

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, oral suspension, oral solution, powder, capsule

Tablet

Captopril (Non-proprietary)

Captopril 12.5 mg Captopril 12.5 mg tablets | 56 tablet | £2.80

Captopril 25 mg Captopril 25 mg tablets | 56 tablet | £4.52

Captopril 50 mg Captopril 50 mg tablets | 56 tablet | £5.83

Captopril 100 mg Captopril 100 mg tablets | 56 tablet | £10.41

Capoten (Bristol-Myers Squibb Pharmaceuticals Ltd)

Captopril 25 mg Captopril 25 mg tablets | 28 tablet | £5.26

Ecospace (AMCo)

Captopril 12.5 mg Ecosp 12.5 mg tablets | 56 tablet | £0.48

Captopril 25 mg Ecosp 25 mg tablets | 56 tablet | £0.60

Captopril 50 mg Ecosp 50 mg tablets | 56 tablet | £0.72

Noyada (Martindale Pharmaceuticals Ltd)

Captopril 1 mg per 1 mL Noyada 1mg/5ml oral solution (sugar-free) | 100 ml | £98.21

ELECTROLYTES: May contain Sodium

BNF 70
Co-zidocapt

The properties listed below are those particular to the combination only. For the properties of the components please consider, captopril p. 126, hydrochlorothiazide p. 160.

INDICATIONS AND DOSE
Mild to moderate hypertension in patients stabilised on the individual components in the same proportions
BY MOUTH
adult: (consult product literature)

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
Tablet
- CO-ZIDOCAPT (non-proprietary)
  Capzide 25 mg, Hydrochlorothiazide 12.5 mg Co-zidocapt 12.5mg/25mg tablets | 28 tablet | £11.00
  Capzide 50 mg, Hydrochlorothiazide 25 mg Co-zidocapt 25mg/50mg tablets | 28 tablet | £14.00
- Capzide (Bristol-Myers Squibb Pharmaceuticals Ltd)
  Capzide 50 mg, Hydrochlorothiazide 25 mg Capzide 25mg/50mg tablets | 30 tablet | £7.52

Enalapril maleate

INDICATIONS AND DOSE
Hypertension
BY MOUTH
adult: Initially 5 mg once daily, lower initial doses may be required when used in addition to diuretic or in renal impairment; maintenance 20 mg once daily; maximum 40 mg per day
Heart failure
BY MOUTH
adult: (under close medical supervision): Initially 2.5 mg once daily, increased if tolerated to 10–20 mg twice daily, dose to be increased gradually over 2–4 weeks
Prevention of symptomatic heart failure in patients with asymptomatic left ventricular dysfunction
BY MOUTH
adult: (under close medical supervision): Initially 2.5 mg once daily, increased if tolerated to 10–20 mg twice daily, dose to be increased gradually over 2–4 weeks

SIDE-EFFECTS
- Common or very common: Asthenia, blurred vision, depression, dyspnoea
- Uncommon: Alopecia, anorexia, arrhythmias, confusion, drowsiness, dry mouth, flushing, hyponatraemia, ileus, impotence, insomnia, muscle cramps, nervousness, palpitation, pericardial pain, sweating, tinnitus, vertigo
- Rare: Abnormal dreams, allergic alveolitis, exfoliative dermatitis, glossitis, gynaecomastia, pemphigus, pulmonary infiltrates, Raynaud’s syndrome, Stevens-Johnson syndrome, stomatitis, toxic epidermal necrolysis
- Very rare: Gastro-intestinal angioedema

BREAST FEEDING
Avoid in first few weeks after delivery, particularly in preterm infants—risk of profound neonatal hypotension; can be used in mothers breast-feeding older infants if essential but monitor infant’s blood pressure.

HEPATIC IMPAIRMENT
Enalapril is a prodrug and requires close monitoring in patients with hepatic impairment.

RENAL IMPAIRMENT
Max. initial dose 2.5 mg daily if eGFR less than 30 mL/minute/1.73 m².

DIRECTIONS FOR ADMINISTRATION
Tablets may be crushed and suspended in water immediately before use.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension
Tablet
- ENALAPRIL MALEATE (non-proprietary)
  Enalapril maleate 2.5 mg | 28 tablet | £0.84 DT price = £1.51
  Enalapril maleate 5 mg | 28 tablet | £4.13 DT price = £0.99
  Enalapril maleate 10 mg | 28 tablet | £5.64 DT price = £1.02
  Enalapril maleate 20 mg | 28 tablet | £6.63 DT price = £1.18
- Innovace (Merck Sharp & Dohme Ltd)
  Enalapril maleate 2.5 mg | 28 tablet | £5.35 DT price = £1.51
  Enalapril maleate 5 mg | 28 tablet | £7.51 DT price = £0.99
  Enalapril maleate 10 mg | 28 tablet | £10.51 DT price = £1.02
  Enalapril maleate 20 mg | 28 tablet | £12.51 DT price = £1.18

Enalapril with hydrochlorothiazide

The properties listed below are those particular to the combination only. For the properties of the components please consider, enalapril maleate above, hydrochlorothiazide p. 160.

INDICATIONS AND DOSE
Mild to moderate hypertension in patients stabilised on the individual components in the same proportions
BY MOUTH
adult: (consult product literature)

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
Tablet
- ENALAPRIL WITH HYDROCHLOROTHIAZIDE (non-proprietary)
  Enalapril maleate 20 mg, Hydrochlorothiazide 12.5 mg | 28 tablet | £20.00 DT price = £13.94
  Innozide (Merck Sharp & Dohme Ltd)
  Enalapril maleate 20 mg, Hydrochlorothiazide 12.5 mg | 28 tablet | £13.90 DT price = £13.94

Fosinopril sodium

INDICATIONS AND DOSE
Hypertension
BY MOUTH
adult: Initially 10 mg daily for 4 weeks, then increased if necessary up to 40 mg daily, doses over 40 mg not shown to increase efficacy
Congestive heart failure (adjunct) (under close medical supervision)
BY MOUTH
adult: Initially 10 mg once daily, then increased if tolerated to 40 mg once daily, doses to be increased gradually

SIDE-EFFECTS
Chest pain, musculoskeletal pain

BREAST FEEDING
Not recommended; alternative treatment options, with better established safety information during breast-feeding, are available.

HEPATIC IMPAIRMENT
Fosinopril is a prodrug and requires close monitoring in patients with hepatic impairment.
**Imidapril hydrochloride**

**INDICATIONS AND DOSE**

**Essential hypertension**

- Adult: Initially 2.5 mg daily, increased if necessary to 10 mg daily, dose to be increased at intervals of at least 3 weeks, dose to be taken before food; maximum 20 mg per day
- Elderly: Initially 2.5 mg daily, increased if necessary to 10 mg daily, dose to be taken before food, dose to be increased at intervals of at least 3 weeks

**Essential hypertension in patients with heart failure, angina or cerebrovascular disease, or in renal or hepatic impairment**

- Adult: Initially 2.5 mg daily, increased if necessary to 10 mg daily, dose to be taken before food, dose to be increased at intervals of at least 3 weeks; maximum 20 mg per day

**SIDE-EFFECTS**

- Blurred vision
- Bronchitis
- Confusion
- Depression
- Dry mouth
- Dysphonia
- Glossitis
- Ileus
- Impotence
- Sleep disturbances
- Tinnitus

**BREAST FEEDING**

Not recommended; alternative treatment options, with better established safety information during breast-feeding, are available.

**HEPATIC IMPAIRMENT**

Imidapril is a prodrug and requires close monitoring in patients with hepatic impairment.

**RENAL IMPAIRMENT**

Initial dose 2.5 mg daily if eGFR 30–80 mL/minute/1.73 m². Avoid if eGFR less than 30 mL/minute/1.73 m².

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Tanatril (Chiesi Ltd)
  - Imidapril hydrochloride 5 mg Tanatril 5 mg tablets | 28 tablet £6.40 DT price = £6.40
  - Imidapril hydrochloride 10 mg Tanatril 10 mg tablets | 28 tablet £7.22 DT price = £7.22
  - Imidapril hydrochloride 20 mg Tanatril 20 mg tablets | 28 tablet £8.67 DT price = £8.67

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**Lisinopril**

**INDICATIONS AND DOSE**

**Hypertension**

- Adult: Initially 10 mg once daily; maintenance 20 mg once daily; maximum 80 mg per day
- Adult: Initially 2.5–5 mg once daily; maintenance 20 mg once daily; maximum 80 mg per day

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

**Tablet**

- Lisinopril (Non-proprietary)
  - Lisinopril 2.5 mg Lisinopril 2.5 mg tablets | 28 tablet £6.16 DT price = £6.36
  - Lisinopril 5 mg Lisinopril 5 mg tablets | 28 tablet £7.80 DT price = £7.96
  - Lisinopril 10 mg Lisinopril 10 mg tablets | 28 tablet £9.60 DT price = £9.76
  - Lisinopril 20 mg Lisinopril 20 mg tablets | 28 tablet £10.90 DT price = £11.00
  - Zestril (AstraZeneca UK Ltd)
  - Lisinopril 5 mg Zestril 5 mg tablets | 28 tablet £4.71 DT price = £4.66

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**Short-term treatment following myocardial infarction in haemodynamically stable patients—systolic blood pressure over 120 mmHg**

**BY MOUTH**

- Adult: Initially 5 mg, taken within 24 hours of myocardial infarction, followed by 5 mg, to be taken 24 hours after initial dose, then 10 mg once daily, to be taken 24 hours after second dose, then 10 mg once daily for 5 weeks (or continued if heart failure), temporarily reduce maintenance dose to 5 mg and if necessary 2.5 mg daily if systolic blood pressure 100 mmHg or less during treatment. Withdraw if prolonged hypotension occurs during treatment (systolic blood pressure less than 90 mmHg for more than 1 hour)

**Renal complications of diabetes mellitus**

**BY MOUTH**

- Adult: Initially 2.5–5 mg once daily, adjusted according to response; maintenance 10–20 mg once daily

**Heart failure (adjunct) (under expert supervision)**

**BY MOUTH**

- Adult: Initially 2.5 mg once daily; increased in steps of up to 10 mg at least every 2 weeks; maximum 35 mg per day

**SIDE-EFFECTS**

- Uncommon Raynaud’s syndrome, vertigo, asthenia, cerebrovascular accident, confusion, impotence, mood changes, myocardial infarction, palpitation, sleep disturbances, tachycardia
- Rare Alopecia, dry mouth, gynaecomastia, psoriasis
- Very rare Allergic alveolitis, pemphigus, profuse sweating, pulmonary infiltrates, Stevens-Johnson syndrome, toxic epidermal necrolysis

**BREAST FEEDING**

Not recommended; alternative treatment options, with better established safety information during breast-feeding, are available.

**RENAL IMPAIRMENT**

Max. initial doses 5–10 mg daily if eGFR 30–80 mL/minute/1.73 m² (max. 40 mg daily); 2.5–5 mg daily if eGFR 10–30 mL/minute/1.73 m² (max. 40 mg daily); 2.5 mg daily if eGFR less than 10 mL/minute/1.73 m².

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**Lisinopril**

**INDICATIONS AND DOSE**

**Hypertension**

- Adult: Initially 10 mg once daily; maintenance 20 mg once daily; maximum 80 mg per day
- Hypertension, when used in addition to diuretic, in cardiac decompensation or in volume depletion

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

**Tablet**

- Lisinopril (Non-proprietary)
  - Lisinopril 2.5 mg Lisinopril 2.5 mg tablets | 28 tablet £6.16 DT price = £6.36
  - Lisinopril 5 mg Lisinopril 5 mg tablets | 28 tablet £7.80 DT price = £7.96
  - Lisinopril 10 mg Lisinopril 10 mg tablets | 28 tablet £9.60 DT price = £9.76
  - Lisinopril 20 mg Lisinopril 20 mg tablets | 28 tablet £10.90 DT price = £11.00
  - Zestril (AstraZeneca UK Ltd)
  - Lisinopril 5 mg Zestril 5 mg tablets | 28 tablet £4.71 DT price = £4.66
Hydrochlorothiazide with lisinopril

The properties listed below are those particular to the combination only. For the properties of the individual components please consider, lisinopril p. 128, hydrochlorothiazide p. 160.

INDICATIONS AND DOSE
Mild to moderate hypertension in patients stabilised on the individual components in the same proportions

BY MOUTH

Adult: (consult product literature)

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet

HYDROCHLOROTHIAZIDE WITH LISISNOPRIL (Non-proprietary)
Hydrochlorothiazide 12.5 mg, Lisinopril 10 mg
Lisinopril 10mg / Hydrochlorothiazide 12.5mg tablets | 28 tablet (£0.30) £4.65 DT price = £4.99
Hydrochlorothiazide 12.5 mg, Lisinopril 20 mg
Lisinopril 20mg / Hydrochlorothiazide 12.5mg tablets | 28 tablet (£0.30) £4.65 DT price = £6.63
Carace Plus (Merck Sharp & Dohme Ltd)
Hydrochlorothiazide 12.5 mg, Lisinopril 20 mg
Carace 20 Plus tablets | 28 tablet (£0.40) £1.43 DT price = £2.63
Zestoretic 10 (AstraZeneca UK Ltd)
Hydrochlorothiazide 12.5 mg, Lisinopril 10 mg
Zestoretic 10 tablets | 28 tablet (£0.25) £0.81 DT price = £4.99
Zestoretic 20 (AstraZeneca UK Ltd)
Hydrochlorothiazide 12.5 mg, Lisinopril 20 mg
Zestoretic 20 tablets | 28 tablet (£0.50) £1.52 DT price = £2.63

MOEXIPRIL HYDROCHLORIDE

INDICATIONS AND DOSE
Essential hypertension (monotherapy)

BY MOUTH

Adult: Initially 7.5 mg once daily, adjusted according to response; maintenance 7.5–15 mg once daily; maximum 30 mg per day

Elderly: Initially 3.75 mg once daily, adjusted according to response; maintenance 7.5–15 mg once daily; maximum 30 mg per day

Essential hypertension when used in addition with nifedipine or other antihypertensive drug

BY MOUTH

Adult: Initially 3.75 mg once daily, adjusted according to response; maintenance 7.5–15 mg once daily; maximum 30 mg per day

CAUTIONS
Significant mitral valve stenosis

SIDE-EFFECTS
Very rare
Numbness

Frequency not known
Alopecia, angina, appetite, arrhythmias, blurred vision, cerebrovascular accident, confusion, depression, drowsiness, dry mouth, dyspnoea, flushing, hyperuricaemia, impotence, myocardial infarction, palpitation, pemetrex, sleep disturbance, Stevens-Johnson syndrome, sweating, syncope, tachycardia, tinnitus, toxic epidermal necrolysis, weight changes

BREAST FEEDING
Not recommended; alternative treatment options, with better established safety information during breast-feeding, are available.

HEPATIC IMPAIRMENT
Initial dose 3.75 mg once daily. Moexipril is a prodrug and requires close monitoring in patients with hepatic impairment.

RENAL IMPAIRMENT
If eGFR less than 40 mL/minute/1.73 m², initial dose 3.75 mg once daily titrated to max. 15 mg once daily.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet

Perdix (UCB Pharma Ltd)
Moexipril hydrochloride 7.5 mg
Perdix 7.5mg tablets | 28 tablet (£0.10) £0.60
Moexipril hydrochloride 15 mg
Perdix 15mg tablets | 28 tablet (£0.25) £1.42

PERINDOPRIL ARGININE

INDICATIONS AND DOSE
Hypertension

BY MOUTH

Adult: Initially 5 mg once daily for 1 month, then, adjusted according to response; maximum 10 mg per day

Elderly: Initially 2.5 mg once daily, then, adjusted according to response; maximum 10 mg per day

Hypertension, if used in addition to diuretic, or in renal impairment, cardiac decompensation or volume depletion

BY MOUTH

Adult: Initially 2.5 mg once daily, then, adjusted according to response; maximum 10 mg per day

Symptomatic heart failure (adjunct) (under close medical supervision)

BY MOUTH

Adult: Initially 2.5 mg once daily for 2 weeks, then increased if tolerated to 5 mg once daily, dose to be taken in the morning

Prophylaxis of cardiac events following myocardial infarction or revascularisation in stable coronary artery disease

BY MOUTH

Adult: Initially 5 mg once daily for 2 weeks, then increased if tolerated to 10 mg once daily, dose to be taken in the morning

SIDE-EFFECTS
Asthenia, mood disturbances, sleep disturbances

HEPATIC IMPAIRMENT
Perindopril is a prodrug and requires close monitoring in patients with hepatic impairment.

RENAL IMPAIRMENT
Max. initial dose 2.5 mg once daily if eGFR 30–60 mL/minute/1.73 m²; 2.5 mg once daily on alternate days if eGFR 15–30 mL/minute/1.73 m².

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 22

Coversyl Arginine (Servier Laboratories Ltd)
Perindopril arginine 2.5 mg
Coversyl Arginine 2.5mg tablets | 30 tablet (£0.35) £4.43 DT price = £4.43
Perindopril arginine 5 mg
Coversyl Arginine 5mg tablets | 30 tablet (£0.70) £6.28 DT price = £6.28
Perindopril arginine 10 mg
Coversyl Arginine 10mg tablets | 30 tablet (£1.05) £10.65 DT price = £10.65
Indapamide with perindopril arginine

The properties listed below are those particular to the combination only. For the properties of the components please consider, perindopril arginine p. 129, indapamide p. 160.

**INDICATIONS AND DOSE**

Hypertension not adequately controlled by perindopril alone

**BY MOUTH**

- Adult: (consult product literature)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension, powder

**Tablet**

**CAUTIONARY AND ADVISORY LABELS** 22

- **PERINDOPRIL ERBUMINE (Non-proprietary)**
  - Perindopril erbumine 2 mg Perindopril erbumine 2mg tablets | 30 tablet [Psd] £4.41 DT price = £1.15 | 56 tablet [Psd] £3.34
  - 60 tablet [Psd] £3.90

- Perindopril erbumine 4 mg Perindopril erbumine 4mg tablets | 30 tablet [Psd] £4.50 DT price = £1.56 | 56 tablet [Psd] £3.38
  - 60 tablet [Psd] £2.80

- Perindopril erbumine 8 mg Perindopril erbumine 8mg tablets | 30 tablet [Psd] £5.95 DT price = £1.52 | 56 tablet [Psd] £3.88 | 60 tablet [Psd] £4.00

Quinapril

**INDICATIONS AND DOSE**

**Essential hypertension**

**BY MOUTH**

- Adult: Initially 10 mg once daily; maintenance 20–40 mg daily in up to 2 divided doses; maximum 80 mg per day
- Elderly: Initially 2.5 mg once daily; maintenance 20–40 mg daily in up to 2 divided doses; maximum 80 mg per day

**Essential hypertension if used in addition to diuretic**

**BY MOUTH**

- Adult: Initially 2.5 mg once daily; maintenance 20–40 mg daily in up to 2 divided doses; maximum 80 mg per day

**Heart failure (adjunct) (under close medical supervision)**

**BY MOUTH**

- Adult: Initially 2.5 mg daily, increased if tolerated to 10–20 mg daily in 1–2 divided doses, doses to be increased gradually; maximum 40 mg per day

**SIDE-EFFECTS** impotence · asthenia · back pain · blurred vision · chest pain · depression · flatulence · insomnia · nervousness · oedema

**BREAST FEEDING** Avoid in the first few weeks after delivery, particularly in preterm infants, due to the risk of profound neonatal hypotension; if essential, may be used in mothers breast-feeding older infants—the infant’s blood pressure should be monitored.

**HEPATIC IMPAIRMENT** Quinapril is a prodrug and requires close monitoring in patients with hepatic impairment.

**RENAL IMPAIRMENT** Max. initial dose 2.5 mg once daily if eGFR less than 40 mL/minute/1.73 m².

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **QUINAPRIL (Non-proprietary)**
  - Quinapril (as Quinapril hydrochloride) 5 mg Quinapril 5mg tablets | 28 tablet [Psd] £8.59 DT price = £8.47
  - Quinapril (as Quinapril hydrochloride) 10 mg Quinapril 10mg tablets | 28 tablet [Psd] £8.59 DT price = £8.46
  - Quinapril (as Quinapril hydrochloride) 20 mg Quinapril 20mg tablets | 28 tablet [Psd] £6.00 DT price = £1.86
  - Quinapril (as Quinapril hydrochloride) 40 mg Quinapril 40mg tablets | 28 tablet [Psd] £8.00 DT price = £2.41

- **Accupro** (Pfizer Ltd)
  - Quinapril (as Quinapril hydrochloride) 5 mg Accupro 5mg tablets | 28 tablet [Psd] £8.60 DT price = £8.47
  - Quinapril (as Quinapril hydrochloride) 10 mg Accupro 10mg tablets | 28 tablet [Psd] £8.60 DT price = £8.46
  - Quinapril (as Quinapril hydrochloride) 20 mg Accupro 20mg tablets | 28 tablet [Psd] £10.79 DT price = £1.86

Perindopril erbumine

**INDICATIONS AND DOSE**

Hypertension

**BY MOUTH**

- Adult: Initially 4 mg once daily for 1 month, dose to be taken in the morning, then, adjusted according to response; maximum 8 mg per day
- Elderly: Initially 2 mg once daily, dose to be taken in the morning, then, adjusted according to response; maximum 8 mg per day

Hypertension, if used in addition to diuretic, in renal impairment, in cardiac decompensation, or in volume depletion

**BY MOUTH**

- Adult: Initially 2 mg once daily, dose to be taken in the morning, then, adjusted according to response; maximum 8 mg per day

**Heart failure (adjunct) (under close medical supervision)**

**BY MOUTH**

- Adult: Initially 2 mg once daily for 2 weeks, dose to be taken in the morning, then increased if necessary up to 4 mg once daily

**Prophylaxis of cardiac events following myocardial infarction or revascularisation in stable coronary artery disease**

**BY MOUTH**

- Adult: Initially 4 mg once daily for 2 weeks, dose to be taken in the morning, then increased if tolerated to 8 mg once daily
- Elderly: Initially 2 mg once daily for 1 week, then increased if tolerated to 4 mg once daily for 1 week, then increased if tolerated to 8 mg once daily

**SIDE-EFFECTS** Asthenia · mood disturbances · sleep disturbances

**BREAST FEEDING** Not recommended; alternative treatment options, with better established safety information during breast-feeding, are available.

**HEPATIC IMPAIRMENT** Perindopril is a prodrug and requires close monitoring in patients with hepatic impairment.

**RENAL IMPAIRMENT** Max. initial dose 2 mg once daily if eGFR 30–60 mL/minute/1.73 m²; 2 mg once daily on alternate days if eGFR 15–30 mL/minute/1.73 m².
Hydrochlorothiazide with quinapril
The properties listed below are those particular to the combination only. For the properties of the components please consider, quinapril p. 130, hydrochlorothiazide p. 160.

INDICATIONS AND DOSE
Hypertension in patients stabilised on the individual components in the same proportions

BY MOUTH

Adult: (consult product literature)

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet

HYDROCHLOROTHIAZIDE WITH QUINAPRIL (Non-proprietary)
Hydrochlorothiazide 12.5 mg, Quinapril (as Quinapril hydrochloride) 10 mg Quinapril 10mg / Hydrochlorothiazide 12.5mg tablets | 28 tablet (PSt) £11.75 DT price = £11.75
Accuretic (Pfizer Ltd)
Hydrochlorothiazide 12.5 mg, Quinapril (as Quinapril hydrochloride) 10 mg Accuretic 12.5mg/10mg tablets | 28 tablet (PSt) £11.75 DT price = £11.75

Ramipril

INDICATIONS AND DOSE
Hypertension

BY MOUTH

Adult: Initially 1.25–2.5 mg daily, increased if necessary up to 10 mg daily, dose to be increased at intervals of 2–4 weeks
Symptomatic heart failure (adjunct) (under close medical supervision)

BY MOUTH

Adult: Initially 1.25 mg daily, increased if necessary up to 10 mg daily, preferably taken in 2 divided doses, increase dose gradually at intervals of 1–2 weeks
Prophylaxis after myocardial infarction in patients with clinical evidence of heart failure (started at least 48 hours after infarction)

BY MOUTH

Adult: Initially 2.5 mg twice daily for 3 days, then increased to 5 mg twice daily
Prophylaxis after myocardial infarction in patients with clinical evidence of heart failure (started at least 48 hours after infarction) when initial dose not tolerated

BY MOUTH

Adult: Initially 1.25 mg twice daily for 2 days, then increased to 2.5 mg twice daily, then increased to 5 mg twice daily, withdraw treatment if dose cannot be increased to 2.5 mg twice daily
Prevention of cardiovascular events in patients with atherosclerotic cardiovascular disease or with diabetes mellitus and at least one additional risk factor for cardiovascular disease

BY MOUTH

Adult: Initially 2.5 mg daily for 1–2 weeks, then increased to 5 mg daily for a further 2–3 weeks, then increased to 10 mg daily
Nephropathy (consult product literature)

BY MOUTH

Adult: Initially 1.25 mg daily for 2 weeks, then increased to 2.5 mg daily for a further 2 weeks, then increased if tolerated to 5 mg daily

SIDE-EFFECTS

- Common or very common Bronchitis · dyspnoea · muscle cramps · stomatitis · syncope
- Uncommon Angina · anxiety · arrhythmias · chest pain · decreased libido · depression · dry mouth · flushing · impotence · loss of appetite · myocardial infarction · nervousness · palpitations · peripheral oedema · sweating · tachycardia · visual disturbances
- Rare Confusion · conjunctivitis · impaired hearing · onycholysis · tinnitus · tremor

Frequency not known Alopoeia · cerebrovascular accident · erythema multiforme · gynaecomastia · hyponatraemia · pempigoid exanthema · precipitation or exacerbation of Raynaud’s syndrome · skin reactions · sleep disturbance · Stevens-Johnson syndrome · toxic epidermal necrolysis

BREAST FEEDING
Not recommended; alternative treatment options, with better established safety information during breast-feeding, are available.

HEPATIC IMPAIRMENT
Max. daily dose 2.5 mg.
Ramipril is a prodrug and requires close monitoring in patients with hepatic impairment.

RENAL IMPAIRMENT
Max. daily dose 5 mg if eGFR 30–60 mL/minute/1.73 m²; max. initial dose 1.25 mg once daily (do not exceed 5 mg daily) if eGFR less than 30 mL/minute/1.73 m².

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet

RAMIPRIL (Non-proprietary)
Ramipril 1.25 mg Ramipril 1.25mg tablets | 28 tablet (PSt) £5.25 DT price = £5.25
Ramipril 2.5 mg Ramipril 2.5mg tablets | 28 tablet (PSt) £7.49 DT price = £7.49
Ramipril 5 mg Ramipril 5mg tablets | 28 tablet (PSt) £10.40 DT price = £10.40
Ramipril 10 mg Ramipril 10mg tablets | 28 tablet (PSt) £14.20 DT price = £14.20

TRITACE (Sanofi)

TRITACE 2.5 mg Tritace 2.5mg tablets | 28 tablet (PSt) £2.12 DT price = £2.12
TRITACE 5 mg Tritace 5mg tablets | 28 tablet (PSt) £2.72 DT price = £2.72
TRITACE 10 mg Tritace 10mg tablets | 28 tablet (PSt) £3.68 DT price = £3.68

Capsule

RAMIPRIL (Non-proprietary)
Ramipril 1.25 mg Ramipril 1.25mg capsules | 28 capsule (PSt) £1.31 DT price = £1.31
Ramipril 2.5 mg Ramipril 2.5mg capsules | 28 capsule (PSt) £1.24 DT price = £1.24
Ramipril 10 mg Ramipril 10mg capsules | 28 capsule (PSt) £2.10 DT price = £2.10

Oral solution

RAMIPRIL (Non-proprietary)
Ramipril 500 microgram per 1 ml Ramipril 2.5mg/5ml oral solution sugar free (sugar-free) | 150 ml (PSt) £96.00 DT price = £96.00

Feldipine with ramipril
The properties listed below are those particular to the combination only. For the properties of the components please consider, feldipine p. 151, ramipril above.
Cardiovascular system

INDICATIONS AND DOSE
Hypertension in patients stabilised on the individual components in the same proportions

BY MOUTH
Adult: (consult product literature)

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Modified-release tablet

CAUTIONARY AND ADVISORY LABELS 25

Triapin (Sanofi)

Feldopine 2.5 mg, Ramipril 2.5 mg Triapin 2.5mg/2.5mg modified-release tablets | 28 tablet | £24.55
Feldopine 5 mg, Ramipril 5 mg Triapin 5mg/5mg modified-release tablets | 28 tablet | £16.13 DT price = £16.13

Trandolapril

INDICATIONS AND DOSE
Mild to moderate hypertension

BY MOUTH
Adult: Initially 500 micrograms once daily; increased to 1–2 mg once daily, dose to be increased at intervals of 2–4 weeks; maximum 4 mg per day

Prophylaxis after myocardial infarction in patients with left ventricular dysfunction (starting as early as 3 days after infarction)

BY MOUTH
Adult: Initially 500 micrograms once daily, then increased to up to 4 mg once daily, doses to be increased gradually

● SIDE-EFFECTS
Alopecia • angina • arrhythmias • asthenia • bronchitis • cerebral haemorrhage • dry mouth • dyspnoea • hot flushes • ileus • myocardial infarction • nervousness • palpitation • psoriasis-like efflorescence • skin reactions • sleep disturbances • Stevens-Johnson syndrome • sweating • syncope • tachycardia • toxic epidermal necrolysis • transient ischaemic attacks

SIDE-EFFECTS, FURTHER INFORMATION
Symptomatic hypotension If symptomatic hypotension develops during titration, do not increase dose further; if possible, reduce dose of any adjunctive treatment and if this is not effective or feasible, reduce dose of trandolapril.

● BREAST FEEDING
Not recommended; alternative treatment options, with better established safety information during breast-feeding, are available.

● HEPATIC IMPAIRMENT
Trandolapril is a prodrug and requires close monitoring in patients with hepatic impairment.

● RENAL IMPAIRMENT
Max. 2 mg daily if eGFR less than 10 mL/minute/1.73 m².

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Capsule

TRANDOLAPRIL (Non-proprietary)

Trandolapril 500 microgram Trandolapril 500microgram capsules | 14 capsule | £1.92 DT price = £1.87
Trandolapril 1 mg Trandolapril 1mg capsules | 28 capsule | £20.00 DT price = £19.99
Trandolapril 2 mg Trandolapril 2mg capsules | 28 capsule | £10.40 DT price = £7.60
Trandolapril 4 mg Trandolapril 4mg capsules | 28 capsule | £14.19 DT price = £14.01

Azilsartan medoxomil

INDICATIONS AND DOSE
Hypertension

BY MOUTH
Adult 18-74 years: Initially 40 mg once daily, increased if necessary to 80 mg once daily
Adult 75 years and over: Initially 20–40 mg once daily, increased if necessary to 80 mg once daily

Hypertension with intravascular volume depletion

BY MOUTH
Adult: Initially 20–40 mg daily, increased if necessary to 80 mg daily

● CAUTIONS
Heart failure

● SIDE-EFFECTS
Common or very common Diarrhoea • raised creatinine kinase
Uncommon Hyperuricaemia • peripheral oedema • raised creatinine • malaise

● HEPATIC IMPAIRMENT
Manufacturer advises to consider initial dose of 20 mg in mild to moderate impairment (limited information available).
Manufacturer advises avoid in severe impairment (no information available). Manufacturer advises monitor closely in mild to moderate hepatic impairment (limited information available).

ANGIOTENSIN-II RECEPTOR ANTAGONISTS

Angiotensin-II receptor antagonists

● CONTRA-INDICATIONS
The combination of an angiotensin-II receptor antagonist with aliskiren is contra-indicated in patients with an eGFR less than 60 mL/minute/1.73 m². The combination of an angiotensin-II receptor antagonist with aliskiren is contra-indicated in patients with diabetes mellitus

● CAUTIONS
Afro-Caribbean patients—particularly those with left ventricular hypertrophy (may not benefit from an angiotensin-II receptor antagonist) • aortic or mitral valve stenosis—elderly (lower initial doses may be appropriate) • hypertrophic cardiomyopathy—patients with a history of angioedema • patients with primary aldosteronism (may not benefit from an angiotensin-II receptor antagonist) • renal artery stenosis

● INTERACTIONS
Appendix 1 (angiotensin-II receptor antagonists).

● SIDE-EFFECTS
Hyperkalaemia • angioedema (may be delayed onset) • symptomatic hypotension including dizziness (particularly in patients with intravascular volume depletion, e.g. those taking high-dose diuretics)

● PREGNANCY
Angiotensin-II receptor antagonists should be avoided in pregnancy unless essential. They may adversely affect fetal and neonatal blood pressure control and renal function; neonatal skull defects and oligohydramnios have also been reported.

BREAST FEEDING
Information on the use of angiotensin-II receptor antagonists in breast-feeding is limited. They are not recommended in breast-feeding and alternative treatment options, with better established safety information during breast-feeding, are available.

RENAL IMPAIRMENT
Use with caution, starting with low dose, and adjust according to response.

MONITORING REQUIREMENTS
Monitor plasma-potassium concentration, particularly in the elderly and in patients with renal impairment.
Candesartan cilexetil

INDICATIONS AND DOSE

Hypertension

BY MOUTH

Adult: Initially 8 mg once daily, increased if necessary up to 32 mg daily, doses to be increased at intervals of 4 weeks; usual dose 8 mg once daily

Hypertension with intravascular volume depletion

BY MOUTH

Adult: Initially 4 mg once daily, increased if necessary up to 32 mg daily, doses to be increased at intervals of 4 weeks; usual dose 8 mg once daily

Heart failure with impaired left ventricular systolic function when ACE inhibitors are not tolerated: Heart failure with impaired left ventricular systolic function in conjunction with an ACE inhibitor (under expert supervision)

BY MOUTH

Adult: Initially 4 mg once daily, increased at intervals of at least 2 weeks to ‘target’ dose of 32 mg once daily or to maximum tolerated dose

CONTRA-INDICATIONS

Cholestasis

SIDE-EFFECTS

Common or very common: Headache, vertigo

Very rare: Arthralgia, back pain, blood disorders, cough, hepatitis, hypoglycaemia, myalgia, nausea, pruritus, rash, urticaria

HEPATIC IMPAIRMENT

Initially 4 mg once daily in mild or moderate liver impairment. Avoid in severe hepatic impairment.

RENAL IMPAIRMENT

Initially 4 mg daily. Use with caution if eGFR less than 15 mL/minute/1.73 m²—limited experience.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

Tablet

Candesartan cilexetil 2 mg Candesartan 2 mg tablets | 7 tablet POM £3.40 DT price = £1.53

Candesartan cilexetil 4 mg Candesartan 4 mg tablets | 7 tablet POM £3.88 DT price = £0.83 | 28 tablet POM £9.78

Candesartan cilexetil 8 mg Candesartan 8 mg tablets | 28 tablet POM £9.89 DT price = £1.23

Candesartan cilexetil 16 mg Candesartan 16 mg tablets | 28 tablet POM £12.72 DT price = £1.57

Candesartan cilexetil 32 mg Candesartan 32 mg tablets | 28 tablet POM £16.13 DT price = £2.20

Amias (Takeda UK Ltd)

Candesartan cilexetil 2 mg Amias 2 mg tablets | 7 tablet POM £3.58 DT price = £1.53

Candesartan cilexetil 4 mg Amias 4 mg tablets | 7 tablet POM £3.88 DT price = £0.83 | 28 tablet POM £9.78

Candesartan cilexetil 8 mg Amias 8 mg tablets | 28 tablet POM £9.89 DT price = £1.23

Eprosartan

INDICATIONS AND DOSE

Hypertension

BY MOUTH

Adult: 600 mg once daily

SIDE-EFFECTS

Common or very common: Headache, vertigo

Uncommon: Arthralgia, back pain, blood disorders, cough, hepatitis, hypoglycaemia, myalgia, nausea, pruritus, rash, urticaria

HEPATIC IMPAIRMENT

Caution in mild or moderate liver impairment. Avoid in severe impairment.

RENAL IMPAIRMENT

Caution if eGFR less than 30 mL/minute/1.73 m².

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

Tablet

Candesartan (as Eprosartan mesilate) 300 mg Eprosartan 300 mg tablets | 28 tablet POM £7.31 DT price = £7.31

Eprosartan (as Eprosartan mesilate) 400 mg Eprosartan 400 mg tablets | 56 tablet POM £25.98 DT price = £25.85

Eprosartan (as Eprosartan mesilate) 600 mg Eprosartan 600 mg tablets | 28 tablet POM £14.31 DT price = £14.31

Teveten (BGP Products Ltd)

Eprosartan (as Eprosartan mesilate) 300 mg Teveten 300 mg tablets | 28 tablet POM £7.31 DT price = £7.31

Eprosartan (as Eprosartan mesilate) 600 mg Teveten 600 mg tablets | 28 tablet POM £14.31 DT price = £14.31

Irbesartan

INDICATIONS AND DOSE

Hypertension

BY MOUTH

Adult 18-74 years: Initially 150 mg once daily, increased if necessary to 300 mg once daily

Adult 75 years and over: Initially 75–150 mg once daily, increased if necessary to 300 mg once daily

Hypertension in patients receiving haemodialysis

BY MOUTH

Adult: Initially 75–150 mg once daily, increased if necessary to 300 mg once daily

Renal disease in hypertensive type 2 diabetes mellitus

BY MOUTH

Adult 18-74 years: Initially 150 mg once daily, increased if tolerated to 300 mg once daily

Adult 75 years and over: Initially 75–150 mg once daily, increased if tolerated to 300 mg once daily

Renal disease in hypertensive type 2 diabetes mellitus in patients receiving haemodialysis

BY MOUTH

Adult: Initially 75–150 mg once daily, increased if tolerated to 300 mg once daily

SIDE-EFFECTS

Common or very common: Fatigue, musculoskeletal pain, nausea, vomiting

Uncommon: Chest pain, cough, diarrhoea, dyspepsia, flushing, sexual dysfunction, tachycardia

Rare: Rash, urticaria
Hydrochlorothiazide with irbesartan

The properties listed below are those particular to the combination only. For the properties of the components please consider, irbesartan p. 133, hydrochlorothiazide p. 160.

INDICATIONS AND DOSE
Hypertension not adequately controlled with irbesartan alone
BY MOUTH
- Adult: (consult product literature)

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
- HYDROCHLOROTHIAZIDE WITH IRBESARTAN (Non-proprietary)
  Hydrochlorothiazide 12.5 mg, Irbesartan 150 mg  Irbesartan 150mg / Hydrochlorothiazide 12.5mg tablets  |  28 tablet  POM  £11.25 DT price = £1.36
  Hydrochlorothiazide 25 mg, Irbesartan 300 mg  Irbesartan 300mg / Hydrochlorothiazide 25mg tablets  |  28 tablet  POM  £13.54 DT price = £1.78
  Hydrochlorothiazide 12.5 mg, Irbesartan 300 mg  Irbesartan 300mg / Hydrochlorothiazide 12.5mg tablets  |  28 tablet  POM  £15.13 DT price = £2.10
- Aprovel (Sanofi)
  Hydrochlorothiazide 12.5 mg, Irbesartan 150 mg  CoAprovel 150mg/12.5mg tablets  |  28 tablet  POM  £11.84 DT price = £1.72
  Hydrochlorothiazide 25 mg, Irbesartan 300 mg  CoAprovel 300mg/25mg tablets  |  28 tablet  POM  £15.93 DT price = £2.87
  Hydrochlorothiazide 12.5 mg, Irbesartan 300 mg  CoAprovel 300mg/12.5mg tablets  |  28 tablet  POM  £15.93 DT price = £2.87

Losartan potassium

INDICATIONS AND DOSE
Diabetic nephropathy in type 2 diabetes mellitus
BY MOUTH
- Adult 18–75 years: Initially 50 mg once daily for several weeks, then increased if necessary to 100 mg once daily
- Adult 76 years and over: Initially 25 mg once daily

Chronic heart failure when ACE inhibitors are unsuitable or contra-indicated
BY MOUTH
- Adult: Initially 12.5 mg once daily, increased if tolerated to up to 150 mg once daily, doses to be increased at weekly intervals

Hypertension
BY MOUTH
- Adult 18–75 years: Initially 50 mg once daily for several weeks, then increased if necessary to 100 mg once daily
- Adult 76 years and over: Initially 25 mg daily

Hypertension with intravascular volume depletion
BY MOUTH
- Adult 18–75 years: Initially 25 mg once daily for several weeks, then increased if necessary up to 100 mg once daily

CAUTIONS
Severe heart failure
SIDE-EFFECTS
- Common or very common Vertigo
- Very rare Arthralgia - cutaneous vasculitis - headache - hepatitis - myalgia - renal dysfunction - taste disturbance - tinnitus

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, powder

Tablet
- IRBESARTAN (Non-proprietary)
  Irbesartan 75 mg  Irbesartan 75mg tablets  |  28 tablet  POM  £0.92 DT price = £0.13
  Irbesartan 150 mg  Irbesartan 150mg tablets  |  28 tablet  POM  £1.125 DT price = £0.16
  Irbesartan 300 mg  Irbesartan 300mg tablets  |  28 tablet  POM  £1.575 DT price = £0.235
- Aprovel (Sanofi)
  Irbesartan 75 mg  Aprovel 75mg tablets  |  28 tablet  POM  £0.92 DT price = £0.13
  Irbesartan 150 mg  Aprovel 150mg tablets  |  28 tablet  POM  £1.125 DT price = £0.16
  Irbesartan 300 mg  Aprovel 300mg tablets  |  28 tablet  POM  £1.575 DT price = £0.235
- Ifirmasta (Consilient Health Ltd)
  Irbesartan 75 mg  Ifirmasta 75mg tablets  |  28 tablet  POM  £0.82 DT price = £0.12
  Irbesartan 150 mg  Ifirmasta 150mg tablets  |  28 tablet  POM  £1.06 DT price = £0.16
  Irbesartan 300 mg  Ifirmasta 300mg tablets  |  28 tablet  POM  £1.575 DT price = £0.235
- Sabeval (Aspire Pharma Ltd)
  Irbesartan 75 mg  Sabeval 75mg tablets  |  28 tablet  POM  £0.92 DT price = £0.13
  Irbesartan 150 mg  Sabeval 150mg tablets  |  28 tablet  POM  £1.125 DT price = £0.16
  Irbesartan 300 mg  Sabeval 300mg tablets  |  28 tablet  POM  £1.575 DT price = £0.235

Hydrochlorothiazide with irbesartan

The properties listed below are those particular to the combination only. For the properties of the components please consider, irbesartan p. 133, hydrochlorothiazide p. 160.

INDICATIONS AND DOSE
Hypertension not adequately controlled with irbesartan alone
BY MOUTH
- Adult: (consult product literature)
Hydrochlorothiazide with losartan

The properties listed below are those particular to the combination only. For the properties of the components please consider, losartan potassium p. 134, hydrochlorothiazide p. 160.

**INDICATIONS AND DOSE**

Hypertension not adequately controlled with losartan alone

**BY MOUTH**

- Adult: (consult product literature)

- **MEDICINAL FORMS**
  
  There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**
  
  - HYDROCHLOROTHIAZIDE WITH LOSARTAN (Non-proprietary)
  
  - Hydrochlorothiazide 12.5 mg, Losartan potassium 50 mg / Hydrochlorothiazide 12.5mg tablets | 28 tablet (POM) £13.75 DT price = £1.65
  
  - Hydrochlorothiazide 25 mg, Losartan potassium 100 mg / Losartan 100mg / Hydrochlorothiazide 25mg tablets | 28 tablet (POM) £16.18 DT price = £2.06
  
  - Hydrochlorothiazide 12.5 mg, Losartan potassium 100 mg / Losartan 100mg / Hydrochlorothiazide 12.5mg tablets | 28 tablet (POM) £16.18 DT price = £13.69
  
  - **Cozaar-Comp** (Merck Sharp & Dohme Ltd)
  
  - Hydrochlorothiazide 12.5 mg, Losartan potassium 50 mg / Cozaar-Comp 50mg/12.5mg tablets | 28 tablet (POM) £12.80 DT price = £1.65
  
  - Hydrochlorothiazide 25 mg, Losartan potassium 100 mg / Cozaar-Comp 100mg/25mg tablets | 28 tablet (POM) £16.18 DT price = £2.06
  
  - Hydrochlorothiazide 12.5 mg, Losartan potassium 100 mg / Cozaar-Comp 100mg/12.5mg tablets | 28 tablet (POM) £16.18 DT price = £13.69

- **SIDE-EFFECTS**

  - **Very common** Headache - abdominal pain - hyponatraemia - hyperkalaemia - hyperuricaemia - liver function tests abnormal
  
  - **Common** Angina - chest pain - cough - myalgia - pruritus - thrombocytopenia - urticaria
  

- **HEPATIC IMPAIRMENT** Dose should not exceed 20 mg daily in moderate impairment. Manufacturer advises avoid in severe impairment—no information available.

- **RENAL IMPAIRMENT** Max. 20 mg daily if eGFR 20–60 mL/minute/1.73 m². Avoid if eGFR less than 20 mL/minute/1.73 m².

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

  **Tablet**

  - **Olmetec** (Daiichi Sankyo UK Ltd)
  
  - Olmesartan medoxomil 10 mg / Olmetec 10mg tablets | 28 tablet (POM) £10.95 DT price = £10.95
  
  - Olmesartan medoxomil 20 mg / Olmetec 20mg tablets | 28 tablet (POM) £12.95 DT price = £12.95
  
  - Olmesartan medoxomil 40 mg / Olmetec 40mg tablets | 28 tablet (POM) £17.50 DT price = £17.50

Amlodipine with olmesartan

The properties listed below are those particular to the combination only. For the properties of the components please consider, amlodipine p. 148, olmesartan medoxomil p. 160.

**INDICATIONS AND DOSE**

Hypertension in patients stabilised on the individual components in the same proportions

**BY MOUTH**

- Adult: (consult product literature)

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**

  - **Sevikar** (Daiichi Sankyo UK Ltd)
  
  - Amlodipine (as Amlodipine besilate) 5 mg, Olmesartan medoxomil 20 mg / Sevikar 20mg/5mg tablets | 28 tablet (POM) £16.95
  
  - Amlodipine (as Amlodipine besilate) 10 mg, Olmesartan medoxomil 40 mg / Sevikar 40mg/10mg tablets | 28 tablet (POM) £16.95
  
  - Amlodipine (as Amlodipine besilate) 5 mg, Olmesartan medoxomil 40 mg / Sevikar 40mg/5mg tablets | 28 tablet (POM) £16.95

Amlodipine with hydrochlorothiazide and olmesartan

The properties listed below are those particular to the combination only. For the properties of the components please consider, amlodipine p. 148, olmesartan medoxomil p. 160.

**INDICATIONS AND DOSE**

Hypertension in patients stabilised on the individual components in the same proportions, or for hypertension not adequately controlled with olmesartan and amlodipine

**BY MOUTH**

- Adult: (consult product literature)

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**

  - **Sevikar HCT** (Daiichi Sankyo UK Ltd)
  
  - Amlodipine besilate 5 mg, Hydrochlorothiazide 12.5 mg, Olmesartan medoxomil 20 mg / Sevikar HCT 20mg/5mg/12.5mg tablets | 28 tablet (POM) £16.95
  
  - Amlodipine besilate 5 mg, Hydrochlorothiazide 25 mg, Olmesartan medoxomil 40 mg / Sevikar HCT 40mg/5mg/25mg tablets | 28 tablet (POM) £16.95
  
  - Amlodipine besilate 10 mg, Hydrochlorothiazide 25 mg, Olmesartan medoxomil 40 mg / Sevikar HCT 40mg/10mg/25mg tablets | 28 tablet (POM) £16.95
  
  - Amlodipine besilate 5 mg, Hydrochlorothiazide 12.5 mg, Olmesartan medoxomil 40 mg / Sevikar HCT 40mg/5mg/12.5mg tablets | 28 tablet (POM) £16.95
Hydrochlorothiazide with olmesartan

The properties listed below are those particular to the combination only. For the properties of the components please consider, olmesartan medoxomil p. 135, hydrochlorothiazide p. 160.

INDICATIONS AND DOSE

Hypertension not adequately controlled with olmesartan alone

BY MOUTH

Adult: (consult product literature)

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

- Olmetec Plus (Daichi Sankyo UK Ltd)
  
  Hydrochlorothiazide 12.5 mg, Olmesartan medoxomil
  
  20 mg Olmetec Plus 20mg/12.5mg tablets | 28 tablet [PMB] £12.95
  DT price = £12.95

  Hydrochlorothiazide 25 mg, Olmesartan medoxomil
  
  20 mg Olmetec Plus 20mg/25mg tablets | 28 tablet [PMB] £12.95
  DT price = £12.95

  Hydrochlorothiazide 12.5 mg, Olmesartan medoxomil
  
  40 mg Olmetec Plus 40mg/12.5mg tablets | 28 tablet [PMB] £17.50
  DT price = £17.50

Telmisartan

INDICATIONS AND DOSE

Hypertension

BY MOUTH

Adult: Initially 20–40 mg once daily for at least 4 weeks, increased if necessary up to 80 mg once daily

Prevention of cardiovascular events in patients with established atherosclerotic cardiovascular disease, or type 2 diabetes mellitus with target-organ damage

BY MOUTH

Adult: 80 mg once daily

SIDE-EFFECTS

- Common or very common Arthralgia - back pain - chest pain - eczema - gastro-intestinal disturbances - influenza-like symptoms - leg cramps - myalgia - pharyngitis - sinusitis - urinary-tract infection

- Uncommon Abnormal vision - anxiety - dry mouth - flatulence - increased sweating - tendinitis-like symptoms - vertigo

- Rare Blood disorders - bradycardia - depression - dyspnoea - eosinophilia - increase in uric acid - insomnia - pruritus - rash - tachycardia

- Frequency not known Asthenia - syncope

HEPATIC IMPAIRMENT 20–40 mg once daily in mild or moderate impairment. Avoid in severe impairment or biliary obstruction.

RENAL IMPAIRMENT Manufacturer advises initial dose of 20 mg once daily in severe impairment.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

- TELMISARTAN (Non-proprietary)
  
  Telmisartan 20 mg Telmisartan 20mg tablets | 28 tablet [PMB] £1.35–£12.93
  DT price = £1.49

  Telmisartan 40 mg Telmisartan 40mg tablets | 28 tablet [PMB] £1.35–£12.93
  DT price = £1.49

  Telmisartan 80 mg Telmisartan 80mg tablets | 28 tablet [PMB] £1.96–£16.15
  DT price = £1.98

  Micardis (Boehringer Ingelheim Ltd)
  
  Telmisartan 20 mg Micardis 20mg tablets | 28 tablet [PMB] £11.10
  DT price = £1.44

Hydrochlorothiazide with telmisartan

The properties listed below are those particular to the combination only. For the properties of the components please consider, telmisartan above, hydrochlorothiazide p. 160.

INDICATIONS AND DOSE

Hypertension not adequately controlled by telmisartan alone

BY MOUTH

Adult: (consult product literature)

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

- HYDROCHLOROTHIAZIDE WITH TELMISARTAN (Non-proprietary)
  
  Hydrochlorothiazide 12.5 mg, Telmisartan 40 mg Telmisartan 40mg / Hydrochlorothiazide 12.5mg tablets | 28 tablet [PMB] £13.61
  DT price = £13.61

  Hydrochlorothiazide 25 mg, Telmisartan 80 mg Telmisartan 80mg / Hydrochlorothiazide 25mg tablets | 28 tablet [PMB] £16.15–£17.00
  DT price = £17.00

  Hydrochlorothiazide 12.5 mg, Telmisartan 80 mg Telmisartan 80mg / Hydrochlorothiazide 12.5mg tablets | 28 tablet [PMB] £16.15–£17.00
  DT price = £17.00

  Actelsar HCT (Actavis UK Ltd)
  
  Hydrochlorothiazide 12.5 mg, Telmisartan 40 mg Actelsar HCT 40mg/12.5mg tablets | 28 tablet [PMB] £13.61
  DT price = £13.61

  Hydrochlorothiazide 25 mg, Telmisartan 80 mg Actelsar HCT 80mg/25mg tablets | 28 tablet [PMB] £17.00
  DT price = £17.00

  Hydrochlorothiazide 12.5 mg, Telmisartan 80 mg Actelsar HCT 80mg/12.5mg tablets | 28 tablet [PMB] £17.00
  DT price = £17.00

  MicardisPlus (Boehringer Ingelheim Ltd)
  
  Hydrochlorothiazide 12.5 mg, Telmisartan 40 mg MicardisPlus 40mg/12.5mg tablets | 28 tablet [PMB] £13.61
  DT price = £13.61

  Hydrochlorothiazide 25 mg, Telmisartan 80 mg MicardisPlus 80mg/25mg tablets | 28 tablet [PMB] £17.00
  DT price = £17.00

  Hydrochlorothiazide 12.5 mg, Telmisartan 80 mg MicardisPlus 80mg/12.5mg tablets | 28 tablet [PMB] £17.00
  DT price = £17.00

  Tolucombi (Consilient Health Ltd)
  
  Hydrochlorothiazide 12.5 mg, Telmisartan 40 mg Tolucombi 40mg/12.5mg tablets | 28 tablet [PMB] £13.61
  DT price = £13.61

  Hydrochlorothiazide 25 mg, Telmisartan 80 mg Tolucombi 80mg/25mg tablets | 28 tablet [PMB] £17.00
  DT price = £17.00

  Hydrochlorothiazide 12.5 mg, Telmisartan 80 mg Tolucombi 80mg/12.5mg tablets | 28 tablet [PMB] £17.00
  DT price = £17.00

Valsartan

INDICATIONS AND DOSE

Hypertension

BY MOUTH

Adult: Initially 80 mg once daily, increased if necessary up to 320 mg daily, doses to be increased at intervals of 4 weeks

Hypertension with intravascular volume depletion

BY MOUTH

Adult: Initially 40 mg once daily, increased if necessary up to 320 mg daily, dose to be increased at intervals of 4 weeks
Heart failure when ACE inhibitors cannot be used, or in conjunction with an ACE inhibitor when a beta-blocker cannot be used. Heart failure, in conjunction with an ACE inhibitor when a beta-blocker cannot be used (under expert supervision).

**BY MOUTH**
- **Adult:** Initially 40 mg twice daily, increased to up to 160 mg twice daily, dose to be increased at intervals of at least 2 weeks.

**RENAL IMPAIRMENT**
- Use with caution if eGFR less than 30 ml/minute/1.73 m².

**SIDE-EFFECTS**

**CONTRA-INDICATIONS** Biliary cirrhosis - cholestasis

**SIDE-EFFECTS**
- **Common or very common** Renal impairment
- **Uncommon** Acute renal failure - cough - fatigue - gastrointestinal disturbance - headache - syncope
- **Frequency not known** Hypersensitivity reactions - myalgia - neutropenia - pruritus - rash - serum sickness - thrombocytopenia - vasculitis

**HEPATIC IMPAIRMENT** Max. dose 80 mg daily in mild to moderate impairment. Avoid in severe hepatic impairment.

**RENALE IMPAIRMENT** Use with caution if eGFR less than 10 ml/minute/1.73 m²—no information available.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

**Tablet**
- **VALSARTAN (Non-proprietary)**
  - Valsartan 40 mg Valsartan 40mg tablets | 7 tablet [Pom] £3.49 DT price = £2.79 | 28 tablet [Pom] no price available
  - Valsartan 80 mg Valsartan 80mg tablets | 28 tablet [Pom] £13.69
  - Valsartan 160 mg Valsartan 160mg tablets | 28 tablet [Pom] £14.69
  - Valsartan 320 mg Valsartan 320mg tablets | 28 tablet [Pom] £20.23
- **Diovan (Novartis Pharmaceuticals UK Ltd)**
  - Valsartan 320 mg Diovan 320mg tablets | 28 tablet [Pom] £20.23
  - **DT price = £15.09**

**Capsule**
- **VALSARTAN (Non-proprietary)**
  - Valsartan 40 mg Valsartan 40mg capsules | 28 capsule [Pom] £11.97 DT price = £6.38
  - Valsartan 80 mg Valsartan 80mg capsules | 28 capsule [Pom] £13.97 DT price = £6.65
  - Valsartan 160 mg Valsartan 160mg capsules | 28 capsule [Pom] £18.41 DT price = £6.01
- **Diovan (Novartis Pharmaceuticals UK Ltd)**
  - Valsartan 40 mg Diovan 40mg capsules | 28 capsule [Pom] £11.97 DT price = £6.38
  - Valsartan 80 mg Diovan 80mg capsules | 28 capsule [Pom] £13.97 DT price = £6.65
  - Valsartan 160 mg Diovan 160mg capsules | 28 capsule [Pom] £18.41 DT price = £6.01

**Oral solution**
- **Diovan (Novartis Pharmaceuticals UK Ltd)**
  - Valsartan 3 mg per 1 ml Diovan 3mg/1ml oral solution | 160 ml [Pom] £1.72
  - **Also available in combination with amlopidine, p. 149 and hydrochlorothiazide, below**

**Hydrochlorothiazide with valsartan**

The properties listed below are those particular to the combination only. For the properties of the components please consider, valsartan p. 136, hydrochlorothiazide p. 160.

**INDICATIONS AND DOSE**

Hypertension not adequately controlled by valsartan alone by mouth
- **Adult:** (consult product literature)

**MEDICINAL FORMS**

**Tablet**
- **HYDROCHLOROTHIAZIDE WITH VALSARTAN (Non-proprietary)**
  - Hydrochlorothiazide 12.5 mg, Valsartan 80 mg Valsartan 80mg / Hydrochlorothiazide 12.5mg tablets | 28 tablet [Pom] £13.97 DT price = £8.47
  - Hydrochlorothiazide 25 mg, Valsartan 160 mg Valsartan 160mg / Hydrochlorothiazide 25mg tablets | 28 tablet [Pom] £18.41 DT price = £11.21
  - Hydrochlorothiazide 12.5 mg, Valsartan 160 mg Valsartan 160mg / Hydrochlorothiazide 12.5mg tablets | 28 tablet [Pom] £18.41 DT price = £2.52
- Co-Diovan (Novartis Pharmaceuticals UK Ltd)
  - Hydrochlorothiazide 12.5 mg, Valsartan 80 mg Co-Diovan 80mg/12.5mg tablets | 28 tablet [Pom] £13.97 DT price = £8.47
  - Hydrochlorothiazide 25 mg, Valsartan 160 mg Co-Diovan 160mg/25mg tablets | 28 tablet [Pom] £18.41 DT price = £11.21
  - Hydrochlorothiazide 12.5 mg, Valsartan 160 mg Co-Diovan 160mg/12.5mg tablets | 28 tablet [Pom] £18.41 DT price = £2.52

**ANTIHYPERTENSIVES (CENTRALLY ACTING)**

**Clonidine hydrochloride**

**INDICATIONS AND DOSE**

Hypertension by mouth
- **Adult:** Initially 50–100 micrograms 3 times a day, increase initial dose every second or third day, usual maximum dose 1.2 mg daily.

Prevention of recurrent migraine | Prevention of vascular headache by mouth
- **Adult:** Initially 50 micrograms twice daily for 2 weeks, then increased if necessary to 75 micrograms twice daily.

**UNLICENSED USE** Clonidine may also be used for Tourette syndrome and sedation—unlicensed indications.

**CONTRA-INDICATIONS** Severe bradyarrhythmia secondary to second- or third-degree AV block or sick sinus syndrome.

**CAUTIONS** Cerebrovascular disease - constipation - heart failure - history of depression - mild to moderate bradyarrhythmia - polyneuropathy - Raynaud’s syndrome or other occlusive peripheral vascular disease

**INTERACTIONS** → Appendix 1 (clonidine).

**SIDE-EFFECTS**
- **Common or very common** Constipation - depression - dizziness - drowsiness - dry mouth - headache - malaise - nausea - postural hypotension - salivary gland pain - sexual dysfunction - sleep disturbances - vomiting
- **Uncommon** Bradycardia - delusion - hallucination - paraesthesia - pruritus - rash - Raynaud’s syndrome - urticaria
- **Rare** Alopecia - AV block - colonic pseudo-obstruction - decreased lacrimation - gynaecomastia - nasal dryness
- **Frequency not known** Bradyarrhythmia - confusion - fluid retention - hepatitis - impaired visual accommodation

**PREGNANCY** May lower fetal heart rate. Avoid oral use unless potential benefit outweighs risk. Avoid using injection.

**BREAST FEEDING** Avoid—present in milk.

**RENALE IMPAIRMENT** Use with caution in severe impairment—reduce initial dose and increase gradually.
Methyldopa

INDICATIONS AND DOSE

Hypertension

BY MOUTH
- Adult: Initially 250 mg 2–3 times a day, dose should be increased gradually at intervals of at least 2 days; maximum 3 g per day
- Elderly: Initially 125 mg twice daily, dose should be increased gradually; maximum 2 g per day

CONTRA-INDICATIONS
Acute porphyria; depression; phaeochromocytoma

CAUTIONS
History of depression

INTERACTIONS → Appendix 1 (methyldopa).

SIDE-EFFECTS
- Aenorrhoea; arthralgia; asthma; Bell’s palsy; bone-marrow depression; bradycardia; decreased libido; depression; dizziness; drug fever; dry mouth; eosinophilia; exacerbation of angina; failure of ejaculation; gastrointestinal disturbances; gynaecomastia; haemolytic anaemia; headache; hepatitis; hyperprolactinaemia; hypersensitivity reactions; impaired mental acuity; impotence; jaundice; leucopenia; lupus erythematosus-like syndrome; mild psychosis; myalgia; myocarditis; nasal congestion; nightmares; oedema; pancreatitis; paraesthesia; Parkinsonism; pericarditis; postural hypotension; rashes; sedation; siadadenitis; stomatitis; thrombocytopenia; toxic epidermal necrolysis

SIDE-EFFECTS, FURTHER INFORMATION
Side-effects are minimised if the daily dose is kept below 4 g.

PREGNANCY
Not known to be harmful.

BREAST FEEDING
Amount too small to be harmful.

HEPATIC IMPAIRMENT
Manufacturer advises caution in history of liver disease. Avoid in active liver disease.

RENAL IMPAIRMENT
Increased sensitivity to hypertensive and sedative effect. Start with small dose.

MONITORING REQUIREMENTS
Monitor blood counts and liver-function before treatment and at intervals during first 6–12 weeks or if unexplained fever occurs.

EFFECT ON LABORATORY TESTS
Interference with laboratory tests. Positive direct Coombs’ test in up to 20% of patients (may affect blood cross-matching).

PATIENT AND CARER ADVICE
Driving and skilled tasks Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol may be enhanced.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension, solution for infusion, oral solution, transdermal patch

Tablet

CAUTIONARY AND ADVISORY LABELS 3, 8

METHYLDOPA (Non-proprietary)

Methyldopa anhydrous 125 mg Methyldopa 125mg tablets | 56 tablet (£0.75–£1.16) DT price = £1.27
Methyldopa anhydrous 250 mg Methyldopa 250mg tablets | 56 tablet (£1.25) DT price = £6.33
Methyldopa anhydrous 500 mg Methyldopa 500mg tablets | 56 tablet (£18.05) DT price = £3.94
Aldomet (Aspen Pharma Trading Ltd) Moxonidine anhydrous 250 mg Aldomet 250mg tablets | 60 tablet (£0.65)
Methyldopa anhydrous 500 mg Aldomet 500mg tablets | 30 tablet (£4.55

Moxonidine

INDICATIONS AND DOSE
Mild to moderate essential hypertension

BY MOUTH
- Adult: 200 micrograms once daily for 3 weeks, dose to be taken in the morning, then increased if necessary to 400 micrograms daily in 1–2 divided doses (max. per dose 400 micrograms); maximum 600 micrograms per day in 2 divided doses

CONTRA-INDICATIONS
Bradyarrhythmia; conduction disorders; second- or third-degree AV block; severe heart failure; sick sinus syndrome; sino-atrial block

CAUTIONS
First-degree AV block; moderate heart failure; severe coronary artery disease; unstable angina

INTERACTIONS → Appendix 1 (moxonidine).

SIDE-EFFECTS
- Common or very common Back pain; diarrhoea; dizziness; dry mouth; dyspepsia; insomnia; nausea; pruritus; rash; somnolence; vomiting
- Uncommon Angioedema; bradycardia; neck pain; nervousness; oedema; tinnitus

PREGNANCY
Manufacturer advises avoid—no information available.

BREAST FEEDING
Present in milk—manufacturer advises avoid.

RENAL IMPAIRMENT
Max. single dose 200 micrograms and max. daily dose 400 micrograms if eGFR 30–60 mL/minute/1.73 m². Avoid if eGFR less than 30 mL/minute/1.73 m².

TREATMENT CESSATION
Avoid abrupt withdrawal (if concomitant treatment with beta-blocker has to be stopped, discontinue beta-blocker first, then moxonidine after a few days).

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 3

MOXONIDINE (Non-proprietary)

Moxonidine 200 microgram Moxonidine 200microgram tablets | 28 tablet (£10.40) DT price = £2.20
Moxonidine 300 microgram Moxonidine 300microgram tablets | 28 tablet (£13.85) DT price = £2.26
Moxonidine 400 microgram Moxonidine 400microgram tablets | 28 tablet (£14.24) DT price = £2.38
dosage reduction is often necessary in renal impairment. Water-soluble beta-blockers are excreted by the kidneys and soluble; they are less likely to enter the brain, and may block beta-blockers, such as atenolol, bisoprolol fumarate, metoprolol tartrate, propranolol hydrochloride, and nadolol, have an intrinsically lesser effect on the beta-adrenoceptors in the heart, peripheral vasculature, myocardium; they are contra-indicated in patients with uncontrolled heart failure, hypotension, bradyarrhythmias, and (to a lesser extent) acebutolol, have less effect on the beta; (bronchial) receptors and are, therefore, relatively cardioselective, but they are not cardiospecific. They have a lesser effect on airways resistance but are not free of this side-effect.

Beta-blockers are also associated with fatigue, coldness of the extremities (may be less common with those with ISA), and sleep disturbances with nightmares (may be less common with the water-soluble beta-blockers).

Beta-blockers can affect carbohydrate metabolism, causing hypoglycaemia or hyperglycaemia in patients with or without diabetes; they can also interfere with metabolic and autonomic responses to hypoglycaemia, thereby masking symptoms such as tachycardia. However, beta-blockers are not contra-indicated in diabetes, although the cardioselective beta-blockers may be preferred. Beta-blockers should be avoided altogether in those with frequent episodes of hypoglycaemia. Beta-blockers, especially when combined with a thiazide diuretic, should be avoided for the routine treatment of uncomplicated hypertension in patients with diabetes or in those at high risk of developing diabetes.

BETA-ADRENOCEPTOR BLOCKERS

Beta-adrenoceptor blocking drugs (beta-blockers) block the beta-adrenoceptors in the heart, peripheral vasculature, bronchi, pancreas, and liver.

Many beta-blockers are now available and in general they are equally effective. There are, however, differences between them, which may affect choice in treating particular diseases or individual patients.

Intrinsic sympathomimetic activity (ISA, partial agonist activity) represents the capacity of beta-blockers to stimulate as well as to block adrenergic receptors. Oxprenolol hydrochloride, p.145, pindolol p.146, acebutolol p.141, and celiprolol hydrochloride p.143 have intrinsic sympathomimetic activity; they tend to cause less bradycardia than the other beta-blockers and may also cause less coldness of the extremities.

Some beta-blockers are lipid soluble and some are water soluble. Atenolol p.141, celiprolol hydrochloride, nadolol p.145, and sotalol hydrochloride p.93 are the most water-soluble; they are less likely to enter the brain, and may therefore cause less sleep disturbance and nightmares.

Water-soluble beta-blockers are excreted by the kidneys and dosage reduction is often necessary in renal impairment.

Beta-blockers with a relatively short duration of action have to be given two or three times daily. Many of these are, however, available in modified-release formulations so that administration once daily is adequate for hypertension. For angina twice-daily treatment may sometimes be needed even with a modified-release formulation. Some beta-blockers, such as metoprolol tartrate, bisoprolol fumarate p.142, celiprolol hydrochloride, and nadolol, have an intrinsically longer duration of action and need to be given only once daily.

Beta-blockers slow the heart and can depress the myocardium; they are contra-indicated in patients with second- or third-degree heart block. Beta-blockers should also be avoided in patients with worsening unstable heart failure; care is required when initiating a beta-blocker in those with stable heart failure.

Labeltolol hydrochloride p.143, celiprolol hydrochloride, carvedilol p.142, and nebivolol p.145 are beta-blockers that have, in addition, an arteriolar vasodilating action, by diverse mechanisms, and thus lower peripheral resistance.

There is no evidence that these drugs have important advantages over other beta-blockers in the treatment of hypertension.

Beta-blockers can precipitate bronchospasm and should therefore usually be avoided in patients with a history of asthma. When there is no suitable alternative, it may be necessary for a patient with well-controlled asthma, or chronic obstructive pulmonary disease (without significant reversible airways obstruction), to receive treatment with a beta-blocker for a co-existing condition (e.g. heart failure or following myocardial infarction). In this situation, a cardioselective beta-blocker should be selected and initiated at a low dose by a specialist; the patient should be closely monitored for adverse effects. Atenolol, bisoprolol fumarate, metoprolol tartrate p.144, nebivolol, and (to a lesser extent) acebutolol, have less effect on the beta; (bronchial) receptors and are, therefore, relatively cardioselective, but they are not cardiospecific. They have a lesser effect on airways resistance but are not free of this side-effect.

Beta-blockers are also associated with fatigue, coldness of the extremities (may be less common with those with ISA), and sleep disturbances with nightmares (may be less common with the water-soluble beta-blockers).

Beta-blockers can affect carbohydrate metabolism, causing hypoglycaemia or hyperglycaemia in patients with or without diabetes; they can also interfere with metabolic and autonomic responses to hypoglycaemia, thereby masking symptoms such as tachycardia. However, beta-blockers are not contra-indicated in diabetes, although the cardioselective beta-blockers may be preferred. Beta-blockers should be avoided altogether in those with frequent episodes of hypoglycaemia. Beta-blockers, especially when combined with a thiazide diuretic, should be avoided for the routine treatment of uncomplicated hypertension in patients with diabetes or in those at high risk of developing diabetes.

Hypertension

The mode of action of beta-blockers in hypertension is not understood, but they reduce cardiac output, alter baroreceptor reflex sensitivity, and block peripheral adrenoceptors. Some beta-blockers depress plasma renin secretion. It is possible that a central effect may also partly explain their mode of action.

Beta-blockers are effective for reducing blood pressure but other antihypertensives are usually more effective for reducing the incidence of stroke, myocardial infarction, and cardiovascular mortality, especially in the elderly. Other antihypertensives are therefore preferred for routine initial treatment of uncomplicated hypertension.

In general, the dose of a beta-blocker does not have to be high.

Beta-blockers can be used to control the pulse rate in patients with phaeochromocytoma. However, they should never be used alone as beta-blockade without concurrent alpha-blockade may lead to a hypertensive crisis. For this reason phenoxybenzamine hydrochloride p.161 should always be used together with the beta-blocker.

Angina

By reducing cardiac work beta-blockers improve exercise tolerance and relieve symptoms in patients with angina (see management of stable angina and acute coronary syndromes for further details). As with hypertension there is no good evidence of the superiority of any one drug, although occasionally a patient will respond better to one beta-blocker than to another. There is some evidence that sudden withdrawal may cause an exacerbation of angina and therefore gradual reduction of dose is preferable when beta-blockers are to be stopped. There is a risk of precipitating heart failure when beta-blockers and verapamil are used together in established ischaemic heart disease.

Myocardial infarction

For specific comments see management of ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction.

Several studies have shown that some beta-blockers can reduce the recurrence rate of myocardial infarction. However, uncontrolled heart failure, hypotension, bradycardia, and obstructive airways disease render beta-blockers unsuitable in some patients following a myocardial infarction. Atenolol p.141 and metoprolol tartrate p.144 may reduce early mortality after intravenous and subsequent oral administration in the acute phase, while acebutolol p.141, metoprolol tartrate, propranolol hydrochloride p.146, and timolol maleate p.147 have protective value when started in the early convalescent phase. The evidence relating to other beta-blockers is less

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Hypertension 139

Cardiovascular system

Physiotens (BGP Products Ltd)

Moxonidine 200 microgram Physiotens 200microgram tablets
28 tablet(s) £5.72 DT price = £2.20

Moxonidine 300 microgram Physiotens 300microgram tablets
28 tablet(s) £13.49 DT price = £2.26

Moxonidine 400 microgram Physiotens 400microgram tablets
28 tablet(s) £13.26 DT price = £2.38
convincing; some have not been tested in trials of secondary prevention.

Arrhythmias
Beta-blockers act as anti-arrhythmic drugs principally by attenuating the effects of the sympathetic system on automaticity and conductivity within the heart. They can be used in conjunction with digoxin to control the ventricular response in atrial fibrillation, especially in patients with thyrotoxicosis. Beta-blockers are also useful in the management of supraventricular arrhythmias, and are used to control those following myocardial infarction.

Esmolol hydrochloride p. 143 is a relatively cardioselective beta-blocker with a very short duration of action, used intravenously for the short-term treatment of supraventricular arrhythmias, sinus tachycardia, or hypertension, particularly in the peri-operative period. It may also be used in other situations, such as acute myocardial infarction, when sustained beta-blockade might be hazardous.

Sotalol hydrochloride p. 93, a non-cardioselective beta-blocker with additional class III anti-arrhythmic activity, is used for prophylaxis in paroxysmal supraventricular arrhythmias. It also suppresses ventricular ectopic beats and non-sustained ventricular tachycardia. It has been shown to be more effective than lidocaine in the termination of spontaneous sustained ventricular tachycardia due to coronary disease or cardiomyopathy. However, it may induce torsade de pointes in susceptible patients.

Heart failure
Beta-blockers may produce benefit in heart failure by blocking sympathetic activity. Bisoprolol fumarate p. 142 and carvedilol p. 142 reduce mortality in any grade of stable heart failure; nebivolol p. 145 is licensed for stable mild to moderate heart failure in patients over 70 years. Treatment should be initiated by those experienced in the management of heart failure.

Thyrotoxicosis
Beta-blockers are used in pre-operative preparation for thyroidectomy. Administration of propranolol hydrochloride p. 146 can reverse clinical symptoms of thyrotoxicosis within 4 days. Routine tests of increased thyroid function remain unaltered. The thyroid gland is rendered less vascular thus making surgery easier.

Other uses
Beta-blockers have been used to alleviate some symptoms of anxiety; probably patients with palpitation, tremor, and tachycardia respond best. Beta-blockers are also used in the prophylaxis of migraine. Betaxolol p. 963, carteolol hydrochloride p. 963, levobunolol hydrochloride p. 964, and timolol maleate p. 965 are used topically in glaucoma.

Beta-adrenoceptor blockers (systemic)

- CONTRA-INDICATIONS Asthma - cardiogenic shock - hypotension - marked bradycardia - metabolic acidosis - phaeochromocytoma (apart from specific use with alpha-blockers) - Prinzmetal’s angina - second-degree AV block - severe peripheral arterial disease - sick sinus syndrome - third-degree AV block - uncontrolled heart failure

CONTRA-INDICATIONS, FURTHER INFORMATION

Bronchospasm Beta-blockers, including those considered to be cardioselective, should usually be avoided in patients with a history of asthma, bronchospasm or a history of obstructive airways disease. However, when there is no alternative, a cardioselective beta-blocker can be given to these patients with caution and under specialist supervision. In such cases the risk of inducing bronchospasm should be appreciated and appropriate precautions taken.

- CAUTIONS Diabetes - first-degree AV block - history of obstructive airways disease (introduce cautiously) - myasthenia gravis - portal hypertension (risk of deterioration in liver function) - psoriasis - symptoms of hypoglycaemia may be masked - symptoms of thyrotoxicosis may be masked

- INTERACTIONS → Appendix 1 (beta-blockers).

- Verapamil and beta-blockers Verapamil injection should not be given to patients recently treated with beta-blockers because of the risk of hypotension and asystole. The suggestion that when verapamil injection has been given first, an interval of 30 minutes before giving a beta-blocker is sufficient has not been confirmed. It may also be hazardous to give verapamil and a beta-blocker together by mouth (should only be contemplated if myocardial function well preserved). There is a risk of precipitating heart failure when beta-blockers and verapamil are used together in established ischaemic heart disease.

- SIDE-EFFECTS
  - Rare Dry eyes (reversible on withdrawal) - rashes (reversible on withdrawal)
  - Frequency not known Alopecia - bradycardia - bronchospasm - coldness of the extremities - conduction disorders - dizziness - dyspnœa - exacerbation of intermittent claudication - exacerbation of psoriasis - exacerbation of Raynaud’s phenomenon - fatigue - gastrointestinal disturbances - headache - heart failure - hyperglycaemia (in patients with or without diabetes) - hypoglycaemia (in patients with or without diabetes) - hypotension - paraesthesia - peripheral vasoconstriction - psychoses - purpura - sexual dysfunction - sleep disturbances (with nightmares) - symptoms of hypoglycaemia masked - thrombocytopenia - vertigo - visual disturbances

SIDE-EFFECTS, FURTHER INFORMATION

Bradycardia With administration by intravenous injection, excessive bradycardia can occur and may be countered with intravenous injection of atropine sulfate.

Overdose Therapeutic overdosages with beta-blockers may cause lightheadedness, dizziness, and possibly syncope as a result of bradycardia and hypotension; heart failure may be precipitated or exacerbated. For details on the management of poisoning, see Beta-blockers, under Emergency treatment of poisoning p. 1123.

- ALLERGY AND CROSS-SENSITIVITY Caution is advised in patients with a history of hypersensitivity—may increase sensitivity to allergens and result in more serious hypersensitivity response. Furthermore beta-adrenoceptor blockers may reduce response to adrenaline (epinephrine).

- PREGNANCY Beta-blockers may cause intra-uterine growth restriction, neonatal hypoglycaemia, and bradycardia; the risk is greater in severe hypertension.

- BREAST FEEDING With systemic use in the mother, infants should be monitored as there is a risk of possible toxicity due to beta-blockade. However, the amount of most beta-blockers present in milk is too small to affect infants.

- MONITORING REQUIREMENTS Monitor lung function (in patients with a history of obstructive airway disease).

- TREATMENT CESSATION Avoid abrupt withdrawal especially in ischaemic heart disease. Sudden cessation of a beta-blocker can cause a rebound worsening of myocardial ischaemia and therefore gradual reduction of dose is preferable when beta-blockers are to be stopped.
Acebutolol

**INDICATIONS AND DOSE**

**Hypertension**
- Adult: Initially 400 mg daily for 2 weeks, alternatively initially 200 mg twice daily for 2 weeks, then increased if necessary to 400 mg twice daily; maximum 1.2 g per day.

**Angina**
- Adult: Initially 400 mg daily, alternatively initially 200 mg twice daily; maximum 1.2 g per day

**Arrhythmias**
- Adult: 0.4–1.2 g daily in 2–3 divided doses

**Severe angina**
- Adult: Initially 300 mg 3 times a day; maximum 1.2 g per day

**BREAST FEEDING**
Acebutolol and water soluble beta-blockers are present in breast milk in greater amounts than other beta-blockers.

**RENAL IMPAIRMENT**
- Half dose if eGFR 25–50 mL/minute/1.73 m²; use quarter dose if eGFR less than 25 mL/minute/1.73 m²; do not administer more than once daily.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- CAUTIONARY AND ADVISORY LABELS 8
  - ACEBUTOLOL (Non-proprietary)
    - Acebutolol (as Acebutolol hydrochloride) 400 mg Acebutolol 400mg tablets 28 | price = £18.62

**Capsule**
- CAUTIONARY AND ADVISORY LABELS 8
  - ACEBUTOLOL (Non-proprietary)
    - Acebutolol (as Acebutolol hydrochloride) 100 mg Acebutolol 100mg tablets 84 | price = £14.97
    - Acebutolol (as Acebutolol hydrochloride) 200 mg Acebutolol 200mg tablets 56 | price = £13.18

**Solution for injection**
- Acebutolol 500 microgram per 1 ml

**Atenolol**

**INDICATIONS AND DOSE**

**Hypertension**
- Adult: 25–50 mg daily, higher doses are rarely necessary

**Angina**
- Adult: 100 mg daily in 1–2 divided doses

**Arrhythmias**
- Adult: 50–100 mg daily

**BY INTRAVENOUS INJECTION**
- Adult: 2.5 mg every 5 minutes (max. per dose 10 mg), repeated if necessary, given at a rate of 1 mg/minute

**BY INTRAVENOUS INFUSION**
- Adult: 150 micrograms/kg every 12 hours if required, to be given over 20 minutes

**Migraine prophylaxis**
- Adult: 50–200 mg daily in divided doses

**Early intervention within 12 hours of myocardial infarction initially by intravenous injection**
- Adult: Initially 5 mg, to be given over 5 minutes, followed by (by mouth) 50 mg after 15 minutes, then (by mouth) 50 mg after 12 hours, then (by mouth) 100 mg daily

**UNLICENSED USE**
- Use of atenolol for migraine prophylaxis is an unlicensed indication.

**BREAST FEEDING**
- Water soluble beta-blockers such as atenolol are present in breast milk in greater amounts than other beta blockers.

**RENAL IMPAIRMENT**
- With oral use Max. 50 mg daily if eGFR 15–35 mL/minute/1.73 m²; max. 25 mg daily or 50 mg on alternate days if eGFR less than 15 mL/minute/1.73 m².
- With intravenous use Max. 10 mg on alternate days if eGFR 15–35 mL/minute/1.73 m²; max. 10 mg every 4 days if eGFR less than 15 mL/minute/1.73 m².

**DIRECTIONS FOR ADMINISTRATION**
- For intravenous infusion (Tenormin®), give intermittently in Glucose 5% or Sodium chloride 0.9%. Suggested infusion time 20 minutes.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**
- CAUTIONARY AND ADVISORY LABELS 8
  - ATENOLOL (Non-proprietary)
    - Atenolol 25 mg Atenolol 25mg tablets 28 | price = £1.39
    - Atenolol 50 mg Atenolol 50mg tablets 28 | price = £0.93
    - Atenolol 100 mg Atenolol 100mg tablets 28 | price = £0.93

**Capsule**
- ATENOLOL (Non-proprietary)
  - Atenolol (as Atenolol hydrochloride) 100 mg Atenolol 100mg tablets 56 | price = £0.93
  - Atenolol (as Atenolol hydrochloride) 200 mg Atenolol 200mg tablets 56 | price = £0.93

**Solution for injection**
- ATENOLOL (Non-proprietary)

**Atenolol with nifedipine**

The properties listed below are those particular to the combination only. For the properties of the components please consider, atenolol above, nifedipine p. 154.

**INDICATIONS AND DOSE**

**Hypertension**
- Adult: 1 capsule daily, increased if necessary to 1 capsule twice daily
- Elderly: 1 capsule daily
Cardiovascular system

Bisoprolol fumarate

INDICATIONS AND DOSE

Hypertension | Angina
BY MOUTH
> Adult: Initially 1.25 mg twice daily for 2 days, then increased to 2.5 mg once daily, dose to be increased at intervals of at least 2 weeks and can be given as a single dose or in divided doses
> Elderly: Initially 1.25 mg daily, initial dose may provide satisfactory control

Angina
BY MOUTH
> Adult: Initially 1.25 mg twice daily for 2 days, then increased to 2.5 mg twice daily

Adjunct to diuretics, digoxin, or ACE inhibitors in symptomatic chronic heart failure
BY MOUTH
> Adult: Initially 3.125 mg twice daily, dose to be taken with food, then increased to 6.25 mg twice daily, then increased to 12.5 mg twice daily, then increased to 25 mg twice daily, dose should be increased at intervals of at least 2 weeks up to the highest tolerated dose, max. 25 mg twice daily in patients with severe heart failure or body-weight less than 85 kg; max. 50 mg twice daily in patients over 85 kg

CONTRA-INDICATIONS Acute or decompensated heart failure requiring intravenous inotropes - sino–atrial block

CAUTIONS Ensure heart failure not worsening before increasing dose

SIDE-EFFECTS
> Uncommon Cramp - depression - muscle weakness
> Rare Hearing impairment - hypertriglyceridaemia - syncope
> Very rare Conjunctivitis

HEPATIC IMPAIRMENT Max. 10 mg daily in severe impairment.

RENAL IMPAIRMENT Reduce dose if eGFR less than 20 mL/minute/1.73 m² (max. 10 mg daily).

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

Tablet

CAUTIONARY AND ADVISORY LABELS 8
> Bisoprolol fumarate (Non-proprietary)
> Bisoprolol fumarate 1.25 mg Bisoprol 1.25mg tablets | 28 tablet (PO) £7.43 DT price = £1.21
> Bisoprolol fumarate 2.5 mg Bisoprol 2.5mg tablets | 28 tablet (PO) £4.39 DT price = £1.12
> Bisoprolol fumarate 3.75 mg Bisoprol 3.75mg tablets | 28 tablet (PO) £6.50 DT price = £1.72
> Bisoprolol fumarate 5 mg Bisoprol 5mg tablets | 28 tablet (PO) £5.89 DT price = £0.98
> Bisoprolol fumarate 7.5 mg Bisoprol 7.5mg tablets | 28 tablet (PO) £5.89 DT price = £1.09
> Bisoprolol fumarate 10 mg Bisoprol 10mg tablets | 28 tablet (PO) £5.89 DT price = £1.02
> Cardicor (Merck Serono Ltd)
> Cardicor 1.25 mg Cardicor 1.25mg tablets | 28 tablet (PO) £2.35 DT price = £1.21

Bisoprolol fumarate 2.5 mg Cardicor 2.5mg tablets | 28 tablet (PO) £2.35 DT price = £1.12
> Bisoprolol fumarate 3.75 mg Cardicor 3.75mg tablets | 28 tablet (PO) £4.90 DT price = £1.72
> Bisoprolol fumarate 5 mg Cardicor 5mg tablets | 28 tablet (PO) £5.90 DT price = £0.98
> Bisoprolol fumarate 7.5 mg Cardicor 7.5mg tablets | 28 tablet (PO) £5.90 DT price = £4.32
> Bisoprolol fumarate 10 mg Cardicor 10mg tablets | 28 tablet (PO) £5.90 DT price = £1.02
> Congescor (Tillomed Laboratories Ltd)
> Bisoprolol fumarate 1.25 mg Congescor 1.25mg tablets | 28 tablet (PO) £5.90 DT price = £1.21
> Bisoprolol fumarate 2.5 mg Congescor 2.5mg tablets | 28 tablet (PO) £3.90 DT price = £1.12

Carvedilol

INDICATIONS AND DOSE

Hypertension
BY MOUTH
> Adult: Initially 12.5 mg once daily for 2 days, then increased to 25 mg once daily; increased if necessary up to 50 mg daily, dose to be increased at intervals of at least 2 weeks and can be given as a single dose or in divided doses

PREGNANCY Information on the safety of carvedilol during pregnancy is lacking. If carvedilol is used close to delivery, infants should be monitored for signs of alpha-blockade (as well as beta-blockade).

BREAST FEEDING Infants should be monitored as there is a risk of possible toxicity due to alpha-blockade (in addition to beta-blockade).

HEPATIC IMPAIRMENT Avoid in hepatic impairment.

MONITORING REQUIREMENTS Monitor renal function during dose titration in patients with heart failure who also have renal impairment, low blood pressure, ischaemic heart disease, or diffuse vascular disease.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, suppository

CONTRA-INDICATIONS Acute or decompensated heart failure requiring intravenous inotropes

SIDE-EFFECTS Allergic skin reactions - angina - AV block - changes in liver enzymes - depressed mood - disturbances of micturition - influenza-like symptoms - leucopenia - nasal stuffiness - postural hypotension - thrombocytopaenia - wheezing

CAUTIONS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

REFERENCES

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, suppository

REFERENCES

CONTRA-INDICATIONS Acute or decompensated heart failure requiring intravenous inotropes

SIDE-EFFECTS Allergic skin reactions - angina - AV block - changes in liver enzymes - depressed mood - disturbances of micturition - influenza-like symptoms - leucopenia - nasal stuffiness - postural hypotension - thrombocytopaenia - wheezing
Celiprolol hydrochloride

**INDICATIONS AND DOSE**
Mild to moderate hypertension

- Adult: 200 mg once daily, dose to be taken in the morning, then increased if necessary to 400 mg once daily

- **SIDE-EFFECTS**
  - Rare: Depression, pneumonia
  - Frequency not known: Hot flushes

- **BREAST FEEDING**: Manufacturers advise avoidance.

- **HEPATIC IMPAIRMENT**: Consider dose reduction.

- **RENA! IMPAIRMENT**: Reduce dose by half if eGFR 15–40 mL/minute/1.73 m². Avoid if eGFR less than 15 mL/minute/1.73 m².

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**

- CARVEDILOL (Non-proprietary)
  - Celiprolol hydrochloride 200 mg: Celiprolol 200mg tablets | 28 tablet [PO] £9.25 DT price = £3.88
  - Celiprolol hydrochloride 400 mg: Celiprolol 400mg tablets | 28 tablet [PO] £39.63 DT price = £10.32
  - Celectol (Zeneca)
    - Celiprolol hydrochloride 200 mg: Celectol 200mg tablets | 28 tablet [PO] £19.83 DT price = £3.88
    - Celiprolol hydrochloride 400 mg: Celectol 400mg tablets | 28 tablet [PO] £39.65 DT price = £10.32

Co-tenidone

Also consider properties of the Thiazides class, p. 159

**INDICATIONS AND DOSE**
Hypertension

- Adult: 50/12.5 mg daily, alternatively increased if necessary to 100/25 mg daily, doses higher than 50 mg atenolol rarely necessary

Dose equivalence and conversion
A mixture of atenolol and chlortalidone in mass proportions corresponding to 4 parts of atenolol and 1 part chlortalidone.

- **SIDE-EFFECTS**
  - Allergic interstitial nephritis - jaundice
  - **PREGNANCY**: Avoid. Diuretics not used to treat hypertension in pregnancy.
  - **BREAST FEEDING**: Atenolol present in milk in greater amounts than some other beta-blockers. Possible toxicity due to beta-blockade—monitor infant. Large doses of chlortalidone may suppress lactation.
  - **RENA! IMPAIRMENT**: Avoid if eGFR less than 30 mL/minute/1.73 m²—consider alternative treatment.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

**Tablet**

- CO-TENIDONE (Non-proprietary)
  - Atenolol 50 mg, Chlortalidone 12.5 mg: Co-tenidone 50mg/12.5mg tablets | 28 tablet [PO] £5.92 DT price = £4.14
  - Atenolol 100 mg, Chlortalidone 25 mg: Co-tenidone 100mg/25mg tablets | 28 tablet [PO] £4.85 DT price = £3.72
  - Tenoret (AstraZeneca UK Ltd)
    - Atenolol 50 mg, Chlortalidone 12.5 mg: Tenoret 50mg/12.5mg tablets | 28 tablet [PO] £3.14 DT price = £2.14
  - Tenoretic (AstraZeneca UK Ltd)
    - Atenolol 100 mg, Chlortalidone 25 mg: Tenoretic 100mg/25mg tablets | 28 tablet [PO] £5.18 DT price = £3.72

Esmolol hydrochloride

**INDICATIONS AND DOSE**
Short-term treatment of supraventricular arrhythmias (including atrial fibrillation, atrial flutter, sinus tachycardia) Tachycardia and hypertension in peri-operative period

- **BY INTRAVENOUS INFUSION**
  - Adult: 50–200 micrograms/kg/minute, consult product literature for details of dose titration and doses during peri-operative period

- **SIDE-EFFECTS**
  - Thrombophlebitis - venous irritation

- **BREAST FEEDING**: Manufacturer advises avoidance.

- **RENA! IMPAIRMENT**: Manufacturer advises caution.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Brevibloc** (Baxter Healthcare Ltd)
  - Esmolol hydrochloride 10 mg per 1 ml: Brevibloc Premixed 100mg/10ml solution for injection vials | 5 vial [PO] no price available

**Solution for infusion**

- **Brevibloc** (Baxter Healthcare Ltd)
  - Esmolol hydrochloride 10 mg per 1 ml: Brevibloc Premixed 2.5g/250ml infusion bags | 1 bag [PO] £83.89

Labetalol hydrochloride

**INDICATIONS AND DOSE**
Controlled hypotension in anaesthesia

- **BY INTRAVENOUS INFUSION OR BY INTRAVENOUS INJECTION**
  - Adult: (consult product literature or local protocols)

Hypertension of pregnancy

- **BY INTRAVENOUS INFUSION**
  - Adult: Initially 20 mg/hour, then increased if necessary to 40 mg/hour after 30 minutes, then increased if necessary to 80 mg/hour after 30 minutes, then increased if necessary to 150 mg/hour after 30 minutes, adjusted according to response; Usual maximum 160 mg/hour

- **BY MOUTH**
  - Adult: Use dose for hypertension

Hypertension following myocardial infarction

- **BY INTRAVENOUS INFUSION**
  - Adult: 15 mg/hour, then increased to up to 120 mg/hour, dose to be increased gradually—continued
**Hypertensive emergencies**

**BY INTRAVENOUS INJECTION**
- Adult: 50 mg, to be given over at least 1 minute, then 50 mg every 5 minutes if required until a satisfactory response occurs; maximum 200 mg per course

**BY INTRAVENOUS INFUSION**
- Adult: Initially 2 mg/minute until a satisfactory response is achieved, then discontinue; usual dose 50–200 mg

**Hypertension**

**BY MOUTH**
- Adult: Initially 100 mg twice daily, dose to be increased at intervals of 14 days; usual dose 200 mg twice daily, increased if necessary up to 800 mg daily in 2 divided doses, to be taken with food, higher doses to be given in 3–4 divided doses; maximum 2.4 g per day
- Elderly: Initially 50 mg twice daily, dose to be increased at intervals of 14 days; usual dose 200 mg twice daily, increased if necessary up to 800 mg daily in 2 divided doses, to be taken with food, higher doses to be given in 3–4 divided doses; maximum 2.4 g per day

**BY INTRAVENOUS INJECTION**
- Adult: 50 mg, dose to be given over at least 1 minute, then 50 mg after 5 minutes if required; maximum 200 mg per course

**BY INTRAVENOUS INFUSION**
- Adult: Initially 2 mg/minute until a satisfactory response is achieved, then discontinue; usual dose 50–200 mg

- **CAUTIONS** Liver damage
- **SIDE-EFFECTS**
  - Rare Lichenoid rash
  - Frequency not known Difficulty in micturition · epigastric pain · liver damage · nausea · postural hypotension · vomiting · weakness

- **PREGNANCY** The use of labetalol in maternal hypertension is not known to be harmful, except possibly in the first trimester. If labetalol is used close to delivery, infants should be monitored for signs of alpha-blockade (as well as beta blockade).

- **BREAST FEEDING** Infants should be monitored as there is a risk of possible toxicity due to alpha-blockade (in addition to beta-blockade).

- **HEPATIC IMPAIRMENT** Avoid—severe hepatocellular injury reported.

- **RENAL IMPAIRMENT** Dose reduction may be required.

- **MONITORING REQUIREMENTS**
  - Liver damage Severe hepatocellular damage reported after both short-term and long-term treatment. Appropriate laboratory testing needed at first symptom of liver dysfunction and if laboratory evidence of damage (or if jaundice) labetalol should be stopped and not restarted.

- **EFFECT ON LABORATORY TESTS** Interferes with laboratory tests for catecholamines.

- **DIRECTIONS FOR ADMINISTRATION** Avoid upright position during and for 3 hours after intravenous administration. For intravenous infusion, give intermittently in Glucose 5% or Sodium chloride and glucose. Dilute to a concentration of 1 mg/mL; suggested volume 200 mL; adjust rate with in-line burette.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

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### Metoprolol tartrate

**INDICATIONS AND DOSE**

**Hypertension**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
- Adult: Initially 100 mg daily, increased if necessary to 200 mg daily in 1–2 divided doses, high doses are rarely required; maximum 400 mg per day

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**
- Adult: 200 mg once daily

**Angina**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
- Adult: 50–100 mg 2–3 times a day

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**
- Adult: 200–400 mg daily

**Arrhythmias**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
- Adult: Usual dose 50 mg 2–3 times a day, then increased if necessary up to 300 mg daily in divided doses

**BY INTRAVENOUS INJECTION**
- Adult: Up to 5 mg, dose to be given at a rate of 1–2 mg/minute, then up to 5 mg after 5 minutes if required, total dose of 10–15 mg

**Migraine prophylaxis**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
- Adult: 100–200 mg daily in divided doses

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**
- Adult: 200 mg daily

**Hyperthyroidism (adjunct)**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
- Adult: 50 mg 4 times a day

**In surgery**

**BY SLOW INTRAVENOUS INJECTION**
- Adult: Initially 2–4 mg, given at induction or to control arrhythmias developing during anaesthesia, then 2 mg, repeated if necessary; maximum 10 mg per course

**Early intervention within 12 hours of infarction**

**INITIALLY BY INTRAVENOUS INJECTION**
- Adult: Initially 5 mg every 2 minutes to a max. of 15 mg, followed after 15 minutes by (by mouth) 50 mg every 6 hours for 48 hours; (by mouth) maintenance 200 mg daily in divided doses

- **HEPATIC IMPAIRMENT** Reduce dose in severe impairment.
Nadolol

**INDICATIONS AND DOSE**

**Hypertension**

- Adult: Initially 80 mg daily, then increased in steps of up to 80 mg every 1 week if required; doses higher than the maximum are rarely necessary; maximum 240 mg per day

- Angina

- Adult: Initially 40 mg daily, then increased if necessary up to 160 mg daily; doses should be increased at weekly intervals; maximum dose rarely is used; maximum 240 mg per day

- Arrhythmias

- Adult: Initially 40 mg daily, then increased if necessary up to 160 mg daily; doses should be increased at weekly intervals; reduced to 40 mg daily if bradycardia occurs

- Migraine prophylaxis

- Adult: Initially 40 mg daily, then increased in steps of 40 mg every 1 week, according to the response of the patient: maintenance 80–160 mg per day

- Thyrotoxicosis (adjunct)

- Adult: 80–160 mg daily

**CONTRA-INDICATIONS**

- Acute or decompensated heart failure requiring intravenous inotropes

**SIDE-EFFECTS**

- Depression - oedema

**BREAST FEEDING**

- Manufacturers advise avoidance.

**HEPATIC IMPAIRMENT**

- No information available—manufacturer advises avoid.

**RENAL IMPAIRMENT**

- Manufacturer advises avoid in heart failure if serum creatinine greater than 250 micromol/litre.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS 8**

- **METOPROLOL TARTRATE (Non-proprietary)**

- Metoprolol tartrate 50 mg | 28 tablet (£5.00 DT price = £1.09) | 56 tablet (£5.00 DT price = £1.18)

- Metoprolol tartrate 100 mg | 28 tablet (£5.00 DT price = £1.18) | 56 tablet (£10.00)

- **Lopresor (Recordati Pharmaceuticals Ltd)**

- Metoprolol tartrate 50 mg | Lopresor 50mg tablets | 56 tablet (£2.57)

- Metoprolol tartrate 100 mg | Lopresor 100mg tablets | 56 tablet (£6.68)

- **Modified-release tablet**

- **CAUTIONARY AND ADVISORY LABELS 8, 25**

- Metoprolol tartrate 200 mg | Lopresor SR 200mg tablets | 28 tablet (£9.80)

**Solution for injection**

- Betaloc (AstraZeneca UK Ltd)

- Metoprolol tartrate 1 mg per 1 ml | 5 ampoule (£5.02) (Hospital only)

Oxrenolol hydrochloride

**INDICATIONS AND DOSE**

**Hypertension**

- Adult: 80–160 mg daily in 2–3 divided doses, then increased if necessary up to 320 mg daily

- Angina

- Adult: 80–160 mg daily in 2–3 divided doses; maximum 320 mg per day

- Arrhythmias

- Adult: 40–240 mg daily in 2–3 divided doses; maximum 240 mg per day

- Anxiety symptoms (short-term use)

- Adult: 40–80 mg daily in 1–2 divided doses

- **Hypertension / Angina**

- Adult: Initially 160 mg once daily, then increased if necessary up to 320 mg daily

**HEPATIC IMPAIRMENT**

- Reduce dose.
Propranolol hydrochloride

INDICATIONS AND DOSE
Thyrotoxicosis
BY MOUTH
▶ Adult: 10–40 mg 3–4 times a day
Thyrotoxic crisis
BY INTRAVENOUS INJECTION
▶ Adult: 1 mg, to be given over 1 minute, dose may be repeated if necessary at intervals of 2 minutes, maximum total dose is 5 mg in anaesthesia; maximum 10 mg per course

Hypertension
BY MOUTH
▶ Adult: Initially 80 mg twice daily, dose should be increased at weekly intervals as required; maintenance 160–320 mg daily

Prophylaxis of variceal bleeding in portal hypertension
BY MOUTH
▶ Adult: Initially 40 mg twice daily, then increased to 80 mg twice daily (max. per dose 160 mg twice daily), dose to be adjusted according to heart rate

Phaeochromocytoma (only with an alpha-blocker) in preparation for surgery
BY MOUTH
▶ Adult: 60 mg daily for 3 days before surgery
Phaeochromocytoma (only with an alpha-blocker) in patients unsuitable for surgery
BY MOUTH
▶ Adult: 30 mg daily

Angina
BY MOUTH
▶ Adult: Initially 40 mg 2–3 times a day; maintenance 120–240 mg daily

Hypertrophic cardiomyopathy | Anxiety tachycardia
BY MOUTH
▶ Adult: 10–40 mg 3–4 times a day

Anxiety with symptoms such as palpitation, sweating and tremor
BY MOUTH
▶ Adult: 40 mg once daily, then increased if necessary to 40 mg 3 times a day

Prophylaxis after myocardial infarction
BY MOUTH
▶ Adult: Initially 40 mg 4 times a day for 2–3 days, then 80 mg twice daily, start treatment 5 to 21 days after infarction

Essential tremor
BY MOUTH
▶ Adult: Initially 40 mg 2–3 times a day; maintenance 80–160 mg daily

Migraine prophylaxis
BY MOUTH
▶ Adult: 80–240 mg daily in divided doses

Arrhythmias
BY INTRAVENOUS INJECTION
▶ Adult: 1 mg, to be given over 1 minute, dose may be repeated if necessary at intervals of 2 minutes, maximum total dose is 5 mg in anaesthesia; maximum 10 mg per course

SIDE-EFFECTS
▶ Rare: Dry eyes (reversible on withdrawal)

HEPATIC IMPAIRMENT
Reduce oral dose.

RENAL IMPAIRMENT
Manufacturer advises caution; dose reduction may be required.
Timolol maleate 10 mg

INDICATIONS AND DOSE

Hypertension
BY MOUTH
- Adult: 10–20 mg daily in 1–2 divided doses

Amiloride with hydrochlorothiazide and timolol

The properties listed below are those particular to the combination only. For the properties of the components please consider, amiloride hydrochlorothiazide p. 203, timolol maleate above.

INDICATIONS AND DOSE

Hypertension
BY MOUTH
- Adult: 1–2 tablets daily

Bendroflumethiazide with timolol

The properties listed below are those particular to the combination only. For the properties of the components please consider, timolol maleate above, bendroflumethiazide p. 159.

INDICATIONS AND DOSE

Hypertension
BY MOUTH
- Adult: 1–2 tablets daily; maximum 4 tablets per day

Calcium-channel blockers

Calcium-channel blockers differ in their predilection for the various possible sites of action and, therefore, their therapeutic effects are disparate, with much greater variation than those of beta-blockers. There are important
differences between verapamil hydrochloride p. 156, diltiazem hydrochloride p. 149, and the dihydropyridine calcium-channel blockers (amlodipine below, felodipine p. 151, lacidipine p. 152, lercanidipine hydrochloride p. 153, nicardipine hydrochloride p. 153, nifedipine p. 154, and nimodipine p. 99). Verapamil hydrochloride and diltiazem hydrochloride should usually be avoided in heart failure because they may further depress cardiac function and cause clinically significant deterioration. Verapamil hydrochloride is used for the treatment of angina, hypertension, and arrhythmias. It is a highly negatively inotropic calcium channel-blocker and it reduces cardiac output, slows the heart rate, and may impair atrioventricular conduction. It may precipitate heart failure, exacerbate conduction disorders, and cause hypotension at high doses and should not be used with beta-blockers. Constipation is the most common side-effect. Nifedipine relaxes vascular smooth muscle and dilates coronary and peripheral arteries. It has more influence on vessels and less on the myocardium than does verapamil hydrochloride, and unlike verapamil hydrochloride has no anti-arrhythmic activity. It rarely precipitates heart failure because any negative inotropic effect is offset by a reduction in left ventricular work.

Nifedipine hydrochloride has similar effects to those of nifedipine and may produce less reduction of myocardial contractility. Amlodipine and felodipine also resemble nifedipine and nicardipine hydrochloride in their effects and do not reduce myocardial contractility and they do not produce clinical deterioration in heart failure. They have a longer duration of action and can be given once daily. Nifedipine, nicardipine hydrochloride, amlodipine, and felodipine are used for the treatment of angina or hypertension. All are valuable in forms of angina associated with coronary vasospasm. Side-effects associated with vasodilatation such as flushing and headache (which become less obtrusive after a few days), and ankle swelling (which may respond only partially to diuretics) are common.

Intravenous nicardipine hydrochloride is licensed for the treatment of acute life-threatening hypertension, for example in the event of malignant arterial hypertension or hypertensive encephalopathy; aortic dissection, when a short-acting beta-blocker is not suitable, or in combination with a beta-blocker when beta-blockade alone is not effective; severe pre-eclampsia, when other intravenous anti-hypertensives are not recommended or are contra-indicated; and for treatment of postoperative hypertension.

Isradipine, lacidipine and lercanidipine hydrochloride have similar effects to those of nifedipine and nicardipine hydrochloride; they are indicated for hypertension only.

Nimodipine is related to nifedipine but the smooth muscle relaxant effect preferentially acts on cerebral arteries. Its use is confined to prevention and treatment of vascular spasm following aneurysmal subarachnoid haemorrhage.

Diltiazem hydrochloride is effective in most forms of angina; the longer-acting formulation is also used for hypertension. It may be used in patients for whom beta-blockers are contra-indicated or ineffective. It has a less negative inotropic effect than verapamil hydrochloride and significant myocardial depression occurs rarely. Nevertheless because of the risk of bradycardia it should be used with caution in association with beta-blockers.

**Unstable angina**

Calcium-channel blockers do not reduce the risk of myocardial infarction in unstable angina. The use of diltiazem hydrochloride or verapamil hydrochloride should be reserved for patients resistant to treatment with beta-blockers.

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**Calcium-channel blockers**

- **DRUG ACTION** Calcium-channel blockers (less correctly called ‘calcium-antagonists’) interfere with the inward displacement of calcium ions through the slow channels of active cell membranes. They influence the myocardial cells, the cells within the specialised conducting system of the heart, and the cells of vascular smooth muscle. Thus, myocardial contractility may be reduced, the formation and propagation of electrical impulses within the heart may be depressed, and coronary or systemic vascular tone may be diminished.

- **SIDE-EFFECTS**
  - **Overdose** Features of calcium-channel blocker poisoning include nausea, vomiting, dizziness, agitation, confusion, and coma in severe poisoning. Metabolic acidosis and hyperglycaemia may occur. For details on the management of poisoning, see Calcium-channel blockers, under Emergency treatment of poisoning p. 1123.
  - **TREATMENT CESSATION** There is some evidence that sudden withdrawal of calcium-channel blockers may be associated with an exacerbation of myocardial ischaemia.

**Amlodipine**

- **DRUG ACTION** Amlodipine is a dihydropyridine calcium-channel blocker.

**INDICATIONS AND DOSE**

- **Angina**
  - **BY MOUTH**
    - **Adult:** Initially 5 mg once daily; maximum 10 mg per day

- **Hypertension**
  - **BY MOUTH**
    - **Adult:** Initially 5 mg once daily; maximum 10 mg per day

- **Dose equivalence and conversion**
  - Tablets from various suppliers may contain different salts (e.g. amlodipine besilate, amlodipine maleate, and amlodipine mesilate) but the strength is expressed in terms of amlodipine (base); tablets containing different salts are considered interchangeable.

- **CONTRA-INDICATIONS** Cardiogenic shock - significant aortic stenosis - unstable angina

- **INTERACTIONS** → Appendix 1 (calcium-channel blockers).

- **SIDE-EFFECTS**
  - **Common or very common** Abdominal pain, dizziness, fatigue, flushing, headache, nausea, oedema, palpitation, sleep disturbances
  - **Uncommon** Alopecia, arthralgia, asthenia, back pain, chest pain, dry mouth, dyspnoea, gastro-intestinal disturbances, gynaecomastia, hypotension, impotence, mood changes, muscle cramps, myalgia, paraesthesia, pruritus, purpura, rashes, rhinitis, skin discoloration, sweating, syncope, taste disturbances, tinnitus, tremor, urinary disturbances, visual disturbances, weight changes
  - **Very rare** Angioedema, arrhythmias, cholestasis, coughing, gastritis, gingival hyperplasia, hepatitis, hyperglycaemia, jaundice, myocardial infarction, pancreatitis, peripheral neuropathy, tachycardia, thrombocytopenia, urticaria, vasculitis
  - **Frequency not known** Erythema multiforme

- **Overdose** In overdose, the dihydropyridine calcium-channel blockers cause severe hypotension secondary to profound peripheral vasodilatation.

- **PREGNANCY** No information available—manufacturer advises avoid, but risk to fetus should be balanced against risk of uncontrolled maternal hypertension.
Diltiazem hydrochloride

**INDICATIONS AND DOSE**

**Angina**

- **BY MOUTH**
  - Adult: Initially 60 mg 3 times a day, adjusted according to response; maximum 360 mg per day
  - Elderly: Initially 60 mg twice daily, adjusted according to response; maximum 360 mg per day

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**Amlodipine with valsartan**

The properties of the components please consider, amlodipine p. 148, valsartan p. 136.

**INDICATIONS AND DOSE**

Hypertension in patients stabilised on the individual components in the same proportions

- **BY MOUTH**
  - Adult: (consult product literature)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

**Tablet**

- **AMLODIPINE (Non-proprietary)**
  - Amlodipine 5 mg | tablet | £0.98
  - Amlodipine 10 mg | tablet | £1.00

- **Amlostin (Discovery Pharmaceuticals Ltd)**
  - Amlodipine 5 mg | tablet | £0.88
  - Amlodipine 10 mg | tablet | £0.90

- **Istin (Pfizer Ltd)**
  - Amlodipine 5 mg | tablet | £0.98
  - Amlodipine 10 mg | tablet | £1.00

**Oral solution**

- **AMLODIPINE (Non-proprietary)**
  - Amlodipine 1 mg per 1 ml | oral solution | £1.10
  - Amlodipine 2 mg per 1 ml | oral solution | £1.15

Also available in combination with olmesartan, p. 135 - hydrochlorothiazide and olmesartan, p. 135 - valsartan, below

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**Dose equivalence and conversion**

The standard formulations containing 60 mg diltiazem hydrochloride are licensed as generics and there is no requirement for brand name dispensing. Although their means of formulation has called for the strict designation ‘modified-release’, their duration of action corresponds to that of tablets requiring administration more frequently.

**TILDIEM RETARD**

Mild to moderate hypertension

- **BY MOUTH**
  - Adult: Initially 90–120 mg twice daily; increased if necessary to 360 mg daily in divided doses
  - Elderly: Initially 120 mg daily; increased if necessary to 120 mg twice daily

**ANGINA**

- **BY MOUTH**
  - Adult: Initially 90–120 mg twice daily; increased if necessary to 480 mg daily in divided doses
  - Elderly: Up to 120 mg twice daily, dose form not appropriate for initial dose titration

**ADIZEM-SR**

Mild to moderate hypertension

- **BY MOUTH**
  - Adult: 120 mg twice daily, dose form not appropriate for initial dose titration

**ANGINA**

- **BY MOUTH**
  - Adult: Initially 90 mg twice daily; increased if necessary to 180 mg twice daily, dose form not appropriate for initial dose titration in the elderly

**ADIZEM-SR**

Mild to moderate hypertension

- **CAPSULES**
  - Adult: 120 mg twice daily, dose form not appropriate for initial dose titration

**ANGINA**

- **BY MOUTH**
  - Adult: Initially 90 mg twice daily; increased if necessary to 180 mg twice daily, dose form not appropriate for initial dose titration in the elderly

**TILDIEM LA**

- **ANGINA**| Mild to moderate hypertension
  - **BY MOUTH**
    - Adult: Initially 200 mg daily, to be taken with or before food, increased if necessary to 300–400 mg daily; maximum 500 mg per day
    - Elderly: Initially 200 mg daily, increased if necessary to 300 mg daily

**VIAZEM XL**

- **ANGINA**| Mild to moderate hypertension
  - **BY MOUTH**
    - Adult: Initially 180 mg once daily, adjusted according to response to 240 mg once daily; maximum 360 mg per day
    - Elderly: Initially 120 mg once daily, adjusted according to response

**DILZEM XL**

- **ANGINA**| Mild to moderate hypertension
  - **BY MOUTH**
    - Adult: Initially 180 mg daily; increased if necessary to 360 mg daily
    - Elderly: Initially 120 mg daily; increased if necessary to 360 mg daily
Blood pressure conditions

DILZEM® SR
Angina | Mild to moderate hypertension
BY MOUTH
» Adult: Initially 90 mg twice daily; increased if necessary up to 180 mg twice daily
» Elderly: Initially 60 mg twice daily; increased if necessary up to 180 mg twice daily

ADIZEM-XL®
Angina | Mild to moderate hypertension
BY MOUTH
» Adult: Initially 240 mg daily; increased if necessary to 300 mg daily
» Elderly: Initially 120 mg daily; increased if necessary up to 300 mg daily

ANGITIL® SR
Angina | Mild to moderate hypertension
BY MOUTH
» Adult: Initially 90 mg twice daily; increased if necessary to 120–180 mg twice daily

ZEMTARD®
Angina
BY MOUTH
» Adult: 180–300 mg daily, increased if necessary to 480 mg daily
» Elderly: Initially 120 mg daily, increased if necessary to 480 mg daily

Mild to moderate hypertension
BY MOUTH
» Adult: 180–300 mg daily, increased if necessary to 360 mg daily
» Elderly: Initially 120 mg daily, increased if necessary to 360 mg daily

SLOZEM®
Angina | Mild to moderate hypertension
BY MOUTH
» Adult: Initially 240 mg daily; increased if necessary to 360 mg daily
» Elderly: Initially 120 mg daily; increased if necessary to 360 mg daily

ANGITIL® XL
Angina | Mild to moderate hypertension
BY MOUTH
» Adult: Initially 240 mg daily; increased if necessary to 300 mg daily, dose form not appropriate for initial dose titration in the elderly

DILCARDIA® SR
Angina | Mild to moderate hypertension
BY MOUTH
» Adult: Initially 90 mg twice daily; increased if necessary to 180 mg twice daily
» Elderly: Initially 60 mg twice daily; increased if necessary to 90 mg twice daily

Frequency not known
Depression • extrapyramidal symptoms • gum hyperplasia • gynaecomastia • hepatitis
Overdose
In overdose, diltiazem has a profound cardiac depressant effect causing hypotension and arrhythmias, including complete heart block and asystole.

PREGNANCY
Avoid.

BREAST FEEDING
Significant amount present in milk—no evidence of harm but avoid unless no safer alternative.

HEPATIC IMPAIRMENT
Reduce dose.

TILDIE RETARD®
Dose for mild to moderate hypertension—initially 120 mg once a day. For treatment of angina, dose form not appropriate for initial titration; up to 120 mg twice a day may be required.

TILDIE® LA
Dose for angina and mild to moderate hypertension—initially 200 mg daily; increased if necessary to 300 mg daily.

VIAZEM® XL, DILZEM® XL, ADIZEM-XL®, ZEMTARD®, SLOZEM®
Dose for angina and mild to moderate hypertension—initially 120 mg once daily, adjusted according to response.

ANGITIL® XL
Dose form not appropriate for initial dose titration.

DILCARDIA® SR
Dose for angina and mild to moderate hypertension—initially 60 mg twice a day; maximum 90 mg twice a day.

RENA IMPAIRMENT
Start with smaller dose.

TILDIE RETARD®
Dose for mild to moderate hypertension—initially 120 mg once a day; increased if necessary to 120 mg twice a day. For treatment of angina, dose form not appropriate for initial titration; up to 120 mg twice a day may be required.

TILDIE® LA
Dose for angina and mild to moderate hypertension—initially 200 mg daily; increased if necessary to 300 mg daily.

VIAZEM® XL, DILZEM® XL, ADIZEM-XL®, ZEMTARD®, SLOZEM®
Dose for angina and mild to moderate hypertension—initially 120 mg once daily, adjusted according to response.

ANGITIL® XL
Dose form not appropriate for initial dose titration.

DILCARDIA® SR
Dose for angina and mild to moderate hypertension—initially 60 mg twice a day; maximum 90 mg twice a day.

PRESCRIBING AND DISPENSING INFORMATION
Different versions of modified-release preparations containing more than 60 mg diltiazem hydrochloride may not have the same clinical effect. To avoid confusion between these different formulations of diltiazem, prescribers should specify the brand to be dispensed.

PATIENT AND CARER ADVICE
TILDIE RETARD®
Tablet membrane may pass through gastro-intestinal tract unchanged, but being porous has no effect on efficacy.

CONTRA-INDICATIONS
Acute porphyrias p. 864 • left ventricular failure with pulmonary congestion • second- or third-degree AV block (unless pacemaker fitted) • severe bradycardia • sick sinus syndrome

CAUTIONS
Bradycardia (avoid if severe) • first degree AV block • heart failure • prolonged PR interval • significantly impaired left ventricular function

INTERACTIONS
Appendix 1 (calcium-channel blockers).

SIDE-EFFECTS
Common or very common • Asthenia • AV block • bradycardia • dizziness • gastro-intestinal disturbances • headache • hot flushes • hypotension • malaise • oedema (notably of ankles) • palpitation • sino-atrial block

Rare
Erythema multiforme • exfoliative dermatitis • photosensitivity • rashes

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Modified-release tablet
CAUTIONARY AND ADVISORY LABELS 25

DILTIAZEM HYDROCHLORIDE (Non-proprietary)
Diltiazem hydrochloride 60 mg
Diltiazem 60mg modified-release tablets | 84 tablet [GBP] £36.26 DT price = £30.55 | 100 tablet [GBP] £43.16
Diltiazem hydrochloride 90 mg
Diltiazem 90mg modified-release tablets | 56 tablet [GBP] £42.80
## Hypertension 151

### Felodipine

**Drug Action** Felodipine is a dihydropyridine calcium-channel blocker.

### INDICATIONS AND DOSE

#### Angina

**BY MOUTH**

- **Adult:** Initially 5 mg daily; increased if necessary to 10 mg daily, to be taken in the morning.
- **Elderly:** Initially 2.5 mg daily; increased if necessary to 10 mg daily, to be taken in the morning.

#### Hypertension

**BY MOUTH**

- **Adult:** Initially 5 mg daily, to be taken in the morning; usual maintenance 5–10 mg once daily, doses above 20 mg daily rarely needed.
- **Elderly:** Initially 2.5 mg daily, to be taken in the morning; usual maintenance 5–10 mg once daily, doses above 20 mg daily rarely needed.

### CONTRA-INDICATIONS

Cardiac outflow obstruction - significant cardiac valvular obstruction (e.g. aortic stenosis) - uncontrolled heart failure - unstable angina - within 1 month of myocardial infarction.

<table>
<thead>
<tr>
<th>Felodipine</th>
<th><strong>Indication</strong></th>
<th><strong>Dose</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Angina</strong></td>
<td>BY MOUTH</td>
<td>Adult: Initially 5 mg daily; increased if necessary to 10 mg daily, to be taken in the morning. Elderly: Initially 2.5 mg daily; increased if necessary to 10 mg daily, to be taken in the morning.</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>BY MOUTH</td>
<td>Adult: Initially 5 mg daily, to be taken in the morning; usual maintenance 5–10 mg once daily, doses above 20 mg daily rarely needed. Elderly: Initially 2.5 mg daily, to be taken in the morning; usual maintenance 5–10 mg once daily, doses above 20 mg daily rarely needed.</td>
</tr>
<tr>
<td><strong>CONTRA-INDICATIONS</strong></td>
<td></td>
<td>Cardiac outflow obstruction - significant cardiac valvular obstruction (e.g. aortic stenosis) - uncontrolled heart failure - unstable angina - within 1 month of myocardial infarction.</td>
</tr>
</tbody>
</table>
Isradipine

**INDICATIONS AND DOSE**

**Hypertension**

**BY MOUTH**

- **Adult:** 2.5 mg twice daily for 3–4 weeks, then increased if necessary to 5 mg twice daily, dose increased exceptionally up to 10 mg twice daily
- **Elderly:** 1.25 mg twice daily, increased if necessary after 3–4 weeks according to response; maintenance 2.5–5 mg once daily

**CONTRA-INDICATIONS**

- Acute porphyrias p. 864 • aortic stenosis • avoid within 1 month of myocardial infarction • cardiogenic shock • unstable angina
- **CAUTIONS**

  - Cardiac conduction abnormalities • poor cardiac reserve
  - **INTERACTIONS**

    → Appendix 1 (calcium-channel blockers).
  - **SIDE-EFFECTS**

    - **Common or very common** Abdominal discomfort • dizziness • dyspnoea • fatigue • flushing • headache • palpitation • peripheral oedema • polyuria • rash • tachycardia
    - **Uncommon** Hypotension • weight gain
    - **Very rare** Anaemia • anorexia • anxiety • arrhythmia • arthralgia • blood disorders • bradycardia • cough • depression • drowsiness • erectile dysfunction • gum hyperplasia • heart failure • hypersensitivity reactions • leucopenia • nausea • paraesthesia • thrombocytopenia • visual disturbance • vomiting

  - **Frequency not known** Gynaecomastia • hepatitis

  - **Overdose** In overdose, the dihydropyridine calcium-channel blockers cause severe hypotension secondary to profound peripheral vasodilatation.
  - **PREGNANCY** May inhibit labour. Risk to fetus should be balanced against risk of uncontrolled maternal hypertension.
  - **BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.
  - **HEPATIC IMPAIRMENT** 1.25 mg twice daily, increased if necessary after 3–4 weeks according to response; maintenance dose of 2.5 mg or 5 mg once daily may be sufficient.
  - **RENAL IMPAIRMENT** Use with caution.

**MEDITINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **ISRADIPINE (Non-proprietary)**

  Isradipine 2.5 mg Isradipine 2.5mg tablets | 56 tablet p. 131

  DT price = £184.01–£211.01 DT price = £185.94

**Lacidipine**

**DRUG ACTION**

Lacidipine is a dihydropyridine calcium-channel blocker.

**INDICATIONS AND DOSE**

**Hypertension**

**BY MOUTH**

- **Adult:** Initially 2 mg daily; increased if necessary to 4 mg daily, then increased if necessary to 6 mg daily, dose increases should occur at intervals of 3–4 weeks, to be taken preferably in the morning

  - **CONTRA-INDICATIONS**

    - Acute porphyrias p. 864 • aortic stenosis • avoid within 1 month of myocardial infarction • cardiogenic shock • unstable angina
    - **CAUTIONS**

      - Cardiac conduction abnormalities • poor cardiac reserve
      - **INTERACTIONS**

        → Appendix 1 (calcium-channel blockers).
      - **SIDE-EFFECTS**

        - **Common or very common** Dizziness • flushing • headache • oedema • palpitation
        - **Rare** Aggravation of angina • asthenia • erythema • gastro-intestinal disturbances • gum hyperplasia • mood disturbances • muscle cramps • polyuria • pruritus • skin rash

  - **Overdose** In overdose, the dihydropyridine calcium-channel blockers cause severe hypotension secondary to profound peripheral vasodilatation.
  - **PREGNANCY** Manufacturer advises avoid may inhibit labour.
  - **BREAST FEEDING** Manufacturer advises avoid—no information available.
  - **HEPATIC IMPAIRMENT** Antihypertensive effect possibly increased.

**MEDITINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **LACIDIPINE (Non-proprietary)**

  Lacidipine 2 mg Lacidipine 2mg tablets | 28 tablet DT price = £2.90

  also available in combination with ramipril, p. 131
Lercanidipine hydrochloride

**DRUG ACTION** Lercanidipine is a dihydropyridine calcium-channel blocker.

**INDICATIONS AND DOSE**

**Mild to moderate hypertension**

**BY MOUTH**

- **Adult:** Initially 10 mg once daily; increased if necessary up to 20 mg daily, dose can be adjusted after 2 weeks

**CONTRA-INDICATIONS**

- Acute porphyrias p. 864
- Aortic stenosis
- Uncontrolled heart failure
- Unstable angina
- within 1 month of myocardial infarction

**CAUTIONS**

- Left ventricular dysfunction
- Sick sinus syndrome (if pacemaker not fitted)

**INTERACTIONS**

- Appendix 1 (calcium-channel blockers)

**SIDE-EFFECTS**

- **Uncommon**
  - Dizziness, flushing, headache, palpitation, peripheral oedema, tachycardia
- **Rare**
  - Angina, asthenia, drowsiness, gastrointestinal disturbances, myalgia, polyuria, rash
- **Very rare**
  - Gingival hyperplasia
  - Hypotension
  - Myocardial infarction

**Overdose**

In overdose, the dihydropyridine calcium-channel blockers cause severe hypotension secondary to profound peripheral vasodilatation.

**PREGNANCY**

Manufacturer advises avoid—no information available.

**BREAST FEEDING**

Manufacturer advises avoid.

**HEPATIC IMPAIRMENT**

Avoid in severe disease.

**RENAL IMPAIRMENT**

Avoid if eGFR less than 30 mL/minute/1.73 m².

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>LERCANIDIPINE HYDROCHLORIDE (Non-proprietary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lercanidipine hydrochloride 10 mg</td>
<td><a href="%C2%A35.89">28 tablet</a> price = £1.57</td>
</tr>
<tr>
<td>Lercanidipine hydrochloride 20 mg</td>
<td><a href="%C2%A310.82">28 tablet</a> price = £1.84</td>
</tr>
<tr>
<td>Zanidip (Recordati Pharmaceuticals Ltd)</td>
<td></td>
</tr>
<tr>
<td>Lercanidipine hydrochloride 10 mg</td>
<td><a href="%C2%A32.95">28 tablet</a> price = £2.90</td>
</tr>
<tr>
<td>Lercanidipine hydrochloride 20 mg</td>
<td><a href="%C2%A33.10">28 tablet</a> price = £3.02</td>
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Nicardipine hydrochloride

**DRUG ACTION** Nicardipine is a dihydropyridine calcium-channel blocker.

**INDICATIONS AND DOSE**

**Prophylaxis of angina**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

- **Adult:** Initially 20 mg 3 times a day, then increased to 30 mg 3 times a day, dose increased after at least 3 days; usual dose 60–120 mg daily

**CONTRA-INDICATIONS**

**GENERAL CONTRA-INDICATIONS**

- Acute porphyrias p. 864
- Aortic stenosis
- Significant or advanced aortic stenosis
- Unstable or acute attacks of angina

**SPECIFIC CONTRA-INDICATIONS:**

- With intravenous use
  - Avoid within 8 days of myocardial infarction
- With oral use
  - Avoid within 1 month of myocardial infarction

**CAUTIONS**

- Congestive heart failure
- Elderly–elevated intracranial pressure
- Portal hypertension
- Pulmonary oedema
- Significantly impaired left ventricular function

**SIDE-EFFECTS**

- Atrophic ventricular block
- Depression
- Dizziness
- Drowsiness
- Dyspnoea
- Flushing
- Frequency of micturition
- Gastro-intestinal disturbances
- Gingival hyperplasia
- Headache
- Hypotension
- Impotence
- Insomnia
- Nausea
- Palpitations
- Paraesthesia
- Paralytic ileus
- Peripheral oedema
- Pruritus
- Pulmonary oedema
- Rash
- Tachycardia
- Thrombocytopenia
- Tinnitus
- Vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

**Hypotension and reflex tachycardia**

Systemic hypotension and reflex tachycardia with rapid reduction of blood pressure may occur—during intravenous use consider stopping infusion or decreasing dose by half.

**OVERDOSE**

In overdose, the dihydropyridine calcium-channel blockers cause severe hypotension secondary to profound peripheral vasodilatation.

**PREGNANCY**

For treatment of acute life-threatening hypertension only. May inhibit labour. Not to be used in...
multiple pregnancy (twins or more) unless there is no other acceptable alternative. Toxicity in animal studies. Risk of severe maternal hypotension and fatal foetal hypoxia—avoid excessive decrease in blood pressure.

- **BREAST FEEDING** Manufacturer advises avoid—present in breast milk.

- **HEPATIC IMPAIRMENT**
  - With oral use Use with caution—consider using lowest initial dose and extending dosing interval according to individual response.
  - With intravenous use Use with caution—use lower initial dose.

- **RENAL IMPAIRMENT**
  - With intravenous use Monitor blood pressure and heart rate at least every 5 minutes during intravenous infusion, and then until stable, and continue monitoring for at least 12 hours after end of infusion.

- **DIRECTIONS FOR ADMINISTRATION** Intravenous nicardipine should only be administered under the supervision of a specialist and in a hospital or intensive care setting in which patients can be closely monitored. For intravenous infusion give continuously in Glucose 5%; dilute dose in infusion fluid to a final concentration of 100–200 micrograms/mL (undiluted solution via central venous line only) and give via volumetric infusion pump or syringe driver; protect from light; to minimise peripheral venous irritation, change site of infusion every 12 hours; risk of adsorption on to plastic of infusion set in the presence of saline solutions; incompatible with bicarbonate or alkaline solutions—consult product literature.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

- **Capsule**
  - NICARDINE HYDROCHLORIDE (Non-proprietary)
    - Nicardipine hydrochloride 20 mg Nicardipine 20mg capsules | 56 capsule [Price] £8.38 DT price = £6.00
    - Nicardipine hydrochloride 30 mg Nicardipine 30mg capsules | 56 capsule [Price] £9.73 DT price = £6.37
  - Cardene (Astellas Pharma Ltd)
    - Nicardipine hydrochloride 20 mg Cardene 20mg capsules | 56 capsule [Price] £6.00 DT price = £6.00
    - Nicardipine hydrochloride 30 mg Cardene 30mg capsules | 56 capsule [Price] £6.96 DT price = £6.37

- **Modified-release capsule**
  - CAUTIONARY AND ADVISORY LABELS 25
  - Cardene SR (Astellas Pharma Ltd)
    - Nicardipine hydrochloride 30 mg Cardene SR 30mg capsules | 56 capsule [Price] £7.15 DT price = £7.15
    - Nicardipine hydrochloride 45 mg Cardene SR 45mg capsules | 56 capsule [Price] £10.40 DT price = £10.40

- **Solution for infusion**
  - NICARDINE HYDROCHLORIDE (Non-proprietary)
    - Nicardipine hydrochloride 1 mg per 1 ml Nicardipine 10mg/10ml solution for injection ampoules | 5 ampoule [Price] £5.00

**Nifedipine**

- **DRUG ACTION** Nifedipine is a dihydropyridine calcium-channel blocker.
**TENSIPINE**® MR
Hypertension | Angina prophylaxis
BY MOUTH
▶ Adult: Initially 10 mg twice daily, adjusted according to response to 40 mg twice daily

**CORACTEN**® SR
Hypertension | Angina prophylaxis
BY MOUTH
▶ Adult: Initially 10 mg twice daily, increased if necessary up to 40 mg twice daily

**CORACTEN**® XL
Hypertension | Angina prophylaxis
BY MOUTH
▶ Adult: Initially 30 mg daily, increased if necessary up to 90 mg daily

**UNLICENSED USE** Not licensed for use in postponing premature labour.

**CONTRA-INDICATIONS** Acute attacks of angina - cardiogenic shock - significant aortic stenosis - unstable angina - within 1 month of myocardial infarction

**CAUTIONS** Diabetes mellitus - elderly - heart failure - poor cardiac reserve - severe hypotension - short-acting formulations are not recommended for angina or long-term management of hypertension; their use may be associated with large variations in blood pressure and reflex tachycardia - significantly impaired left ventricular function (heart failure deterioration observed) - withdrawn if ischaemic pain occurs or existing pain worsens shortly after initiating treatment

**ADALAT**® LA
Crohn's disease - decreased lumen diameter of the gastro-intestinal tract - history of gastro-intestinal obstruction - inflammatory bowel disease

**CAUTIONS, FURTHER INFORMATION**
**ADALAT**® LA, **VALNI**® XL
Dose form not appropriate for use where there is a history of oesophageal obstruction - inflammatory bowel disease (including Crohn's disease).

**INTERACTIONS** → Appendix 1 (calcium-channel blockers).

**SIDE-EFFECTS**
▶ Common or very common Asthenia - dizziness - gastrointestinal disturbance - headache - hypotension - lethargy - oedema - palpitation - vasodilatation
▶ Rare Anorexia - gum hyperplasia - hyperglycaemia - male infertility - mood disturbances - photosensitivity reactions - purpura
▶ Frequency not known Agranulocytosis - anaphylaxis - bezoar formation (with some modified-release preparations) - dysphagia - gynaecomastia - intestinal obstruction - intestinal ulcer

**Overdose** In overdose, the dihydropyridine calcium-channel blockers cause severe hypotension secondary to profound peripheral vasodilatation.

**PREGNANCY** May inhibit labour; manufacturer advises avoid before week 20, but risk to fetus should be balanced against risk of uncontrolled maternal hypertension. Use only if other treatment options are not indicated or have failed.

**BREAST FEEDING** Amount too small to be harmful but manufacturers advise avoid.

**HEPATIC IMPAIRMENT** Dose reduction may be required in severe liver disease. Some modified-release formulations may not be suitable for dose titration in hepatic disease—consult product literature.

**ADALAT**® LA, **VALNI**® XL. Dose form not appropriate.

**DIRECTIONS FOR ADMINISTRATION**
**FORTIPINE** LA 40 Take with or just after food, or a meal.

**PRESCRIBING AND DISPENSING INFORMATION** Different versions of modified-release preparations may not have the same clinical effect. To avoid confusion between these different formulations of nifedipine, prescribers should specify the brand to be dispensed.

**PATIENT AND CARER ADVICE**
**ADALAT**® LA. Tablet membrane may pass through gastro-intestinal tract unchanged, but being porous has no effect on efficacy.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral drops

**Modified-release tablet**

**CAUTIONARY AND ADVISORY LABELS 25**
▶ **NIFEDIPINE** (Non-proprietary)

| Nifedipine 10 mg | Nifedipine 10mg modified-release tablets | 56 tablet (P01) £7.34 DT price = £7.34 |
| Nifedipine 20 mg | Nifedipine 20mg modified-release tablets | 28 tablet (P01) no price available | 56 tablet (P01) £10.06 |
| Nifedipine 30 mg | Nifedipine 30mg modified-release tablets | 28 tablet (P01) no price available | DT price = £6.85 |
| Nifedipine 40 mg | Nifedipine 40mg modified-release tablets | 30 tablet (P01) no price available |
| Adalat LA (Bayer Plc) | Nifedipine 20 mg | Adalat LA 20 tablets | 28 tablet (P01) £5.27 |
| Adalat 30 mg | Adalat LA 30 tablets | 28 tablet (P01) £6.85 DT price = £6.85 |
| Nifedipine 60 mg | Adalat LA 60 tablets | 28 tablet (P01) £9.03 DT price = £9.03 |
| Nifedipine 30 mg | Adalat retard 20mg tablets | 56 tablet (P01) £8.81 |
| Adipine MR (Chesi Ltd) | Nifedipine 10 mg | Adipine MR 10 tablets | 56 tablet (P01) £3.73 DT price = £3.74 |
| Nifedipine 20 mg | Adipine MR 20 tablets | 56 tablet (P01) £5.21 |
| Adipine XL (Chesi Ltd) | Nifedipine 30 mg | Adipine XL 30mg tablets | 28 tablet (P01) £4.70 DT price = £6.85 |
| Nifedipine 60 mg | Adipine XL 60mg tablets | 28 tablet (P01) £7.10 DT price = £9.03 |
| Fortipine LA (AMCo) | Nifedipine 40 mg | Fortipine LA 40 tablets | 30 tablet (P01) £14.40 |
| Nifedipress MR (Dexcel-Pharma Ltd) | Nifedipine 10 mg | Nifedipress MR 10 tablets | 56 tablet (P01) £9.23 DT price = £7.34 |
| Nifedipine 20 mg | Nifedipress MR 20 tablets | 56 tablet (P01) £10.06 |
| Tensipine MR (Genus Pharmaceuticals Ltd) | Nifedipine 10 mg | Tensipine MR 10 tablets | 56 tablet (P01) £4.30 DT price = £7.34 |
| Nifedipine 20 mg | Tensipine MR 20 tablets | 56 tablet (P01) £5.49 |
| Valni XL (Zentiva) | Nifedipine 30 mg | Valni XL 30mg tablets | 28 tablet (P01) £7.29 DT price = £6.85 |
| Nifedipine 60 mg | Valni XL 60mg tablets | 28 tablet (P01) £9.14 DT price = £9.03 |
| Brands may include Adalyn XL; Kentipine MR; Neazipine XL; Nifopress Retard; Valni Retard |

**Capsule**
▶ **NIFEDIPINE** (Non-proprietary)

| Nifedipine 5 mg | Nifedipine 5mg capsules | 84 capsule (P01) £19.99 DT price = £15.20 |
Verapamil hydrochloride

INDICATIONS AND DOSE

Treatment of supraventricular arrhythmias
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
▶ Adult: 40–120 mg 3 times a day
BY SLOW INTRAVENOUS INJECTION
▶ Adult: 5–10 mg, to be given over 2 minutes, preferably with ECG monitoring
▶ Elderly: 5–10 mg, to be given over 3 minutes, preferably with ECG monitoring

Paroxysmal tachyarrhythmias
BY SLOW INTRAVENOUS INJECTION
▶ Adult: Initially 5–10 mg, followed by 5 mg after 5–10 minutes if required, to be given over 2 minutes, preferably with ECG monitoring
▶ Elderly: Initially 5–10 mg, followed by 5 mg after 5–10 minutes if required, to be given over 3 minutes, preferably with ECG monitoring

Angina
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
▶ Adult: 80–120 mg 3 times a day

Hypertension
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
▶ Adult: 240–480 mg daily in 2–3 divided doses

Prophylaxis of cluster headache (initiated under specialist supervision)
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
▶ Adult: 240–960 mg daily in 3–4 divided doses

HALF SECURON® SR
Hypertension (in patients new to verapamil)
BY MOUTH
▶ Adult: Initially 120 mg daily, increased if necessary up to 480 mg daily, doses above 240 mg daily as 2 divided doses

Hypertension
BY MOUTH
▶ Adult: 240 mg daily, increased if necessary up to 480 mg daily, doses above 240 mg daily as 2 divided doses

Angina
BY MOUTH
▶ Adult: 240 mg twice daily, may sometimes be reduced to once daily

Prophylaxis after myocardial infarction where beta-blockers not appropriate
BY MOUTH
▶ Adult: 360 mg daily in divided doses, started at least 1 week after infarction, given as either 240 mg in the morning and 120 mg in the evening or 120 mg 3 times daily

SECURON® SR
Hypertension (in patients new to verapamil)
BY MOUTH
▶ Adult: Initially 120 mg daily, increased if necessary up to 480 mg daily, doses above 240 mg daily as 2 divided doses

Hypertension
BY MOUTH
▶ Adult: 240 mg daily, increased if necessary up to 480 mg daily, doses above 240 mg daily as 2 divided doses

Angina
BY MOUTH
▶ Adult: 240 mg twice daily, may sometimes be reduced to once daily

Prophylaxis after myocardial infarction where beta-blockers not appropriate
BY MOUTH
▶ Adult: 360 mg daily; maximum 480 mg per day

VERTAB® SR 240
Mild to moderate hypertension
BY MOUTH
▶ Adult: 240 mg daily, increased if necessary to 240 mg twice daily

Angina
BY MOUTH
▶ Adult: 240 mg twice daily, dose frequency may sometimes be reduced to once daily

VERAPRESS® MR
Hypertension
BY MOUTH
▶ Adult: 240 mg daily, increased if necessary to 240 mg twice daily

Angina
BY MOUTH
▶ Adult: 240 mg twice daily, may sometimes be reduced to once daily

UNIVER®
Hypertension (in patients new to verapamil)
BY MOUTH
▶ Adult: 120 mg daily; maximum 480 mg per day

Hypertension
BY MOUTH
▶ Adult: 240 mg daily; maximum 480 mg per day

Angina
BY MOUTH
▶ Adult: 360 mg daily; maximum 480 mg per day

● UNLICENSED USE
  ● With oral use Prophylaxis of cluster headaches is an unlicensed indication.

● CONTRA-INDICATIONS  Acute porphyrias p. 864 · atrial flutter or fibrillation associated with accessory conducting pathways (e.g. Wolff-Parkinson-White-syndrome) · bradycardia · cardiogenic shock · history of heart failure (even if controlled by therapy) · history of significantly impaired left ventricular function (even if controlled by therapy) · hypotension · second- and third-degree AV block · sick sinus syndrome · sino-atrial block

● CAUTIONS  Acute phase of myocardial infarction (avoid if bradycardia, hypotension, left ventricular failure) · first-degree AV block

● INTERACTIONS → Appendix 1 (calcium-channel blockers).
Verapamil and beta-blockers  Verapamil injection should not be given to patients recently treated with beta-blockers because of the risk of hypotension and asystole. The suggestion that when verapamil injection has been given first, an interval of 30 minutes before giving a beta-blocker is sufficient has not been confirmed. It may also be hazardous to give verapamil and a beta-blocker together by mouth (should only be contemplated if myocardial function well preserved).

SIDE-EFFECTS

Common or very common  Constipation
Uncommon  Ankle oedema, dizziness, fatigue, flushing, headache, nausea, vomiting
Rare  Allergic reactions - angioedema, arthralgia, asystole, bradycardia, erythema, erythrocalalgia, gingival hyperplasia after long-term treatment, gynaecomastia after long-term treatment, heart block, heart failure, hypotension, increased prolactin concentration, myalgia, paraesthesia, pruritus, Stevens-Johnson syndrome, urticaria

SIDE-EFFECTS, FURTHER INFORMATION

Intravenous administration or high doses  Hypotension, heart failure, bradycardia, heart block, and asystole are side-effects associated with intravenous administration or high doses.

Overdose  In overdose, verapamil has a profound cardiac depressant effect causing hypotension and arrhythmias, including complete heart block and asystole.

PREGNANCY  May reduce uterine blood flow with fetal hypoxia. Manufacturer advises avoid in first trimester unless absolutely necessary. May inhibit labour.

BREAST FEEDING  Amount too small to be harmful.

HEPATIC IMPAIRMENT  Oral dose may need to be reduced.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet

VERAPAMIL HYDROCHLORIDE (Non-proprietary)

Verapamil hydrochloride 40 mg Verapamil 40mg tablets 84 tablet (£3.18 DT price = £2.06
Verapamil hydrochloride 80 mg Verapamil 80mg tablets 84 tablet (£3.65 DT price = £2.38
Verapamil hydrochloride 120 mg Verapamil 120mg tablets 28 tablet (£2.80 DT price = £1.81
Verapamil hydrochloride 160 mg Verapamil 160mg tablets 56 tablet (£28.20 DT price = £28.20

Modified-release tablet

CAUTIONARY AND ADVISORY LABELS 25

VERAPAMIL HYDROCHLORIDE (Non-proprietary)

Verapamil hydrochloride 120 mg Verapamil 120mg modified-release tablets 28 tablet (£7.71 DT price = £7.71
Verapamil hydrochloride 240 mg Verapamil 240mg modified-release tablets 28 tablet (£5.55 DT price = £5.55
Half Securon (BGP Products Ltd)
Verapamil hydrochloride 120 mg Half Securon SR 120mg tablets 28 tablet (£7.71 DT price = £7.71
Securon (BGP Products Ltd)
Verapamil hydrochloride 240 mg Securon SR 240mg tablets 28 tablet (£5.55 DT price = £5.55
Brands may include Vera-Til SR

Verapress MR (Dexcel-Pharma Ltd)
Verapress hydrochloride 240 mg Verapress MR 240mg tablets 28 tablet (£5.55 DT price = £5.55
Verapress hydrochloride 240 mg Verapress SR 240mg tablets 28 tablet (£3.90 DT price = £3.55
Vertab SR (Chiesi Ltd)
Vertab hydrochloride 240 mg Vertab SR 240 tablets 28 tablet (£5.45 DT price = £5.45
Brands may include Vera-Til SR

Modified-release capsule

CAUTIONARY AND ADVISORY LABELS 25

EXCIPIENTS: May contain Propylene glycol

Univer (Teva UK Ltd)
Verapamil hydrochloride 120 mg Univer 120mg modified-release capsules 28 capsule (£4.86 DT price = £4.86

Hydralazine hydrochloride

INDICATIONS AND DOSE

BY MOUTH

Moderate to severe hypertension (adjunct)

Adult: Initially 25 mg twice daily, increased if necessary up to 50 mg twice daily

Heart failure (with long acting nitrate) (initiated in hospital or under specialist supervision)

BY MOUTH

Adult: Initially 25 mg 3–4 times a day, then increased if necessary to every 2 days; maintenance 50–75 mg 4 times a day

Hypertensive emergencies (including during pregnancy)

Hypertension with renal complications

BY INTRAVENOUS INFUSION

Adult: Initially 200–300 micrograms/minute; maintenance 50–150 micrograms/minute

Hypertensive emergencies (including during pregnancy)

Hypertension with renal complications

BY SLOW INTRAVENOUS INJECTION

Adult: 5–10 mg, to be diluted with 10 mL sodium chloride 0.9%, dose may be repeated after 20–30 minutes

CONTRA-INDICATIONS

Acute porphyrias

Pulmonary

Dissecting aortic aneurysm

High output heart failure

Idiopathic systemic lupus erythematosus

Myocardial insufficiency due to mechanical obstruction

Severe tachycardia

CAUTIONS

Cerebrovascular disease - coronary artery disease (may provoke angina, avoid after myocardial infarction until stabilised) - occasionally blood pressure reduction too rapid even with low parenteral doses

INTERACTIONS  Appendix 1 (hydralazine)

SIDE-EFFECTS

Rare  Rash

Frequency not known

Abnormal liver function - agitation - anorexia - anxiety - arthralgia - blood disorders - dizziness - dyspnoea - fever - fluid retention - flushing - gastrointestinal disturbances - haematuria - haemolytic anaemia - headache - hypotension - increased lactation - jaundice - leucopenia - myalgia - nasal congestion - palpitation - paraesthesia - peripheral neuritis - polyneuritis - proteinuria - raised plasma creatinine - systemic lupus erythematosus-like syndrome after long-term therapy with over 100 mg daily (or less in women and in slow acetylator individuals) - tachycardia - thrombocytopenia

SIDE-EFFECTS, FURTHER INFORMATION

The incidence of side-effects is lower if the dose is kept below 100 mg daily, but systemic lupus erythematosus should be suspected if there is unexplained weight loss, arthritis, or any other unexplained ill health.
Minoxidil

INDICATIONS AND DOSE
Severe hypertension, in addition to a diuretic and a beta-blocker

BY MOUTH
- Adult: Initially 5 mg daily in 1–2 divided doses, then increased in steps of 5–10 mg, increased at intervals of at least 3 days, seldom necessary to exceed 50 mg daily; maximum 100 mg per day
- Elderly: Initially 2.5 mg daily in 1–2 divided doses, then increased in steps of 5–10 mg, increased at intervals of at least 3 days, seldom necessary to exceed 50 mg daily; maximum 100 mg per day

CONTRA-INDICATIONS Phaeochromocytoma

CAUTIONS Acute porphyrias p. 864 · after myocardial infarction (until stabilised) · angina

INTERACTIONS Appendix 1 (vasodilator antihypertensives).

SIDE-EFFECTS Breast tenderness · gastro-intestinal disturbances · hypertrichosis · hyperpigmentation · rashes · reversible rise in creatinine and blood urea nitrogen · sodium retention · tachycardia · water retention · weight gain

PREGNANCY Avoid—possible toxicity including reduced placental perfusion. Neonatal hirsutism reported.

BREAST FEEDING Present in milk but not known to be harmful.

RENAI IMPAIRMENT Use with caution in significant impairment.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
Thiazides and related diuretics

- **CONTRA-INDICATIONS** Addison’s disease, hypercalcaemia, hypernatraemia, refractory hypokalaemia, symptomatic hyperuricaemia
- **CAUTIONS** Diabetes, gout, hyperaldaosteronism, malnourishment, nephrotic syndrome, systemic lupus erythematosus

**CAUTIONS, FURTHER INFORMATION**

**Potassium loss** Hypokalaemia can occur with both thiazide and loop diuretics. The risk of hypokalaemia depends on the duration of action as well as the potency and is thus greater with thiazides than with an equipotent dose of a loop diuretic.

Hypokalaemia is dangerous in severe cardiovascular disease and in patients also being treated with cardiac glycosides. Often the use of potassium-sparing diuretics avoids the need to take potassium supplements. Potassium supplements or potassium-sparing diuretics are seldom necessary when thiazides are used in the routine treatment of hypertension. In hepatic failure, hypokalaemia caused by diuretics can precipitate encephalopathy, particularly in alcoholic cirrhosis.

**Elderly** Lower initial doses of diuretics should be used in the elderly because they are particularly susceptible to the side-effects. The dose should then be adjusted according to renal function. Diuretics should not be used continuously on a long-term basis to treat simple gravitational oedema (which will usually respond to increased movement, raising the legs, and support stockings).

**Existing conditions** Thiazides and related diuretics can exacerbate diabetes, gout, and systemic lupus erythematosus.

**INTERACTIONS** → Appendix 1 (diuretics).

**SIDE-EFFECTS**
- **Common or very common** Altered plasma-lipid concentrations - gout - hypercalcaemia - hyperglycaemia - hyperuricaemia - hypochloraemic alkalosis - hypokalaemia - hypomagnesaemia - hyponatraemia - metabolic and electrolyte disturbances - mild gastrointestinal disturbances - postural hypotension
- **Uncommon** Agranulocytosis - blood disorders - impotence - leucopenia - thrombocytopenia

**Frequency not known** Cardiac arrhythmias - dizziness - headache - hypersensitivity reactions - intrahepatic cholestasis - pancreatitis - paraesthesia - photosensitivity - pneumonitis - pulmonary oedema - severe skin reactions - visual disturbances

**PREGNANCY** Thiazides and related diuretics should not be used to treat gestational hypertension. They may cause neonatal thrombocytopenia, bone marrow suppression, jaundice, electrolyte disturbances, and hypoglycaemia; placental perfusion may also be reduced. Stimulation of labour, uterine inertia, and meconium staining have also been reported.

**HEPATIC IMPAIRMENT** Caution in mild to moderate impairment. Avoid in severe liver disease. Hypokalaemia may precipitate coma in hepatic impairment, although hypokalaemia can be prevented by using a potassium-sparing diuretic. There is an increased risk of hypomagnesaemia in alcoholic cirrhosis.

**RENAL IMPAIRMENT** Thiazides and related diuretics are ineffective if eGFR is less than 30 mL/minute/1.73 m² and should be avoided. Metolozane remains effective if eGFR is less than 30 mL/minute/1.73 m² but is associated with a risk of excessive diuresis. Electrolytes should be monitored in renal impairment.

**MONITORING REQUIREMENTS** Electrolytes should be monitored, particularly with high doses and long-term use.

#### Bendroflumethiazide (Bendrofluzide)

**INDICATIONS AND DOSE**

- **Oedema**
  - **BY MOUTH**
    - Adult: Initially 5–10 mg once daily or on alternate days, dose to be taken in the morning, then maintenance 5–10 mg 1–3 times a week
  - **Hypertension**
    - **BY MOUTH**
      - Adult: 2.5 mg daily, dose to be taken in the morning, higher doses are rarely necessary

**BREAST FEEDING** The amount present in milk is too small to be harmful. Large doses may suppress lactation.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

**Tablet**

- **BENDROFLUMETHIAZIDE (Non-proprietary)**
  - Bendroflumethiazide 2.5 mg Bendroflumethiazide 2.5mg tablets | 28 tablet (PS) £3.68 DT price = 10.08 | 500 tablet (PS) £65.71
  - Bendroflumethiazide 5 mg Bendroflumethiazide 5mg tablets | 28 tablet (PS) £7.36 DT price = 0.97 | 500 tablet (PS) £73.60
  - Aprinox (AMCo)
    - Bendroflumethiazide 2.5 mg Aprinox 2.5mg tablets | 500 tablet (PS) £27.31
Co-amilozide

**INDICATIONS AND DOSE**

**Hypertension**
- **BY MOUTH**
  - Adult: Initially 2.5/25 mg daily, increased if necessary up to 5/50 mg daily

**Congestive heart failure**
- **BY MOUTH**
  - Adult: Initially 2.5/25 mg daily; increased if necessary up to 10/100 mg daily, reduce dose for maintenance if possible

**Oedema and ascites in cirrhosis of the liver**
- **BY MOUTH**
  - Adult: Initially 5/50 mg daily; increased if necessary up to 10/100 mg daily, reduce dose for maintenance if possible

**Dose equivalence and conversion**
A mixture of amiloride hydrochloride and hydrochlorothiazide in the mass proportions of 1 part amiloride hydrochloride to 10 parts hydrochlorothiazide.

**CONTRA-INDICATIONS**
- Anuria - hyperkalaemia

**CAUTIONS**
- Diabetes mellitus - elderly

**SIDE-EFFECTS**

**BREAST FEEDING**
- Avoid—no information regarding amiloride component available. Amount of hydrochlorothiazide in milk probably too small to be harmful. Large doses of hydrochlorothiazide may suppress lactation.

**RENAral IMPAIRMENT**
- Manufacturers advise avoid in severe impairment. Monitor plasma-potassium concentration (high risk of hyperkalaemia in renal impairment).

**MONITORING REQUIREMENTS**
- Monitor electrolytes.

**MEDICINAL FORMS**
- Present in milk—manufacturer advises avoid.

**Hydrochlorothiazide**

**INDICATIONS AND DOSE**

**Essential hypertension**
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: 2.5 mg daily, dose to be taken preferably in the morning
- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Adult: 1.5 mg daily, dose to be taken preferably in the morning

**SIDE-EFFECTS**
- Diuresis (with doses above 2.5 mg daily) - paresthesia

**ALLERGY AND CROSS-SENSITIVITY**
- Contraindicated if history of hypersensitivity to sulfonamides.

**BREAST FEEDING**
- Present in milk—manufacturer advises avoid.

**INDAPAMIDE**

**INDICATIONS AND DOSE**

**Essential hypertension**
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: 2.5 mg daily, dose to be taken preferably in the morning
- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Adult: 1.5 mg daily, dose to be taken preferably in the morning

**SIDE-EFFECTS**
- Acute porphyrias p. 864

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution suspended

**Tablet**
- **INDAPAMIDE (Non-proprietary)**
  - Indapamide hemihydrate 2.5 mg Indapamide 2.5mg tablets | 28 tablet (PO) £40.99 DT price = £1.56 | 30 tablet (PO) £27.99 | 56 tablet (PO) £52.00
4.2 Hypertension associated with phaeochromocytoma

**Drugs used for Hypertension associated with phaeochromocytoma not listed below; Propranolol hydrochloride, p. 146**

**ALPHA-ADRENOCEPTOR BLOCKERS**

### Phenoxbenzamine hydrochloride

**INDICATIONS AND DOSE**

**Hypertension in phaeochromocytoma**

**BY MOUTH**

- **Adults:** Initially 10 mg daily, increased in steps of 10 mg daily until hypertension controlled or treatment not tolerated; maintenance 1–2 mg/kg daily in 2 divided doses

- **SIDE-EFFECTS**
  - Gastro-intestinal disturbances
  - Frequency not known: Inhibition of ejaculation, lassitude, miosis, nasal congestion, postural hypotension (with dizziness and marked compensatory tachycardia)
  - PREGNANCY Hypotension may occur in newborn.

- **CAUTIONS**
  - Avoid contact with skin (risk of contact sensitisation) - avoid in acute porphyrias p. 864.
  - Carcinogenic in animals. Cerebrovascular disease, congestive heart failure, elderly, severe ischaemic heart disease. Avoid contact with skin (risk of contact sensitisation) - avoid in acute porphyrias p. 864.

- **CONTRA-INDICATIONS**
  - History of cerebrovascular accident

- **INTERACTIONS**
  - Appendix 1 (alpha-blockers).

- **MEDICINAL FORMS**
  - Medicines not identified.

**INDICATIONS AND DOSE**

**Hypertensive crises**

**PERIPHERAL VASODILATORS**

### Sodium nitroprusside

**INDICATIONS AND DOSE**

**Hypertensive emergences**

**BY INTRAVENOUS INFUSION**

- **Adults:** Initially 0.5–1.5 micrograms/kg/minute, adjusted in steps of 500 nanograms/kg/minute every 5 minutes, usual dose 0.5–8 micrograms/kg/minute, use lower doses if already receiving other antihypertensives, stop if response unsatisfactory with max. dose in 10 minutes, lower initial dose of up to 1.5 micrograms/kg/minute has been used.

- **Controlled hypotension in anaesthesia during surgery**

- **BY INTRAVENOUS INFUSION**
  - **Adults:** Up to 1.5 micrograms/kg/minute.

- **Heart failure**

- **BY INTRAVENOUS INFUSION**
  - **Adults:** Initially 10–15 micrograms/minute, increased every 5–10 minutes as necessary, usual dose 10–200 micrograms/minute normally for max. 3 days.
Guanethidine monosulfate

**INDICATIONS AND DOSE**

**Hypertensive crisis (but no longer recommended)**

**BY INTRAMUSCULAR INJECTION**

- Adult: 10–20 mg, dose may be repeated after 3 hours if necessary

**CONTRA-INDICATIONS** Heart failure, phaeochromocytoma

**CAUTIONS** Asthma, cerebral arteriosclerosis, coronary arteriosclerosis, history of peptic ulceration

**INTERACTIONS** Appendix 1 (adrenergic neurone blockers).

**SIDE-EFFECTS** Diarrhoea, drowsiness, failure of ejaculation, fluid retention, headache, nasal congestion, postural hypotension

**PREGNANCY** Postural hypotension and reduced uteroplacental perfusion. Should not be used to treat hypertension in pregnancy.

**RENAI IMPAIRMENT** Reduce dose if eGFR 40–65 mL/minute/1.73 m². Avoid if eGFR less than 40 mL/minute/1.73 m².

**LESS SUITABLE FOR PRESCRIBING** Guanethidine monosulfate is less suitable for prescribing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

GUANETHIDINE MONOSULFATE (Non-proprietary) Guanethidine monosulfate 10 mg per 1 ml

10mg/1ml solution for injection ampoules | 5 ampoule £224.15

**ENDOTHELIN RECEPTOR ANTAGONISTS**

**Ambrisentan**

**INDICATIONS AND DOSE**

Pulmonary arterial hypertension

**BY MOUTH**

- Adult: 5 mg once daily, increased if necessary to 10 mg once daily

Dose adjustments due to interactions

Max. 5 mg daily with concomitant ciclosporin.

**CONTRA-INDICATIONS** Idiopathic pulmonary fibrosis

**CAUTIONS** Not to be initiated in significant anaemia

**INTERACTIONS** Appendix 1 (ambrisentan).

**SIDE-EFFECTS**

- Common or very common Abdominal pain, anaemia, chest pain, constipation, diarrhoea, dizziness, dyspnoea, epistaxis, flushing, headache, heart failure, hypotension, malaise, nausea, palpitation, peripheral oedema, upper respiratory tract disorders, vomiting

- Uncommon Autoimmune hepatitis, hepatic injury, syncope

**CONCEPTION AND CONTRACEPTION** Exclude pregnancy before treatment and ensure effective contraception during treatment. Monthly pregnancy tests advised.

**PREGNANCY** Avoid (teratogenic in animal studies).

**BREAST FEEDING** Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT** Avoid in severe impairment.

**RENAI IMPAIRMENT** Use with caution if eGFR less than 30 mL/minute/1.73 m².

**MONITORING REQUIREMENTS**

- Monitor haemoglobin concentration or haematocrit observed). Treatment if significant decrease in haemoglobin concentration or haematocrit observed.

- Discontinue if liver enzymes raised

- Monthly pregnancy tests advised.

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium (SMC) Decisions has advised (October 2008) that ambrisentan (Vlibris®) should be prescribed only by specialists in the Scottish Pulmonary Vascular Unit or other similar specialists.
**Bosentan**

**INDICATIONS AND DOSE**

**Pulmonary arterial hypertension**

BY MOUTH

- Adult: Initially 62.5 mg twice daily for 4 weeks, then increased to 125 mg twice daily (max. per dose 250 mg); maximum 500 mg per day

Systemic sclerosis with ongoing digital ulcer disease (to reduce number of new digital ulcers)

BY MOUTH

- Adult: Initially 62.5 mg twice daily for 4 weeks, then increased to 125 mg twice daily

**SIDE-EFFECTS**

- Common or very common Anaemia, diarrhoea, flushing, gastro-oesophageal reflux, headache, hypotension, oedema, palpititation, syncope

- Uncommon Leucopenia, neutropenia, thrombocytopenia

- Rare Liver cirrhosis, liver failure

**CONCEPTION AND CONTRACEPTION** Effective contraception required during administration (hormonal contraception not considered effective). Monthly pregnancy tests advised.

**PREGNANCY** Avoid (teratogenic in animal studies).

**BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT** Avoid if serum transaminases exceed 3 times upper limit of normal. Avoid in moderate and severe impairment.

**RENAL IMPAIRMENT** Manufacturer advises caution in severe impairment and avoid in patients undergoing dialysis (no information available). In renal impairment consider monitoring blood pressure (risk of hypotension).

**CONTRA-INDICATIONS** Acute porphyrias p. 864

**CAUTIONS** Not to be initiated if systemic systolic blood pressure is below 85 mmHg

**INTERACTIONS** → Appendix 1 (bosentan).

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Volibris (GlaxoSmithKline UK Ltd)
  - Bosentan 5 mg Volibris 5mg tablets | 30 tablet [POM] £1,618.08
  - Bosentan 10 mg Volibris 10mg tablets | 30 tablet [POM] £1,618.08

**Macitentan**

**INDICATIONS AND DOSE**

**Pulmonary arterial hypertension**

BY MOUTH

- Adult: 10 mg daily

**CONTRA-INDICATIONS** Severe anaemia

**CAUTIONS** Patients over 75 years - pulmonary veno-occlusive disease

**INTERACTIONS** → Appendix 1 (macitentan).

**SIDE-EFFECTS**

- Common or very common Anaemia, bronchitis, headache, hypotension, upper respiratory-tract disorders - urinary-tract infection

- Frequency not known Leucopenia, thrombocytopenia

**CONCEPTION AND CONTRACEPTION** Manufacturer advises exclude pregnancy before treatment and ensure effective contraception during and for one month after stopping treatment. Monthly pregnancy tests advised.

**PREGNANCY** Toxicity in animal studies.

**BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT** Do not initiate if serum transaminases or signs of hepatic injury—can restart on advice on hepatologist if liver function tests return to normal and no hepatic injury.

**RENAL IMPAIRMENT** Toxin studies.

**CONTRA-INDICATIONS** Severe anaemia

**CAUTIONS** Patients over 75 years - pulmonary veno-occlusive disease

**INTERACTIONS** → Appendix 1 (macitentan).

**SIDE-EFFECTS**

- Common or very common Anaemia, bronchitis, headache, hypotension, upper respiratory-tract disorders - urinary-tract infection

- Frequency not known Leucopenia, thrombocytopenia

**CONCEPTION AND CONTRACEPTION** Manufacturer advises exclude pregnancy before treatment and ensure effective contraception during and for one month after stopping treatment. Monthly pregnancy tests advised.

**PREGNANCY** Toxicity in animal studies.

**BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT** Do not initiate if serum transaminases exceed 3 times upper limit of normal. Avoid in moderate and severe impairment.

**RENAL IMPAIRMENT** Manufacturer advises caution in severe impairment and avoid in patients undergoing dialysis (no information available). In renal impairment consider monitoring blood pressure (risk of hypotension).

**CONTRA-INDICATIONS** Acute porphyrias p. 864

**CAUTIONS** Not to be initiated if systemic systolic blood pressure is below 85 mmHg

**INTERACTIONS** → Appendix 1 (bosentan).

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Tracleer (Actelion Pharmaceuticals UK Ltd)
  - Bosentan (as Bosentan monohydrate) 62.5 mg Tracleer 62.5mg tablets | 56 tablet [POM] £1,510.21
  - Bosentan (as Bosentan monohydrate) 125 mg Tracleer 125mg tablets | 56 tablet [POM] £1,510.21

**Riociguat**

**INDICATIONS AND DOSE**

Chronic thromboembolic pulmonary hypertension that is recurrent or persistent following surgery, or is inoperable (initiated under specialist supervision) | Monotherapy or in combination with an endothelin receptor antagonist for idiopathic or hereditary pulmonary arterial hypertension, or pulmonary arterial hypertension associated with connective tissue disease (initiated under specialist supervision)

**BY MOUTH**

- Adult: Initially 1 mg 3 times a day for 2 weeks, increased in steps of 0.5 mg 3 times a day, dose to be increased every 2 weeks, increased up to 2.5 mg 3 times a day, increase up to maximum dose continued
only if systolic blood pressure > 95 mmHg and no signs of hypotension, if treatment interrupted for 3 or more days, restart at 1 mg three times daily for 2 weeks and titrate as before, during titration, reduce dose by 0.5 mg three times daily if systolic blood pressure falls below 95 mmHg and patient shows signs of hypotension

- **CONTRA-INDICATIONS** History of serious haemoptysis - previous bronchial artery embolisation - pulmonary veno-occlusive disease
- **CAUTIONS** Autonomic dysfunciton - elderly (risk of hypotension) - hypotension (do not initiate if systolic blood pressure below 95 mmHg) - hypovolaemia - severe left ventricular outflow obstruction

**SIDE-EFFECTS**
- **Common or very common** Anaemia - constipation - diarrhoea - dizziness - dyspepsia - dysphagia - epistaxis - gastritis - gastro-oesophageal reflux - haemoptysis - headache - hypotension - nasal congestion - nausea - palpatation - peripheral oedema - vomiting
- **Uncommon** Pulmonary haemorrhage

**CONCEPTION AND CONTRACEPTION** Effective contraception required during treatment. Monthly pregnancy tests advised.

**PREGNANCY** Avoid — toxicity in animal studies.

**BREAST FEEDING** Manufacturer advises avoid — present in milk in animal studies.

**HEPATIC IMPAIRMENT** Titrate dose cautiously in moderate impairment. Manufacturer advises avoid in severe impairment — no information available.

**RENAL IMPAIRMENT** Titrate dose cautiously — risk of hypotension. Manufacturer advises avoid if eGFR less than 30 mL/minute/1.73 m² — limited information available.

**PATIENT AND CARER ADVICE** Smoking cessation advised (response possibly reduced). Patients should inform prescriber if smoking started or stopped during treatment; dose adjustment may be necessary.

**NATIONAL FUNDING/ACCESS DECISIONS**

### Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (November 2014) that riociguat (Adempas®) is accepted for restricted use within NHS Scotland for the treatment of chronic thromboembolic pulmonary hypertension in patients for whom a phosphodiesterase type-5 inhibitor is inappropriate, not tolerated, or ineffective, and should only be prescribed by specialists in the Scottish Pulmonary Vascular Unit.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Tablet**
  - **Adempas** (Bayer Plc)
    - Riociguat 500 microgram 42 tablet [£997.36] | 84 tablet [£1,994.72]
    - Riociguat 1 mg 42 tablet [£997.36] | 84 tablet [£1,994.72]
    - Riociguat 1.5 mg 42 tablet [£997.36] | 84 tablet [£1,994.72]
    - Riociguat 2 mg 42 tablet [£997.36] | 84 tablet [£1,994.72]

**PROSTAGLANDINS (CARDIOVASCULAR)**

### Iloprost

**INDICATIONS AND DOSE**

Idiopathic or familial pulmonary arterial hypertension (initiated under specialist supervision)

- **Adult**
  - Initially 2.5 micrograms for 1 dose, increased to 5 micrograms for 1 dose, if tolerated maintain at 5 micrograms 6–9 times a day, according to response; reduced if higher dose not tolerated to 2.5 micrograms 6–9 times a day

- **CONTRA-INDICATIONS** Conditions which increase risk of haemorrhage - congenital or acquired valvular defects of the myocardium - decompensated cardiac failure (unless under close medical supervision) - pulmonary veno-occlusive disease - severe arrhythmias - unstable angina - within 3 months of cerebrovascular events - within 6 months of myocardial infarction

- **CAUTIONS**
  - **GENERAL CAUTIONS**
    - Hypotension (do not initiate if systolic blood pressure below 85 mmHg) - unstable pulmonary hypertension with advanced right heart failure - acute pulmonary infection - chronic obstructive pulmonary disease - severe asthma
  - **INTERACTIONS** to Appendix 1 (Iloprost).
  - **SIDE-EFFECTS**
    - **Common or very common** Chest pain - cough - diarrhoea - dyspnoea - haemorrhage - headache - hypotension - jaw pain - nausea - oral irritation - rash - throat pain - vomiting
    - **Frequency not known** Bronchospasm - taste disturbance - thrombocytopenia - wheezing
  - **PREGNANCY** Use if potential benefit outweighs risk.
  - **BREAST FEEDING** Manufacturer advises avoid — no information available.
  - **HEPATIC IMPAIRMENT** Elimination reduced. Initially 2.5 micrograms at intervals of 3–4 hours (max. 6 times daily), adjusted according to response (consult product literature).
  - **DIRECTIONS FOR ADMINISTRATION** To minimise accidental exposure use only with nebulisers listed in Ventavis® product literature in a well ventilated room.
  - **PRESCRIBING AND DISPENSING INFORMATION** Delivery characteristics of nebuliser devices may vary — only switch devices under medical supervision.
  - **NATIONAL FUNDING/ACCESS DECISIONS**
    - **Scottish Medicines Consortium (SMC) Decisions**
      - The Scottish Medicines Consortium has advised (November 2005) that ioprost (Ventavis®) is accepted for restricted use within NHS Scotland in patients in whom bosentan is ineffective or not tolerated, and should only be prescribed by specialists in the Scottish Pulmonary Vascular Unit.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Nebuliser liquid**
  - **Ventavis** (Bayer Plc)
    - Iloprost (as ioprost trometamol) 10 microgram per 1 ml Ventavis 10 micrograms/ml nebuliser solution 1ml ampoules | 30 ampoule [£1,400.19] | 168 ampoule [£2,241.08]
4.5 Hypotension and shock

**Sympathomimetics**

**Inotropic sympathomimetics**

**Shock**

Shock is a medical emergency associated with a high mortality. The underlying causes of shock such as haemorrhage, sepsis, or myocardial insufficiency should be corrected. The profound hypotension of shock must be treated promptly to prevent tissue hypoxia and organ failure. Volume replacement is essential to correct the hypovolaemia associated with haemorrhage and sepsis but may be detrimental in cardiogenic shock. Depending on haemodynamic status, cardiac output may be improved by the use of sympathomimetic inotropes such as adrenaline/epinephrine, dobutamine, or dopamine hydrochloride below. In septic shock, when fluid replacement and inotropic support fail to maintain blood pressure, the vasoconstrictor noradrenaline/norepinephrine may be considered. In cardiogenic shock peripheral resistance is frequently high and to raise it further may worsen myocardial performance and exacerbate tissue ischaemia.

The use of sympathomimetic inotropes and vasoconstrictors should preferably be confined to the intensive care setting and undertaken with invasive haemodynamic monitoring.

See also advice on the management of anaphylactic shock on p. 242.

**Vasoconstrictor sympathomimetics**

Vasoconstrictor sympathomimetics raise blood pressure transiently by acting on alpha-adrenergic receptors to constrict peripheral vessels. They are sometimes used as an emergency method of elevating blood pressure where other measures have failed. The danger of vasoconstrictors is that although they raise blood pressure they also reduce perfusion of vital organs such as the kidney.

Spinal and epidural anaesthesia may result in sympathetic block with resultant hypotension. Management may include intravenous fluids (which are usually given prophylactically), oxygen, elevation of the legs, and injection of a pressor drug such as ephedrine hydrochloride p. 237. As well as constricting peripheral vessels ephedrine hydrochloride p. 237 also accelerates the heart rate (by acting on beta receptors). Use is made of this dual action of ephedrine hydrochloride p. 237 to manage associated bradycardia (although intravenous injection of atropine sulfate p. 949 may also be required if bradycardia persists).

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**Drugs used for Hypotension and shock not listed below; Dopamine hydrochloride 800 mg/5 ml concentrate for solution for infusion ampoule £19.42–£20.00 Dopamine hydrochloride 160 mg per 1 ml solution for infusion ampoule £4.2–£4.49**

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**Sympathomimetics (Inotropic)**

**Dopamine hydrochloride**

**Drug Action**

Dopamine is a cardiac stimulant which acts on beta, receptors in cardiac muscle, and increases contractility with little effect on rate.

**Indications and Dose**

Cardiogenic shock in infarction or cardiac surgery

BY INTRAVENOUS INFUSION

- Adult: Initially 2–5 micrograms/kg/minute

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**Contra-Indications**

Phaeochromocytoma, tachyarrhythmia

**Caution**

Correct hypovolaemia, hyperthyroidism, low dose in shock due to acute myocardial infarction

**Interactions**

Appendix 1 (sympathomimetics)

**Side-effects**

- Common or very common Chest pain, dyspnoea, headache, hypotension, nausea, palpitation, tachycardia, vasoconstriction, vomiting

- Uncommon Bradycardia, gangrene, hypertension, mydriasis

- Rare Fatal ventricular arrhythmias

**Pregnancy**

No evidence of harm in animal studies—manufacturer advises use only if potential benefit outweighs risk.

**Breastfeeding**

May suppress lactation—not known to be harmful.

**Directions for Administration**

For intravenous infusion give continuously in Glucose 5% or Sodium chloride 0.9%. Dilute to max. concentration of 3.2 mg/mL; incompatible with bicarbonate. Dopamine concentrate for intravenous infusion to be diluted before use.

**Medicinal Forms**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for infusion

**Solution for Infusion**

- Dopamine hydrochloride (Non-proprietary)
  - Dopamine hydrochloride 40 mg per 1 ml
  - Dopamine 200 mg/5 ml solution for infusion ampoules
    - 5 ampoules [BNF] £19.42–£20.00
  - Dopamine hydrochloride 160 mg per 1 ml
    - 5 ampoules [BNF] £4.2–£4.49

**Sympathomimetics (Vasoconstrictor)**

**Metaraminol**

**Indications and Dose**

Acute hypotension

BY INTRAVENOUS INFUSION

- Adult: 15–100 mg, adjusted according to response

Emergency treatment of acute hypotension

INITIALLY BY INTRAVENOUS INJECTION

- Adult: Initially 0.5–5 mg, then (by intravenous infusion) 15–100 mg, adjusted according to response

Priapism (alternative to intracavernosal injections of phenylephrine and adrenaline)

BY INTRACAVERNOSAL INJECTION

- Adult: 1 mg every 15 minutes

**Unlicensed Use**

Use for priapism is an unlicensed indication.

**Contra-Indications**

Hypertension

**Caution**

General Caution: Cirsosis, coronary vascular thrombosis, diabetes mellitus, elderly, extravasation at injection site may cause necrosis, following myocardial infarction, hypercapnia, hyperthyroidism, hypoxia, mesenteric vascular thrombosis, peripheral vascular thrombosis, Prinzmetal’s variant angina, uncorrected hypovolaemia

**Specific Caution:**

- With intracavernosal use Associated with fatal hypertensive crises

**Caution, Further Information**

Hypertensive response Metaraminol has a longer duration of action than noradrenaline, and an excessive
vasoressor response may cause a prolonged rise in blood pressure.

- **INTERACTIONS** → Appendix 1 (sympathomimetics).
- **SIDE-EFFECTS** Angle-closure glaucoma, anorexia, anxiety, arrhythmias, bradycardia, confusion, dyspnoea, fatal ventricular arrhythmia reported in Lennec’s cirrhosis, headache, hypertension, hypoxia, insomnia, nausea, palpitation, peripheral ischaemia, psychosis, tachycardia, tremor, urinary retention, vomiting, weakness
- **PREGNANCY** May reduce placental perfusion—manufacturer advises use only if potential benefit outweighs risk.
- **BREAST FEEDING** Manufacturer advises caution—no information available.
- **MONITORING REQUIREMENTS** Monitor blood pressure and rate of flow frequently.
- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Aramine®), give continuously or via drip tubing in Glucose 5% or Sodium chloride 0.9%. Suggested volume 500 mL.

For intracavernosal injection, dilute 1 mg (0.1 mL of 10 mg/mL metaraminol injection to 5 mL with Sodium chloride injection 0.9% and give carefully by slow injection into the corpora in 5–10 mL injections.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion, solution for infusion

**Solution for infusion**

- **NORADRENALINE/NOREPINEPHRINE (Non-proprietary)**
  - Noradrenaline (as Noradrenaline acid tartrate) 1 mg per 1 ml Noradrenaline (base) 4mg/4ml concentrate for solution for infusion ampoules | 10 ampoule (£8) no price available
  - Noradrenaline (base) 4mg/4ml solution for infusion ampoules | 5 ampoule (£22) (Hospital only)
  - Noradrenaline (base) 2mg/2ml solution for infusion ampoules | 5 ampoule (£22) (Hospital only)
  - Noradrenaline (base) 8mg/8ml concentrate for solution for infusion ampoules | 10 ampoule (£8) no price available

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**Phenylephrine hydrochloride**

**INDICATIONS AND DOSE**

**Acute hypotension**

- **BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION**
  - Adult: Initially 2–5 mg, followed by further doses of 1–10 mg, after at least 15 minutes if required.

- **BY INTRAVENOUS INFUSION**
  - Adult: 100–500 micrograms, repeated as necessary after at least 15 minutes; a 1 mg/1 mL solution to be used

- **BY INTRAVENOUS INFUSION**
  - Adult: Initially up to 180 micrograms/minute, reduced to 30–60 micrograms/minute, adjusted according to response

**Priapism**

- **BY INTRACAVERNOSAL INJECTION**
  - Adult: 100–200 micrograms every 5–10 minutes; maximum 1 mg per course

**UNLICENSED USE** Use of phenylephrine hydrochloride injection in priapism is an unlicensed indication.

**CONTRA-INDICATIONS** Hypertension, severe hyperthyroidism

**CAUTIONS** Coronary disease, severe hypertension, severe peripheral ischaemia, peripheral vascular thrombosis, Prinzmetal’s variant angina, uncorrected hypovolaemia

**INTERACTIONS** → Appendix 1 (sympathomimetics).

**SIDE-EFFECTS** Angle-closure glaucoma, anorexia, anxiety, arrhythmias, bradycardia, confusion, dyspnoea, headache, hypertension, hypoxia, insomnia, nausea, palpitation, peripheral ischaemia, psychosis, tachycardia, tremor, urinary retention, vomiting, weakness

**PREGNANCY** Avoid—may reduce placental perfusion.

**MONITORING REQUIREMENTS** Monitor blood pressure and rate of flow frequently.

**DIRECTIONS FOR ADMINISTRATION** For treatment of acute hypotension in adults, use a solution containing noradrenaline 40 micrograms (base)/mL. For intravenous infusion, give continuously in Glucose 5% or Sodium Chloride and glucose via a controlled infusion device. For administration via syringe pump, dilute 2 mg (2 mL of solution) noradrenaline base with 48 mL infusion fluid. For administration via drip counter dilute 20 mg (20 mL of solution) noradrenaline base with 480 mL infusion fluid; give through a central venous catheter; incompatible with alkalis.

**PRESCRIBING AND DISPENSING INFORMATION** For a period of time, preparations on the UK market may be described as either noradrenaline base or noradrenaline acid tartrate; doses in the BNF are expressed as the base.

**MONITORING REQUIREMENTS**
5 Heart failure

Heart failure

Drug treatment of heart failure associated with a reduced left ventricular ejection fraction (left ventricular systolic dysfunction) is covered below; optimal management of heart failure with a preserved left ventricular ejection fraction has not been established.

The treatment of chronic heart failure aims to relieve symptoms, improve exercise tolerance, reduce the incidence of acute exacerbations, and reduce mortality. An ACE inhibitor, titrated to a ‘target dose’ (or the maximum tolerated dose if lower), together with a beta-blocker, form the basis of treatment for all patients with heart failure due to left ventricular systolic dysfunction.

An ACE inhibitor is generally advised for patients with asymptomatic left ventricular systolic dysfunction or symptomatic heart failure. An angiotensin-II receptor antagonist may be a useful alternative for patients who, because of side-effects such as cough, cannot tolerate ACE inhibitors; a relatively high dose of the angiotensin-II receptor antagonist may be required to produce benefit. Candesartan cilexetil p. 133 or valsartan p. 136 may be given under specialist supervision as adjuncts to an ACE inhibitor in the treatment of heart failure when other treatments are unsuitable; the concomitant use of this combination, together with an aldosterone antagonist or a potassium-sparing diuretic is not recommended.

The beta-blockers bisoprolol fumarate p. 142 and carvedilol p. 142 are of value in any grade of stable heart failure due to left ventricular systolic dysfunction; nebivolol p. 145 is licensed for stable mild to moderate heart failure in patients over 70 years. Beta-blocker treatment should be started by those experienced in the management of heart failure, at a very low dose and titrated very slowly over a period of weeks or months. Symptoms may deteriorate initially, calling for adjustment of concomitant therapy.

The aldosterone antagonist spironolactone p. 168 can be added to an ACE inhibitor and a beta-blocker in patients who continue to remain symptomatic (particularly in those with moderate to severe heart failure); low doses of spironolactone reduce symptoms and mortality in these patients. If spironolactone cannot be used, eplerenone below may be considered for the management of heart failure after an acute myocardial infarction with evidence of left ventricular systolic dysfunction, or for chronic mild heart failure with left ventricular systolic dysfunction. Close monitoring of serum creatinine, eGFR, and potassium is necessary, particularly following any change in treatment or any change in the patient’s clinical condition.

Patients who cannot tolerate an ACE inhibitor or an angiotensin-II receptor antagonist, or in whom they are contra-indicated, may be given isosorbide dinitrate p. 191 with hydralazine hydrochloride p. 157 but this combination may be poorly tolerated. The combination of isosorbide dinitrate p. 191 and hydralazine hydrochloride p. 157 may be considered in addition to standard therapy with an ACE inhibitor and a beta-blocker in patients who continue to remain symptomatic (particularly in patients of African or Caribbean origin who have moderate to severe heart failure).

Digoxin p. 94 improves symptoms of heart failure and exercise tolerance and reduces hospitalisation due to acute exacerbations but it does not reduce mortality. Digoxin is reserved for patients with worsening or severe heart failure due to left ventricular systolic dysfunction who remain symptomatic despite treatment with an ACE inhibitor and a beta-blocker in combination with either an aldosterone antagonist, candesartan cilexetil, or isosorbide dinitrate with hydralazine hydrochloride.

Patients with fluid overload should also receive either a loop or a thiazide diuretic (with salt or fluid restriction where appropriate). A thiazide diuretic may be of benefit in patients with mild heart failure and good renal function; however, thiazide diuretics are ineffective in patients with poor renal function (eGFR less than 30 mL/minute/1.73 m²) and a loop diuretic is preferred. If diuresis with a single diuretic is insufficient, a combination of a loop diuretic and a thiazide diuretic may be tried; addition of metolazone p. 205 may also be considered but the resulting diuresis may be profound and care is needed to avoid potentially dangerous electrolyte disturbances.

Drugs used for Heart failure not listed below; Bendroflumethiazide, p. 159 · Bisoprolol fumarate, p. 142 · Candesartan cilexetil, p. 133 · Captopril, p. 126 · Chlortalidone, p. 204 · Co-amoxiclav, p. 150 · Cyclopenthiazide, p. 204 · Digoxin, p. 94 · Enalapril maleate, p. 127 · Glyceryl trinitrate, p. 190 · Hydralazine hydrochloride, p. 157 · Isosorbide dinitrate, p. 191 · Isosorbide mononitrate, p. 192 · Ibubradine, p. 185 · Lisinopril, p. 128 · Losartan potassium, p. 134 · Metoprolol tartrate, p. 144 · Nebivolol, p. 145 · Perindopril arginine, p. 129 · Perindopril erbumine, p. 130 · Prazosin, p. 674 · Quinapril, p. 130 · Ramipril, p. 131 · Sodium nitroprusside, p. 161 · Valsartan, p. 136

ALDOSTERONE ANTAGONISTS

Eplerenone

INDICATIONS AND DOSE

Adjunct in stable patients with left ventricular ejection fraction <40% with evidence of heart failure, following myocardial infarction (start therapy within 3–14 days of event) | Adjunct in chronic mild heart failure with left ventricular ejection fraction ≤30%

BY MOUTH

- Adult: Initially 25 mg daily, then increased to 50 mg daily, increased within 4 weeks of initial treatment

CONTRA-INDICATIONS

Hyperkalaemia

CAUTIONS

Elderly

INTERACTIONS

→ Appendix 1 (diuretics).

Concomitant use of potassium-sparing diuretics or potassium supplements is contra-indicated.

SIDE-EFFECTS

- Common or very common Azotaemia · constipation · cough · diarrhoea · dizziness · hyperkalaemia · hypotension

Cardiovascular system
Spironolactone

INDICATIONS AND DOSE

Oedema / Ascites in cirrhosis of the liver
BY MOUTH
Adult: 100–400 mg daily, adjusted according to response

Malignant ascites
BY MOUTH
Adult: Initially 100–200 mg daily, then increased if necessary to 400 mg daily, maintenance dose adjusted according to response

Nephrotic syndrome
BY MOUTH
Adult: 100–200 mg daily

Oedema in congestive heart failure
BY MOUTH
Adult: Initially 100 mg daily, alternatively initially 25–200 mg daily, dose may be taken as a single dose or divided doses, maintenance dose adjusted according to response

Moderate to severe heart failure (adjunct)
BY MOUTH
Adult: Initially 25 mg once daily, then adjusted according to response to 50 mg once daily

Resistant hypertension (adjunct)
BY MOUTH
Adult: 25 mg once daily

Primary hyperaldosteronism in patients awaiting surgery
BY MOUTH
Adult: 100–400 mg daily, may be used for long-term maintenance if surgery inappropriate, use lowest effective dose

- UNLICENSED USE Resistant hypertension (adjunct) unlicensed indication.
- CONTRA-INDICATIONS Addison’s disease - anuria - hyperkalaemia
- CAUTIONS Acute porphyrias p. 864 - elderly - potential metabolic products carcinogenic in rodents
- INTERACTIONS → Appendix 1 (diuretics).
  Potassium supplements must not be given with potassium-sparing diuretics. Administration of a potassium-sparing diuretic to a patient receiving an ACE inhibitor or an angiotensin-II receptor antagonist can also cause severe hyperkalaemia.

PREGNANCY
Use only if potential benefit outweighs risk—feminisation of male fetus in animal studies.

BREAST FEEDING
Metabolites present in milk, but amount probably too small to be harmful.

RENAL IMPAIRMENT
Avoid in acute renal insufficiency or severe impairment. Monitor plasma-potassium concentration (high risk of hyperkalaemia in renal impairment).

MONITORING REQUIREMENTS
Monitor electrolytes—discontinue if hyperkalaemia occurs (in severe heart failure monitor potassium and creatinine 1 week after initiation and after any dose increase, monthly for first 3 months, then every 3 months for 1 year, and then every 6 months).

MALIGNANCY
Avoid in patients with bone marrow depression.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
- EPLERENONE (Non-proprietary)
  Eplerenone 25 mg Eplerenone 25mg tablets | 28 tablet [POM] £35.45-£42.72 DT price = £39.04
  Eplerenone 50 mg Eplerenone 50mg tablets | 28 tablet [POM] £35.45-£42.72 DT price = £38.95
  → Inspira (Pfizer Ltd)
  Eplerenone 25 mg Inspira 25mg tablets | 28 tablet [POM] £42.72 DT price = £39.04
  Eplerenone 50 mg Inspira 50mg tablets | 28 tablet [POM] £42.72 DT price = £38.95

Co-flumactone

The properties listed below are those particular to the combination only. For the properties of the components please consider, spironolactone above and Thiazides, p. 159.
**INDICATIONS AND DOSE**

**Congestive heart failure**

**BY MOUTH**

- Adult: Initially 100/100 mg daily; maintenance 25/25–200/200 mg daily, maintenance dose not recommended because spironolactone generally given in lower dose

**LESS SUITABLE FOR PRESCRIBING** Co-flumactone tablets are less suitable for prescribing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Aldactide (Pfizer Ltd)
  - Hydroflumethiazide 25 mg, Spironolactone 25 mg Aldactide 25 tablets | 100 tablet (Primacor®) £20.23 DT price = £20.23
  - Hydroflumethiazide 50 mg, Spironolactone 50 mg Aldactide 50 tablets | 28 tablet (Primacor®) £10.70 | 100 tablet (Primacor®) £38.23 DT price = £38.23

**PHOSPHODIESTERASE TYPE-3 INHIBITORS**

**Enoximone**

**DRUG ACTION** Enoximone is a phosphodiesterase type-3 inhibitor that exerts most effect on the myocardium; it has positive inotropic properties and vasodilator activity.

**INDICATIONS AND DOSE**

Congestive heart failure where cardiac output reduced and filling pressures increased

**BY SLOW INTRAVENOUS INJECTION (RATE NOT EXCEEDING 12.5 MG/MINUTE)**

- Adult: Initially 0.5–1 mg/kg, then 500 micrograms/kg every 30 minutes until a satisfactory response is achieved or a total dose of 3 mg/kg is reached; maintenance, initial dose of up to 3 mg/kg every 3–6 hours as required

**BY INTRAVENOUS INFUSION**

- Adult: Initially 90 micrograms/kg/minute, dose to be given over 10–30 minutes, followed by 5–20 micrograms/kg/minute, dose to be given as either a continuous or intermittent infusion; maximum 24 mg/kg per day

**CAUTIONS** Heart failure associated with hypertrophic cardiomyopathy, stenotic or obstructive valvar disease or other outlet obstruction

**INTERACTIONS** → Appendix 1 (phosphodiesterase type-3 inhibitors).

**SIDE-EFFECTS**

- Chills
- Diarrhoea
- Ectopic beats
- Fever
- Headache
- Hypotension
- Insomnia
- Nausea
- Oliguria
- Supraventricular arrhythmias (more likely in patients with pre-existing arrhythmias)
- Upper and lower limb pain
- Urinary retention
- Ventricular tachycardia (more likely in patients with pre-existing arrhythmias)
- Vomiting

**PREGNANCY**

Manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING**

Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT**

Dose reduction may be required.

**RENAL IMPAIRMENT**

Consider dose reduction.

**MONITORING REQUIREMENTS**

Monitor blood pressure, heart rate, ECG, central venous pressure, fluid and electrolyte status, renal function, platelet count and hepatic enzymes.

**DIRECTIONS FOR ADMINISTRATION**

Incompatible with glucose solutions. Use only plastic containers or syringes; crystal formation if glass used. Avoid extravasation.

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For intravenous infusion (Primacor®), give continuously or intermittently in Sodium chloride 0.9% or Water for injections; dilute to a concentration of 2.5 mg/mL.

**PRESCRIBING AND DISPENSING INFORMATION**

Sustained haemodynamic benefit has been observed after administration of phosphodiesterase type-3 inhibitors, but there is no evidence of any beneficial effect on survival.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

**EXCIPIENTS:** May contain Alcohol, propylene glycol

- **Perfan** (Myogen GmbH)
  - Enoximone 5 mg per 1 ml Perfan 100mg/20ml solution for injection ampoules | 10 ampoule (Primacor®) no price available (Hospital only)

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**Milrinone**

**DRUG ACTION** Milrinone is a phosphodiesterase type-3 inhibitor that exerts most effect on the myocardium; it has positive inotropic properties and vasodilator activity.

**INDICATIONS AND DOSE**

Short-term treatment of severe congestive heart failure unresponsive to conventional maintenance therapy (not immediately after myocardial infarction) / Acute heart failure, including low output states following heart surgery

**INITIALLY BY INTRAVENOUS INJECTION**

- Adult: Initially 50 micrograms/kg, given over 10 minutes, followed by (by intravenous infusion) 375–750 nanograms/kg/minute usually given following surgery for up to 12 hours or in congestive heart failure for 48–72 hours; maximum 1.13 mg/kg per day

**CONTRA-INDICATIONS**

Severe hypovolaemia

**CAUTIONS**

Correct hypokalaemia - heart failure associated with hypertrophic cardiomyopathy, stenotic or obstructive valvar disease or other outlet obstruction

**INTERACTIONS** → Appendix 1 (phosphodiesterase type-3 inhibitors).

**SIDE-EFFECTS**

- Common or very common
  - Ectopic beats
  - Headache
  - Hypotension
  - Supraventricular arrhythmias (more likely in patients with pre-existing arrhythmias)
  - Upper and lower limb pain
  - Urinary retention
  - Ventricular tachycardia (more likely in patients with pre-existing arrhythmias)
  - Vomiting

**PREGNANCY**

Manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING**

Manufacturer advises avoid—no information available.

**RENSAL IMPAIRMENT**

Reduce dose and monitor response if eGFR less than 50 mL/minute/1.73 m²—consult product literature for details.

**MONITORING REQUIREMENTS**

Monitor blood pressure, heart rate, ECG, central venous pressure, fluid and electrolyte status, renal function, platelet count and hepatic enzymes.

**DIRECTIONS FOR ADMINISTRATION**

Avoid extravasation. For intravenous injection, may be given either undiluted or diluted before use. For intravenous infusion (Primacor®) give continuously in Glucose 5% or Sodium chloride 0.9%; dilute to a suggested concentration of 200 micrograms/mL.
### Hyperlipidaemia

**Lipid-regulating drugs**

**Primary and secondary prevention of cardiovascular disease**

Preventative measures should be taken in individuals with a high risk of developing cardiovascular disease (primary prevention) and to prevent recurrence of events in those with established cardiovascular disease (secondary prevention).

**Primary prevention**

Individuals at high risk of developing cardiovascular disease include those who have diabetes mellitus, chronic kidney disease (eGFR < 60 mL/minute/1.73 m²) and/or albuminuria, and those with familial hypercholesterolaemia. The risk also increases with age; those aged 85 years and over are at particularly high risk, especially if they smoke or have hypertension. Preventative measures are also required for other individuals who are considered to be at high risk of developing atherosclerotic cardiovascular disease based on risk estimated using risk calculators (see Risk calculators); those with a 10-year risk of cardiovascular disease of 10% or more stand to benefit most from drug treatment. Patients with a 10-year cardiovascular risk of less than 10% may benefit from an assessment of their lifetime risk (using the JBS3 tool—see Risk calculators for more detail), discussion on the impact of lifestyle interventions and, if necessary, drug therapy.

**Risk calculators**

Risk assessment calculators are recommended by both NICE (clinical guideline 181 (July 2014). Lipid Modification—Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease) and JBS3 (Joint British Societies’ consensus recommendations for the prevention of cardiovascular disease 2014). They should not be used in patients at high cardiovascular risk. Both calculators are unsuitable for assessing risk in those aged 85 years and over, and NICE advises against using a risk assessment tool in those with type 1 diabetes mellitus.

The QRISK² risk calculator [www.qrisk.org/](http://www.qrisk.org/) is recommended by NICE clinical guideline 181, and the JBS3 risk calculator [www.jbs3risk.com/pages/risk_calculator.htm](http://www.jbs3risk.com/pages/risk_calculator.htm) is endorsed by JBS3. Both tools assess cardiovascular risk—coronary heart disease (angina and myocardial infarction), stroke, and transient ischaemic attack, on the basis of lipid profile, systolic blood pressure, gender, age, ethnicity, smoking status, BMI, chronic kidney disease, diabetes mellitus, atrial fibrillation, treated hypertension, rheumatoid arthritis, or a family history of premature cardiovascular disease. Risk assessment tools underestimate risk in patients with additional risk due to existing conditions or medication, such as:

- serious mental disorder
- autoimmune disorders such as systemic lupus erythematosus and other systemic inflammatory disorders
- antiretroviral treatment
- medication causing dyslipidaemia as a side-effect e.g. antipsychotics, corticosteroids, or immunosuppressants
- triglyceride concentration > 4.5 mmol/litre

Cardiovascular disease risk is also underestimated in those who are already taking antihypertensive or lipid-regulating drugs, and in those who have recently stopped smoking. Severe obesity (BMI > 40 kg/m²) also increases cardiovascular risk; the need for further treatment of risk...
factors in patients below the cardiovascular risk threshold for treatment should be based on clinical judgement.

**Preventative measures for primary prevention**

All patients at high risk of cardiovascular disease should be advised to make lifestyle modifications that include beneficial changes to diet, exercise, weight management, alcohol consumption, and smoking cessation. Offer a statin as first-line drug treatment if lifestyle modifications are inappropriate or ineffective (see also Statins for the prevention of cardiovascular disease). Lipid-regulating drug treatment must be combined with advice on diet and lifestyle measures, and where appropriate, treatment of comorbidities and secondary causes of dyslipidaemia.

**Secondary prevention**

Statins should be offered to all patients, including the elderly, with cardiovascular disease such as those with coronary heart disease (including history of angina or acute myocardial infarction), occlusive arterial disease (including peripheral vascular disease, non-haemorrhagic stroke, or transient ischaemic attacks).

**Preventative measures for secondary prevention**

Patients should be advised to make lifestyle modifications that include beneficial changes to diet, exercise, weight management, alcohol consumption, and smoking cessation, however, initiation of lipid-regulating drug treatment should not be delayed to manage modifiable risk factors, and must be combined with advice on diet and lifestyle measures, and where appropriate, treatment of comorbidities and secondary causes of dyslipidaemia.

**Statins for the prevention of cardiovascular disease**

A statin reduces the risk of cardiovascular disease events, and is the drug of first choice for primary and secondary prevention of cardiovascular disease. Before starting treatment with statins, secondary causes of dyslipidaemia should be addressed; these include uncontrolled diabetes mellitus, hepatic disease, nephrotic syndrome, and excessive alcohol consumption. Patients with hypothyroidism should receive adequate thyroid replacement therapy (before assessing the requirement for lipid-regulating treatment if for primary prevention) because correcting hypothyroidism itself may resolve the lipid abnormality. Untreated hypothyroidism increases the risk of myositis with lipid-regulating drugs.

For the purpose of reducing cardiovascular risk, NICE Clinical Guideline 181 (NICE clinical guideline 181 (July 2014). Lipid Modification—Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease) defines statins by the percentage reduction in LDL-cholesterol they achieve:

For primary prevention, NICE Clinical Guideline 181 recommends that atorvastatin p. 179 a high-intensity statin (when prescribed at a dose of at least 20 mg/day), should be offered to those with a 10-year risk of cardiovascular disease of 10% or more; patients aged 85 years and over may benefit from atorvastatin to reduce the risk of non-fatal myocardial infarction. For secondary prevention, atorvastatin is also recommended. Patients taking a low- or medium-intensity statin should discuss the benefits and risks of switching to a high intensity statin at their next medication review.

A statin should be considered for all adults with type 1 diabetes mellitus, particularly those aged 40 years and over, or who have had diabetes for more than 10 years, or who have established nephropathy, or other risk factors for cardiovascular disease. JBS3 recommendations (Joint British Societies’ consensus recommendations for the prevention of cardiovascular disease (JBS3) 2014) in diabetes mellitus differ in certain respects from NICE Clinical Guideline 181 (NICE clinical guideline 181 (July 2014). Lipid Modification—Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease)—see JBS3 recommendations for further details. In type 2 diabetes, assess level of risk using the risk calculator and treat for primary prevention if necessary.

Total cholesterol, HDL-cholesterol, and non-HDL cholesterol concentrations should be checked 3 months after starting treatment with a high intensity statin. NICE Clinical Guideline 181 recommends aiming for a reduction in non-HDL cholesterol concentration below 2.5 mmol/litre. If these are not achieved, ensure lifestyle modifications are optimised and consider increasing the dose of the statin if started on less than atorvastatin 80 mg and the patient is judged to be at higher risk because of comorbidities, risk score or, using clinical judgement.

Expert advice should be sought about treatment options for patients at high risk of cardiovascular disease or those with existing cardiovascular disease, who are intolerant of three different statins.

**Fibrates** should not be routinely used for primary or secondary prevention. Nicotinic acid p. 177, bile acid sequestrants, and omega-3 fatty acid compounds are not recommended for primary or secondary prevention.

**Hypercholesterolaemia, hypertriglyceridaemia, and familial hypercholesterolaemia**

A statin is also the drug of first choice for treating hypercholesterolaemia and moderate hypertriglyceridaemia. Severe hyperlipidaemia not adequately controlled with a maximal dose of a statin may require the use of an additional lipid-regulating drug such as ezetimibe p. 173; such treatment should generally be supervised by a specialist.
A number of conditions, some familial, are characterised by very high LDL-cholesterol concentration, high triglyceride concentration, or both. Fenofibrate p. 175 may be added to statin therapy if triglycerides remain high even after the LDL-cholesterol concentration has been reduced adequately; nicotinic acid may also be used to further lower triglyceride or LDL-cholesterol concentration.

Combination of a statin with a fibrate or with nicotinic acid carries an increased risk of side-effects (including rhabdomyolysis) and should be used under specialist supervision; monitoring of liver function and creatine kinase should also be considered. The concomitant administration of gemfibrozil with a statin increases the risk of rhabdomyolysis considerably—this combination should not be used.

A statin is recommended for all patients with familial hypercholesterolaemia. A ‘high-intensity’ statin (as defined in NICE Clinical Guideline 71, August 2008. Identification and management of familial hypercholesterolaemia) e.g. rosuvastatin p. 180 (initiated by a specialist) or atorvastatin should be considered in order to achieve the recommended reduction in LDL-cholesterol concentration of greater than 50% from baseline; a ‘high-intensity’ statin is one that produces a greater LDL-cholesterol reduction than simvastatin 40 mg. Patients with heterozygous familial hypercholesterolaemia who have contra-indications to, or are intolerant of, statins should receive ezetimibe p. 173. The combination of a statin and ezetimibe can be considered if a statin alone fails to provide adequate control (or if intolerance limits dose titration), and when a switch to an alternative statin is being considered. Patients for whom statins and ezetimibe are inappropriate, should be referred to a specialist for the consideration of treatment with a bile acid sequestrant, nicotinic acid, or a fibrate.

The prescribing of drug therapy in homozygous familial hypercholesterolaemia should be undertaken in a specialist centre.

Bile acid sequestrants
Bile acid sequestrants effectively reduce LDL-cholesterol but can aggravate hypertriglyceridaemia. Treatment with bile acid sequestrants may be appropriate under specialist supervision if statins and ezetimibe are inappropriate, and when LDL-cholesterol is severely raised, for example in familial hypercholesterolaemia.

Fibrates
Fibrates are mainly used in those whose serum-triglyceride concentration is greater than 10 mmol/litre or in those who cannot tolerate a statin (specialist use).

Lomitapide
Lomitapide p. 176 is licensed as an adjunct to dietary measures and other lipid-regulating drugs for the treatment of homozygous familial hypercholesterolaemia.

Nicotinic acid group
The value of nicotinic acid p. 177 is limited by its side-effects, especially vasodilatation. Nicotinic acid is used by specialists in combination with a statin if the statin alone cannot adequately control dyslipidaemia (raised LDL-cholesterol, triglyceridaemia, and low HDL-cholesterol).

Acipimox p. 177 seems to have fewer side-effects than nicotinic acid but may be less effective in its lipid-regulating capabilities.

Omega-3 fatty acid compounds
There is no evidence that omega-3 fatty acid compounds reduce the risk of cardiovascular disease.

Statins
Statins are more effective than other lipid-regulating drugs at lowering LDL-cholesterol concentration but they are less effective than the fibrates in reducing triglyceride concentration. However, statins reduce cardiovascular disease events and total mortality irrespective of the initial cholesterol concentration.

BILE ACID SEQUESTRANTS

Bile acid sequestrants

• **DRUG ACTION** Bile acid sequestrants act by binding bile acids, preventing their reabsorption; this promotes hepatic conversion of cholesterol into bile acids; the resultant increased LDL-receptor activity of liver cells increases the clearance of LDL-cholesterol from the plasma.

• **CAUTIONS** Interference with the absorption of fat-soluble vitamins (supplements of vitamins A, D, K, and folic acid may be required when treatment is prolonged).

• **SIDE-EFFECTS** Constipation, diarrhoea, gastro-intestinal discomfort, hypertriglyceridaemia (aggravation), hypoprothrombinaemia associated with vitamin K deficiency, increased risk of bleeding, nausea, vomiting.

• **PREGNANCY** Bile acid sequestrants should be used with caution as although the drugs are not absorbed, they may cause fat-soluble vitamin deficiency on prolonged use.

• **BREAST FEEDING** Bile acid sequestrants should be used with caution as although the drugs are not absorbed, they may cause fat-soluble vitamin deficiency on prolonged use.

Coleselam hydrochloride

**INDICATIONS AND DOSE**
Primary hypercholesterolaemia as an adjunct to dietary measures (monotherapy)

**BY MOUTH**

- **Adult:** 3.75 g daily in 1–2 divided doses; maximum 4.375 g per day

Primary hypercholesterolaemia as an adjunct to dietary measures, in combination with a statin **Primary and familial hypercholesterolaemia, in combination with ezetimibe, either with or without a statin**

**BY MOUTH**

- **Adult:** 2.5–3.75 g daily in 1–2 divided doses, may be taken at the same time as the statin and ezetimibe

• **CONTRA-INDICATIONS** Biliary obstruction · bowel obstruction

• **CAUTIONS** Gastro-intestinal motility disorders · inflammatory bowel disease · major gastro-intestinal surgery

• **INTERACTIONS** → Appendix 1 (coleselam).

• **SIDE-EFFECTS** Headache · myalgia

• **HEPATIC IMPAIRMENT** Manufacturer advises caution.

• **MONITORING REQUIREMENTS** Patients receiving ciclosporin should have their blood-ciclosporin concentration monitored before, during, and after treatment with coleselam.

• **DIRECTIONS FOR ADMINISTRATION** Other drugs should be taken at least 4 hours before or after coleselam to reduce possible interference with absorption.

• **PATIENT AND CARER ADVICE** Patient counselling on administration is advised for coleselam hydrochloride tablets (avoid other drugs at same time).
Colestipol hydrochloride

INDICATIONS AND DOSE
Hyperlipidaemias, particularly type IIa, in patients who have not responded adequately to diet and other appropriate measures

BY MOUTH
- Adults: Initially 5 g 1–2 times a day, increased in steps of 5 g every 1 month if required, total daily dose may be given in 1–2 divided doses; maximum 30 g per day

INTERACTIONS → Appendix 1 (colestipol).

DIRECTIONS FOR ADMINISTRATION The contents of each sachet should be mixed with at least 100 mL of water or other suitable liquid such as fruit juice, skimmed milk, thin soups, and pulpy fruits with a high moisture content. Alternatively it can be mixed with thin soups, cereals, yoghurt, or pulpy fruits ensuring at least 100 mL of liquid is provided. Other drugs should be taken at least 1 hour before or 4–6 hours after colestipol to reduce possible interference with absorption.

PATIENT AND CARER ADVICE Patient counselling on administration is advised for colestipol hydrochloride granules (avoid other drugs at same time).

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Granules
- Colestipol hydrochloride 5 gram Colestipol 5 g granules sachets plain (sugar-free) | 30 sachet (£15.05)
- Colestipol Orange 5 g granules sachets (sugar-free) | 30 sachet (£15.05)

Cholestagel

- Tablet
  - Colestipol hydrochloride 625 mg Cholestel 625 mg tablets | 180 tablet (£96.10 DT price = £96.10

Colestyramine

(Cholestyramine)

INDICATIONS AND DOSE
Hyperlipidaemias, particularly type IIa, in patients who have not responded adequately to diet and other appropriate measures

BY MOUTH
- Adult: Initially 4 g daily, increased in steps of 4 g every 1 week; 12–24 g daily in 1–4 divided doses, adjusted according to response; maximum 36 g per day

PRURITUS ASSOCIATED WITH PARTIAL BILIARY OBSTRUCTION AND PRIMARY BILIARY CIRRHOSIS

BY MOUTH
- Adult: 4–8 g once daily

DIARRHOEA ASSOCIATED WITH CROHN’S DISEASE, ILEAL RESECTION, VOGATOMY, DIABETIC VAGAL NEUROPATHY, AND RADIATION

BY MOUTH
- Adult: Initially 4 g daily, increased in steps of 4 g every 1 week; 12–24 g daily in 1–4 divided doses, adjusted according to response, if no response within 3 days an alternative therapy should be initiated; maximum 36 mg per day

Accelerated elimination of teriflunomide

BY MOUTH
- Adult: 8 g 3 times a day for 11 days; reduced to 4 g 3 times a day, dose should only be reduced if not tolerated

Accelerated elimination of leflunomide (washout procedure)

BY MOUTH
- Adult: 8 g 3 times a day for 11 days

CONTRA-INDICATIONS Complete biliary obstruction (not likely to be effective)

INTERACTIONS → Appendix 1 (colestipol).

SIDE-EFFECTS
- Rare Intestinal obstruction
- Frequency not known Hyperchloraemic acidosis (on prolonged use)

DIRECTIONS FOR ADMINISTRATION The contents of each sachet should be mixed with at least 150 mL of water or other suitable liquid such as fruit juice, skimmed milk, thin soups, and pulpy fruits with a high moisture content. Other drugs should be taken at least 1 hour before or 4–6 hours after colestyramine to reduce possible interference with absorption.

PATIENT AND CARER ADVICE Patient counselling on administration is advised for colestyramine powder (avoid other drugs at same time).

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension, cream

Powder
- Colestyramine (Non-proprietary) Colestyramine 4g oral powder sachets sugar free (sugar-free) | 50 sachet (£30.00–£32.78 DT price = £31.85
- Questran (Bristol-Myers Squibb Pharmaceuticals Ltd) Colestyramine anhydrous 4 gram Questran 4g oral powder sachets | 50 sachet (£10.76
- Questran Light (Bristol-Myers Squibb Pharmaceuticals Ltd) Colestyramine anhydrous 4 gram Questran Light 4g oral powder sachets (sugar-free) | 50 sachet (£16.15 DT price = £31.85

CHOLESTEROL ABSORPTION INHIBITORS

Ezetimibe

- DRUG ACTION Ezetimibe inhibits the intestinal absorption of cholesterol. If used alone, it has a modest effect on lowering LDL-cholesterol, with little effect on other lipoproteins.

INDICATIONS AND DOSE
Adjunct to dietary measures and statin treatment in primary hypercholesterolaemia | Adjunct to dietary measures and statin in homozygous familial hypercholesterolaemia | Primary hypercholesterolaemia (if statin inappropriate or not tolerated) | Adjunct to dietary measures in homozygous sitosterolaemia

BY MOUTH
- Adult: 10 mg daily

INTERACTIONS → Appendix 1 (ezetimibe).

There is an increased risk of rhabdomyolysis if ezetimibe is used in combination with a statin.

SIDE-EFFECTS
- Common or very common Fatigue · gastro-intestinal disturbances · headache · myalgia
Hyperlipidaemia

Fibrates

**DRUG ACTION** Fibrates act by decreasing serum triglycerides; they have variable effect on LDL-cholesterol.

**INDICATIONS AND DOSE** Adjunct to diet and other appropriate measures in mixed hyperlipidaemia if statin contra-indicated or not tolerated | Adjunct to diet and other appropriate measures in severe hypertriglyceridaemia

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

- Adult: 200 mg 3 times a day

BY MOUTH USING MODIFIED-RELEASE MEDICINES

- Adult: 400 mg once daily, modified-release dose form is not appropriate in patients with renal impairment

**CONTRA-INDICATIONS** Gall bladder disease · hyperalimentation - nephrotic syndrome · photosensitivity to fibrates

**CAUTIONS** Correct hypothyroidism before initiating treatment

**INTERACTIONS** → Appendix 1 (fibrates).

Combination of a fibrate with a statin increases the risk of muscle effects (especially rhabdomyolysis) and should be used with caution.

**SIDE-EFFECTS**

- Common or very common Abdominal distension · anorexia · diarrhoea · nausea

- Uncommon Alopecia · cholestasis · dizziness · erectile dysfunction · headache · myotoxicity (with myasthenia, myalgia, or very rarely rhabdomyolysis)—special risk in renal impairment · photosensitivity reactions · pruritus · rash · renal failure · urticaria

- Rare Pancreatitis · peripheral neuropathy

- Very rare Anaemia · gallstones · increased platelet count · interstitial lung disease · leucopenia · pancytopenia · Stevens-Johnson syndrome · thrombocytopenic purpura · toxic epidermal necrolysis

**PREGNANCY** Manufacturers advise avoid—no information available.

**LIVER FEEDING** Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT** Avoid in moderate and severe impairment—may accumulate.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Ezetimibe for the treatment of primary hypercholesterolaemia (November 2007) NICE TA132

Ezetimibe, used in accordance with the licensed indications for Ezetrol®, is an option for the treatment of adults with primary hypercholesterolaemia. www.nice.org.uk/TA132

**MEDICINAL Forms**

- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Ezetrol (Merck Sharp & Dohme Ltd)
  - Ezetimibe 10 mg Ezetrol 10mg tablets | 28 tablet | £26.31 DT price = £26.31

Also available in combination with simvastatin, p. 182

Ciprofibrate

**DRUG ACTION** Fibrates act by decreasing serum triglycerides; they have variable effect on LDL-cholesterol.

**INDICATIONS AND DOSE** Adjunct to diet and other appropriate measures in mixed hyperlipidaemia if statin contra-indicated or not tolerated | Adjunct to diet and other appropriate measures in severe hypertriglyceridaemia

BY MOUTH

- Adult: 100 mg daily

**CONTRA-INDICATIONS** Gall bladder disease · hyperalimentation - nephrotic syndrome · photosensitivity to fibrates

**CAUTIONS** Correct hypothyroidism before initiating treatment

**INTERACTIONS** → Appendix 1 (fibrates).

Combination of a fibrate with a statin increases the risk of muscle effects (especially rhabdomyolysis) and should be used with caution.

**SIDE-EFFECTS**

- Common or very common Abdominal distension · anorexia · diarrhoea · nausea
• **Uncommon** Alopecia - cholestasis - dizziness - erectile dysfunction - headache - myotoxicity (with myasthenia, myalgia, or very rarely rhabdomyolysis)—special risk in renal impairment - photosensitivity reactions - pruritus - rash - renal failure - urticaria

• **Rare** Pancreatitis - peripheral neuropathy

• **Very rare** Anaemia - gallstones - increased platelet count - interstitial lung disease - leucopenia - pancytopenia - Stevens-Johnson syndrome - thrombocytopenic purpura - toxic epidermal necrolysis

• **Frequency not known** Pneumonitis - pulmonary fibrosis

• **PREGNANCY** Manufacturers advise avoid—■ toxicity in animal studies.

• **BREAST FEEDING** Manufacturer advises avoid—■ in milk in animal studies.

• **HEPATIC IMPAIRMENT** Use with caution in mild to moderate impairment. Avoid in severe impairment.

• **RENAL IMPAIRMENT** Reduce dose to 100 mg on alternate days in moderate impairment. Avoid in severe impairment.

Myotoxicity Special care needed in patients with renal disease, as progressive increases in serum creatinine concentration or failure to follow dosage guidelines may result in myotoxicity (rhabdomyolysis); discontinue if myotoxicity suspected or creatine kinase concentration increases significantly.

• **MONITORING REQUIREMENTS**

º Liver function tests recommended every 3 months for first year (discontinue treatment if significantly raised).

º Consider monitoring liver function and creatine kinase when fibrates used in combination with a statin.

• **PRESCRIBING AND DISPENSING INFORMATION**

Fibrates are mainly used in those whose serum-triglyceride concentration is greater than 10 mmol/litre or in those who cannot tolerate a statin (specialist use).

• **MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

º **CIPROFIBRATE (Non-proprietary)**

Ciprofibrate 100 mg Ciprofibrate 100mg tablets | 28 tablet £6.69 DT price = £10.31

**Fenofibrate**

• **DRUG ACTION** Fibrates act by decreasing serum triglycerides; they have variable effect on LDL-cholesterol.

**INDICATIONS AND DOSE**

Adjunct to diet and other appropriate measures in mixed hyperlipidaemia if statin contraindicated or not tolerated | Adjunct to diet and other appropriate measures in severe hypertriglyceridaemia | Adjunct to statin in mixed hyperlipidaemia if triglycerides and HDL-cholesterol inadequately controlled in patients at high cardiovascular risk

**BY MOUTH USING CAPSULES**

º Adult: Initially 200 mg daily, then increased if necessary to 267 mg daily, maximum 200 mg daily with concomitant statin; 200 mg capsules not appropriate for use in renal impairment; 267 mg capsules not appropriate for initial dose titration or in renal impairment

**BY MOUTH USING TABLETS**

º Adult: 160 mg daily, tablets not appropriate in renal impairment

• **CONTRA-INDICATIONS** Gall bladder disease - pancreatitis (unless due to severe hypertriglyceridaemia) - photosensitivity to ketoprofen

• **CAUTIONS** Correct hypothyroidism before initiating treatment

• **INTERACTIONS** → Appendix 1 (fibrates).

Combination of a fibrate with a statin increases the risk of muscle effects (especially rhabdomyolysis) and should be used with caution.

• **SIDE-EFFECTS**

º **Common or very common** Abdominal distension - anorexia - diarrhoea - nausea

º **Uncommon** Alopecia - cholestasis - dizziness - erectile dysfunction - headache - myotoxicity (with myasthenia, myalgia, or very rarely rhabdomyolysis)—special risk in renal impairment - pancreatitis - photosensitivity reactions - pruritus - pulmonary embolism - rash - renal failure - urticaria

º **Rare** Hepatitis - peripheral neuropathy

º **Very rare** Anaemia - gallstones - increased platelet count - interstitial lung disease - leucopenia - pancytopenia - Stevens-Johnson syndrome - thrombocytopenic purpura - toxic epidermal necrolysis

º **Frequency not known** Interstitial pneumopathies

º **PREGNANCY** Avoid—■embryotoxicity in animal studies.

º **BREAST FEEDING** Manufacturers advise avoid—no information available.

• **HEPATIC IMPAIRMENT** Avoid.

• **RENAL IMPAIRMENT** Reduce dose to 134 mg daily if eGFR less than 60 mL/minute/1.73 m². Reduce dose to 67 mg daily if eGFR less than 20 mL/minute/1.73 m². Avoid if eGFR less than 15 mL/minute/1.73 m².

Myotoxicity Special care needed in patients with renal disease, as progressive increases in serum creatinine concentration or failure to follow dosage guidelines may result in myotoxicity (rhabdomyolysis); discontinue if myotoxicity suspected or creatine kinase concentration increases significantly.

• **MONITORING REQUIREMENTS**

º Liver function tests recommended every 3 months for first year (discontinue treatment if significantly raised).

º Consider monitoring liver function and creatine kinase when fibrates used in combination with a statin.

• **PRESCRIBING AND DISPENSING INFORMATION**

Fibrates are mainly used in those whose serum-triglyceride concentration is greater than 10 mmol/litre or in those who cannot tolerate a statin (specialist use).

• **MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

º **CAUTIONARY AND ADVISORY LABELS 21**

º **FENOFIBRATE (Non-proprietary)**

Fenofibrate micronised 160 mg Fenofibrate micronised 160mg tablets | 28 tablet £6.69 DT price = £6.69

Supralip (BGP Products Ltd) Fenofibrate micronised 160 mg Supralip 160mg tablets | 28 tablet £6.69 DT price = £6.69

**Capsule**

º **CAUTIONARY AND ADVISORY LABELS 21**

º **FENOFIBRATE (Non-proprietary)**

Fenofibrate micronised 67 mg Fenofibrate micronised 67mg capsules | 90 capsule £23.30 DT price = £13.00

Fenofibrate micronised 200 mg Fenofibrate micronised 200mg capsules | 28 capsule £21.75 DT price = £14.57

Fenofibrate micronised 267 mg Fenofibrate micronised 267mg capsules | 28 capsule £21.75 DT price = £5.29

Lipantil Micro (BGP Products Ltd) Lipantil Micro 67 capsules | 90 capsule £23.30 DT price = £19.00

Fenofibrate micronised 200 mg Lipantil Micro 200 capsules | 28 capsule £14.23 DT price = £14.57

Fenofibrate micronised 267 mg Lipantil Micro 267 capsules | 28 capsule £21.75 DT price = £5.29
Gemfibrozil

**DRUG ACTION** Fibrates act by decreasing serum triglycerides; they have variable effect on LDL-cholesterol.

**INDICATIONS AND DOSE**
Adjunct to diet and other appropriate measures in mixed hyperlipidaemia if statin contra-indicated or not tolerated. Adjunct to diet and other appropriate measures in primary hypercholesterolaemia if statin contra-indicated or not tolerated. Adjunct to diet and other appropriate measures in severe hypertriglyceridaemia.

**CONTRA-INDICATIONS** History of gall-bladder or biliary tract disease including gallstones, photosensitivity to fibrates.

**CAUTIONS** Correct hypothyroidism before initiating treatment - elderly.

**INTERACTIONS** Appendix 1 (fibrates).

The combination of gemfibrozil and a statin should preferably be avoided; high risk of muscle effects (especially rhabdomyolysis).

**SIDE-EFFECTS**
- **Common or very common** Abdominal pain, constipation, diarrhoea, dyspepsia, eczema, fatigue, flatulence, headache, nausea, rash, vertigo, vomiting.
- **Uncommon** Atrial fibrillation.
- **Rare** Hepatitis, paraesthesia, alopecia, anaemia, angioedema, appendicitis, blurred vision, bone-marrow suppression, cholestatic jaundice, depression, disturbances in hepatic function, dizziness, drowsiness, eosinophilia, exfoliative dermatitis, leucopenia, myalgia, myasthenia, myopathy, myositis accompanied by increase in creatine kinase (discontinue if raised significantly), pancreatitis, photosensitivity, pruritus, sexual dysfunction, thrombocytopenia, urticaria.

**PREGNANCY** Manufacturers advise avoid unless essential — toxicity in animal studies.

**BREAST FEEDING** Manufacturer advises avoid—no information available.

**RENALError** Avoid.

**RENAL IMPAIRMENT** Initially 900 mg daily if eGFR 30–80 mL/minute/1.73 m². Avoid if eGFR less than 30 mL/minute/1.73 m².

**Myotoxicity** Special care needed in patients with renal disease, as progressive increases in serum creatinine concentration or failure to follow dosage guidelines may result in myotoxicity (rhabdomyolysis); discontinue if myotoxicity suspected or creatine kinase concentration increases significantly.

**MONITORING REQUIREMENTS**
- Monitor blood counts for first year.
- Monitor liver-function (discontinue treatment if abnormalities persist).
- Consider monitoring creatine kinase if used in combination with a statin.

**PRESCRIBING AND DISPENSING INFORMATION** Fibrates are mainly used in those whose serum-triglyceride concentration is greater than 10 mmol/litre or in those who cannot tolerate a statin (specialist use).

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

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<td><strong>GEMFIBROZIL (Non-proprietary)</strong></td>
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<tr>
<td>Gemfibrozil 600 mg</td>
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<tr>
<td>56 tablet [P] £34.95 DT price = £34.95</td>
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<td>Lopid (Pfizer Ltd)</td>
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<td>Gemfibrozil 300 mg</td>
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**MICROSOMAL TRIGLYCERIDE TRANSFER PROTEIN INHIBITORS**

Lomitapide

**DRUG ACTION** Lomitapide, an inhibitor of microsomal triglyceride transfer protein (MTP), reduces lipoprotein secretion and circulating concentrations of lipoprotein-borne lipids such as cholesterol and triglycerides.

**INDICATIONS AND DOSE**
Adjunct to dietary measures and other lipid-regulating drugs with or without low-density lipoprotein apheresis in homozygous familial hypercholesterolaemia (under expert supervision)

**BY MOUTH**
- Adult: Initially 5 mg daily for 2 weeks, dose to be taken at least 2 hours after evening meal, then increased if necessary to 10 mg daily, for at least 4 weeks, then increased to 20 mg daily for at least 4 weeks, then increased in steps of 20 mg daily, adjusted at intervals of at least 4 weeks; maximum 60 mg per day

**CONTRA-INDICATIONS** Significant or chronic bowel disease.

**CAUTIONS** Concomitant use of hepatotoxic drugs - lomitapide can interfere with the absorption of fat-soluble nutrients and supplementation of vitamin E and fatty acids is required - patients over 65 years.

**INTERACTIONS** Appendix 1 (fibrates).

**SIDE-EFFECTS**
- **Common or very common** Bloating, abdominal pain, appetite changes, constipation, diarrhoea, dizziness, dyspepsia, eczema, erythematous rash, flatulence, gastro-oesophageal reflux disease, gastroenteritis, haemorrhoids, headache, hepatic steatosis, hepatomegaly, hyperkalaemia, leucopenia, malaise, migraine, muscle spasms, nausea, neutropenia, raised serum transaminases, tenesmus, vomiting, weight loss.
- **Uncommon** Abnormal gait, anaemia, arthralgia, chest pain, drowsiness, dry mouth, dry skin, eye swelling, gastro-intestinal haemorrhage, haematemeses, haematuria, hyperbilirubinaemia, joint swelling, myalgia, pain in extremities, paraesthesia, proteinuria, pyrexia, sweating, vertigo.

**SIDE-EFFECTS, FURTHER INFORMATION**

**Raised transaminases** Reduce dose if serum transaminases raised during treatment (consult product literature).

**CONCEPTION AND CONTRACEPTION** Manufacturer advises exclude pregnancy before treatment and ensure effective contraception used.

**PREGNANCY** Avoid — teratogenicity and embryotoxicity in animal studies.

**BREAST FEEDING** Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT** Reduce dose if serum transaminases raised during treatment (consult product literature). Max. 40 mg daily in mild impairment.
Avoid in moderate to severe impairment, or if unexplained persistent abnormal liver function tests.

- **RENAL IMPAIRMENT** Max. 40 mg daily in end-stage renal disease.

- **MONITORING REQUIREMENTS**
  - Monitor liver function tests before treatment, then at least monthly and before each dose increase for first year, then at least every 3 months and before each dose increase thereafter.
  - Screen for hepatic steatosis and fibrosis before treatment, then annually thereafter.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Capsule**
    - Lojuxta (Aegerion Pharmaceuticals Ltd)
      - Lojuxta 5 mg capsules | 28 capsule [POD]
      - £17,765.00
    - Lojuxta 10 mg Lojuxta 10 mg capsules | 28 capsule [POD]
      - £17,765.00
    - Lojuxta 20 mg Lojuxta 20 mg capsules | 28 capsule [POD]
      - £17,765.00

### NICOTINIC ACID DERIVATIVES

#### Acipimox

**INDICATIONS AND DOSE**
Adjunct or alternative treatment in hyperlipidaemias of types IIb and IV in patients who have not responded adequately to other lipid-regulating drugs such as a statin or fibrate, and lifestyle changes (including diet, exercise, and weight reduction)

**BY MOUTH**
- Adult: 250 mg 2–3 times a day

- **CONTRA-INDICATIONS** Peptic ulcer
- **SIDE-EFFECTS**
  - Common or very common Abdominal pain · dyspepsia · flushing · headache · malaise · rash · urticaria
  - Uncommon Anaphylactoid reaction · arthralgia · bronchospasm · erythema · myalgia · myositis · pruritus · rash
  - Frequency not known Diarrhoea · dry eyes · vasodilatation

- **PREGNANCY** Manufacturer advises avoid—no information available.
- **BREAST FEEDING** Manufacturer advises avoid—no information available.
- **RENAL IMPAIRMENT** Reduce dose to 250 mg 1–2 times daily if eGFR 30–60 mL/minute/1.73 m². Avoid if eGFR less than 30 mL/minute/1.73 m².

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

- **Capsule**
  - Olbetam (Pfizer Ltd)
    - Acipimox 250 mg Olbetam 250 mg capsules | 90 capsule [POD]
      - £46.33 DT price = £46.33

#### Nicotinic acid

- **DRUG ACTION** In doses of 1.5 to 3 g daily, it lowers both cholesterol and triglyceride concentrations by inhibiting synthesis, it also increases HDL-cholesterol.

### SIDE-EFFECTS

- **COMMON**
  - Rash
  - Headache
  - Cardiovascular system

- **FURTHER INFORMATION**

- **OMEGA-3 FATTY ACIDS**

#### Omega-3-acid ethyl esters

**INDICATIONS AND DOSE**
Adjunct to diet and statin in type IIb or III hypertriglyceridaemia | Adjunct to diet in type IV hypertriglyceridaemia

**BY MOUTH**
- Adult: Initially 2 capsules daily, dose to be taken with food, increased if necessary to 4 capsules daily

Adjunct in secondary prevention in those who have had a myocardial infarction in the preceding 3 months

**BY MOUTH**
- Adult: 1 capsule daily, dose to be taken with food

- **CAUTIONS** Anticoagulant treatment (bleeding time increased) · haemorrhagic disorders

- **SIDE-EFFECTS**
  - Common or very common Dyspepsia · nausea
  - Uncommon Abdominal pain · dizziness · gastritis · taste disturbances
  - Rare Acne · headache · hepatic disorders · hyperglycaemia · rash
  - Very rare Gastro-intestinal haemorrhage · hypotension · increased white cell count · nasal dryness · urticaria
HYPERLIPIDAEMIA

Cardiovascular system

- **PREGNANCY** Manufacturers advise use only if potential benefit outweighs risks—no information available.
- **BREAST FEEDING** Manufacturers advise avoid—no information available.
- **HEPATIC IMPAIRMENT** Monitor liver function in hepatic impairment.
- **NATIONAL FUNDING/ACCESS DECISIONS**
- **SCOTTISH MEDICATIONS CONSORTIUM (SMC) DECISIONS** The Scottish Medicines Consortium has advised (November 2002) that omega-3 acid ethyl esters are not recommended for use within NHS Scotland for the treatment of hypertriglyceridaemia.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Capsule**
    - **CAUTIONARY AND ADVISORY LABELS**
      - **OMEGA-3 ACID ETHYL ESTERS (NON-PROPRIETARY)**
        - Docosahexaenoic acid 380 mg, Eicosapentaenoic acid 460 mg
        - Docosahexaenoic acid 380 mg capsules
          - Frequency not known
          - Very rare
          - Rare
          - **INTERACTIONS** Appendix 1 (statins).
          - **SIDE-EFFECTS** Further Information
          - **CONCEPTION AND CONTRACEPTION**
            - Hypothyroidism should be managed adequately before starting treatment with a statin.
            - **INTERACTIONS** Appendix 1 (statins).
            - **SIDE-EFFECTS** Further Information
          - **PREPARATIONS**
            - **Hepatitis**
              - **SIDE-EFFECTS** Further Information
              - **CONCEPTION AND CONTRACEPTION**
            - **Pregnancy**
              - **SIDE-EFFECTS** Further Information
              - **CONCEPTION AND CONTRACEPTION**
            - **Hypothyroidism**
              - **SIDE-EFFECTS** Further Information
              - **CONCEPTION AND CONTRACEPTION**
            - **Drug Action**
              - Statins competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, an enzyme involved in cholesterol synthesis, especially in the liver.
            - **Caution**
              - Elderly, high alcohol intake, history of liver disease, hypothyroidism, patients at increased risk of muscle toxicity, including myopathy or rhabdomyolysis (e.g. those with a personal or family history of muscular disorders, previous history of muscular toxicity and a high alcohol intake).
            - **Caution, Further Information**
              - **Muscle effects** Muscle toxicity can occur with all statins, however the likelihood increases with higher doses and in certain patients (see below). Statins should be used with caution in patients at increased risk of muscle toxicity, including those with a personal or family history of muscular disorders, previous history of muscular toxicity, a high alcohol intake, renal impairment or hypothyroidism.
              - In patients at increased risk of muscle effects, a statin should not usually be started if the baseline creatine kinase concentration is more than 5 times the upper limit of normal (some patients may present with an extremely elevated baseline creatine kinase concentration, for example because of a physical occupation or rigorous exercise—specialist advice should be sought regarding consideration of statin therapy in these patients).

- **STATINS**
  - **Drug Action** Statins competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, an enzyme involved in cholesterol synthesis, especially in the liver.
  - **Caution** Elderly, high alcohol intake, history of liver disease, hypothyroidism, patients at increased risk of muscle toxicity, including myopathy or rhabdomyolysis (e.g. those with a personal or family history of muscular disorders, previous history of muscular toxicity and a high alcohol intake).
  - **Caution, Further Information**
    - **Muscle effects** Muscle toxicity can occur with all statins, however the likelihood increases with higher doses and in certain patients (see below). Statins should be used with caution in patients at increased risk of muscle toxicity, including those with a personal or family history of muscular disorders, previous history of muscular toxicity, a high alcohol intake, renal impairment or hypothyroidism.
    - In patients at increased risk of muscle effects, a statin should not usually be started if the baseline creatine kinase concentration is more than 5 times the upper limit of normal (some patients may present with an extremely elevated baseline creatine kinase concentration, for example because of a physical occupation or rigorous exercise—specialist advice should be sought regarding consideration of statin therapy in these patients).

**SIDE-EFFECTS**
- Rare
  - Hepatitis, jaundice
- Very rare
  - Hepatic failure, interstitial lung disease, lupus erythematosus-like reactions, pancreatitis
- Frequency not known
  - Alopeica, altered liver function tests
  - Anemia, arthralgia, asthenia, depression, dizziness, fatigue, gastrointestinal disturbances, headache, hyperglycaemia, hypersensitivity reactions may be associated with the development of diabetes mellitus (particularly in those already at risk of the condition), myalgia, myopathy, myositis, paraesthesia, peripheral neuropathy, pruritus, rash, rhabdomyolysis, sexual dysfunction, sleep disturbance, thrombocytopenia, urticaria, visual disturbance

**SIDE-EFFECTS, FURTHER INFORMATION**
- Muscle effects The risk of myopathy, myositis, and rhabdomyolysis associated with statin use is rare. Although myalgia has been reported commonly in patients receiving statins, muscle toxicity truly attributable to statin use is rare. Muscle toxicity can occur with all statins, however the likelihood increases with higher doses.
- If muscular symptoms or raised creatine kinase occur during treatment, other possible causes (e.g. rigorous physical activity, hypothyroidism, infection, recent trauma, and drug or alcohol addiction) should be excluded before statin therapy is implicated, particularly if statin treatment has previously been tolerated for more than 3 months. When a statin is suspected to be the cause of myopathy, creatine kinase concentration is markedly elevated (more than 5 times upper limit of normal), or if muscular symptoms are severe, treatment should be discontinued. If symptoms resolve and creatine kinase concentrations return to normal, the statin should be reintroduced at a lower dose and the patient monitored closely; an alternative statin should be prescribed if unacceptable side-effects are experienced with a particular statin. Statins should not be discontinued in the event of small, asymptomatic elevations of creatine kinase. Routine monitoring of creatine kinase is unnecessary in asymptomatic patients.
- Statins should not be discontinued if there is an increase in the blood-glucose concentration or HbA1C as the benefits continue to outweigh the risks.
- **INTERSTITIAL LUNG DISEASE** If patients develop symptoms such as dyspnoea, cough, and weight loss, they should seek medical attention.
- **CONCEPTION AND CONTRACEPTION** Adequate contraception is required during treatment and for 1 month afterwards.
- **PREGNANCY** Statins should be avoided in pregnancy (discontinue 3 months before attempting to conceive) as congenital anomalies have been reported and the decreased synthesis of cholesterol possibly affects fetal development.
Primary prevention of cardiovascular events in patients at high risk of a first cardiovascular event

BY MOUTH

Adult: 20 mg daily, dose can be increased if necessary

Secondary prevention of cardiovascular events

BY MOUTH

Adult: 80 mg once daily

Dose adjustments due to interactions

Reduced dose required (max. 10 mg daily) with concomitant ciclosporin, or tipranavir combined with ritonavir—seek specialist advice.

Maximum dose of 40 mg once daily when combined with anion-exchange resin for heterozygous familial hypercholesterolaemia.

**UNLICENSED USE** Not licensed for use in secondary prevention of cardiovascular events. Starting dose of 20 mg once daily is not licensed for the primary prevention of cardiovascular events.

**CAUTIONS** Haemorrhagic stroke

**SIDE-EFFECTS**

Common or very common

Back pain, epistaxis, hyperglycaemia, nasopharyngitis, pharyngolaryngeal pain.

Uncommon

Anorexia, blurred vision, chest pain, hypoglycaemia, malaise, neck pain, peripheral oedema, pyrexia, tinnitus, weight gain.

Rare

Cholestasis, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Very rare

Cynaesmaostasia, hearing loss.

**BREAST FEEDING** Manufacturer advises avoid—for no information available.

**RENAL IMPAIRMENT** In chronic kidney disease, for primary and secondary prevention of cardiovascular events [unlicensed starting dose in primary prevention; unlicensed in secondary prevention], initially 20 mg once daily, increased if necessary (on specialist advice if eGFR < 30 mL/minute/L.73 m²); max. 80 mg once daily.

**PATIENT AND CARER ADVICE** Patient counselling is advised for atorvastatin tablets (muscle effects).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension.

**Tablet**

- ATORVASTATIN (Non-proprietary)
  - 10 mg: Atorvastatin 10mg tablets | 28 tablet | £13.00 DT price = £1.18 | 90 tablet | £41.78
  - 20 mg: Atorvastatin 20mg tablets | 28 tablet | £24.64 DT price = £1.41 | 90 tablet | £79.20
  - 30 mg: Atorvastatin 30mg tablets | 28 tablet | £24.50
  - 40 mg: Atorvastatin 40mg tablets | 28 tablet | £24.64 DT price = £1.59 | 90 tablet | £79.20
  - 60 mg: Atorvastatin 60mg tablets | 28 tablet | £28.00
  - 80 mg: Atorvastatin 80mg tablets | 28 tablet | £28.21 DT price = £2.71 | 90 tablet | £90.67
  - Lipitor (Pfizer Ltd)
    - 10 mg: Lipitor 10mg tablets | 28 tablet | £13.00 DT price = £1.18
    - 20 mg: Lipitor 20mg tablets | 28 tablet | £24.64 DT price = £1.41
    - 40 mg: Lipitor 40mg tablets | 28 tablet | £24.64 DT price = £1.59

- Lipitor (Atorvastatin calcium trihydrate) 10 mg: Lipitor 10mg tablets | 28 tablet | £13.00 DT price = £1.18
- Lipitor (Atorvastatin calcium trihydrate) 20 mg: Lipitor 20mg tablets | 28 tablet | £24.64 DT price = £1.41
- Lipitor (Atorvastatin calcium trihydrate) 40 mg: Lipitor 40mg tablets | 28 tablet | £24.64 DT price = £1.59
Fluvastatin

INDICATIONS AND DOSE

Adjunct to diet in primary hypercholesterolaemia or combined (mixed) hyperlipidaemia (types IIA and IIB)

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
- Adult: Initially 20–40 mg daily, dose to be taken in the evening, increased if necessary up to 80 mg daily in 2 divided doses, dose to be adjusted at intervals of at least 4 weeks
- Adult: 80 mg daily
- Adult: 80 mg daily, dose is not appropriate for initial dose titration

Prevention of coronary events after percutaneous coronary intervention
- Adult: 80 mg daily
- Adult: 80 mg daily
- Adult: 80 mg daily, dose is not appropriate for initial dose titration

SIDE-EFFECTS
- Very rare Vasculitis
- BREAST FEEDING Manufacturer advises avoid—no information available.
- RENAL IMPAIRMENT Manufacturer advises doses above 40 mg daily should be initiated with caution if eGFR less than 30 mL/minute/1.73 m²
- PATIENT AND CARER ADVICE Patient counselling is advised for fluvastatin tablets/capsules (main side effects).
- NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (February 2004) that fluvastatin is accepted for restricted use for the secondary prevention of coronary events after percutaneous coronary angioplasty; if the patient has previously been receiving another statin, then there is no need to change the statin.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Modified-release tablet

CAUTIONARY AND ADVISORY LABELS 25
- FLUVASTATIN (Non-proprietary)
  Fluvastatin (as Fluvastatin sodium) 80 mg Fluvastatin 80mg modified-release tablets 28 tablet (PO) no price available DT price = £13.20
  Lescol XL (Novartis Pharmaceuticals UK Ltd) Fluvastatin (as Fluvastatin sodium) 80 mg Lescol XL 80mg tablets 28 tablet (PO) £13.20 DT price = £13.20
  Brands may include Dorisil XL; Lescol XL; Luvivista XL; Nandovar XL; Pinnmatix; Stefluvin XL

Capsule
- FLUVASTATIN (Non-proprietary)
  Fluvastatin (as Fluvastatin sodium) 20 mg Fluvastatin 20mg capsules 28 capsule (PO) £6.96 DT price = £2.48
  Fluvastatin (as Fluvastatin sodium) 40 mg Fluvastatin 40mg capsules 28 capsule (PO) £7.42 DT price = £2.72
  Lescol (Novartis Pharmaceuticals UK Ltd)
  Fluvastatin (as Fluvastatin sodium) 20 mg Lescol 20mg capsules 28 capsule (PO) £7.29 DT price = £2.48
  Fluvastatin (as Fluvastatin sodium) 40 mg Lescol 40mg capsules 28 capsule (PO) £15.26 DT price = £2.72

Pravastatin sodium

INDICATIONS AND DOSE

Adjunct to diet for primary hypercholesterolaemia or combined (mixed) hyperlipidaemias in patients who have not responded adequately to dietary control

BY MOUTH
- Adult: 10–40 mg daily, dose to be taken at night, dose to be adjusted at intervals of at least 4 weeks
- Prevention of cardiovascular events in patients with previous myocardial infarction or unstable angina
- Adjunct to diet to prevent cardiovascular events in patients with hypercholesterolaemia

BY MOUTH
- Adult: 40 mg daily, dose to be taken at night
- Reduction of hyperlipidaemia in patients receiving immunosuppressive therapy following solid-organ transplantation

BY MOUTH
- Adult: Initially 20 mg daily, then increased if necessary up to 40 mg daily, dose to be taken at night, close medical supervision is required if dose is increased to maximum dose

SIDE-EFFECTS
- Uncommon Abnormal urination · dysuria · nocturia · urinary frequency
- Very rare Fulminant hepatic necrosis

BREAST FEEDING Manufacturer advises avoid—small amount of drug present in breast milk.

RENA L IMPAIRMENT Manufacturer advises initial dose of 10 mg once daily in moderate to severe impairment.

PATIENT AND CARER ADVICE Patient counselling is advised for pravastatin tablets (muscle effects).

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension, powder

Tablet
- PRAVASTATIN SODIUM (Non-proprietary)
  Pravastatin sodium 10 mg Pravastatin 10mg tablets 28 tablet (PO) £6.62 DT price = £1.31
  Pravastatin sodium 20 mg Pravastatin 20mg tablets 28 tablet (PO) £29.60 DT price = £1.57
  Pravastatin sodium 40 mg Pravastatin 40mg tablets 28 tablet (PO) £59.60 DT price = £1.93
- Lipostat (Bristol-Myers Squibb Pharmaceuticals Ltd)
  Pravastatin sodium 10 mg Lipostat 10mg tablets 28 tablet (PO) £14.18 DT price = £1.31
  Pravastatin sodium 20 mg Lipostat 20mg tablets 28 tablet (PO) £26.01 DT price = £1.57
  Pravastatin sodium 40 mg Lipostat 40mg tablets 28 tablet (PO) £56.01 DT price = £1.93

Rosuvastatin

INDICATIONS AND DOSE

Primary hypercholesterolaemia (type IIA including heterozygous familial hypercholesterolaemia), mixed dyslipidaemia (type IIB), or homozygous familial hypercholesterolaemia in patients who have not responded adequately to diet and other appropriate measures

BY MOUTH
- Adult 18–69 years: Initially 5–10 mg once daily, then increased if necessary to 20 mg once daily, dose to be increased at intervals of at least 4 weeks
- Adult (patients of Asian origin): Initially 5 mg once daily, then increased if necessary up to 20 mg once daily, dose to be increased at intervals of at least 4 weeks.
Hyperlipidaemia

**INDICATIONS AND DOSE**

**Primary hypercholesterolaemia, or combined (mixed) hyperlipidaemia in patients who have not responded adequately to diet and other appropriate measures**

**BY MOUTH**

- Adult: Initially 10–20 mg once daily, then increased if necessary up to 80 mg once daily, adjusted at intervals of at least 4 weeks, dose to be taken at night; 80 mg dose only for those with severe hypercholesterolaemia and at high risk of cardiovascular complications

**Prevention of cardiovascular events in patients with atherosclerotic cardiovascular disease or diabetes mellitus**

- Adult: Initially 10–20 mg once daily, then increased if necessary up to 80 mg once daily, adjusted at intervals of at least 4 weeks, dose to be taken at night; 80 mg dose only for those with severe hypercholesterolaemia and at high risk of cardiovascular complications

**Dose adjustments due to interactions**

Max. 10 mg daily with concomitant bezafibrate or ciprofibrate.

Max. 20 mg daily with concomitant amiodarone, verapamil, diltiazem, amiodipine, or ranolazine.

Max. 40 mg daily with concomitant lomitapide.

**SIDE-EFFECTS**

- Rare  Anaemia
- Frequency not known  Tendinopathy

**BREAST FEEDING**  Manufacturer advises avoid—no information available.

**RENAL IMPAIRMENT**  Doses above 10 mg daily should be used with caution if eGFR less than 30 mL/minute/1.73 m².

**PATIENT AND CARER ADVICE**  Patient counselling is advised for simvastatin tablets/oral suspension (muscle effects).

**EXCEPTIONS TO LEGAL CATEGORY**  Simvastatin 10 mg tablets can be sold to the public to reduce risk of first coronary event in individuals at moderate risk of coronary heart disease (approx. 10–15 % risk of major event in 10 years), max. daily dose 10 mg and pack size of 28 tablets; treatment should form part of a programme to reduce risk of coronary heart disease.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**

- SIMVASTATIN (Non-proprietary) 10 mg | Simvastatin 10mg tablets | 28 tablet | £18.00 DT price = £0.90
- SIMVASTATIN (Non-proprietary) 20 mg | Simvastatin 20mg tablets | 28 tablet | £29.60 DT price = £1.02
Acute attacks of stable angina should be managed with risk of cardiovascular events. Management to prevent angina attacks and to reduce the exertion and relieved by rest. Treatment involves plaques in the coronary arteries that restrict blood flow and angina.

Stable angina

Myocardial ischaemia

Ezetimibe with simvastatin

The properties listed below are those particular to the combination only. For the properties of the components please consider, ezetimibe p. 173, simvastatin p. 181.

**INdications and dose**

Homozygous familial hypercholesterolaemia, primary hypercholesterolaemia, and mixed hyperlipidaemia in patients stabilised on the individual components in the same proportions, or for patients not adequately controlled by statin alone

**By mouth**

- Adult: (consult product literature)

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug.

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| Ezetimibe 10 mg, Simvastatin 40 mg | Inegy 10mg/40mg tablets | 28 tablet [GBP] £38.98 DT price = £38.98 |

| Ezetimibe 10 mg, Simvastatin 80 mg | Inegy 10mg/80mg tablets | 28 tablet [GBP] £41.21 DT price = £41.21 |

7 Myocardial ischaemia

Stable angina

It is important to distinguish stable angina from unstable angina. Stable angina usually results from atherosclerotic plaques in the coronary arteries that restrict blood flow and oxygen supply to the heart; it is often precipitated by exertion and relieved by rest. Treatment involves management of acute anginal pain, and long term management to prevent angina attacks and to reduce the risk of cardiovascular events.

**Management**

Acute attacks of stable angina should be managed with sublingual glyceryl trinitrate p. 190 which can be taken immediately before performing activities that are known to bring on an attack. If attacks occur more than twice a week, regular drug therapy is required and should be introduced in a step-wise manner according to response.

Patients with stable angina should be given a beta-blocker or a calcium-channel blocker. In those with left-ventricular dysfunction, beta-blocker treatment should be started at a very low dose and titrated very slowly over a period of weeks or months. If a beta-blocker or a calcium-channel blocker alone fails to control symptoms adequately, a combination of a beta-blocker and a dihydropyridine calcium-channel blocker (e.g. amlodipine p. 148, felodipine p. 151, modified-release nifedipine p. 154) should be used; if this combination is not appropriate due to intolerance of, or contra-indication to, either beta-blockers or calcium-channel blockers, addition of a long-acting nitrate, ivabradine p. 185, nicorandil p. 185, or ranolazine p. 184 can be considered.

For those patients in whom both beta-blockers and calcium-channel blockers are not tolerated or are contra-indicated, monotherapy with a long-acting nitrate, ivabradine, nicorandil, or ranolazine should be considered.

Response to treatment should be assessed every 2–4 weeks after initiating or changing drug therapy; the drug should be titrated (according to symptom control) to the maximum tolerated dose. Consider referring the patient to a specialist if a combination of two drugs fails to control symptoms. Addition of a third antianginal drug should only be considered if symptom control is not achieved with two drugs and the patient is either due to undergo a revascularisation procedure, or a revascularisation procedure is considered inappropriate. See the use of antiplatelet drugs in patients undergoing coronary stenting.

For long-term prevention of cardiovascular events, see Prevention of cardiovascular events.

**Antiangular drugs**

Nitrates, calcium-channel blockers, and potassium channel activators (use in adults only) have a vasodilating and, consequently, blood pressure lowering effect. Vasodilators can act in heart failure by arteriolar dilatation which reduces both peripheral vascular resistance and left ventricular pressure during systole resulting in improved cardiac output. They can also cause venous dilatation which results in dilatation of capacitance vessels, increase of venous pooling, and diminution of venous return to the heart (decreasing left ventricular end-diastolic pressure).

Nicorandil p. 185, a potassium-channel activator with a nitrate component, has both arterial and venous vasodilating properties and is licensed for the prevention and long-term treatment of angina. Nicorandil has similar efficacy to other antiangular drugs in controlling symptoms; it may produce additional symptomatic benefit in combination with other antiangular drugs [unlicensed indication].

Ivabradine p. 185 lowers the heart rate by its action on the sinus node. It is licensed for the treatment of angina in patients who are in normal sinus rhythm in combination with a beta-blocker, or when beta-blockers are contraindicated or not tolerated. Ivabradine, in combination with standard therapy including a beta-blocker (unless contra-indicated or not tolerated), is also licensed for mild to severe stable chronic heart failure in patients who are in sinus rhythm.

Ranolazine p. 184 is licensed as adjunctive therapy in patients who are inadequately controlled or intolerant of first-line antiangular drugs.

**Drugs used for Myocardial ischaemia not listed below**

- Acebutolol, p. 141
- Amlodipine, p. 148
- Atenolol, p. 141
- Bisoprolol fumarate, p. 142
- Bivalirudin, p. 116
- Carvedilol, p. 142
- Diltiazem hydrochloride, p. 149
- Felodipine, p. 151
- Fondaparinux sodium, p. 109
- Metoprolol tartrate, p. 144
- Nadolol, p. 145
- Nicardipine hydrochloride, p. 153
- Nifedipine, p. 154
- Oxeprolol hydrochloride, p. 145
- Pindolol, p. 146
- Propranolol hydrochloride, p. 146
- Timolol maleate, p. 147
- Venctamyl hydrochloride, p. 156
### Glycoprotein IIB/IIIa Inhibitors

**Abciximab**

**INDICATIONS AND DOSE**
Prevention of ischaemic cardiac complications in patients undergoing percutaneous coronary intervention (specialist use only)

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 250 micrograms/kg, to be given over 1 minute, then (by intravenous infusion) 125 nanograms/kg/minute (max. 10 micrograms/minute), to be started 10–60 minutes before percutaneous coronary intervention and continue for 12 hours

**Short-term prevention of myocardial infarction in patients with unstable angina not responding to conventional treatment and who are scheduled for percutaneous coronary intervention (specialist use only)**

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 250 micrograms/kg, to be given over 1 minute, then (by intravenous infusion) 125 nanograms/kg/minute (max. 10 micrograms/minute), to be started up to 24 hours before possible percutaneous coronary intervention and continue infusion for 12 hours after intervention

**SIDE-EFFECTS**
Common or very common Back pain · bleeding manifestations · bradycardia · chest pain · fever · headache · hypotension · nausea · puncture site pain · thrombocytopenia · vomiting

- Rare Adult respiratory distress · cardiac tamponade · hypersensitivity reactions

**PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk — no information available.

**BREAST FEEDING** Manufacturer advises avoid — no information available.

**HEPATIC IMPAIRMENT** Avoid in severe liver disease — increased risk of bleeding.

**RENAI IMPAIRMENT** Caution in severe impairment — increased risk of bleeding.

**MONITORING REQUIREMENTS**
- Measure baseline prothrombin time, activated clotting time, activated partial thromboplastin time, platelet count, haemoglobin and haematocrit.
- Monitor haemoglobin and haematocrit 12 hours and 24 hours after start of treatment and platelet count 2–4 hours and 24 hours after start of treatment.

**DIRECTIONS FOR ADMINISTRATION**
For intravenous infusion (ReoPro®), give continuously in Glucose 5% or Sodium Chloride 0.9%. Dilute requisite dose in infusion fluid and give via infusion pump; filter upon dilution through a non-pyrogenic low protein-binding 0.2 or 0.22, or 5 micron filter or upon administration through an in-line non-pyrogenic low protein-binding 0.2 or 0.22 micron filter

**CONTRA-INDICATIONS**
- Active internal bleeding · arteriovenous malformation or aneurysm · haemorrhagic diathesis · hypertensive retinopathy · intracranial neoplasm · intracranial or intraspinal surgery or trauma within last 2 months · major surgery within last 2 months · severe hypertension · stroke within last 2 years · thrombocytopenia · vasculitis

**CAUTIONS** Discontinue if uncontrolled serious bleeding occurs or emergency cardiac surgery needed (consult product literature for details of procedures to minimise bleeding) · elderly

**INTERACTIONS**
Caution with concomitant use of drugs that increase risk of bleeding.

**CONTRA-INDICATIONS**
Abnormal bleeding within 30 days · aneurysm · arteriovenous malformation · haemorrhagic diathesis · history of haemorrhagic stroke · increased INR · increased prothrombin time · intracranial disease · major surgery or severe trauma within 6 weeks · neoplasm · severe hypertension · stroke within last 30 days · thrombocytopenia

**CAUTIONS** Discontinue if emergency cardiac surgery necessary · discontinue if intra-aortic balloon pump necessary · discontinue if thrombolytic therapy necessary · risk of bleeding — discontinue immediately if uncontrolled serious bleeding

**INTERACTIONS**
Caution with concomitant drugs that increase risk of bleeding — discontinue immediately if uncontrolled serious bleeding.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**SOLUTION FOR INJECTION**
- **ReoPro** (Eli Lilly and Company Ltd)
  - Abciximab 2 mg per 1 ml ReoPro 10mg/5ml solution for injection vials | 1 vial (Rx) £15.50

**Eptifibatide**

**INDICATIONS AND DOSE**
In combination with aspirin and unfractionated heparin for the prevention of early myocardial infarction in patients with unstable angina or non-ST-segment-elevation myocardial infarction and with last episode of chest pain within 24 hours (specialist use only)

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 180 micrograms/kg, then (by intravenous infusion) 2 micrograms/kg/minute for up to 72 hours (up to 96 hours if percutaneous coronary intervention during treatment)

**CONTRA-INDICATIONS**
Abnormal bleeding within 30 days · aneurysm · arteriovenous malformation · haemorrhagic diathesis · history of haemorrhagic stroke · increased INR · increased prothrombin time · intracranial disease · major surgery or severe trauma within 6 weeks · neoplasm · severe hypertension · stroke within last 30 days · thrombocytopenia

**CAUTIONS**
Discontinue if emergency cardiac surgery necessary · discontinue if intra-aortic balloon pump necessary · discontinue if thrombolytic therapy necessary · risk of bleeding — discontinue immediately if uncontrolled serious bleeding

**INTERACTIONS**
Caution with concomitant drugs that increase risk of bleeding — discontinue immediately if uncontrolled serious bleeding.

**SIDE-EFFECTS**
Common or very common Bleeding manifestations

- Rare Anaphylaxis · rash

**PREGNANCY**
Manufacturer advises use only if potential benefit outweighs risk — no information available.

**BREAST FEEDING**
Manufacturer advises avoid — no information available.

**HEPATIC IMPAIRMENT**
Avoid in severe liver disease — increased risk of bleeding.

**RENAL IMPAIRMENT**
Reduce infusion to 50–100 micrograms/kg · monitor haemoglobin and haematocrit 12 hours and 24 hours after start of treatment

**MONITORING REQUIREMENTS**
- Measure baseline prothrombin time, activated partial thromboplastin time, platelet count, haemoglobin, haematocrit and serum creatinine.
- Monitor haemoglobin, haematocrit and platelets within 6 hours after start of treatment, then at least once daily.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**SOLUTION FOR INJECTION**
- **Integrillin** (GlaxoSmithKline UK Ltd)
  - Eptifibatide 2 mg per 1 ml Integrillin 20mg/10ml solution for injection vials | 1 vial (Rx) £13.61 (Hospital only)

**Solution for infusion**
- **Integrillin** (GlaxoSmithKline UK Ltd)
  - Eptifibatide 750 microgram per 1 ml Integrillin 75mg/100ml solution for infusion vials | 1 vial (Rx) £42.79 (Hospital only)
Tirofiban

**INDICATIONS AND DOSE**

In combination with unfractionated heparin, aspirin, and clopidogrel for prevention of early myocardial infarction in patients with unstable angina or non-ST-segment-elevation myocardial infarction (NSTE-MI) and with last episode of chest pain within 12 hours (with angiography planned for 4–48 hours after diagnosis (initiated under specialist supervision))

BY INTRAVENOUS INFUSION

- Adult: Initially 400 nanograms/kg/minute for 30 minutes, then 100 nanograms/kg/minute for at least 48 hours (continue during and for 12–24 hours after percutaneous coronary intervention), maximum duration of treatment 108 hours

In combination with unfractionated heparin, aspirin, and clopidogrel for prevention of early myocardial infarction in patients with unstable angina or non-ST-segment-elevation myocardial infarction (NSTE-MI) and with last episode of chest pain within 12 hours (with angiography within 4 hours of diagnosis) (initiated under specialist supervision)

INITIALLY BY INTRAVENOUS INJECTION

- Adult: 25 micrograms/kg, to be given over 3 minutes at start of percutaneous coronary intervention, then (by intravenous infusion) 150 nanograms/kg/minute for 12–24 hours, maximum duration of treatment 48 hours

In combination with unfractionated heparin, aspirin, and clopidogrel for reduction of major cardiovascular events in patients with ST-segment elevation myocardial infarction (STEMI) intended for primary percutaneous coronary intervention (PCI) (initiated under specialist supervision) INITIALLY BY INTRAVENOUS INJECTION

- Adult: 25 micrograms/kg, to be given over 3 minutes at start of percutaneous coronary intervention, then (by intravenous infusion) 150 nanograms/kg/minute for 12–24 hours, maximum duration of treatment 48 hours

**CONTRA-INDICATIONS**

Abnormal bleeding within 30 days - history of aneurysm - history of arteriovenous malformation - history of haemorrhagic stroke - history of intracranial disease - history of neoplasm - increased INR - increased prothrombin time - severe hypertension - stroke within 50 days - thrombocytopenia

**CAUTIONS**

- Active peptic ulcer (within 3 months) - acute pericarditis - anaemia - aortic dissection - cardiogenic shock - discontinue if intra-aortic balloon pump necessary - discontinue if thrombolytic therapy necessary - discontinue immediately if serious or uncontrollable bleeding occurs - discontinue if emergency cardiac surgery necessary - elderly - faecal occult blood - haematuria - haemorrhagic retinopathy - low body-weight - major surgery within 5 months (avoid if within 6 weeks) - organ biopsy or lithotripsy within last 2 weeks - puncture of non-compressible vessel within 24 hours - risk of bleeding (within 3 months) - severe heart failure - severe trauma within 5 months (avoid if within 6 weeks) - traumatic or protracted cardiopulmonary resuscitation within last 2 weeks - uncontrollable severe hypertension - vasculitis

**INTERACTIONS**

Appendix 1 (tirofiban).

Concomitant drugs that increase risk of bleeding (including within 48 hours of thrombolytic administration).

**SIDE-EFFECTS**

- Bleeding manifestations - fever - headache - nausea - reversible thrombocytopenia

**PREGNANCY**

Manufacturer advises use only if potential benefit outweighs risk—no information available.

**BREAST FEEDING**

Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT**

Caution in mild to moderate liver disease. Avoid in severe liver disease—increased risk of bleeding.

**RENAL IMPAIRMENT**

Increased risk of bleeding. Use half normal dose if eGFR less than 30 mL/minute/1.73 m².

Monitor carefully if eGFR less than 60 mL/minute/1.73 m².

**MONITORING REQUIREMENTS**

Monitor platelet count, haemoglobin and haematocrit before treatment, 2–6 hours after start of treatment and then at least once daily.

**DIRECTIONS FOR ADMINISTRATION**

For intravenous infusion (Aggrastat®), give continuously in Glucose 5% or Sodium chloride 0.9%. Withdraw 50 mL infusion fluid from 250 mL bag and replace with 50 mL tirofiban concentrate (250 micrograms/mL) to give a final concentration of 50 micrograms/mL.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Infusion**

ELECTROLYTES: May contain Sodium 

- Aggrastat (Correvio GmbH)

  Tirofiban (as Tirofiban hydrochloride) 50 microgram per 1 mL Aggrastat 12.5mg/250ml infusion bags 1 bag.price no price available (Hospital only)

**Solution for infusion**

ELECTROLYTES: May contain Sodium 

- Aggrastat (Correvio GmbH)

  Tirofiban (as Tirofiban hydrochloride) 250 microgram per 1 mL Aggrastat 12.5mg/50ml concentrate for solution for infusion vials 1 vial.price no price available (Hospital only)

**Piperazine derivatives**

Ranolazine

**INDICATIONS AND DOSE**

As adjunctive therapy in the treatment of stable angina in patients inadequately controlled or intolerant of first-line antianginal therapies

BY MOUTH

- Adult: Initially 375 mg twice daily for 2–4 weeks, then increased to 500 mg twice daily, then increased if necessary up to 750 mg twice daily; reduced if not tolerated to 375–500 mg twice daily

**CAUTIONS**

Body-weight less than 60 kg - elderly - moderate to severe congestive heart failure - QT interval prolongation

**INTERACTIONS**

Appendix 1 (ranolazine).

**SIDE-EFFECTS**

- Common or very common Asthenia - constipation - dizziness - headache - nausea - vomiting


- Rare Allergic dermatitis - anemia - angioedema - cold extremities - erectile dysfunction - erogenous dysesthesia - impaired hearing - loss of consciousness - pancreatitis - parosmia - rash - renal failure - throat tightness - urticaria - Weight loss

**PREGNANCY**

Manufacturer advises avoid unless essential—no information available.
PATIENT AND CARER ADVICE

BREAST FEEDING
Manufacturer advises avoid—no information available.

HEPATIC IMPAIRMENT
Use with caution in mild impairment; avoid in moderate and severe impairment.

RENAL IMPAIRMENT
Use with caution if eGFR 30–80 mL/minute/1.73 m²; avoid if eGFR less than 30 mL/minute/1.73 m².

PATIENT AND CARER ADVICE
Patient alert card to be provided.

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (October 2012) that ranolazine (Ranexa) is not recommended for use within NHS Scotland.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Modified-release tablet

CAUTIONARY AND ADVISORY LABELS 25

Ranolazine 375 mg Ranexa 375 mg modified-release tablets
60 tablet $48.98 DT price = $48.98

Ranolazine 500 mg Ranexa 500 mg modified-release tablets
60 tablet $48.98 DT price = $48.98

Ranolazine 750 mg Ranexa 750 mg modified-release tablets
60 tablet $48.98 DT price = $48.98

HEPATIC IMPAIRMENT

CAUTIONS
Acute myocardial infarction with acute left ventricular failure and low filling pressures - acute pulmonary oedema - hypovolaemia - low systolic blood pressure

INTERACTIONS
Appendix 1 (nicorandil).

SIDE-EFFECTS
Common or very common Cutaneous vasodilation with flushing - dizziness - headache (especially on initiation, usually transitory) - increase in heart rate (at high doses) - nausea - rectal bleeding - vomiting - weakness

Uncommon Angioedema - hypotension - myalgia - oral ulceration

Rare Abdominal pain - anal ulceration - cholestasis - hepatitis - intestinal ulceration - jaundice - pruritus - rash - skin ulceration

PREGNANCY
Manufacturer advises use only if potential benefit outweighs risk—no information available.

BREAST FEEDING
No information available—manufacturer advises avoid.

PATIENT AND CARER ADVICE
Patients should be warned not to drive or operate machinery until it is established that their performance is unimpaired.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: powder

SELECTIVE SINUS NODE I F INHIBITORS

Ivabradine

INDICATIONS AND DOSE
Treatment of angina in patients in normal sinus rhythm

BY MOUTH

Adult: Initially 5 mg twice daily for 2–4 weeks, then increased if necessary to 7.5 mg twice daily; reduced if not tolerated to 2.5–5 mg twice daily, heart rate at rest should not be allowed to fall below 50 beats per minute

Elderly: Initially 2.5 mg twice daily, heart rate at rest should not be allowed to fall below 50 beats per minute

Mild to severe chronic heart failure

BY MOUTH

Adult: Initially 5 mg twice daily for 2 weeks, then increased if necessary to 7.5 mg twice daily; reduced if not tolerated to 2.5 mg twice daily, heart rate at rest should not be allowed to fall below 50 beats per minute

CONTRA-INDICATIONS
Acute myocardial infarction - cardiogenic shock - congenital QT syndrome - do not initiate for angina if heart rate below 70 beats per minute - do not initiate for chronic heart failure if heart rate below 75 beats per minute - immediately after cerebrovascular accident - patients dependent on pacemaker - second- and third-degree heart block - severe hypotension - sick-sinus syndrome - sino-atrial block - unstable angina - unstable or acute heart failure

CAUTIONS
Atrial fibrillation or other arrhythmias (treatment ineffective) - elderly - in angina, consider stopping if there is no or limited symptom improvement after 5 months - intraventricular conduction defects - mild to moderate hypotension (avoid if severe) - retinitis pigmentosa

INTERACTIONS
Appendix 1 (ivabradine).

SIDE-EFFECTS
Common or very common Atrial fibrillation - blurred vision - bradycardia - dizziness - first-degree heart block - headache - phosphates - ventricular extrasystoles - visual disturbances

Uncommon Angioedema - constipation - diarrhoea - dysphonia - eosinophilia - hyperuricaemia - muscle cramps - nausea - palpitations - raised plasma-creatinine concentration - rash - supraventricular extrasystoles - vertigo

Very rare Second and third-degree heart block - sick sinus syndrome

PREGNANCY
Manufacturer advises avoid—toxicity in animal studies.

BREAST FEEDING
Present in milk in animal studies—manufacturer advises avoid.

HEPATIC IMPAIRMENT
Manufacturer advises caution in moderate impairment. Avoid in severe impairment.
Evidence of myocardial necrosis, whereas in NSTEMI, severe angina. Patients with unstable angina have no recurring or prolonged angina at rest, or new onset of ischaemia, with irreversible necrosis of the heart muscle, often leading to long-term complications. STEMI can also myocardial necrosis (less significant than with STEMI) will be evident. There is a risk of progression to STEMI or sudden death, particularly in patients who experience pain at rest.

Management of unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI)

These conditions are managed similarly; the aims of management are to provide supportive care and pain relief during the acute attack and to prevent further cardiac events and death. For advice on the management of patients with acute ST-segment elevation myocardial infarction (STEMI), see below.

Initial management

Oxygen should be administered if there is evidence of hypoxia, pulmonary oedema, or continuing myocardial ischaemia; hypoxia should be avoided and particular care is required in patients with chronic obstructive airways disease.

NitrateS are used to relieve ischaemic pain. If sublingual glyceryl trinitrate p. 190 is not effective, intravenous or buccal glyceryl trinitrate or intravenous isosorbide dinitrate p. 191 is given. If pain continues, drowsiness, hydrochloride p. 361 or morphine p. 367 can be given by slow intravenous injection; an antiemetic such as metoclopramide hydrochloride p. 347 should also be given.

Aspirin p. 104 (chewed or dispersed in water) is given for its antiplatelet effect. If aspirin is given before arrival at hospital, a note saying that it has been given should be sent with the patient. Clopidogrel p. 106 should also be given.

Prasugrel p. 188 is an alternative to clopidogrel in certain patients undergoing percutaneous coronary intervention (see NICE guidance p. 188). Ticagrelor p. 188 is also an alternative to clopidogrel (see NICE guidance p. 188).

Patients should also receive either heparin (unfractionated) p. 114, a low molecular weight heparin, or fondaparinux sodium p. 109. Patients without contra-indications should receive beta-blockers which should be continued indefinitely. In patients without left ventricular dysfunction and in whom beta-blockers are inappropriate, diltiazem hydrochloride p. 149 or verapamil hydrochloride p. 156 can be given.

The glycoprotein Ib/IIa inhibitors epifibatide p. 183 (in combination with heparin (unfractionated) p. 114 and aspirin) and tirofiban p. 184 (in combination with heparin (unfractionated) aspirin, and clopidogrel) can be used for unstable angina or for NSTEMI in patients at a high risk of either myocardial infarction or death.

In intermediate- and high-risk patients, abciximab or epifibatide (in combination with heparin (unfractionated) and aspirin), or tirofiban (in combination with heparin (unfractionated), aspirin, and clopidogrel) can also be used in patients undergoing percutaneous coronary intervention, to reduce the immediate risk of vascular occlusion. In intermediate- and high-risk patients in whom early intervention is planned, bivalirudin p. 116 can be considered as an alternative to the combination of a glycoprotein Ib/IIa inhibitor plus a heparin.

Revascularisation procedures are often appropriate for patients with unstable angina or NSTEMI; the use of antiplatelet drugs in patients undergoing coronary stenting.

Long-term management

The need for long-term angina treatment or for coronary angiography should be assessed. Most patients will require standard angina treatment to prevent recurrence of symptoms.

ST-segment elevation myocardial infarction (STEMI)

This is an acute coronary syndrome where atheromatous plaque rupture leads to thrombosis and myocardial ischaemia, with irreversible necrosis of the heart muscle,
occasionally occur as a result of coronary spasm or embolism, arteritis, spontaneous thrombosis, or sudden severe elevation in blood pressure.

**Management of ST-segment elevation myocardial infarction (STEMI)**

These notes give an overview of the initial and long-term management of myocardial infarction with ST segment elevation (STEMI). For advice on the management of non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina, see above. The aims of management of STEMI are to provide supportive care and pain relief, to promote reperfusion and to reduce mortality. Oxygen, nitrates, and diphosphonate hydrochloride p. 361 or morphine p. 367 can provide initial support and pain relief; aspirin and percutaneous coronary intervention or thrombolytics promote reperfusion; anticoagulants help to reduce re-occlusion and systemic embolisation; long-term use of aspirin, beta-blockers, ACE inhibitors, and statins help to reduce mortality further.

Local guidelines for the management of myocardial infarction should be followed where they exist.

**Initial management**

**Oxygen** should be administered if there is evidence of hypoxia, pulmonary oedema, or continuing myocardial ischaemia; hyperoxia should be avoided and particular care is required in patients with chronic obstructive airways disease.

The pain (and anxiety) of myocardial infarction is managed with slow intravenous injection of diphosphonate hydrochloride or morphine; an antiemetic such as metoclopramide hydrochloride p. 347 (or, if left ventricular function is not compromised, cyclizine p. 343) by intravenous injection should also be given.

Aspirin (chewed or dispersed in water) is given for its antiplatelet effect. If aspirin is given before arrival at hospital, a note saying that it has been given should be sent with the patient. Clopidogrel p. 106, should also be given. Prasugrel p. 188, is an alternative to clopidogrel in certain patients undergoing percutaneous coronary intervention (see NICE guidance p. 188). Ticagrelor p. 188, is also an alternative to clopidogrel (see NICE guidance p. 188).

Patency of the occluded artery can be restored by percutaneous coronary intervention or by giving a thrombolytic drug, unless contra-indicated. Percutaneous coronary intervention is the preferred method; a glycoprotein IIb/IIIa inhibitor can be used to reduce the risk of immediate vascular occlusion in intermediate- and high-risk patients. Patients undergoing percutaneous coronary intervention should also receive either heparin (unfractionated) or a low molecular weight heparin (e.g. enoxaparin sodium p. 113); bivalirudin p. 116 is an alternative to the combination of a glycoprotein IIb/IIIa inhibitor plus a heparin (see also NICE guidance p. 117). In patients who cannot be offered percutaneous coronary intervention within 90 minutes of diagnosis, a thrombolytic drug should be administered along with either heparin (unfractionated) (for maximum 2 days), a low molecular weight heparin (e.g. enoxaparin sodium), or fondaparinux sodium. See use of antiplatelet drugs in patients undergoing coronary stenting p. 103.

Patients who do not receive reperfusion therapy (with percutaneous coronary intervention or a thrombolytic) should be treated with either fondaparinux sodium, enoxaparin sodium, or heparin (unfractionated). Prescribers should consult product literature and local protocols (where they exist) for details of anticoagulant dose and duration.

**Nitrates** are used to relieve ischaemic pain. If sublingual glyceryl trinitrate p. 190 is not effective, intravenous glyceryl trinitrate or isosorbide dinitrate p. 191 is given. Early administration of some beta-blockers has been shown to be of benefit and should be given to patients without contra-indications.

**ACE inhibitors**, and angiotensin-II receptor antagonists if an ACE inhibitor cannot be used, are also of benefit to patients who have no contra-indications; in hypertensive and normotensive patients treatment with an ACE inhibitor, or an angiotensin-II receptor antagonist, can be started within 24 hours of the myocardial infarction and continued for at least 5–6 weeks (see below for long-term treatment). All patients should be closely monitored for hyperglycaemia; those with diabetes or raised blood-glucose concentration should receive insulin p. 603.

**Long-term management**

Long-term management following STEMI involves the use of several drugs which should ideally be started before the patient is discharged from hospital. Aspirin should be given to all patients, unless contra-indicated. The addition of clopidogrel has been shown to reduce morbidity and mortality. Prasugrel p. 188 or ticagrelor are alternatives to clopidogrel in certain patients. For those intolerant of clopidogrel, and who are at low risk of bleeding, the combination of warfarin sodium p. 121 and aspirin should be considered. In those intolerant of both aspirin and clopidogrel, warfarin sodium alone can be used. Warfarin sodium should be continued for those who are already being treated for another indication, such as atrial fibrillation, with the addition of aspirin if there is a low risk of bleeding. The combination of aspirin with clopidogrel or warfarin sodium increases the risk of bleeding. The combination of aspirin with clopidogrel or warfarin sodium increases the risk of bleeding. Low-dose rivaroxaban p. 109, in combination with aspirin alone or aspirin and clopidogrel, is licensed for the prevention of atherothrombotic events following STEMI—see Prevention of cardiovascular events p. 187. For details of antiplatelet drug duration following coronary stenting—see also Antiplatelet drugs and coronary stents p. 103.

**Beta-blockers** should be given to all patients in whom they are not contra-indicated. Acebutolol p. 141, metoprolol tartrate p. 144, propranolol hydrochloride p. 146 and timolol maleate p. 147 are suitable; for patients with left ventricular dysfunction, carvedilol p. 142, bisoprolol fumarate p. 142, or long-acting metoprolol tartrate may be appropriate.

Diltiazem hydrochloride p. 149 [unlicensed] or verapamil hydrochloride p. 156 can be considered if a beta-blocker cannot be used; however they are contra-indicated in those with left ventricular dysfunction. Other calcium-channel blockers have no place in routine long-term management after a myocardial infarction.

An **ACE inhibitor** should be considered for all patients, especially those with evidence of left ventricular dysfunction. If an ACE inhibitor cannot be used, an angiotensin-II receptor antagonist may be used for patients with heart failure. A relatively high dose of either the ACE inhibitor or angiotensin-II receptor antagonist may be required to produce benefit.

**Nitrates** are used for patients with angina. Eplerenone p. 167 is licensed for use following a myocardial infarction in those with left ventricular dysfunction and evidence of heart failure. See also the role of **statins** in preventing recurrent cardiovascular events p. 178.

**Prevention of cardiovascular events**

Patients with stable angina, unstable angina, or NSTEMI should be given advice and treatments to reduce their cardiovascular risk. The importance of lifestyle changes, especially stopping smoking, should be emphasised. Aspirin should be given indefinitely. Antihypertensive treatment should be initiated if appropriate, and a **statin** should also be given.
In patients with stable angina, addition of an ACE inhibitor should be considered for patients with diabetes (and should be continued if indicated for a co-morbidity).

In patients with unstable angina or NSTEMI, clopidogrel is given, in combination with aspirin, for up to 12 months—most benefit occurs during the first 3 months. Prasugrel below or ticagrelor below are alternatives to clopidogrel in certain patients. An ACE inhibitor should also be given.

Low-dose rivaroxaban p. 109, in combination with aspirin alone or aspirin and clopidogrel, is licensed for the prevention of atherothrombotic events following an acute coronary syndrome with elevated cardiac biomarkers.


**ANTIPLATELETS**

**Prasugrel**

**INDICATIONS AND DOSE**

In combination with aspirin for the prevention of atherothrombotic events in patients with acute coronary syndrome undergoing percutaneous coronary intervention

**BY MOUTH**

- Adult 18-74 years (body-weight up to 60 kg): Initially 60 mg for 1 dose, then 5 mg once daily usually for up to 12 months
- Adult 18-74 years (body-weight 60 kg and above): Initially 60 mg for 1 dose, then 10 mg once daily usually for up to 12 months
- Adult 75 years and over: Initially 60 mg for 1 dose, then 5 mg once daily usually for up to 12 months

Patients undergoing coronary angiography within 48 hours of admission for unstable angina or NSTEMI

**BY MOUTH**

- Adult: Initially 60 mg, to be administered at the time of percutaneous coronary intervention to minimise the risk of bleeding, maintenance dose of 10 mg or 5 mg daily should then be selected as appropriate

**Alternative to clopidogrel in certain patients undergoing percutaneous coronary intervention**

**BY MOUTH**

- Adult: 60 mg as a single dose

- **CONTRA-INDICATIONS** Active bleeding - history of stroke or transient ischaemic attack

- **CAUTIONS** Body-weight less than 60 kg - discontinue at least 7 days before elective surgery if antplatelet effect not desirable - elderly patients at increased risk of bleeding (e.g. from recent trauma, surgery, gastrointestinal bleeding, or active peptic ulcer disease)

- **INTERACTIONS → Appendix 1 (prasugrel).** Caution with concomitant use of drugs that increase risk of bleeding.

- **SIDE-EFFECTS**

  - Common or very common Anaemia, gastro-intestinal haemorrhage, haematoma, haematuria, haemorrhage, intracranial haemorrhage, rash
  - Uncommon Angioedema, hypersensitivity reactions
  - Rare Thrombocytopenia
  - Frequency not known Thrombotic thrombocytopenic purpura

- **ALLERGY AND CROSS-SENSITIVITY** Caution in patients with history of hypersensitivity reactions to thienopyridines (e.g. clopidogrel).

- **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT** Use with caution in moderate impairment—increased risk of bleeding. Avoid in severe impairment.

- **RENAI IMPAIRMENT** Use with caution—increased risk of bleeding.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  - **NICE technology appraisals (TAs)**

    - Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (July 2014) NICE TA317

    Prasugrel 10 mg in combination with aspirin is recommended as an option, within its marketing authorisation, for preventing atherothrombotic events in adults with acute coronary syndrome (unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI) or ST segment elevation myocardial infarction (STEMI)) having primary or delayed percutaneous coronary intervention. [www.nice.org.uk/TA317](http://www.nice.org.uk/TA317)

- **Scottish Medicines Consortium (SMC) Decisions**

  The Scottish Medicines Consortium has advised (August 2009) that prasugrel (Efient®), in combination with aspirin, be accepted for restricted use within NHS Scotland for the prevention of atherothrombotic events in patients with acute coronary syndrome undergoing percutaneous coronary intervention who are eligible to receive the 10 mg dose of prasugrel.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

- **Tablet**

  - **Efient** (Eli Lilly and Company Ltd)

    - Prasugrel (as Prasugrel hydrochloride) 5 mg Efient 5mg tablets | 28 tablet [Pack] £27.56 GT price = £27.56
    - Prasugrel (as Prasugrel hydrochloride) 10 mg Efient 10mg tablets | 28 tablet [Pack] £47.56 GT price = £47.56

- **Ticagrelor**

  **INDICATIONS AND DOSE**

  In combination with aspirin for the prevention of atherothrombotic events in patients with acute coronary syndrome

  **BY MOUTH**

  - Adult: Initially 180 mg for 1 dose, then 90 mg twice daily usually for up to 12 months

  **Alternative to clopidogrel in patients undergoing percutaneous coronary intervention**

  **BY MOUTH**

  - Adult: 180 mg as a single dose

- **CONTRA-INDICATIONS** Active bleeding - history of intracranial haemorrhage

- **CAUTIONS** Asthma - bradycardia (unless pacemaker fitted) - chronic obstructive pulmonary disease - discontinue 7 days before elective surgery if antplatelet effect not desirable - history of hyperuricaemia - patients at increased risk of bleeding (e.g. from recent trauma, surgery, gastrointestinal bleeding, or coagulation disorders) - second- or third-degree AV block (unless pacemaker fitted) - sick sinus syndrome (unless pacemaker fitted)

- **INTERACTIONS** Caution with concomitant use of drugs that increase risk of bleeding.

- **SIDE-EFFECTS**

  - Common or very common Bruising - dyspnoea - haemorrhage
Uncommon Abdominal pain · diarrhoea · dizziness · dyspepsia · gastritis · headache · nausea · pruritus · rash · vomiting

Rare Confusion · constipation · hyperuricaemia · paraesthesia · raised serum creatinine · vertigo

PREGNANCY Manufacturer advises avoid—toxicity in animal studies.

BREAST FEEDING Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT Avoid in moderate or severe impairment—no information available.

MONITORING REQUIREMENTS Monitor renal function 1 month after initiation.

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

Ticagrelor for the treatment of acute coronary syndromes (October 2011) NICE TA236

Ticagrelor, in combination with low-dose aspirin, is recommended for up to 12 months as a treatment option in adults with acute coronary syndromes, that is, people:

- with ST-segment elevation myocardial infarction—defined as ST elevation or new left bundle branch block on electrocardiogram—that cardiologists intend to treat with primary percutaneous coronary intervention, or
- with non-ST-segment elevation myocardial infarction (NSTEMI), or
- admitted to hospital with unstable angina—defined as ST or T wave changes on electrocardiogram suggestive of ischaemia plus one of the characteristics defined below. Before ticagrelor is continued beyond the initial treatment, the diagnosis of unstable angina should first be confirmed, ideally by a cardiologist.

Characteristics to be used in defining treatment with ticagrelor for unstable angina are:

- age 60 years or older;
- previous myocardial infarction or previous coronary artery bypass grafting;
- coronary artery disease with stenosis of 50% or more in at least two vessels;
- previous ischaemic stroke;
- previous transient ischaemic attack, carotid stenosis of at least 50%, or cerebral revascularisation;
- diabetes mellitus;
- peripheral arterial disease, or
- chronic renal dysfunction (creatinine clearance less than 60 mL/minute/1.73 m²).

www.nice.org.uk/TA236

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

- Brilique (AstraZeneca UK Ltd)
  
  Brilique 90 mg Brilique 90mg tablets | 56 tablet pack £54.60 DT price = £54.60

NITRATES

Nitrates

Nitrates have a useful role in angina. Although they are potent coronary vasodilators, their principal benefit follows from a reduction in venous return which reduces left ventricular work. Unwanted effects such as flushing, headache, and postural hypotension may limit therapy, especially when angina is severe or when patients are unusually sensitive to the effects of nitrates.

Sublingual glyceryl trinitrate p. 190 is one of the most effective drugs for providing rapid symptomatic relief of angina, but its effect lasts only for 20 to 30 minutes; the 300-microgram tablet is often appropriate when glyceryl trinitrate is first used. The aerosol spray provides an alternative method of rapid relief of symptoms for those who find difficulty in dissolving sublingual preparations. Duration of action may be prolonged by transdermal preparations (but tolerance may develop).

Isosorbide dinitrate p. 191 is active sublingually and is a more stable preparation for those who only require nitrates infrequently. It is also effective by mouth for prophylaxis; although the effect is slower in onset, it may persist for several hours. Duration of action of up to 12 hours is claimed for modified-release preparations. The activity of isosorbide dinitrate may depend on the production of active metabolites, the most important of which is isosorbide mononitrate p. 192. Isosorbide mononitrate itself is also licensed for angina prophylaxis; modified-release formulations (for once daily administration) are available. Glyceryl trinitrate p. 190 or isosorbide dinitrate may be tried by intravenous injection when the sublingual form is ineffective in patients with chest pain due to myocardial infarction or severe ischaemia. Intravenous injections are also useful in the treatment of congestive heart failure.

CONTRA-INDICATIONS Aortic stenosis · cardiac tamponade · constrictive pericarditis · hypertrophic cardiomyopathy · hypotensive conditions · hypovolaemia · marked anaemia · mitral stenosis · raised intracranial pressure due to cerebral haemorrhage · raised intracranial pressure due to head trauma · toxic pulmonary oedema

CAUTIONS Heart failure due to obstruction · hypothermia · hypothyroidism · hypoxaemia · malnutrition · metal-containing transdermal systems should be removed before magnetic resonance imaging procedures, cardioversion, or diathermy · recent history of myocardial infarction · susceptibility to angle-closure glaucoma · tolerance · ventilation and perfusion abnormalities

CAUTIONS, FURTHER INFORMATION

Tolerance Many patients on long-acting or transdermal nitrates rapidly develop tolerance (with reduced therapeutic effects). Reduction of blood-nitrate concentrations to low levels for 4 to 12 hours each day usually maintains effectiveness in such patients. If tolerance is suspected during the use of transdermal patches they should be left off for 8–12 hours (usually overnight) in each 24 hours; in the case of modified-release tablets of isosorbide dinitrate (and conventional formulations of isosorbide mononitrate), the second of the two daily doses should be given after about 8 hours rather than after 12 hours. Conventional formulations of isosorbide mononitrate should not usually be given more than twice daily unless small doses are used; modified-release formulations of isosorbide mononitrate should only be given once daily, and used in this way do not produce tolerance.

INTERACTIONS Appendix 1 (nitrates).

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

- Common or very common Dizziness · postural hypotension · tachycardia · throbbing headache
- Uncommon Flushing · heartburn · nausea · rash · syncope · temporary hypoxaemia · vomiting
- Very rare Angle-closure glaucoma
- Frequency not known Paradoxical bradycardia

SPECIFIC SIDE-EFFECTS

- Uncommon
  - With transdermal use application site reactions with transdermal patches
  - Frequency not known
Glycerel trinitrate

INDICATIONS AND DOSE
Prophylaxis and treatment of angina
BY SUBLINGUAL ADMINISTRATION USING SUBLINGUAL TABLETS
Adult: 0.3–1 mg; dose may be repeated as required.
Control of hypertension and myocardial ischaemia during and after cardiac surgery | Induction of controlled hypotension during surgery | Congestive heart failure | Unstable angina
BY INTRAVENOUS INFUSION
Adult: 10–200 micrograms/minute (max. per dose 400 micrograms/minute), adjusted according to response, consult product literature for recommended starting doses specific to indication
Treatment or prophylaxis of angina
BY SUBLINGUAL ADMINISTRATION USING AEROSOL SPRAY
Adult: 1–2 sprays, dose be administered under tongue and then close mouth
NITRO-DUR®
Prophylaxis of angina
BY TRANSDERMAL APPLICATION
Adult: One '0.2mg/5h' patch to be applied to chest or outer upper arm and replaced every 24 hours, sitting replacement patch on different area, dose adjusted according to response; maximum 15 mg per day
DEPONIT®
Prophylaxis of angina
BY TRANSDERMAL APPLICATION
Adult: One '5' or one '10' patch to be applied to lateral chest wall, upper arm, thigh, abdomen, or shoulder; increase to two '10' patches every 24 hours if necessary, to be replaced every 24 hours, sitting replacement patch on different area
MINITRAN®
Prophylaxis of angina
BY TRANSDERMAL APPLICATION
Adult: One '5' patch to be applied to chest or upper arm; replace every 24 hours, sitting replacement patch on different area, dose to be adjusted according to response
Maintenance of venous patency ('5' patch only)
BY TRANSDERMAL APPLICATION
Adult: (consult product literature)

SIDE-EFFECTS
With intravenous use | abdominal pain | apprehension | diaphoresis | muscle twitching | palpitation | prolonged administration has been associated with methaemoglobinemia | restlessness | retrosternal discomfort | severe hypotension

SIDE-EFFECTS, FURTHER INFORMATION
With intravenous use | Side-effects may be associated with over rapid administration (reduce rate of injection).

ALLERGY AND CROSS-SENSITIVITY
Contraindicated in nitrate hypersensitivity.

BREAST FEEDING
No information available—manufacturers advise use only if potential benefit outweighs risk.

HEPATIC IMPAIRMENT
Caution in severe impairment.

RENAL IMPAIRMENT
Manufacturers advise use only if potential benefit outweighs risk.

TREATMENT REQUIREMENTS
Monitor blood pressure and heart rate during intravenous infusion.

PREGNANCY
Not known to be harmful.

DIRECTIONS FOR ADMINISTRATION
With intravenous use | Glass or polyethylene apparatus is preferable; loss of potency will occur if PVC is used. For intravenous infusion (Nitrocin®, Nitronal®), give continuously in Glucose 5% or Sodium Chloride 0.9%. For Nitrocine®, suggested infusion concentration 100 micrograms/mL; incompatible with polyvinyl chloride infusion containers such as Viaflex® or Steriflex®; use glass or polyethylene containers or give via a syringe pump.
Glycerel trinitrate 1 mg/ml to be diluted before use or given undiluted with syringe pump. Glycerel trinitrate 5 mg/ml to be diluted before use.

PRESCRIBING AND DISPENSING INFORMATION
With sublingual use | Glyceryl trinitrate tablets should be supplied in glass containers of not more than 100 tablets, closed with a foil-lined cap, and containing no cotton wool wadding; they should be discarded after 8 weeks in use.

PATIENT AND CARER ADVICE
Rectal ointment should be discarded 8 weeks after first opening.

PERCUTOL®
Patients or carers should be given advice on how to administer glyceryl trinitrate ointment.

NATIONAL FUNDING/ACCESS DECISIONS
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (January 2008) that glyceryl trinitrate 0.4% ointment (Rectogesic®) is not recommended for use within NHS Scotland for the relief of pain associated with chronic anal fissure.

MEDECIN FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ointment

TRANSDERM-NITRO®
Prophylaxis of angina
BY TRANSDERMAL APPLICATION
Adult: One '5' or one '10' patch to be applied to lateral chest wall and replaced every 24 hours, sitting replacement patch on different area, max. two '10' patches daily
Prophylaxis of phlebitis and extravasation ('5' patch only)
BY TRANSDERMAL APPLICATION
Adult: (consult product literature)
PERCUTOL®
Prophylaxis of angina (to determine dose)
TO THE SKIN
Adult: ½ inch to be administered on first day then increased by ½ inch/day until headache occurs, then reduced by ½ inch, approx. 800 micrograms/hour absorbed from 1 inch of ointment
Prophylaxis of angina
TO THE SKIN
Adult: 1–2 inches every 3–4 hours as required, to be measured on to Applipure® and applied (usually to chest, arm, or thigh) without rubbing in and secured with surgical tape, approx. 800 micrograms/hour absorbed from 1 inch of ointment.

Anal fissure
BY RECTUM USING RECTAL OINTMENT
Adult: Apply 2.5 centimetres every 12 hours until pain stops. Max. duration of use 8 weeks, apply to anal canal, 2.5 cm of ointment contains 1.5 mg of glyceryl trinitrate

SIDE-EFFECTS
With rectal use | Burning | diarrhoea | itching | rectal bleeding

PREGNANCY
Not known to be harmful.

NATIONAL FUNDING/ACCESS DECISIONS
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (January 2008) that glyceryl trinitrate 0.4% ointment (Rectogesic®) is not recommended for use within NHS Scotland for the relief of pain associated with chronic anal fissure.

MEDECIN FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ointment

190 Myocardial ischaemia

With intravenous use: abdominal pain • apprehension • diaphoresis • muscle twitching • palpitation • prolonged administration has been associated with methaemoglobinemia • restlessness • retrosternal discomfort • severe hypotension.
**Cardiovascular system**

**Acute coronary syndromes** 191

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**Sublingual tablet**

**CAUTIONARY AND ADVISORY LABELS**

- **GLYCERIL TRINITRATE (Non-proprietary)**
  - Glyceril trinitrate 300 microgram GTN 300 microgram sublingual tablets | 100 tablet [P] £2.71 DT price = £2.71
  - Glyceril trinitrate 500 microgram Glyceril trinitrate 500 microgram sublingual tablets | 100 tablet [P] £4.92 DT price = £2.08
  - Glyceril trinitrate 600 microgram Glyceril trinitrate 600 microgram sublingual tablets | 100 tablet [P] no price available

**Sublingual spray**

**CAUTIONARY AND ADVISORY LABELS**

- **GLYCERIL TRINITRATE (Non-proprietary)**
  - Glyceril trinitrate 400 microgram per 1 dose Glyceril trinitrate 400 micrograms/dose pump sublingual spray | 180 dose [P] £3.10 DT price = £3.10 | 200 dose [P] £3.44 DT price = £3.44
  - Glyceril trinitrate 400 micrograms/dose aerosol sublingual spray | 200 dose [P] £3.44
  - **Nitrolingual** (Merck Serono Ltd)
    - Glyceril trinitrate 400 microgram per 1 dose Nitrolingual 400 micrograms/dose pump sublingual spray | 75 dose [P] no price available (Hospital only) | 180 dose [P] £3.10 DT price = £3.10 | 200 dose [P] £3.44 DT price = £3.44
  - **Nitromin** (Teva UK Ltd)
    - Glyceril trinitrate 400 microgram per 1 dose Nitromin 400 micrograms/dose pump sublingual spray | 180 dose [P] £2.63 DT price = £3.10 | 200 dose [P] £2.71 DT price = £3.44

**Solution for infusion**

**EXCIPIENTS:** May contain Ethanol, propylene glycol

- **GLYCERIL TRINITRATE (Non-proprietary)**
  - Glyceril trinitrate 1 mg per 1 ml Glyceril trinitrate 50 mg/ml solution for infusion vials | 1 vial [P] £15.90 | 25 vial [P] no price available
  - Glyceril trinitrate 5 mg per 1 ml Glyceril trinitrate 50 mg/ml solution for infusion ampoules | 15 ampoule [P] £64.90
  - Glyceril trinitrate 25 mg/5 ml solution for infusion ampoules | 5 ampoule [P] £32.45
  - **Nitrocin** (UCB Pharma Ltd)
    - Glyceril trinitrate 1 mg per 1 ml Nitrocin 10 mg/10 ml solution for infusion ampoules | 10 ampoule [P] £58.75 (Hospital only)
  - **Nitronal** (Merck Serono Ltd)
    - Glyceril trinitrate 1 mg per 1 ml Nitronal 5 mg/5 ml solution for infusion ampoules | 10 ampoule [P] £18.04
  - Nitrocin 50 mg/50 ml solution for infusion vials | 1 vial [P] £14.76

**Transdermal patch**

- **GLYCERIL TRINITRATE (Non-proprietary)**
  - Glyceril trinitrate 5 mg per 24 hour Glyceril trinitrate 5 mg/24 hours transdermal patches | 28 patch [P] no price available
  - Glyceril trinitrate 10 mg per 24 hour Glyceril trinitrate 10 mg/24 hours transdermal patches | 28 patch [P] no price available
  - Glyceril trinitrate 15 mg per 24 hour Glyceril trinitrate 15 mg/24 hours transdermal patches | 30 patch [P] no price available
  - **Deponit** (UCB Pharma Ltd)
    - Glyceril trinitrate 5 mg per 24 hour Deponit 5 transdermal patches | 28 patch [P] £12.77
    - Glyceril trinitrate 10 mg per 24 hour Deponit 10 transdermal patches | 28 patch [P] £14.06
  - **Minitrin** (Meda Pharmaceuticals Ltd)
    - Glyceril trinitrate 5 mg per 24 hour Minitrin 5 transdermal patches | 30 patch [P] £11.62
    - Glyceril trinitrate 10 mg per 24 hour Minitrin 10 transdermal patches | 30 patch [P] £12.87
    - Glyceril trinitrate 15 mg per 24 hour Minitrin 15 transdermal patches | 30 patch [P] £14.19
  - **Nitro-Dur** (Merck Sharp & Dohme Ltd)
    - Glyceril trinitrate 5 mg per 24 hour Nitro-Dur 0.2 mg/hour transdermal patches | 28 patch [P] £10.59
    - Glyceril trinitrate 10 mg per 24 hour Nitro-Dur 0.4 mg/hour transdermal patches | 28 patch [P] £11.72
    - Glyceril trinitrate 15 mg per 24 hour Nitro-Dur 0.6 mg/hour transdermal patches | 28 patch [P] £12.90
  - **Transderm-Nitro** (Novartis Pharmaceuticals UK Ltd)
    - Glyceril trinitrate 5 mg per 24 hour Transderm-Nitro 5 transdermal patches | 28 patch [P] £17.05
    - Glyceril trinitrate 10 mg per 24 hour Transderm-Nitro 10 transdermal patches | 28 patch [P] £18.74

**Ointment**

**EXCIPIENTS:** May contain Wool fat and related substances including lanolin

- **Percutol** (Aspire Pharma Ltd)
  - Glyceril trinitrate 20 mg per 1 gram Percutol 2% ointment | 60 gram [P] £70.60 DT price = £70.60

**Rectal ointment**

- **Rectogesic** (Prostrakon Ltd)
  - Glyceril trinitrate 4 mg per 1 gram Rectogesic 0.4% rectal ointment | 30 gram [P] £39.90 DT price = £39.30

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**Isosorbide dinitrate**

**INDICATIONS AND DOSE**

**Prophylaxis and treatment of angina**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

- **Adult:** 30–120 mg daily in divided doses

**BY INTRAVENOUS INFUSION**

- **Adult:** 2–10 mg/hour, increased if necessary up to 20 mg/hour

**BY SUBLINGUAL ADMINISTRATION USING AEROSOL SPRAY**

- **Adult:** 1–3 sprays, to be administered under tongue whilst holding breath, allow a 30 second interval between each dose

**Left ventricular failure**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

- **Adult:** 40–160 mg daily in divided doses, increased if necessary up to 240 mg daily in divided doses

**BY INTRAVENOUS INFUSION**

- **Adult:** Initially 2–10 mg/hour, increased if necessary up to 20 mg/hour

**Prophylaxis of angina**

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

- **Adult:** 40 mg daily in 1–2 divided doses, increased if necessary to 60–80 mg daily in 2–3 divided doses

- **PREGNANCY** May cross placenta—manufacturers advise avoid unless potential benefit outweighs risk.

**DIRECTIONS FOR ADMINISTRATION**

For intravenous infusion (Isoket 0.05%/0. Isoket 0.1%/), give continuously in Glucose 5% or Sodium chloride 0.9%. Adsorbed to some extent by polyvinyl chloride infusion containers; preferably use glass or polyethylene containers or give via a syringe pump; Isoket 0.05% can alternatively be administered undiluted using a syringe pump with a glass or rigid plastic syringe. Glass or polyethylene infusion apparatus is preferable; loss of potency if PVC used.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, solution for infusion, oral solution

**Tablet**

- **ISOSORBIDE DINITRATE (Non-proprietary)**
  - Isosorbide dinitrate 10 mg Isosorbide dinitrate 10 mg tablets | 56 tablet [P] £30.00 DT price = £31.41
  - Isosorbide dinitrate 20 mg Isosorbide dinitrate 20 mg tablets | 56 tablet [P] £36.60 DT price = £34.38

**Modified-release tablet**

**CAUTIONARY AND ADVISORY LABELS**

- **ISOSORBIDE DINITRATE (Non-proprietary)**
  - Isosorbide dinitrate 20 mg Isosorbide dinitrate 20 mg modified-release tablets | 56 tablet [P] no price available
  - Isosorbide dinitrate 40 mg Isosorbide dinitrate 40 mg modified-release tablets | 56 tablet [P] no price available
  - **Isoket Retard** (UCB Pharma Ltd)
    - Isosorbide dinitrate 20 mg Isoket Retard 20 tablets | 56 tablet [P] £2.58
    - Isosorbide dinitrate 40 mg Isoket Retard 40 tablets | 56 tablet [P] £6.36
Cardiovascular system

Isosorbide mononitrate

INDICATIONS AND DOSE

Prophylaxis of angina | Adjunct in congestive heart failure

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

Adult: Initially 0.5 tablet daily for 2–4 days, to minimise possibility of headache, then 1 tablet daily, increased if necessary to 2 tablets daily, dose to be taken in the morning

MONOMIL® XL
Prophylaxis of angina

BY MOUTH

Adult: Initially 0.5 tablet daily for 2–4 days, to be taken if headache occurs, then 1 tablet daily, increased if necessary to 2 tablets daily, dose to be taken in the morning

ISMO RETAR®
Prophylaxis of angina

BY MOUTH

Adult: 1 tablet daily, to be taken in the morning

ISIB® 60XL
Prophylaxis of angina

BY MOUTH

Adult: Initially 0.5 tablet daily for 2–4 days, to be taken in the morning

MONOSORB® XL60
Prophylaxis of angina

BY MOUTH

Adult: Initially 0.5 tablet daily for the first 2–4 days, to minimise the possibility of headache, then 1 tablet daily, increased if necessary to 2 tablets daily, to be taken in the morning

IMDUR®
Prophylaxis of angina

BY MOUTH

Adult: Initially 0.5 tablet daily, to be taken if headache occurs; 1 tablet daily, then increased if necessary to 2 tablets daily, dose to be taken in the morning

MONOMAX® XL
Prophylaxis of angina

BY MOUTH

Adult: Initially 0.5 tablet daily for 2–4 days, to minimise possibility of headache, then 1 tablet daily, increased if necessary to 2 tablets daily, to be taken in the morning

ZEMON®
Prophylaxis of angina

BY MOUTH

Adult: Initially 30 mg daily for 2–4 days, to minimise possibility of headache, then 40–60 mg daily, increased if necessary to 80–120 mg once daily, to be taken in the morning

PREGNANCY

Manufacturers advise avoid unless potential benefit outweighs risk.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet

CAUTIONARY AND ADVISORY LABELS 25

ISOSORBIDE MONONITRATE (Non-proprietary)

| Isosorbide mononitrate 10 mg | Isosorbide mononitrate 10mg tablets | 56 tablet | £48.25 DT price = £4.27
| Isosorbide mononitrate 20 mg | Isosorbide mononitrate 20mg tablets | 56 tablet | no price available DT price = £5.26 | 56 tablet | £62.25 DT price = £5.26

Isosorbide mononitrate 40 mg | Isosorbide mononitrate 40mg tablets | 56 tablet | £36.75 DT price = £6.19 | 56 tablet | no price available DT price = £6.19

Brands may include Ismo

Modified-release tablet

CAUTIONARY AND ADVISORY LABELS 25

ISOSORBIDE MONONITRATE (Non-proprietary)

| Isosorbide mononitrate 40 mg | Isosorbide mononitrate 40mg modified-release tablets | 28 tablet | no price available | 28 tablet | £50.64
| Chemydur 60XL (AMCo)
| Isosorbide mononitrate 60 mg | Chemydur 60XL tablets | 28 tablet | £3.49 DT price = £8.105
| Imdur (AstraZeneca UK Ltd)
| Isosorbide mononitrate 60 mg | Imdur 60mg modified-release tablets | 28 tablet | £10.50 DT price = £10.50
| Isib XL (Sinclair Iris Pharma Pfc)
| Isosorbide mononitrate 60 mg | Isib 60XL tablets | 28 tablet | £8.15 DT price = £10.50
SYMPATHOMIMETICS (INOTROPIC)

Cardiovascular system

Do not hallucinate.

Dobutamine

**DRUG ACTION** Dobutamine is a cardiac stimulant which acts on beta, receptors in cardiac muscle, and increases contractility with little effect on rate.

**INDICATIONS AND DOSE**

Inotropic support in infarction, cardiac surgery, cardiomyopathies, septic shock, cardiogenic shock, and during positive end expiratory pressure ventilation

**BY INTRAVENOUS INFUSION**

- Adult: Usual dose 2.5–10 micrograms/kg/minute, adjusted according to response, alternatively 0.5–40 micrograms/kg/minute

**Cardiac stress testing**

**BY INTRAVENOUS INFUSION**

- Adult: (consult product literature)

**CONTRA-INDICATIONS** Phaeochromocytoma

**CAUTIONS** Acute heart failure - acute myocardial infarction - arrhythmias - correct hypercapnia before starting and during treatment - correct hypovolaemia before starting and during treatment - correct hypoxia before starting and during treatment - correct metabolic acidosis before starting and during treatment - diabetes mellitus - elderly - extravasation may cause tissue necrosis - extreme caution or avoid in marked obstruction of cardiac ejection (such as idiopathic hypertrophic subaortic stenosis) - hypothyroidism - ischaemic heart disease - obliterrative vascular disease - severe hypotension - susceptibility to angle-closure glaucoma - tachycardia - tolerance may develop with continuous infusions longer than 72 hours

**INTERACTIONS** → Appendix 1 (sympathomimetics).

**SIDE-EFFECTS**

- Rare Psychosis

- Very rare Angle-closure glaucoma - AV block - bradycardia - cardiac arrest - coronary artery spasm - hypokalaemia - myocardial infarction - petechial bleeding

- Frequency not known Anxiety - arrhythmias - bronchospasm - cerebral haemorrhage - chest pain - dyspnoea - eosinophilia - fever - headache - hypertension (marked increase in systolic blood pressure indicates overdose) - hypotension - increased urinary urgency - myoclonic spasm - nausea - palpitation - paraesthesia - phlebitis - puritus of scalp - pulmonary oedema - rash - reduced platelet aggregation (on prolonged use) - tachycardia - tremor - vomiting

**PREGNANCY** No evidence of harm in animal studies— manufacturers advise use only if potential benefit outweighs risk.

**BREAST FEEDING** Manufacturers advise avoid—no information available.

**MONITORING REQUIREMENTS** Monitor serum-potassium concentration.

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion, give continuously in Glucose 5% or Sodium chloride 0.9%. Dilute to a concentration of 0.5–1 mg/mL and give via an infusion pump; give higher concentration (max. 5 mg/mL) through central venous catheter; incompatible with bicarbonate and other strong alkaline solutions. Dobutamine injection should be diluted before use or given undiluted with syringe pump. Dobutamine concentrate for intravenous infusion should be diluted before use.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

**EXCIPIENTS:** May contain Sulfites

- Dobutamine (Non-proprietary)
  - Dobutamine (as Dobutamine hydrochloride) 5 mg per 1 mL Dobutamine 250mg/50ml solution for infusion vials | 1 vial (£0.75)
  - Dobutamine (as Dobutamine hydrochloride) 12.5 mg per 1 mL Dobutamine 250mg/20ml concentrate for solution for infusion ampoules | 5 ampoule (£26.00-£26.25)

**Fibrinolytic drugs**

The value of thrombolytic drugs for the treatment of myocardial infarction has been established. Streptokinase p. 195 and alteplase p. 194 have been shown to reduce mortality. Retepase p. 195 and tenecteplase p. 195 are also licensed for acute myocardial infarction. Thrombolytic drugs are indicated for any patient with acute myocardial infarction for whom the benefit is likely to outweigh the risk of treatment. Trials have shown that the benefit is greatest
Alteplase
(rt-PA; Tissue-type plasminogen activator)

INDICATIONS AND DOSE
Acute myocardial infarction, accelerated regimen
INITIALLY BY INTRAVENOUS INJECTION
▶ Adult (body-weight up to 65 kg): Initially 15 mg, to be initiated within 6 hours of symptom onset, followed by (by intravenous infusion) 0.75 mg/kg, to be given over 30 minutes, then (by intravenous infusion) 0.5 mg/kg, to be given over 60 minutes, maximum total dose of 100 mg administered over 90 minutes
▶ Adult (body-weight 65 kg and above): Initially 15 mg, to be initiated within 6 hours of symptom onset, followed by (by intravenous infusion) 50 mg, to be given over 30 minutes, then (by intravenous infusion) 35 mg, to be given over 60 minutes, maximum total dose of 100 mg administered over 90 minutes

Acute myocardial infarction
INITIALLY BY INTRAVENOUS INJECTION
▶ Adult: Initially 10 mg, to be initiated within 6–12 hours of symptom onset, followed by (by intravenous infusion) 50 mg, to be given over 60 minutes, then (by intravenous infusion) 10 mg for 4 infusions, each 10 mg infusion dose to be given over 30 minutes, total dose of 100 mg over 3 hours; maximum 1.5 mg/kg in patients less than 65 kg

Pulmonary embolism
INITIALLY BY INTRAVENOUS INJECTION
▶ Adult: Initially 10 mg, to be given over 1–2 minutes, followed by (by intravenous infusion) 90 mg, to be given over 2 hours, maximum 1.5 mg/kg in patients less than 65 kg

Acute stroke (under specialist neurology physician only)
BY INTRAVENOUS INFUSION
▶ Adult 18-79 years: Initially 900 micrograms/kg (max. per dose 90 mg), treatment must begin within 4.5 hours of symptom onset, to be given over 60 minutes, the initial 10% of dose is to be administered by intravenous injection and the remainder by intravenous infusion

ACTILYSE CATHFL®
Thrombolytic treatment of occluded central venous access devices
BY INTRAVENOUS INJECTION
▶ Adult: (consult product literature)

CONTRA-INDICATIONS
▶ When used for acute ischaemic stroke Convulsion accompanying stroke. history of stroke in patients with diabetes. hyperglycaemia. hypoglycaemia. severe stroke. stroke in last 5 months

INTERACTIONS
Contra-indicated if concomitant treatment with oral anticoagulants.

SIDE-EFFECTS
Risk of cerebral bleeding increased in acute stroke

ALLERGY AND CROSS-SENSITIVITY
Contra-indicated if history of hypersensitivity to gentamicin (residue from manufacturing process).

MONITORING REQUIREMENTS
When used for acute ischaemic stroke Monitor for intracranial haemorrhage, and monitor blood pressure (antihypertensive recommended if systolic above 180 mmHg or diastolic above 105 mmHg).

DIRECTIONS FOR ADMINISTRATION
For intravenous infusion (Actilyse®), give intermittently or continuously in Sodium chloride 0.9%; dissolve in water for injections to a concentration of 1 mg/mL or 2 mg/mL and infuse intravenously; alternatively dilute the solution further in

Fibrinolytics

DRUG ACTION
Fibrinolytic drugs act as thrombolytics by activating plasminogen to form plasmin, which degrades fibrin and so breaks up thrombi.

CONTRA-INDICATIONS
Active pulmonary disease with cavitation. acute pancreatitis. aneurysm. aortic dissection. bacterial endocarditis. bleeding diatheses. coagulation defects. coma. heavy vaginal bleeding. history of cerebrovascular disease (especially recent events or with any residual disability). oesophageal varices. pericarditis. recent haemorrhage. recent surgery (including dental extraction). recent symptoms of possible peptic ulceration. recent trauma. severe hypertension.

CAUTIONS
Conditions in which thrombolysis might give rise to embolic complications such as enlarged left atrium with atrial fibrillation (risk of dissolution of clot and subsequent embolisation). elderly. external chest compression. hypertension. risk of bleeding (including that from venepuncture or invasive procedures).

INTERACTIONS
Caution with recent or concomitant use of drugs that increase the risk of bleeding.

SIDE-EFFECTS
Allergic reactions. anaphylaxis. angina. (when used in myocardial infarction). back pain. bleeding. breathing difficulty (usually limited to the site of injection, but can occur from other sites). cerebral oedema (caused by reperfusion). convulsions. fever. flushing. hypotension. intracerebral haemorrhage. nausea. pulmonary oedema (caused by reperfusion). rash. recurrent ischaemia (when used in myocardial infarction). reperfusion arrhythmias. (when used in myocardial infarction). urticaria. vomiting.

SIDE-EFFECTS, FURTHER INFORMATION
BLEEDING
Serious bleeding calls for discontinuation of the thrombolytic and may require administration of coagulation factors and antifibrinolytic drugs (e.g. tranexamic acid). Rarely further embolism may occur (either due to clots that break away from the original thrombus or to cholesterol crystal emboli).

Hypotension
Hypotension can usually be controlled by elevating the patient’s legs, or by reducing the rate of infusion or stopping it temporarily.

PREGNANCY
Thrombolytic drugs can possibly lead to premature separation of the placenta in the first 18 weeks of pregnancy. There is also a risk of maternal haemorrhage throughout pregnancy and post-partum, and also a theoretical risk of fetal haemorrhage throughout pregnancy.

HEPATIC IMPAIRMENT
Avoid in severe hepatic impairment as there is an increased risk of bleeding.

in those with ECG changes that include ST segment elevation (especially in those with anterior infarction) and in patients with bundle branch block. Patients should not be denied thrombolytic treatment on account of age alone because mortality in the elderly is high and the reduction in mortality is the same as in younger patients. Alteplase should be given within 6–12 hours of symptom onset, reteplase and streptokinase within 12 hours of symptom onset, but ideally all should be given within 1 hour; use after 12 hours requires specialist advice. Tenecteplase should be given as early as possible and usually within 6 hours of symptom onset.

Alteplase, streptokinase and urokinase p. 119 can be used for other thromboembolic disorders such as deep-vein thrombosis and pulmonary embolism. Alteplase is also used for acute ischaemic stroke.

Urokinase p. 119 is also licensed to restore the patency of occluded intravenous catheters and cannulas blocked with fibrin clots.

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Serious bleeding calls for discontinuation of the thrombolytic and may require administration of coagulation factors and antifibrinolytic drugs (e.g. tranexamic acid). Rarely further embolism may occur (either due to clots that break away from the original thrombus or to cholesterol crystal emboli).

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HEPATIC IMPAIRMENT
Avoid in severe hepatic impairment as there is an increased risk of bleeding.

Side-effects
Serious bleeding calls for discontinuation of the thrombolytic and may require administration of coagulation factors and antifibrinolytic drugs (e.g. tranexamic acid). Rarely further embolism may occur (either due to clots that break away from the original thrombus or to cholesterol crystal emboli).

Hypotension
Hypotension can usually be controlled by elevating the patient’s legs, or by reducing the rate of infusion or stopping it temporarily.

Pregnancy
Thrombolytic drugs can possibly lead to premature separation of the placenta in the first 18 weeks of pregnancy. There is also a risk of maternal haemorrhage throughout pregnancy and post-partum, and also a theoretical risk of fetal haemorrhage throughout pregnancy.

Hepatic impairment
Avoid in severe hepatic impairment as there is an increased risk of bleeding.

In those with ECG changes that include ST segment elevation (especially in those with anterior infarction) and in patients with bundle branch block. Patients should not be denied thrombolytic treatment on account of age alone because mortality in the elderly is high and the reduction in mortality is the same as in younger patients. Alteplase should be given within 6–12 hours of symptom onset, reteplase and streptokinase within 12 hours of symptom onset, but ideally all should be given within 1 hour; use after 12 hours requires specialist advice. Tenecteplase should be given as early as possible and usually within 6 hours of symptom onset.

Alteplase, streptokinase and urokinase p. 119 can be used for other thromboembolic disorders such as deep-vein thrombosis and pulmonary embolism. Alteplase is also used for acute ischaemic stroke.

Urokinase p. 119 is also licensed to restore the patency of occluded intravenous catheters and cannulas blocked with fibrin clots.
the infusion fluid to a concentration of not less than 200 micrograms/mL; not to be infused in glucose solution.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE technology appraisals (TAs)**
    - Alteplase for the treatment of acute ischaemic stroke (September 2012) NICE TA264
    - Alteplase is recommended for the treatment of acute ischaemic stroke in adults in accordance with its licensed indication if:
      - treatment is started as early as possible within 4.5 hours of onset of stroke symptoms, and
      - intracranial haemorrhage has been excluded by appropriate imaging techniques. [www.nice.org.uk/TA264](http://www.nice.org.uk/TA264)

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection
    - **Powder and solvent for solution for injection**
      - Actilyse (Boehringer Ingelheim Ltd)
        - Alteplase 10 mg: Actilyse 10mg powder and solvent for solution for injection vials | 1 vial [PPI] £144.00
        - Alteplase 20 mg: Actilyse 20mg powder and solvent for solution for injection vials | 1 vial [PPI] £216.00
      - Actilyse Cathflo (Boehringer Ingelheim Ltd)
        - Alteplase 2 mg: Actilyse Cathflo 2mg powder and solvent for solution for injection vials | 5 vial [PPI] £225.00 (Hospital only)
  - **Powder and solvent for solution for infusion**
    - Actilyse (Boehringer Ingelheim Ltd)
      - Alteplase 50 mg: Actilyse 50mg powder and solvent for solution for infusion vials | 1 vial [PPI] £360.00

- **Retepase**
  - **INDICATIONS AND DOSE**
    - Acute myocardial infarction
      - Adult: 10 units, initiated within 12 hours of onset of symptoms, dose to be given over not more than 2 minutes, followed by 10 units after 30 minutes
  - **BREAST FEEDING**
    - Manufacturer advises avoid breastfeeding for 24 hours after dose (express and discard milk during this time).
  - **MEDICINAL FORMS**
    - There can be variation in the licensing of different medicines containing the same drug.
    - **Powder and solvent for solution for injection**
      - Rapilysin (Actavis UK Ltd)
        - Retepase 10 unit: Rapilysin 10unit powder and solvent for solution for injection vials | 2 vial [PPI] £566.00

- **Streptokinase**
  - **INDICATIONS AND DOSE**
    - Acute myocardial infarction
      - Adult: 1 500 000 units, to be initiated within 12 hours of symptom onset, dose to be given over 60 minutes
      - Deep-vein thrombosis | Pulmonary embolism | Acute arterial thromboembolism | Central retinal venous or arterial thrombosis
        - **BY INTRAVENOUS INJECTION**
          - Adult: 250 000 units, dose to be given over 30 minutes, then 100 000 units every 1 hour for up to 12–72 hours, duration is adjusted according to condition with monitoring of clotting parameters (consult product literature)

- **SIDE-EFFECTS**
  - Rare: Guillain-Barré syndrome

- **ALLERGY AND CROSS-SENSITIVITY**
  - Contra-indicated if previous allergic reaction to either streptokinase or anistreplase (no longer available). Prolonged persistence of antibodies to streptokinase and anistreplase (no longer available) can reduce the effectiveness of subsequent treatment; therefore, streptokinase should not be used again beyond 4 days of first administration of either streptokinase or anistreplase.

- **DIRECTIONS FOR ADMINISTRATION**
  - For intravenous infusion (Streptase®), give continuously or intermittently; reconstitute with sodium chloride 0.9%, then dilute further with Glucose 5% or Sodium Chloride 0.9% after reconstitution.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
    - **Powder for solution for infusion**
      - STREPTOKINASE (Non-proprietary)
        - Streptokinase 1.5 mega u: Biofactor Streptokinase 1.5million unit powder for solution for infusion vials | 1 vial [PPI] £83.44
        - Streptokinase 250000 unit: Biofactor Streptokinase 250,000unit powder for solution for infusion vials | 1 vial [PPI] £15.91
        - Streptokinase 750000 unit: Biofactor Streptokinase 750,000unit powder for solution for infusion vials | 1 vial [PPI] £41.72

### Tenecteplase

- **INDICATIONS AND DOSE**
  - Acute myocardial infarction
    - **BY INTRAVENOUS INJECTION**
      - Adult: 30–50 mg (max. per dose 50 mg), dose to be given over 10 seconds and initiated within 6 hours of symptom onset, dose varies according to body weight—consult product literature
  - **BREAST FEEDING**
    - Manufacturer advises avoid breastfeeding for 24 hours after dose (express and discard milk during this time).
  - **MEDICINAL FORMS**
    - There can be variation in the licensing of different medicines containing the same drug.
    - **Powder and solvent for solution for injection**
      - Metalyse (Boehringer Ingelheim Ltd)
        - Tenecteplase 8000 unit: Metalyse 8,000unit powder and solvent for solution for injection vials | 1 vial [PPI] £502.25
        - Tenecteplase 10000 unit: Metalyse 10,000unit powder and solvent for solution for injection vials | 1 vial [PPI] £502.25

### 7.2 Cardiac arrest

**Cardiopulmonary resuscitation**

The algorithm for cardiopulmonary resuscitation (Life support algorithm) reflects the most recent recommendations of the Resuscitation Council (UK). These guidelines are available at [www.resus.org.uk](http://www.resus.org.uk).

Cardiac arrest can be associated with ventricular fibrillation, pulseless ventricular tachycardia, asystole, and pulseless electrical activity (electromechanical dissociation). Adrenaline/epinephrine p. 196 1 in 10000 (100 micrograms/mL) is recommended by intravenous injection repeated every 3–5 minutes if necessary. Administration through a central line results in a faster response than peripheral administration, however placement of a central line must not interfere with chest...
Adrenaline/epinephrine

**DRUG ACTION** Acts on both alpha and beta receptors and increases both heart rate and contractility (beta, effects); it can cause peripheral vasodilation (a beta, effect) or vasoconstriction (an alpha effect).

**INDICATIONS AND DOSE**

**Cardiopulmonary resuscitation**

*BY INTRAVENOUS INJECTION*
- Adult: 1 mg every 3–5 minutes as required, a 1 in 10 000 (100 micrograms/mL) solution is recommended

**Acute hypotension**

*BY CONTINUOUS INTRAVENOUS INFUSION*
- Neonate: Initially 100 nanograms/kg/minute (up to 1.5 micrograms/kg/minute has been used), adjusted according to response
- Child: Initially 100 nanograms/kg/minute (up to 1.5 micrograms/kg/minute has been used), adjusted according to response

**Emergency treatment of acute anaphylaxis (under expert supervision) Angioedema (if laryngeal oedema is present)**

*BY INTRAMUSCULAR INJECTION*
- Child 1 month–5 years: 150 micrograms, to be injected preferably into the anterolateral aspect of the middle third of the thigh, repeated if necessary, doses may be repeated several times if necessary at 5 minute intervals according to blood pressure, pulse, and respiratory function
- Child 6–11 years: 300 micrograms, to be injected preferably into the anterolateral aspect of the middle third of the thigh, doses may be repeated several times if necessary at 5 minute intervals according to blood pressure, pulse, and respiratory function
- Child 12–17 years: 500 micrograms, to be injected preferably into the anterolateral aspect of the middle third of the thigh, doses may be repeated several times if necessary at 5 minute intervals according to blood pressure, pulse, and respiratory function
- Adult: 500 micrograms, to be injected preferably into the anterolateral aspect of the middle third of the thigh, doses may be repeated several times if necessary at 5 minute intervals according to blood pressure, pulse, and respiratory function

Acute anaphylaxis when there is doubt as to the adequacy of the circulation (specialist use only) Angioedema (if laryngeal oedema is present) (specialist use only)

*BY SLOW INTRAVENOUS INJECTION*
- Adult: 50 micrograms, using 0.5 mL of the dilute 1 in 10 000 adrenaline injection, dose to be repeated according to response, if multiple doses required, adrenaline should be given as a slow intravenous infusion stopping when a response has been obtained

Control of bradycardia in patients with arrhythmias after myocardial infarction, if there is a risk of asystole, or if the patient is unstable and has failed to respond to atropine

*BY INTRAVENOUS INFUSION*
- Adult: 2–10 micrograms/minute, adjusted according to response

**EMERADE® 150 MICROGRAMS**

Acute anaphylaxis (for self-administration)

*BY INTRAMUSCULAR INJECTION*
- Child (body-weight up to 15 kg): 150 micrograms, then 150 micrograms after 5–15 minutes as required
- Child (body-weight 15–30 kg): 150 micrograms, then 150 micrograms after 5–15 minutes as required, on the basis of a dose of 10 micrograms/kg, 300 micrograms may be more appropriate for some children

**EMERADE® 300 MICROGRAMS**

Acute anaphylaxis (for self-administration)

*BY INTRAMUSCULAR INJECTION*
- Child (body-weight up to 15 kg): 300 micrograms, then 300 micrograms after 5–15 minutes as required
- Adult (body-weight 30 kg and above): 300 micrograms, then 300 micrograms after 5–15 minutes as required

**EMERADE® 500 MICROGRAMS**

Acute anaphylaxis (for self-administration for patients at risk of severe anaphylaxis)

*BY INTRAMUSCULAR INJECTION*
- Child 12–17 years: 500 micrograms, then 500 micrograms after 5–15 minutes as required
- Adult: 500 micrograms, then 500 micrograms after 5–15 minutes as required

**EPIPEN® JR AUTO-INJECTOR 0.15MG**

Acute anaphylaxis (for self-administration)

*BY INTRAMUSCULAR INJECTION*
- Child (body-weight up to 15 kg): 150 micrograms, then 150 micrograms after 5–15 minutes as required
- Child (body-weight 15–30 kg): 150 micrograms, then 150 micrograms after 5–15 minutes as required, on the basis of a dose of 10 micrograms/kg, 300 micrograms may be more appropriate for some children

**EPIPEN® AUTO-INJECTOR 0.3MG**

Acute anaphylaxis (for self-administration)

*BY INTRAMUSCULAR INJECTION*
- Child (body-weight up to 15 kg): 300 micrograms, then 300 micrograms after 5–15 minutes as required
- Adult (body-weight 30 kg and above): 300 micrograms, then 300 micrograms after 5–15 minutes as required

**JEXT® 150 MICROGRAMS**

Acute anaphylaxis (for self-administration)

*BY INTRAMUSCULAR INJECTION*
- Child (body-weight up to 15 kg): 150 micrograms, then 150 micrograms after 5–15 minutes as required
- Child (body-weight 15–30 kg): 150 micrograms, then 150 micrograms after 5–15 minutes as required, on the basis of a dose of 10 micrograms/kg, 300 micrograms may be more appropriate for some children

**SYMPATHOMIMETICS (VASOCONSTRICTOR)**

**Adrenaline/epinephrine**

- Drugs administered peripherally must be followed by a flush of at least 20 mL Sodium Chloride 0.9% injection to aid entry into the central circulation.
- Intravenous injection of amiodarone hydrochloride should be considered after adrenaline/epinephrine below to treat ventricular fibrillation or pulseless ventricular tachycardia in cardiac arrest refractory to defibrillation. An additional dose of amiodarone hydrochloride can be given if necessary, followed by an intravenous infusion of amiodarone hydrochloride. Lidocaine hydrochloride p. 91, is an alternative if amiodarone hydrochloride is not available. Atropine sulfate p. 949 is no longer recommended in the treatment of asystole or pulseless electrical activity.
- During cardiopulmonary arrest if intravenous access cannot be obtained, the intraosseous route can be used instead. Drug administration via the endotracheal route is no longer recommended.
- For the management of acute anaphylaxis, see allergic emergencies under Antihistamines, allergen immunotherapy and allergic emergencies p. 241.

- For the management of acute anaphylaxis, see allergic emergencies under Antihistamines, allergen immunotherapy and allergic emergencies p. 241.
**MONITORING REQUIREMENTS**

- **Blood pressure and pulse:** Monitor blood pressure and pulse; maximum 100 micrograms per course

**JEXT® 300 MICROGRAMS**

**Acute anaphylaxis** (for self-administration)

- **By intramuscular injection**
  - Child (body-weight 30 kg and above): 300 micrograms, then 300 micrograms after 5–15 minutes as required
  - Adult (body-weight 30 kg and above): 300 micrograms, then 300 micrograms after 5–15 minutes as required

**Priapism associated with alprostadil, if aspiration and lavage of corpora are unsuccessful (alternative to phenylephrine or metaraminol)**

- **By intracavernosal injection**
  - Adult: 10–20 micrograms every 5–10 minutes, using a 20 microgram/mL solution. **Important:** if suitable strength of adrenaline not available may be specially prepared by diluting 0.1 mL of the adrenaline 1 in 1000 (1 mg/mL) injection to 5 mL with sodium chloride 0.9%, continuously monitor blood pressure and pulse; maximum 100 micrograms per course

**Unlicensed Use**

- With intravenous use: Adrenaline 1 in 1000 (1mg/mL) solution is not licensed for intravenous administration. Auto-injector delivering 150-microgram dose of adrenaline not licensed for use in children body-weight under 15 kg.

**Important safety information**

**Safe Practice**

Intravenous route should be used with extreme care by specialists only.

**Cautions**

- Arteriosclerosis, arrhythmias, cerebrovascular disease, cor pulmonale, diabetes mellitus, elderly, hypercalcaemia, hypereflexia, hypertension, hyperthyroidism, hypokalaemia, ischaemic heart disease, obstructive cardiomyopathy, oesophageal vascular disease, organic brain damage, phaeochromocytoma, prostate disorders, psychosis, severe angina, susceptibility to angle-closure glaucoma

**Cautions, further information**

Cautions listed are only for non-life-threatening situations.

**Interactions**

- Appendix 1 (sympathomimetics)

Severe anaphylaxis in patients taking beta-blockers may not respond to adrenaline—consider bronchodilator therapy. Furthermore, adrenaline can cause severe hypertension and bradycardia in those taking non-cardioselective beta-blockers.

**Side-effects**

- Angina, angle-closure glaucoma, anorexia, anxiety, arrhythmias, cold extremities, confusion, difficulty in micturition, dizziness, dry mouth, dysphonia, headache, hyperglycaemia, hypersalivation, hypertension (risk of cerebral haemorrhage), hypokalaemia, insomnia, metabolic acidosis, mydriasis, myocardial infarction, nausea, pallor, palpitation, psychosis, pulmonary oedema (on excessive dosage or extreme sensitivity), restlessness, sweating, tachycardia, tissue necrosis at injection site, tissue necrosis of bowel, tissue necrosis of extremities, tissue necrosis of kidneys, tissue necrosis of liver, tremor, urination retention, vomiting, weakness

**Pregnancy**

May reduce placental perfusion and cause tachycardia, cardiac irregularities, and extrasystoles in fetus. Can delay second stage of labour. Manufacturers advise use only if benefit outweighs risk.

**Breast feeding**

Present in milk but unlikely to be harmful as poor oral bioavailability.

**Renal impairment**

Manufacturers advise use with caution in severe impairment.

**Monitoring Requirements**

Monitor blood pressure and ECG.

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**Directions for Administration**

- With intravenous use in children: Acute hypotension (same text as above) For **continuous intravenous infusion,** dilute with Glucose 5% or Sodium Chloride 0.9% and give through a central venous catheter. Incompatible with bicarbonate and alkaline solutions. Neonatal intensive care, dilute 3 mg/kg body-weight to a final volume of 50 mL with infusion fluid; an intravenous infusion rate of 0.1 mL/hour provides a dose of 100 nanograms/kg/minute; infuse through a central venous catheter. Incompatible with bicarbonate and alkaline solutions. These infusions are usually made up with adrenaline 1 in 1000 (1 mg/mL) solutions.

- With intravenous use: Administration through a central line results in a faster response than peripheral administration, however placement of a central line must not interfere with chest compressions; drugs administered peripherally must be followed by a flush of at least 20 mL. Sodium Chloride 0.9% injection to aid entry into the central circulation.

**Prescribing and dispensing information**

It is important, in acute anaphylaxis where intramuscular injection might still succeed, time should not be wasted seeking intravenous access. Great vigilance is needed to ensure that the correct strength of adrenaline injection is used; anaphylactic shock kits need to make a very clear distinction between the 1 in 10 000 strength and the 1 in 1000 strength. Patients with severe allergy should be instructed in the self-administration of adrenaline by intramuscular injection.

 Packs for self-administration need to be clearly labelled with instructions on how to administer adrenaline (intramuscularly, preferably at the midpoint of the outer thigh, through light clothing if necessary) so that in the case of rapid collapse someone else is able to give it. It is important to ensure individuals at risk and their carers understand that:

- two injection devices should be carried at all times to treat symptoms until medical assistance is available; if, after the first injection, the individual does not start to feel better, the second injection should be given 5 to 15 minutes after the first;
- an ambulance should be called at every administration, even if symptoms improve;
- the individual should lie down with their legs raised (unless they have breathing difficulties, in which case they should sit up) and should not be left alone. Adrenaline for administration by intramuscular injection is available in ‘auto-injectors’ (e.g. Emerade®, EpiPen®, or Jext®), pre-assembled syringes fitted with a needle suitable for very rapid administration (if necessary by a bystander or a healthcare provider if it is the only preparation available); injection technique is device specific.

To ensure patients receive the auto-injector device that they have been trained to use, prescribers should specify the brand to be dispensed.

**Patient and carer advice**

Individuals at considerable risk of anaphylaxis need to carry (or have available) adrenaline at all times and the patient, or their carers, need to be instructed in advance when and how to inject it.

Medicines for Children leaflet: Adrenaline auto-injector for anaphylaxis www.medicinesforchildren.org.uk/adrenaline-for-anaphylaxis

**EpiPen® Auto-injector 0.15mg, 0.3mg**

1.7 mL of the solution remains in the auto-injector device after use.

**Emerade® 500 Micrograms**

No solution remains in the auto-injector device after use.
EMERADE® 150 MICROGRAMS
0.35 mL of the solution remains in the auto-injector device after use.

EMERADE® 300 MICROGRAMS
0.2 mL of the solution remains in the auto-injector device after use.

JEXT® 300 MICROGRAMS
1.1 mL of the solution remains in the auto-injector device after use.

JEXT® 150 MICROGRAMS
1.25 mL of the solution remains in the auto-injector device after use.

● EXCEPTIONS TO LEGAL CATEGORY POM restriction does not apply to the intramuscular administration of up to 1 mg of adrenaline injection 1 in 1000 (1 mg/mL) for the emergency treatment of anaphylaxis.

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing 500 micrograms/ml and from special-order manufacturers include: solution for injection

Solution for injection
EXCIPIENTS: May contain Sulfites

Adrenaline (as Adrenaline acid tartrate) 100 microgram per 1 mL Adrenaline (base) 1mg/10ml (1 in 10,000) dilute solution for injection ampoules | 1 ampoule (POM) £43.53 | 10 ampoule (POM) £40.30
Adrenaline (base) 500 micrograms/ml (1 in 10,000) dilute solution for injection ampoules | 10 ampoule (POM) £55.43
Adrenaline 100 microgram per 1 mL Adrenaline (base) 100 micrograms/ml (1 in 10,000) dilute solution for injection ampoules | 10 ampoule (POM) £52.03
Adrenaline (base) 1mg/10ml (1 in 10,000) dilute solution for injection pre-filled syringes | 1 pre-filled disposable injection (POM) £6.67-
Adrenaline (base) 1mg/10ml (1 in 10,000) dilute solution for injection pre-filled syringes | 1 pre-filled disposable injection (POM) £6.99

Adrenaline (as Adrenaline acid tartrate) 1 mg per 1 mL Adrenaline (base) 5mg/5ml (1 in 1000) solution for injection ampoules | 10 ampoule (POM) £63.77
Adrenaline (base) 500micrograms/0.5ml (1 in 1000) solution for injection ampoules | 10 ampoule (POM) £50.57 DT price = £50.57
Adrenaline (base) 1mg/10ml (1 in 1000) solution for injection ampoules | 10 ampoule (POM) £4.43 DT price = £4.41

Adrenaline 1 mg per 1 mL Adrenaline (base) for anaphylaxis
1mg/1ml (1 in 1000) solution for injection pre-filled syringes | 1 pre-
Adrenaline (base) 1mg/ml (1 in 1000) solution for injection pre-filled syringes | 1 pre-filled disposable injection (POM) £10.40
Adrenaline (base) 1mg/ml (1 in 1000) solution for injection pre-filled syringes | 1 pre-filled disposable injection (POM) £15.00
Adrenaline (base) 1mg/ml (1 in 1000) solution for injection pre-filled syringes | 1 pre-filled disposable injection (POM) £13.90

Adrenaline (as Adrenaline acid tartrate) 1 mg per 1 mL Emerade (Imed Systems Ltd)
150 micrograms/ml (0.15ml) solution for injection auto-injectors | 1 pre-filled disposable injection (POM) £26.94
Emerade 500micrograms/0.5ml (1 in 1000) solution for injection auto-injectors | 1 pre-filled disposable injection (POM) £27.74

Adrenaline 1 mg per 1 mL Emerade (Imed Systems Ltd)
300 micrograms/ml (0.3ml) in 1 in 1000 solution for injection auto-injectors | 1 pre-filled disposable injection (POM) £26.94

EpiPen (Meda Pharmaceuticals Ltd)
Adrenaline 500 microgram per 1 mL EpiPen Jr.
150 micrograms/ml (0.3ml) solution for injection auto-injectors | 1 pre-filled disposable injection (POM) £26.45 | 2 pre-filled disposable injection (POM) £52.90

Adrenaline 1 mg per 1 mL EpiPen 300 micrograms/ml (0.3ml) in 1 in 1000 solution for injection auto-injectors | 1 pre-filled disposable injection (POM) £26.45 | 2 pre-filled disposable injection (POM) £52.90

Jext (ALK-Abello Ltd)
Adrenaline (as Adrenaline acid tartrate) 1 mg per 1 mL Jext
150 micrograms/ml (0.15ml) solution for injection auto-injectors | 1 pre-filled disposable injection (POM) £23.99

Adrenaline 1 mg per 1 ml Jext 300 micrograms/ml (0.3ml) in 1 in 1000 solution for injection auto-injectors | 1 pre-filled disposable injection (POM) £23.99

8 Oedema

Diuretics

Overview
Thiazides are used to relieve oedema due to chronic heart failure and, in lower doses, to reduce blood pressure. Loop diuretics are used in pulmonary oedema due to left ventricular failure and in patients with chronic heart failure. Combination diuretic therapy may be effective in patients with oedema resistant to treatment with one diuretic. Vigorous diuresis, particularly with loop diuretics, may induce acute hypotension; rapid reduction of plasma volume should be avoided.

Thiazides and related diuretics
Thiazides and related compounds are moderately potent diuretics; they inhibit sodium reabsorption at the beginning of the distal convoluted tubule. They act within 1 to 2 hours of oral administration and most have a duration of action of 12 to 24 hours; they are usually administered early in the day so that the diuresis does not interfere with sleep.

In the management of hypertension a low dose of a thiazide produces a maximal or near-maximal blood pressure lowering effect, with very little biochemical disturbance. Higher doses cause more marked changes in plasma potassium, sodium, uric acid, glucose, and lipids, with little advantage in blood pressure control. Chlorothalidone p. 204 and indapamide p. 160 are the preferred diuretics in the management of hypertension. Thiazides also have a role in chronic heart failure.

Bendroflumethiazide p. 159 can be used for mild or moderate heart failure; it is licensed for the treatment of hypertension but is no longer considered the first-line diuretic for this indication, although patients with stable and controlled blood pressure currently taking bendroflumethiazide can continue treatment.

Chlortalidone, a thiazide-related compound, has a longer duration of action than the thiazides and may be given on alternate days to control oedema. It is also useful if acute retention is liable to be precipitated by a more rapid diuresis or if patients dislike the altered pattern of micturition caused by other diuretics. Chlortalidone can also be used under close supervision for the treatment of ascites due to cirrhosis in stable patients.

Xipamide p. 205 and indapamide are chemically related to chlortalidone. Indapamide is claimed to lower blood pressure with less metabolic disturbance, particularly less aggravation of diabetes mellitus.

Metholozane p. 205 is particularly effective when combined with a loop diuretic (even in renal failure); profound diuresis can occur and the patient should therefore be monitored carefully.

The thiazide diuretics benzthiazide, clopamide, cyclopenhiazide p. 204, hydrochlorothiazide, and hydroflumethiazide do not offer any significant advantage over other thiazides and related diuretics.

Loop diuretics
Loop diuretics are used in pulmonary oedema due to left ventricular failure; intravenous administration produces relief of breathlessness and reduces pre-load sooner than would be expected from the time of onset of diuresis. Loop diuretics are also used in patients with chronic heart failure. Diuretic-resistant oedema (except lymphoedema and
Oedema due to peripheral venous stasis or calcium-channel blockers can be treated with a loop diuretic combined with a thiazide or related diuretic (e.g. bendroflumethiazide or metolazone).

If necessary, a loop diuretic can be added to antihypertensive treatment to achieve better control of blood pressure in those with resistant hypertension, or in patients with impaired renal function or heart failure.

Loop diuretics can exacerbate diabetes (but hyperglycaemia is less likely than with thiazides) and gout. If there is an enlarged prostate, urinary retention can occur, although this is less likely if small doses and less potent diuretics are used initially.

Furosemide and bumetanide are similar in activity; both act within 1 hour of oral administration and diuresis is complete within 6 hours so that, if necessary, they can be given twice in one day without interfering with sleep. Following intravenous administration furosemide has a peak effect within 30 minutes. The diuresis associated with these drugs is dose related.

Torasemide p. 202 has properties similar to those of furosemide and bumetanide, and is indicated for oedema and for hypertension.

Potassium-sparing diuretics and aldosterone antagonists
Amiloride hydrochloride p. 203 and triamterene p. 203 on their own are weak diuretics. They cause retention of potassium and are therefore given with thiazide or loop diuretics as a more effective alternative to potassium supplements. See compound preparations with thiazides or loop diuretics.

Potassium supplements must not be given with potassium-sparing diuretics. Administration of a potassium-sparing diuretic to a patient receiving an ACE inhibitor or an angiotensin-II receptor antagonist can also cause severe hyperkalaemia.

Aldosterone antagonists
Spironolactone p. 168 potentiates thiazide or loop diuretics by antagonising aldosterone; it is a potassium-sparing diuretic. Spironolactone is of value in the treatment of oedema and ascites caused by cirrhosis of the liver; furosemide can be used as an adjunct. Low doses of spironolactone are beneficial in moderate to severe heart failure and when used in resistant hypertension [unlicensed indication]. Spironolactone is also used in primary hyperaldosteronism (Conn’s syndrome). It is given before surgery or if surgery is not appropriate, in the lowest effective dose for maintenance.

Eplerenone p. 167 is licensed for use as an adjunct in left ventricular dysfunction with evidence of heart failure after a myocardial infarction; it is also licensed as an adjunct in chronic mild heart failure with left ventricular systolic dysfunction.

Potassium supplements must not be given with aldosterone antagonists

Potassium-sparing diuretics with other diuretics
Although it is preferable to prescribe thiazides and potassium-sparing diuretics separately, the use of fixed combinations may be justified if compliance is a problem. Potassium-sparing diuretics are not usually necessary in the routine treatment of hypertension, unless hypokalaemia develops.

Other diuretics
Mannitol p. 202 is an osmotic diuretic that can be used to treat cerebral oedema and raised intraocular pressure. Mercurial diuretics are effective but are now almost never used because of their nephrotoxicity.

The carbonic anhydrase inhibitor acetazolamide p. 965 is a weak diuretic and is little used for its diuretic effect. It is used for prophylaxis against mountain sickness [unlicensed indication] but is not a substitute for acclimatisation.

Acetazolamide and eye drops of dorzolamide p. 966 and brinzolamide p. 965 inhibit the formation of aqueous humour and are used in glaucoma.

Diuretics with potassium
Many patients on diuretics do not need potassium supplements. For many of those who do, the amount of potassium in combined preparations may not be enough, and for this reason their use is to be discouraged.

Diuretics with potassium and potassium-sparing diuretics should not usually be given together. Diuretics and potassium supplements should be prescribed separately for children.

LOOP DIURETICS

Loop diuretics

- **DRUG ACTION** Loop diuretics inhibit reabsorption from the ascending limb of the loop of Henlé in the renal tubule and are powerful diuretics.

- **CONTRA-INDICATIONS** Anuria · comatose and precomatose states associated with liver cirrhosis · renal failure due to nephrotic or hepatotoxic drugs · severe hypokalaemia · severe hyponatraemia

- **CAUTIONS** Can exacerbate diabetes (but hyperglycaemia less likely than with thiazides) · can exacerbate gout · hypotension should be corrected before initiation of treatment · hypovolaemia should be corrected before initiation of treatment · urinary retention can occur in prostatic hyperplasia

**CAUTIONS, FURTHER INFORMATION**

**Elderly** Lower initial doses of diuretics should be used in the elderly because they are particularly susceptible to the side-effects. The dose should then be adjusted according to renal function. Diuretics should not be used continuously on a long-term basis to treat simple gravitational oedema (which will usually respond to increased movement, raising the legs, and support stockings).

**Potassium loss** Hypokalaemia can occur with both thiazide and loop diuretics. The risk of hypokalaemia depends on the duration of action as well as the potency and is thus greater with thiazides than with an equipotent dose of a loop diuretic.

Hypokalaemia is dangerous in severe cardiovascular disease and in patients also being treated with cardiac glycosides. Often the use of potassium-sparing diuretics avoids the need to take potassium supplements.

In hepatic failure, hypokalaemia caused by diuretics can precipitate encephalopathy, particularly in alcoholic cirrhosis.

**Urinary retention** If there is an enlarged prostate, urinary retention can occur, although this is less likely if small doses and less potent diuretics are used initially; an adequate urinary output should be established before initiating treatment.

- **INTERACTIONS** → Appendix 1 (diuretics).

- **SIDE-EFFECTS**
  - **Very rare** Hyperuricaemia
  - **Frequency not known** Acute urinary retention · blood disorders · bone-marrow depression · deafness (usually with high doses and rapid intravenous administration, and in renal impairment) · electrolyte disturbances · hepatic encephalopathy · hyperglycaemia (less common than with thiazides) · hypersensitivity reactions ·
hypocalcaemia • hypochloraemia • hypokalaemia • hypomagnesaemia • hyponatraemia • leucopenia • metabolic alkalosis • mild gastro-intestinal disturbances • pancreatitis • photosensitivity • postural hypotension • pruritus • rash • temporary increase in serum-cholesterol and triglyceride concentration • thrombocytopenia • tinnitus (usually with high doses and rapid intravenous administration, and in renal impairment) • visual disturbances

HEPATIC IMPAIRMENT Hypokalaemia induced by loop diuretics may precipitate hepatic encephalopathy and coma—potassium-sparing diuretics can be used to prevent this. Diuretics can increase the risk of hypomagnesaemia in alcoholic cirrhosis, leading to arrhythmias.

RENAL IMPAIRMENT High doses of loop diuretics may occasionally be needed in renal impairment. High doses or rapid intravenous administration can cause tinnitus and deafness.

MONITORING REQUIREMENTS Monitor electrolytes during treatment.

Bumetanide

INDICATIONS AND DOSE

Oedema

BY MOUTH

• Adult: 1 mg, dose to be taken in the morning, then 1 mg after 6–8 hours if required

• Elderly: 500 micrograms daily, this lower dose may be sufficient in elderly patients

Oedema, severe cases

BY MOUTH

• Adult: Initially 5 mg daily, increased in steps of 5 mg every 12–24 hours, adjusted according to response

SIDE-EFFECTS Breast pain • gynaecomastia • musculoskeletal pain (associated with high doses in renal failure)

PREGNANCY Bumetanide should not be used to treat gestational hypertension because of the maternal hypovolaemia associated with this condition.

BREAST FEEDING No information available. May inhibit lactation.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

• BUMETANIDE (Non-proprietary)
  Bumetanide 1 mg Bumetanide 1mg tablets | 28 tablet £2.50 DT price = £1.35
  Bumetanide 5 mg Bumetanide 5mg tablets | 28 tablet £7.00 DT price = £6.98

Oral solution

• BUMETANIDE (Non-proprietary)
  Bumetanide 200 microgram per ml Bumetane 1mg/5ml oral solution sugar free (sugar-free) | 150 ml (PO) £128.00 DT price = £128.00

Also available in combination with amiloride, p. 203

Co-amilofruse

INDICATIONS AND DOSE

Oedema

BY MOUTH

• Adult: 2.5/20–10/80 mg daily, dose to be taken in the morning

Dose equivalence and conversion

A mixture of amiloride hydrochloride and furosemide (frusemide) in the mass proportions of 1 part amiloride hydrochloride to 8 parts furosemide (frusemide).

CONTRA-INDICATIONS Addison’s disease • anuria • comatose or precomatose states associated with liver cirrhosis • dehydration • hyperkalaemia • hypovolaemia • renal failure • severe hypokalaemia • severe hyponatraemia

CAUTIONS Correct hypovolaemia before using in oliguria • diabetes mellitus • elderly • gout • hepatorenal syndrome • hypoproteinaemia • hypotension • impaired micturition • prostatic enlargement

INTERACTIONS ➔ Appendix 1 (diuretics).

SIDE-EFFECTS Agranulocytosis • anaphylaxis • aplastic anaemia • blood disorders • bone marrow depression (withdraw treatment) • confusion • deafness (usually in renal impairment or in hypoproteinaemia) • dry mouth • eosinophilia • exfoliative dermatitis • gastrointestinal disturbances • gout • haemolytic anaemia • hepatic encephalopathy • hyperglycaemia • hypersensitivity reactions • hyperuricaemia • hypokalaemia • hypopkaemia (due to furosemide—may be followed by hyperkalaemia due to amiloride) • hypomagnesaemia • hyponatraemia • hypotension • intrahepatic cholestasis • leucopenia • metabolic alkalosis or acidosis • pancreatitis • paraesthesia • photosensitivity • purpura • rashes • Stevens–Johnson syndrome • temporary increase in serum cholesterol and triglyceride concentrations • thrombocytopenia • tinnitus • toxic epidermal necrolysis

PREGNANCY Not used to treat hypertension in pregnancy.

BREAST FEEDING Manufacturers advise avoid—no information regarding amiloride component available. Amount of furosemide in milk too small to be harmful. Furosemide may inhibit lactation.

HEPATIC IMPAIRMENT Increased risk of hypomagnesaemia in alcoholic cirrhosis.

RENAL IMPAIRMENT Risk of hyperkalaemia in renal impairment but may need higher doses. Monitor plasma-potassium concentration. Avoid if eGFR less than 30 mL/minute/1.73 m².

MONITORING REQUIREMENTS Monitor electrolytes.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

Tablet

• CO-AMILOFRUSE (Non-proprietary)
  Amiloride hydrochloride 2.5 mg, Furosemide 20 mg Co-amilofruse 2.5mg/20mg tablets | 28 tablet (PO) £10.95 DT price = £3.93 | 56 tablet (PO) £8.64
  Amiloride hydrochloride 5 mg, Furosemide 40 mg Co-amilofruse 5mg/40mg tablets | 28 tablet (PO) £13.95 DT price = £5.09 | 56 tablet (PO) £10.18
  Amiloride hydrochloride 10 mg, Furosemide 80 mg Co-amilofruse 10mg/80mg tablets | 28 tablet (PO) £30.00 DT price = £15.51

• Frumil (Sanofi)
  Amiloride hydrochloride 2.5 mg, Furosemide 20 mg Frumil 5LS 20mg/2.5mg tablets | 28 tablet (PO) £4.32 DT price = £3.93 | 56 tablet (PO) £8.49
  Amiloride hydrochloride 5 mg, Furosemide 40 mg Frumil 40mg/5mg tablets | 28 tablet (PO) £5.29 DT price = £5.09 | 56 tablet (PO) £10.35
Furosemide (Fresmide)

**INDICATIONS AND DOSE**

**Oedema**
- **BY MOUTH**
  - Initial: Initially 40 mg daily, dose to be taken in the morning, then maintenance 20–40 mg daily
  - **INITIALLY BY INTRAMUSCULAR INJECTION OR BY SLOW INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION**
  - **Adult:** Initially 20–50 mg, then (by intramuscular injection or by intravenous injection or by intravenous infusion) increased in steps of 20 mg every 2 hours if required, doses greater than 50 mg given by intravenous infusion only; maximum 1.5 g per day

**Resistant oedema**
- **BY MOUTH**
  - Adult: 80–120 mg daily
  - **INITIALLY BY INTRAMUSCULAR INJECTION OR BY SLOW INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION**
  - **Adult:** Initially 20–50 mg, then (by intramuscular injection or by intravenous injection or by intravenous infusion) increased in steps of 20 mg every 2 hours if required, doses greater than 50 mg given by intravenous infusion only; maximum 1.5 g per day

**Resistant hypertension**
- **BY MOUTH**
  - Adult: 40–80 mg daily
  - **INITIALLY BY INTRAMUSCULAR INJECTION OR BY SLOW INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION**
  - **Adult:** Initially 20–50 mg, then (by intramuscular injection or by intravenous injection or by intravenous infusion) increased in steps of 20 mg every 2 hours if required, doses greater than 50 mg given by intravenous infusion only; maximum 1.5 g per day

**CAUTIONS** Hepatorenal syndrome - hypoproteinaemia may reduce diuretic effect and increase risk of side-effects

**SIDE-EFFECTS** Gout - intrahepatic cholestasis

**PREGNANCY** Furosemide should not be used to treat gestational hypertension because of the maternal hypovolaemia associated with this condition.

**BREAST FEEDING** Amount too small to be harmful. May inhibit lactation.

**DIRECTIONS FOR ADMINISTRATION** Intravenous administration rate should not usually exceed 4 mg/minute however single doses of up to 80 mg may be administered more rapidly. A lower rate of infusion may be necessary in renal impairment. For **Intravenous infusion (Lasix®)**, give continuously in Sodium chloride 0.9%; infusion pH must be above 5.5 and rate should not exceed 4 mg/minute; glucose solutions are unsuitable.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, spray, oral solution

**Tablet**
- **Furosemide 20 mg**
  - **Furosemide 40 mg**
  - **Furosemide 500 mg**
  - **Brands may include:**
    - **Duressal**

**Solution for injection**
- **Furosemide 8 mg per 1 ml**
  - **Furosemide 40 mg/5 ml oral solution**
  - **Furosemide 10 mg per 1 ml**

**Brands may include:**
- **Frusol**

**Solution for injection**
- **Furosemide 8 mg per 1 ml**
  - **Furosemide 40 mg/5 ml oral solution**
  - **Furosemide 10 mg per 1 ml**

**Brands may include:**
- **Frusol**

**Furosemide with potassium chloride**

The properties listed below are those particular to the combination only. For the properties of the components please consider, furosemide above, potassium chloride p. 863.

**INDICATIONS AND DOSE**

**Oedema**
- **BY MOUTH**
  - Adult: (consult product literature)

**DIRECTIONS FOR ADMINISTRATION** Furosemide with modified-release potassium chloride tablets should be swallowed whole with plenty of fluid during meals while sitting or standing.

**PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer furosemide with potassium chloride tablets.

**LESS SUITABLE FOR PRESCRIBING** Furosemide with potassium chloride tablets are less suitable for prescribing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Modified-release tablet**

- **Diumide-K Continus** (Teofarma)
  - **Furosemide 40 mg, Potassium chloride 600 mg**
  - **Diumide-K Continus tablets**
  - **30 tablet**

**Furosemide with spironolactone**

The properties listed below are those particular to the combination only. For the properties of the components please consider, furosemide above, spironolactone p. 168.

**INDICATIONS AND DOSE**

**Resistant oedema**
- **BY MOUTH**
  - Adult: 20/50–80/200 mg daily

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**
- **Lasilactone** (Sanofi)
  - **Furosemide 20 mg, Spironolactone 50 mg**

**Capsule**
- **Lasilactone** (Sanofi)
  - **Furosemide 20 mg, Spironolactone 50 mg**

**Furosemide with triamterene**

The properties listed below are those particular to the combination only. For the properties of the components please consider, furosemide above, triamterene p. 203.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.
# Osmotic Diuretics

## Mannitol

### INDICATIONS AND DOSE

**Cerebral oedema**

**BY INTRAVENOUS INFUSION**

- Adult: 0.25–2 g/kg, repeated if necessary, to be administered over 30–60 minutes, dose may be repeated 1–2 times after 4–8 hours

**Raised intra-ocular pressure**

**BY INTRAVENOUS INFUSION**

- Adult: 0.25–2 g/kg, repeated if necessary, to be administered over 30–60 minutes, dose may be repeated 1–2 times after 4–8 hours

### CONTRA-INDICATIONS

- Anuria
- Intracranial bleeding (except during craniotomy)
- Severe cardiac failure
- Severe dehydration
- Severe pulmonary oedema

### CAUTIONS

- Extravasation causes inflammation and thrombophlebitis

### INTERACTIONS

See Appendix 1 (mannitol).

### SIDE-EFFECTS

- Uncommon
  - Electrolyte imbalance
  - Fluid imbalance
  - Hypotension
  - Thrombophlebitis
- Rare
  - Anaphylaxis
  - Arrhythmia
  - Blurred vision
  - Chest pain
  - Chills
  - Convulsions
  - Cramp
  - Dehydration
  - Dizziness
  - Dry mouth
  - Fever
  - Focal osmotic nephrosis
  - Headache
  - Hypersensitivity reactions
  - Hypertension
  - Nausea
  - Oedema
  - Pulmonary oedema
  - Raised intracranial pressure
  - Rhinitis
  - Skin necrosis
  - Thirst
  - Urinary retention
  - Urticaria
  - Vomiting

- Very rare
  - Acute renal failure
  - Congestive heart failure

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

<table>
<thead>
<tr>
<th><strong>TORASEMIDE (Non-proprietary)</strong></th>
<th>28 tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torasemide 5 mg</td>
<td>£14.49 DT price</td>
</tr>
<tr>
<td>Torasemide 10 mg</td>
<td>£18.67 DT price</td>
</tr>
<tr>
<td>Torem (Meda Pharmaceuticals Ltd)</td>
<td>28 tablet</td>
</tr>
<tr>
<td>Torasemide 2.5 mg, Torem 2.5 mg tablets</td>
<td>£3.78 DT price</td>
</tr>
<tr>
<td>Torasemide 5 mg, Torem 5 mg tablets</td>
<td>£5.53 DT price</td>
</tr>
<tr>
<td>Torasemide 10 mg, Torem 10 mg tablets</td>
<td>£8.14 DT price</td>
</tr>
</tbody>
</table>

## Torasemide

### INDICATIONS AND DOSE

**Oedema**

**BY MOUTH**

- Adult: 5 mg once daily, to be taken preferably in the morning, then increased if necessary to 20 mg once daily; maximum 40 mg per day

**Hypertension**

**BY MOUTH**

- Adult: 2.5 mg daily, then increased if necessary to 5 mg once daily

### SIDE-EFFECTS

- Rare
  - Limb paraesthesia

- Frequency not known
  - Dry mouth
  - **PREGNANCY** Manufacturer advises avoid—toxicity in animal studies.
  - **BREAST FEEDING** Manufacturer advises avoid—no information available.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

<table>
<thead>
<tr>
<th><strong>TORASEMIDE (Non-proprietary)</strong></th>
<th>28 tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torasemide 5 mg, Triamterene 50 mg tablets</td>
<td>56 tablet £6.34 DT price</td>
</tr>
<tr>
<td>Furosemide 40 mg, Triamterene 50 mg tablets</td>
<td>56 tablet £4.97 DT price</td>
</tr>
</tbody>
</table>

### DIRECTIONS FOR ADMINISTRATION

For mannitol 20%, an in-line filter is recommended (15-micron filters have been used).
Amiloride hydrochloride

**INDICATIONS AND DOSE**

**Oedema (monotherapy)**  
**BY MOUTH**  
- Adult: Initially 10 mg daily, alternatively initially 5 mg twice daily, adjusted according to response; maximum 20 mg per day

Potassium conservation when used as an adjunct to thiazide or loop diuretics for hypertension or congestive heart failure  
**BY MOUTH**  
- Adult: Initially 5–10 mg daily

Potassium conservation when used as an adjunct to thiazide or loop diuretics for hepatic cirrhosis with ascites  
**BY MOUTH**  
- Adult: Initially 5 mg daily

**CONTRA-INDICATIONS**  
Addison’s disease • anuria • hyperkalaemia

**CAUTIONS**  
Diabetes mellitus • elderly

**INTERACTIONS**  
Appendix 1 (diuretics).

**SIDE-EFFECTS**  
Abdominal pain • agitation • alopecia • angina • anorexia • arthralgia • confusion • constipation • cough • diaphoresis • dizziness • dry mouth • dyspepsia • dysuria • encephalopathy • flatulence • gastrointestinal bleeding • headache • hyperkalaemia • insomnia • jaundice • malaise • muscle cramp • nasal congestion • nausea • palpitation • paraesthesia • postural hypotension • pruritus • raised intracranial pressure • rash • sexual dysfunction • thirst • tinnitus • tremor • urinary disturbances • visual disturbance • vomiting • weakness

**PREGNANCY**  
Not to be used to treat gestational hypertension.

**BREAST FEEDING**  
Manufacturer advises avoid—no information available.

**RENAL IMPAIRMENT**  
Manufacturers advise avoid in severe impairment. Monitor plasma-potassium concentration (high risk of hyperkalaemia in renal impairment).

**MONITORING REQUIREMENTS**  
Monitor electrolytes.

**MEDICINAL FORMS**  
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

**INFUSION**  
- **MANNITOL (Non-proprietary)**  
  - Mannitol 100 mg per 1 ml
    - Mannitol 50g/500ml infusion Viaflo bags  | 1 bag ($P39) no price available  | 20 bag ($P39) no price available
    - Mannitol 500/500ml infusion Viaflex bags  | 1 bag ($P39) no price available  | 20 bag ($P39) no price available
  - Polyfusor K mannitol 20% infusion 500ml bottles  | 1 bottle ($P39) £4.05
  - Mannitol 100 mg/500ml infusion Viaflex bags  | 1 bag ($P39) no price available  | 20 bag ($P39) no price available
  - Mannitol 500/500ml infusion Viaflo bags  | 1 bag ($P39) no price available
  - Mannitol 200 mg per 1 ml
    - Mannitol 100g/500ml infusion Viaflex bags  | 1 bag ($P39) no price available  | 20 bag ($P39) no price available

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

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**Amiloride with bumetanide**

The properties listed below are those particular to the combination only. For the properties of the components please consider, amiloride hydrochloride above, bumetanide p. 200.

**INDICATIONS AND DOSE**

**Oedema**  
**BY MOUTH**
- Adult: 1–2 tablets daily

**Triamterene**

**INDICATIONS AND DOSE**

**Oedema | Potassium conservation with thiazide and loop diuretics**  
**BY MOUTH**  
- Adult: Initially 150–250 mg daily in 2 divided doses, to be taken after breakfast and lunch, lower initial dose when given with other diuretics, then reduced to 150–250 mg once daily on alternate days in 2 divided doses, to be taken after breakfast and lunch, after one week of initial treatment

**CONTRA-INDICATIONS**  
Addison’s disease • anuria • hyperkalaemia

**CAUTIONS**  
Diabetes mellitus • elderly • gout • may cause blue fluorescence of urine

**INTERACTIONS**  
Appendix 1 (triamterene).

**SIDE-EFFECTS**  
Common or very common • Diarrhoea • hyperkalaemia • nausea • vomiting
- Uncommon • Dry mouth • headache • hyperuricaemia • rash
- Rare • Megaloblastic anaemia • pancytopenia • photosensitivity • serum-sickness
- Very rare • Renal failure (reversible on discontinuation) • triamterene found in kidney stones

**FREQUENCY NOT KNOWN**  
Jaundice • malaise • slight decrease in blood pressure

**PREGNANCY**  
Not used to treat gestational hypertension. Avoid unless essential.

**BREAST FEEDING**  
Present in milk—manufacturer advises avoid.

**HEPATIC IMPAIRMENT**  
Use with caution. Avoid in progressive impairment.

**RENAL IMPAIRMENT**  
Avoid in progressive impairment. Monitor plasma-potassium concentration (high risk of hyperkalaemia in renal impairment).

**MONITORING REQUIREMENTS**  
Monitor electrolytes.
Cardiovascular system

**Thiazides and related diuretics**

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Capsule**
CAUTIONARY AND ADVISORY LABELS 14, 21

▶ TRIAMTERENE (Non-proprietary)
Triamterene 50 mg, Triamterene 50mg capsules | 30 capsule | £41.90 DT price = £41.90

Also available in combination with furosemide, p. 201

**PATIENT AND CARER ADVICE**
Urine may look slightly blue in some lights.

**Chlortalidone with triamterene**
The properties listed below are those particular to the combination only. For the properties of the components please consider, triamterene p. 203, chlortalidone below.

**INDICATIONS AND DOSE**
Hypertension | Oedema
BY MOUTH
▶ Adult: 1–2 tablets daily, dose to be taken in the morning

**SIDE-EFFECTS**
▶ Rare Allergic interstitial nephritis · jaundice
▶ BREAST FEEDING The amount present in milk is too small to be harmful. Large doses may suppress lactation.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
CAUTIONARY AND ADVISORY LABELS 14, 21

▶ Chlortalidone 50 mg, Triamterene 50 mg | Kalspare tablets | 28 tablet | £9.90

**Co-triamterzide**
The properties listed below are those particular to the combination only. For the properties of the components please consider, triamterene p. 203, hydrochlorothiazide p. 160.

**INDICATIONS AND DOSE**
Hypertension
BY MOUTH
▶ Adult: 1 tablet daily, increased if necessary up to 4 tablets daily, dose to be taken after breakfast

**SIDE-EFFECTS**
▶ Rare Depression
▶ BREAST FEEDING The amount present in milk is too small to be harmful. Large doses may suppress lactation.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
CAUTIONARY AND ADVISORY LABELS 14, 21

▶ Hydrochlorothiazide 25 mg, Triamterene 50 mg | Dyazide 50mg/25mg tablets | 30 tablet | £0.95 DT price = £0.95

**Chlortalidone**
(Chlorthalidone)
The properties listed below are those particular to the drug only. For properties common to the class, see thiazides and related diuretics, p. 159.

**INDICATIONS AND DOSE**
Ascites due to cirrhosis in stable patients (under close supervision) | Oedema due to nephrotic syndrome
BY MOUTH
▶ Adult: Up to 50 mg daily

Hypertension
BY MOUTH
▶ Adult: 25 mg daily, dose to be taken in the morning, then increased if necessary to 50 mg daily

Mild to moderate chronic heart failure
BY MOUTH
▶ Adult: 25–50 mg daily, dose to be taken in the morning, then increased if necessary to 100–200 mg daily, reduce to lowest effective dose for maintenance

Nephrogenic diabetes insipidus | Partial pituitary diabetes insipidus
BY MOUTH
▶ Adult: Initially 100 mg twice daily, then reduced to 50 mg daily

**SIDE-EFFECTS**
▶ Rare Depresssion
▶ BREAST FEEDING The amount present in milk is too small to be harmful. Large doses may suppress lactation.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
EXCIPIENTS: May contain Gluten

▶ Navidrex (AMCo)
Cyclopenthiazide 500 microgram | Navidrex 500microgram tablets | 28 tablet | £1.27

**Medicinal forms**

**Chlorthalidone with hydrochlorothiazide**
Also available in combination with furosemide, p. 201

**Medicinal forms**

**Chlorthalidone with triamterene**
Also available in combination with furosemide, p. 201

**Chlorthalidone**
(Chlorthalidone)
The properties listed below are those particular to the drug only. For properties common to the class, see thiazides and related diuretics, p. 159.

**INDICATIONS AND DOSE**
Hypertension
BY MOUTH
▶ Adult: Up to 50 mg daily

**Side-effects**
▶ Rare Allergic interstitial nephritis · jaundice
▶ BREAST FEEDING The amount present in milk is too small to be harmful. Large doses may suppress lactation.

**Medicinal forms**

**Cyclopenthiazide**
The properties listed below are those particular to the drug only. For properties common to the class, see thiazides and related diuretics, p. 159.

**INDICATIONS AND DOSE**
Heart failure
BY MOUTH
▶ Adult: 250–500 micrograms daily, take in the morning, then increased if necessary to 1 mg daily, reduce to lowest effective dose for maintenance

**Side-effects**
▶ Rare Depression
▶ BREAST FEEDING The amount present in milk is too small to be harmful. Large doses may suppress lactation.

**Medicinal forms**

**Dyazide**
Tablet

▶ Kalspare (DHP Healthcare Ltd)
Chlortalidone 50 mg, Triamterene 50 mg | Kalspare tablets | 28 tablet | £9.90

**Navidrex**
Tablet

▶ (AMCo)
Cyclopenthiazide 500 microgram | Navidrex 500microgram tablets | 28 tablet | £1.27

**Medicinal forms**

**EXCIPIENTS: May contain Gluten**

**Navidrex**
Tablet

▶ (AMCo)
Cyclopenthiazide 500 microgram | Navidrex 500microgram tablets | 28 tablet | £1.27

**Medicinal forms**
Metolazone

The properties listed below are those particular to the drug only. For properties common to the class, see thiazides and related diuretics, p. 159.

INDICATIONS AND DOSE
Oedema
BY MOUTH
» Adult: 5–10 mg daily, dose to be taken in the morning; dose may be increased in resistant oedema; increased if necessary to 20 mg daily; maximum 80 mg per day

Hypertension
BY MOUTH
» Adult: Initially 5 mg daily, dose to be taken in the morning; maintenance 5 mg once daily on alternate days

● CAUTIONS Acute porphyrias p. 864
● SIDE-EFFECTS Chest pain · chills
● BREAST FEEDING The amount present in milk is too small to be harmful. Large doses may suppress lactation.
● DIRECTIONS FOR ADMINISTRATION Tablets may be crushed and mixed with water immediately before use.

Xipamide

The properties listed below are those particular to the drug only. For properties common to the class, see thiazides and related diuretics, p. 159.

INDICATIONS AND DOSE
Oedema
BY MOUTH
» Adult: Initially 40 mg daily, dose to be taken in the morning, increased if necessary to 80 mg daily, higher dose to be used in resistant cases; maintenance 20 mg daily, dose to be taken in the morning

Hypertension
BY MOUTH
» Adult: 20 mg daily, dose to be taken in the morning

● CAUTIONS Acute porphyrias p. 864
● BREAST FEEDING No information available.

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension, tablet

9 Vascular disease

Peripheral vascular disease

Peripheral vascular disease can be either occlusive (e.g. intermittent claudication) in which occlusion of the peripheral arteries is caused by atherosclerosis, or vasospastic (e.g. Raynaud’s syndrome). Peripheral arterial occlusive disease is associated with an increased risk of cardiovascular events; this risk is reduced by measures such as smoking cessation, effective control of blood pressure, regulating blood lipids, optimising glycaemic control in diabetes, taking aspirin p. 104 in a dose of 75 mg daily, and possibly weight reduction in obesity. Exercise training can improve symptoms of intermittent claudication; revascularisation procedures may be appropriate.

Naftidrofuryl oxalate p. 206 can alleviate symptoms of intermittent claudication and improve pain-free walking distance in moderate disease. Patients taking naftidrofuryl oxalate p. 206 should be assessed for improvement after 3–6 months.

Cilostazol p. 206 is licensed for use in intermittent claudication to improve walking distance in patients without peripheral tissue necrosis who do not have pain at rest; use is restricted to second-line treatment where lifestyle modifications and other appropriate interventions have failed to improve symptoms. Cilostazol should be initiated by those experienced in the management of intermittent claudication. Patients receiving cilostazol should be assessed for improvement after 3 months; consider discontinuation of treatment if there is no clinically relevant improvement in walking distance.

Inositol nicotinate p. 206 and pentoxifylline p. 207 are not established as being effective for the treatment of intermittent claudication.

Management of Raynaud’s syndrome includes avoidance of exposure to cold and stopping smoking. More severe symptoms may require vasodilator treatment, which is most often successful in primary Raynaud’s syndrome. Nifedipine p. 154 is useful for reducing the frequency and severity of vasospastic attacks. Alternatively, naftidrofuryl oxalate p. 206 may produce symptomatic improvement; inositol nicotinate p. 206 (a nicotinic acid derivative) may also be considered. Pentoxifylline, prazosin p. 674, and moxisylyte below are not established as being effective for the treatment of Raynaud’s syndrome.

Vasodilator therapy is not established as being effective for chilblains.

ALPHA-ADRENOCEPTOR BLOCKERS

Moxisylyte
(Thymoxamine)

INDICATIONS AND DOSE
Primary Raynaud’s syndrome (short-term treatment)
BY MOUTH
» Adult: Initially 40 mg 4 times a day, increased if necessary to 80 mg 4 times a day, increase dose if poor initial response, discontinue after 2 weeks if no response

● CONTRA-INDICATIONS Active liver disease
● CAUTIONS Diabetes mellitus
● SIDE-EFFECTS Cholestatic jaundice · diarrhoea · dizziness · flushing · headache · hepatic reactions · hepatitis · nausea
● PREGNANCY Manufacturer advises avoid.
● LESS SUITABLE FOR PRESCRIBING Less suitable for prescribing.

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
» Opilon (Archimedes Pharma UK Ltd)
Moxisylyte (as Moxisylyte hydrochloride) 40 mg Opilon 40mg tablets | 112 tablet (PO) £90.22 DT price = £90.22
FLAVONOIDS

Oxerutins

INDICATIONS AND DOSE
Relief of symptoms of oedema associated with chronic venous insufficiency
BY MOUTH
> Adult: 500 mg twice daily

SIDE-EFFECTS
Flushing • headache • mild gastro-intestinal disturbances • rash

LESS SUITABLE FOR PRESCRIBING
Oxerutins (rutosides) are not vasodilators and are not generally regarded as effective preparations as capillary sealants or for the treatment of cramps; they are less suitable for prescribing.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Capsule
> Paroven (Novartis Consumer Health UK Ltd)
Oxerutins 250 mg Paroven 250mg capsules | 120 capsule £16.81 DT price + £16.81

5HT 2 RECEPTOR ANTAGONISTS

Naftidrofuryl oxalate

INDICATIONS AND DOSE
Peripheral vascular disease
BY MOUTH
> Adult: 100–200 mg 3 times a day, patients taking naftidrofuryl should be assessed for improvement after 3–6 months

Cerebral vascular disease
BY MOUTH
> Adult: 100 mg 3 times a day, patients taking naftidrofuryl should be assessed for improvement after 3–6 months

SIDE-EFFECTS
Epigastric pain • hepatic failure • hepatitis • nausea • rash

NATIONAL FUNDING/ACCESS DECISIONS
NICE Technology appraisals (TAs)
> Cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease (May 2011)
NICE TA223
Naftidrofuryl oxalate is an option for the treatment of intermittent claudication in patients with peripheral arterial disease; patients currently receiving treatment should have the option to continue until they and their clinician consider it appropriate to stop. www.nice.org.uk/TA223

LESS SUITABLE FOR PRESCRIBING
Less suitable for prescribing.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Tablet
> Hexopal (Genus Pharmaceuticals Ltd)
Inositol nicotinate 500 mg Hexopal 500mg tablets | 100 tablet £30.76 DT price = £30.76
Inositol nicotinate 750 mg Hexopal Forte 750mg tablets | 112 tablet £51.03 DT price = £51.03

NICOTINIC ACID DERIVATIVES

Inositol nicotinate

INDICATIONS AND DOSE
Peripheral vascular disease
BY MOUTH
> Adult: 3 g daily in 2–3 divided doses; maximum 4 g per day

CONTRA-INDICATIONS
Acute phase of a cerebrovascular accident • recent myocardial infarction

CAUTIONS
Cerebrovascular insufficiency • unstable angina

SIDE-EFFECTS
Dizziness • flushing • headache • hypotension • nausea • oedema • paraesthesia • rash • syncope • vomiting

PREGNANCY
No information available—manufacturer advises avoid unless potential benefit outweighs risk.

NATIONAL FUNDING/ACCESS DECISIONS
NICE technology appraisals (TAs)
> Cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease (May 2011)
NICE TA223
Inositol nicotinate is not recommended for the treatment of intermittent claudication in patients with peripheral arterial disease; patients currently receiving treatment should have the option to continue until they and their clinician consider it appropriate to stop. www.nice.org.uk/TA223

LESS SUITABLE FOR PRESCRIBING
Less suitable for prescribing.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Tablet
> Hexopal (Genus Pharmaceuticals Ltd)
Inositol nicotinate 500 mg Hexopal 500mg tablets | 100 tablet £30.76 DT price = £30.76
Inositol nicotinate 750 mg Hexopal Forte 750mg tablets | 112 tablet £51.03 DT price = £51.03

PHOSPHODIESTERASE TYPE-3 INHIBITORS

Cilostazol

INDICATIONS AND DOSE
Intermittent claudication in patients without rest pain and no peripheral tissue necrosis
BY MOUTH
> Adult: 100 mg twice daily, to be taken 30 minutes before food, cilostazol should be initiated by those experienced in the management of intermittent claudication, patients receiving cilostazol should be assessed for improvement after 3 months; consider discontinuation of treatment if there is no clinically relevant improvement in walking distance

Dose adjustments due to interactions
Reduce dose to 50 mg twice daily with concomitant use of potent inhibitors of cytochrome P450 enzymes CYP3A4 (e.g. clarithromycin, itraconazole, ketoconazole, protease inhibitors) or CYP2C19, or with erythromycin or omeprazole.

CONTRA-INDICATIONS
Active peptic ulcer • congestive heart failure • coronary intervention in previous 6 months • haemorrhagic stroke in previous 6 months • history of severe tachyarrhythmia • myocardial infarction in previous 6 months • poorly controlled hypertension • predisposition to bleeding • proliferative diabetic retinopathy •
Cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol

NATIONAL FUNDING/ACCESS DECISIONS

RENAL IMPAIRMENT

HEPATIC IMPAIRMENT

BREAST FEEDING

PREGNANCY

INTERACTIONS

CAUTIONS

SIDE-EFFECTS

Common or very common


Uncommon


Rare

Bleeding disorders - increased urinary frequency - renal impairment - thrombocytopenia

Frequency not known


SIDE-EFFECTS, FURTHER INFORMATION

Blood Disorders

A blood count should be performed and the drug stopped immediately if there is suspicion of a blood dyscrasia.

Pregnancy

Avoid - toxicity in animal studies.

Breast Feeding

Present in milk in animal studies - manufacturer advises avoid.

Hepatic Impairment

Avoid in moderate or severe liver disease.

Renal Impairment

Avoid if eGFR less than 25 mL/minute/1.73 m².

Patient and Carer Advice

Blood disorders. Patients should be advised to report any unexplained bleeding, bruising, sore throat, or fever.

National Funding/Access Decisions

NICE Technology Appraisals (TAs)

Cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease (May 2011) NICE TA223

Cilostazol is not recommended for the treatment of intermittent claudication in patients with peripheral arterial disease; patients currently receiving this treatment should have the option to continue until they and their clinician consider it appropriate to stop. www.nice.org.uk/TA223

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (October 2005) that cilostazol is not recommended for the treatment of intermittent claudication within NHS Scotland.

Medicinal Forms

There can be variation in the licensing of different medicines containing the same drug.

Tablet

Cilostazol (Non-proprietary)

Cilostazol 50 mg | 56 tablet POM £40.05 DT price = £39.91
Cilostazol 100 mg | 56 tablet POM £31.70 DT price = £31.70

XANTHINNES

Pentoxifylline (Oxpentifylline)

INDICATIONS AND DOSE

Peripheral vascular disease | Venous leg ulcer (adjunct)

BY MOUTH

Adult: 400 mg 2–3 times a day

Unlicensed Use

Use of pentoxifylline as adjunct therapy for venous leg ulcers is an unlicensed indication.

Contra-Indications

Acute myocardial infarction - cerebral haemorrhage - extensive retinal haemorrhage - severe cardiac arrhythmias

CAUTIONS

Avoid in Acute porphyrias p. 864 - coronary artery disease - hypotension

INTERACTIONS

Rare - Angina - hypotension

Very rare - Bleeding

Frequency not known - Agitation - diarrhoea - dizziness - flushing - headache - intra-hepatic cholestasis - nausea - sleep disturbances - tachycardia - thrombocytopenia - vomiting

Pregnancy

Manufacturer advises avoid — no information available.

Breast Feeding

Present in milk - manufacturer advises use only if potential benefit outweighs risk.

Hepatic Impairment

Manufacturer advises reduce dose in severe impairment.

Renal Impairment

Reduce dose by 30–50% if eGFR less than 30 mL/minute/1.73 m².

National Funding/Access Decisions

NICE Technology Appraisals (TAs)

Cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease (May 2011) NICE TA223

Pentoxifylline is not recommended for the treatment of intermittent claudication in patients with peripheral arterial disease; patients currently receiving this treatment should have the option to continue until they and their clinician consider it appropriate to stop. www.nice.org.uk/TA223

Less Suitable for Prescribing

Less suitable for prescribing.

Medicinal Forms

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

Modified-Release Tablet

Cautionary and Advisory Labels 21, 25

Trental (Sanofi)

Pentoxifylline 400 mg | 90 tablet POM £19.39 DT price = £19.39

Cardiovascular system
9.1 Vein malformations

**SCLEROSANTS**

**Sodium tetradecyl sulfate**

**INDICATIONS AND DOSE**

Sclerotherapy of reticular veins and spider veins in legs and varicose veins

**BY INTRavenous INJECTION**

- **Adult:** Test dose recommended before each treatment (consult product literature)

**CONTRA-INDICATIONS** Acute infection - asthma - blood disorders - deep vein thrombosis - high risk of thromboembolism - hyperthyroidism - inability to walk - neoplasm - occlusive arterial disease - phlebitis - pulmonary embolism - recent acute superficial thrombophlebitis - recent surgery - respiratory disease - significant valvular incompetence in deep veins - skin disease - symptomatic patent foramen ovale (if administered as foam) - uncontrolled diabetes mellitus - varicose veins caused by tumours (unless tumour removed)

**CAUTIONS** Arterial disease - asymptomatic patent foramen ovale (use smaller volumes and avoid Valsalva manoeuvre immediately after administration) - extravasation may cause necrosis of tissues - history of migraine (use smaller volumes) - resuscitation facilities must be available - venous insufficiency with lymphoedema (pain and inflammation may worsen)

**SIDE-EFFECTS**

- **Common or very common** Local burning - local pain - phlebitis - skin discoloration - superficial thrombophlebitis - telangiectatic matting
- **Uncommon** Deep vein thrombosis - scotoma
- **Rare** Chest pain - cough - headache - migraine - paraesthesia - shortness of breath - vasovagal reactions
- **Very rare** Anaphylaxis - circulatory collapse - diarrhoea - dry mouth - fever - hot flushes - hypersensitivity reactions - nausea - necrosis of skin and tissues - palpitation - pulmonary embolism - sloughing of skin and tissues - stroke - swollen tongue - transient ischaemic attack - vasculitis - vomiting - weakness

**PREGNANCY** Avoid unless benefits outweigh risks—no information available.

**BREAST FEEDING** Use with caution—no information available.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

**EXCipients:** May contain Benzyl alcohol

- Fibro-Vein (STD Pharmaceutical Products Ltd)
  - Sodium tetradecyl sulfate 2 mg per 1 ml Fibrovein 0.2% solution for injection 5ml vials | 10 vial £70.00
  - Sodium tetradecyl sulfate 5 mg per 1 ml Fibrovein 0.5% solution for injection 2ml ampoules | 5 ampoule £32.00
  - Sodium tetradecyl sulfate 10 mg per 1 ml Fibrovein 1% solution for injection 2ml ampoules | 5 ampoule £21.50
  - Sodium tetradecyl sulfate 30 mg per 1 ml Fibrovein 3% solution for injection 2ml ampoules | 5 ampoule £32.00
  Fibrovein 3% solution for injection 5ml vials | 10 vial £158.50
Chapter 3
Respiratory system

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Respiratory system

Inhalation
This route delivers the drug directly to the airways; the dose required is smaller than when given by mouth and side-effects are reduced.

Inhaler devices
These include pressurised metered-dose inhalers, breath-actuated inhalers, and dry powder inhalers. Many patients can be taught to use a pressurised metered-dose inhaler effectively but some patients, particularly the elderly and children, find them difficult to use. Spacer devices can help such patients because they remove the need to co-ordinate actuation with inhalation. Dry powder inhalers may be useful in adults and children over 5 years who are unwilling or unable to use a pressurised metered-dose inhaler. Alternatively, breath-actuated inhalers are suitable for adults and older children provided they can use the device effectively.

Pressurised metered-dose inhalers are an effective and convenient method of drug administration in mild to moderate asthma.

On changing from a pressurised metered-dose inhaler to a dry powder inhaler, patients may notice a lack of sensation in the mouth and throat previously associated with each actuation. Coughing may also occur.

The patient should be instructed carefully on the use of the inhaler and it is important to check that the inhaler continues to be used correctly because inadequate inhalation technique may be mistaken for a lack of response to the drug.

Spacer devices
Spacer devices remove the need for coordination between actuation of a pressurised metered-dose inhaler and inhalation. The spacer device reduces the velocity of the aerosol and subsequent impaction on the oropharynx and allows more time for evaporation of the propellant so that a larger proportion of the particles can be inhaled and deposited in the lungs. Spacer devices are particularly useful for patients with poor inhalation technique, for children, for patients requiring high doses of inhaled corticosteroids, for nocturnal asthma, and for patients prone to candidiasis with inhaled corticosteroids. The size of the spacer is important, the larger spacers with a one-way valve (Volumatic®) being most effective. It is important to prescribe a spacer device that is compatible with the metered-dose inhaler, see devices below. Spacer devices should not be regarded as interchangeable; patients should be advised not to switch between spacer devices.

Use and care of spacer devices
Patients should inhale from the spacer device as soon as possible after actuation because the drug aerosol is very short-lived; single-dose actuation is recommended. Tidal breathing is as effective as single breaths. The device should be cleaned once a month by washing in mild detergent and then allowed to dry in air without rinsing; the mouthpiece should be wiped clean of detergent before use. Some manufacturers recommend more frequent cleaning, but this should be avoided since any electrostatic charge may affect drug delivery. Spacer devices should be replaced every 6–12 months.

Nebulisers
Solutions for nebulisation are available for use in severe acute asthma. They are administered over 5–10 minutes from a nebuliser usually driven by oxygen in hospital.

Patients with a severe attack of asthma should preferably have oxygen during nebulisation since beta, agonists can increase arterial hypoxaemia.

A nebuliser converts a solution of a drug into an aerosol for inhalation. It is used to deliver higher doses of drug to the airways than is usual with standard inhalers. The main indications for use of a nebuliser are to deliver:

- a beta, agonist or ipratropium bromide p. 217 to a patient with an acute exacerbation of asthma or of chronic obstructive pulmonary disease;
- a beta2, agonist, corticosteroid, or ipratropium bromide on a regular basis to a patient with severe asthma or reversible airways obstruction when the patient is unable to use other inhalational devices;
- an antibiotic (such as colistimethate sodium p. 489) or a mucolytic to a patient with cystic fibrosis;
- budesonide p. 228 or adrenaline/epinephrine p. 196 to a child with severe croup;
- pentamidine isetionate p. 523 for the prophylaxis and treatment of pneumocystis pneumonia.

The use of nebulisers in chronic persistent asthma and chronic obstructive pulmonary disease should be considered only:

- after a review of the diagnosis;
- after review of therapy (see also Chronic Obstructive Pulmonary Disease p. 214) and the patient’s ability to use hand-held devices;
- after increased doses of inhaled therapy from hand-held inhalers (with a spacer if necessary) have been tried for 2 weeks;
- if the patient remains breathless, despite correctly using optimal therapy.

Before prescribing a nebuliser, a home trial should preferably be undertaken to monitor response for up to 2 weeks on standard treatment and up to 2 weeks on...
nebulised treatment. If prescribed, patients must:

- have clear instructions from a doctor, specialist nurse, physiotherapist, or pharmacist on the use of the nebuliser (including maintenance and cleaning) and on peak-flow monitoring;
- be instructed not to treat acute attacks at home without also seeking help;
- have regular follow up by a doctor, specialist nurse or physiotherapist after about 1 month and annually thereafter.

The proportion of a nebuliser solution that reaches the lungs depends on the type of nebuliser and although it can be as high as 30%, it is more frequently close to 10% and sometimes below 10%. The remaining solution is left in the nebuliser as residual volume or is deposited in the mouthpiece and tubing. The extent to which the nebulised solution is deposited in the airways or alveoli depends on the droplet size, pattern of breath inhalation, and condition of the lungs. Droplets with a mass median diameter of the droplet size, pattern of breath inhalation, and condition of the lung. Droplets with a mass median diameter of 1–5 microns are deposited in the airways and are therefore appropriate for asthma, whereas a particle size of 1–2 microns is needed for alveolar deposition of pentamidine isetionate p. 523 to combat pneumocystis infection. The type of nebuliser is therefore chosen according to the deposition required and according to the viscosity of the solution.

Jet nebulisers

Jet nebulisers are more widely used than ultrasonic nebulisers. Most jet nebulisers require an optimum gas flow rate of 6–8 litres/minute and in hospital can be driven by piped air or oxygen; in acute asthma the nebuliser should be driven by oxygen. Domiciliary oxygen cylinders do not provide an adequate flow rate therefore an electrical compressor is required for domiciliary use.

For patients at risk of hypercapnia, such as those with chronic obstructive pulmonary disease, oxygen can be dangerous and the nebuliser should be driven by air. If oxygen is required, it should be given simultaneously by nasal cannula.

Tubing

The Department of Health has reminded users of the need to use the correct grade of tubing when connecting a nebuliser to a medical gas supply or compressor.

Ultrasonic nebulisers

Ultrasonic nebulisers produce an aerosol by ultrasonic vibration of the drug solution and therefore do not require a gas flow; they are not suitable for the nebulisation of some drugs, such as dornase alfa p. 256 and nebulised suspensions.

Nebuliser diluent

Nebulisation may be carried out using an undiluted nebuliser solution or it may require dilution beforehand. The usual diluent is sterile sodium chloride 0.9% (physiological saline).

In England and Wales nebulisers and compressors are not available on the NHS (but they are free of VAT); some nebulisers (but not compressors) are available on form GP10A in Scotland (for details consult Scottish Drug Tariff).

Oral

The oral route is used when administration by inhalation is not possible. Systemic side-effects occur more frequently when a drug is given orally rather than by inhalation. Drugs given by mouth for the treatment of asthma include beta2 agonists, corticosteroids, theophylline p. 238, and leukotriene receptor antagonists.

Parenteral

Drugs such as beta2 agonists, corticosteroids, and aminophylline p. 237 can be given by injection in acute severe asthma when administration by nebulisation is inadequate or inappropriate. If the patient is being treated in the community, urgent transfer to hospital should be arranged.

NICE technology appraisals (TAs)

Inhaler devices for children under 5 years with chronic asthma (August 2000) NICE TA10

A child’s needs and likelihood of good compliance should govern the choice of inhaler and spacer device; only then should cost be considered.

- corticosteroid and bronchodilator therapy should be delivered by pressurised metered-dose inhaler and spacer device, with a facemask if necessary;
- if this is not effective, and depending on the child’s condition, nebulised therapy may be considered and, in children over 3 years, a dry powder inhaler may also be considered. www.nice.org.uk/TA10

Inhaler devices for children 5–15 years with chronic asthma (March 2002) NICE TA38

A child’s needs, ability to develop and maintain effective technique, and likelihood of good compliance should govern the choice of inhaler and spacer device; only then should cost be considered.

- corticosteroid therapy should be routinely delivered by a pressurised metered-dose inhaler and spacer device;
- for other inhaled drugs, particularly bronchodilators, a wider range of devices should be considered;
- children and their carers should be trained in the use of the chosen device; suitability of the device should be reviewed at least annually. Inhaler technique and compliance should be monitored. www.nice.org.uk/TA38

1 Airways disease, obstructive

Asthma

Drugs used in the management of asthma include beta2 agonists, antimuscarinic bronchodilators, theophylline p. 238, corticosteroids, sodium cromoglicate p. 234 and nedocromil sodium p. 234, leukotriene receptor antagonists, and, in specialist centres, omalizumab p. 235.

Management of acute asthma

Important: Patients with severe or life-threatening acute asthma may not be distressed and may not have all these abnormalities; the presence of any should alert the doctor to regard each emergency consultation as being for severe acute asthma until shown otherwise.

See medical emergencies, for doses of drugs used for the management of acute asthma.

Moderate acute asthma

- Able to talk
- Respiration (breaths/minute) < 25; child 2–5 years < 40, 5–12 years ≤ 30
- Pulse (beats/minute) < 110; child 2–5 years ≤ 140, 5–12 years ≤ 125
- Arterial oxygen saturation ≥ 92%
- Peak flow > 50% of predicted or best; child 5–12 years ≥ 50%

Treat at home or in surgery and assess response to treatment

Treatment

- Inhaled short-acting beta2 agonist via a large-volume spacer or oxygen-driven nebuliser (if available); give salbutamol 100 micrograms/metered inhalation p. 222, and repeat at 10–20 minute intervals if necessary or give nebulised salbutamol or terbutaline sulfate p. 225, and repeat at 20–30 minute intervals if necessary.
Management of severe acute asthma

Important
Regard each emergency consultation as being for severe acute asthma until shown otherwise. Failure to respond adequately at any time requires immediate transfer to hospital.

Severe acute asthma can be fatal and must be treated promptly. All patients with severe acute asthma should be given high-flow oxygen (if available) and an inhaled short-acting beta agonist via a large-volume spacer or nebuliser; give salbutamol 100 micrograms/minute inhalation p. 222, each puff inhaled separately via a large volume spacer, and repeat at 10–20 minute intervals or as necessary. If there are life-threatening features, give salbutamol or terbutaline sulfate p. 225 via an oxygen-driven nebuliser every 20–30 minutes or as necessary. In all cases, a systemic corticosteroid should be given. For adults, give prednisolone by mouth for at least 5 days, or intravenous hydrocortisone (preferably as sodium succinate) every 6 hours until conversion to oral prednisolone is possible. For children, give prednisolone by mouth for up to 3 days, or longer if necessary, or intravenous hydrocortisone (preferably as sodium succinate) every 6 hours until conversion to oral prednisolone is possible. If the child has been taking an oral corticosteroid for more than a few days, then give prednisolone at the upper end of the dose range. In severe or life-threatening asthma, also consider initial treatment with ipratropium bromide by nebuliser.

Most patients do not require and do not benefit from the addition of intravenous aminophylline or of intravenous beta agonist; both cause more adverse effects than nebulised beta agonists. Nevertheless, an occasional patient who has not been taking theophylline may benefit from aminophylline infusion. A single dose of magnesium sulfate [unlicensed indication] by intravenous infusion over 20 minutes can be used for patients with severe acute asthma, but evidence of benefit is limited.

Treatment of severe acute asthma is safer in hospital where resuscitation facilities are immediately available. Treatment should never be delayed for investigations, patients should never be sedated, and the possibility of a pneumothorax should be considered.

If the patient’s condition deteriorates despite pharmacological treatment, intermittent positive pressure ventilation may be needed.

Follow up in all cases
Episodes of acute asthma should be regarded as a failure of preventative therapy. A careful history should be taken to establish the reason for the exacerbation. Monitor symptoms and peak flow. Inhaler technique should be checked and regular treatment should be reviewed, see Management of chronic asthma below. Patients should be given a written asthma action plan aimed at preventing relapse, optimising treatment, and preventing delay in seeking assistance in future exacerbations. Follow-up within 48 hours should be arranged with the general practitioner or appropriate primary care health professional. Patients should also be reviewed by a respiratory specialist within one month of the exacerbation.

Advice on the management of acute asthma is based on the recommendations of the British Thoracic Society and Scottish Intercollegiate Guidelines Network (updated January 2012); updates available at www.brit-thoracic.org.uk.

Management of chronic asthma

Important: Start at step most appropriate to initial severity; before initiating a new drug consider whether diagnosis is correct, check compliance and inhaler technique, and eliminate trigger factors for acute exacerbations.
Advice on the management of chronic asthma is based on the recommendations of the British Thoracic Society and Scottish Intercollegiate Guidelines Network (updated January 2012); updates available at www.brit-thoracic.org.uk

**Respiratory system**

**Lung function measurements cannot be used to guide management of those under 5 years.**

**Step 1: occasional relief bronchodilator**
- Inhaled short-acting beta; agonist as required (up to once daily).
- Move to step 2 if needed more than twice a week, or if night-time symptoms at least once a week, or if exacerbation in the last 2 years.

**Step 2: regular inhaled preventer therapy**
- Inhaled short-acting beta; agonist as required **plus**
- Regular standard-dose inhaled corticosteroid **plus**
- Regular long-acting beta; agonist (alternatives to inhaled corticosteroid are leukotriene receptor antagonists, theophylline, inhaled sodium cromoglicate, or inhaled nedocromil sodium, but are considerably less effective)
**Step 3: inhaled corticosteroid + long-acting inhaled beta; agonist**
- Inhaled short-acting beta; agonist as required **plus**
- Regular standard-dose inhaled corticosteroid **plus**
- Regular inhaled long-acting beta; agonist (salmeterol p. 222 or formoterol fumarate p. 220); if *asthma not controlled* increase dose of inhaled corticosteroid to upper end of standard dose range and **Either** stop long-acting beta; agonist if of no benefit or continue long-acting beta; agonist if of some benefit; if *asthma still not controlled* and long-acting beta; agonist stopped, add one of:
  - Leukotriene receptor antagonist
  - Modified-release oral theophylline
  - Modified-release oral beta; agonist (child under 12 years not recommended).

**Step 4: high-dose inhaled corticosteroid + regular bronchodilators**
- Inhaled short-acting beta; agonist as required **with**
- Regular high-dose inhaled corticosteroid **plus**
- Inhaled long-acting beta; agonist **plus**
- In adults 6-week sequential therapeutic trial of one or more of:
  - Leukotriene receptor antagonist
  - Modified-release oral theophylline
  - Modified-release oral beta; agonist

**Step 5: regular corticosteroid tablets (refer to a respiratory specialist)**
- Inhaled short-acting beta; agonist as required **with**
- Regular high-dose inhaled corticosteroid **and**
- One or more long-acting bronchodilators (see step 4) **plus**
- Regular prednisolone p. 585 tablets (as single daily dose); in addition to regular prednisolone, continue high-dose inhaled corticosteroid (in exceptional cases may exceed licensed doses); these patients should normally be referred to an asthma clinic

**Step 2: regular preventer therapy**
- Inhaled short-acting beta; agonist as required **plus**
- *Either* regular standard-dose inhaled corticosteroid
- 0r (if inhaled corticosteroid cannot be used) leukotriene receptor antagonist.

**Step 3: add-on therapy**
- Child under 2 years: Refer to respiratory paediatrician
- Child 2–5 years: Inhaled short-acting beta, agonist as required **plus**
- Regular inhaled corticosteroid in standard dose **plus**
- Leukotriene receptor antagonist

**Step 4: persistent poor control**
- Refer to respiratory paediatrician.

**Step down**
- Regularly review need for treatment.

**Standard-dose inhaled corticosteroids**

**Beclometasone dipropionate or budesonide:**
- Adult and child over 12 years 100–400 micrograms twice daily
- Child under 12 years 100–200 micrograms twice daily

**Fluticasone propionate:**
- Adult and child over 12 years 50–200 micrograms twice daily
- Child 4–12 years 50–100 micrograms twice daily

**Mometasone furoate:**
- Adult and child over 12 years 400 micrograms as a single dose in the evening or in 2 divided doses
- Child under 12 years not recommended

Dose adjustments may be required for some inhaler devices, see individual preparations.

**High-dose inhaled corticosteroids**

**Beclometasone dipropionate or budesonide:**
- Adult and child over 12 years 0.4–1 mg twice daily
- Child 5–12 years 200–400 micrograms twice daily

**Fluticasone propionate:**
- Adult and child over 12 years 200–500 micrograms twice daily
- Child 5–12 years 100–200 micrograms twice daily

**Mometasone furoate:**
- Adult and child over 12 years 400 micrograms twice daily
- Child under 12 years not recommended

Dose adjustments may be required for some inhaler devices, see individual preparations.

Failure to achieve control with these doses is unusual.

**Pregnancy and breast-feeding**

It is particularly important that asthma should be well controlled during pregnancy; when this is achieved asthma has no important effects on pregnancy, labour, or on the fetus. Drugs for asthma should preferably be administered by inhalation to minimise exposure of the fetus. Inhaled drugs, theophylline p. 236, and prednisolone can be taken as normal during pregnancy and breast-feeding. See individual leukotriene receptor antagonists for information on their use during pregnancy. Women planning to become pregnant should be counselled about the importance of taking their asthma medication regularly to maintain good control.

Severe acute exacerbations of asthma can have an adverse effect on pregnancy and should be treated promptly in hospital with conventional therapy, including nebulisation of a beta2 agonist and oral or parenteral administration of a corticosteroid; prednisolone is the preferred corticosteroid for oral administration since very little of the drug reaches the fetus. Oxygen should be given immediately to maintain arterial oxygen saturation of 94–98% and prevent maternal and fetal hypoxia. An intravenous beta, agonist, aminophylline p. 237, or magnesium sulfate p. 858 can be used during pregnancy if necessary; parenteral beta2 agonists can affect the myometrium.
**Peak flow meters**

When used in addition to symptom-based monitoring, peak flow monitoring has not been proven to improve asthma control in either adults or children, however measurement of peak flow may be of benefit in adult patients who are ‘poor perceivers’ and hence slow to detect deterioration in their asthma, and for those with more severe asthma.

When peak flow meters are used, patients must be given clear guidelines as to the action they should take if their peak flow falls below a certain level. Patients can be encouraged to adjust some of their own treatment (within specified limits) according to changes in peak flow rate.

Peak flow charts should be issued to patients where appropriate, and are available to purchase from:

3M Security Print and Systems Limited, Gorse Street, Chadderton, Oldham, OL9 9QH. Tel: 0845 610 1112

GP practices can obtain supplies through their Area Team stores.

NHS Hospitals can order supplies from [www.nhsforms.co.uk](http://www.nhsforms.co.uk) or by emailing nhsforms@mmm.com.

In Scotland, peak flow charts can be obtained by emailing stockorders.dppas@apsgroup.co.uk.

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**Bronchodilators**

**Adrenoceptor agonists (sympathomimetics)**

Selective $\beta_2$ agonists produce bronchodilation. A short-acting $\beta_2$ agonist is used for immediate relief of asthma symptoms while some long-acting $\beta_2$ agonists are added to an inhaled corticosteroid in patients requiring prophylactic treatment.

The selective $\beta_2$ agonists (selective $\beta_2$-adrenoceptor agonists, selective $\beta_2$ stimulants) such as salbutamol p. 222 or terbutaline sulfate p. 225 are the safest and most effective short-acting $\beta_2$ agonists for asthma. Less selective $\beta_2$ agonists such as ephedrine hydrochloride p. 226 is less suitable and less safe for use as a bronchodilator than the selective $\beta_2$ agonists, because it is more likely to cause arrhythmias and other side-effects; it should be avoided whenever possible.

Adrenaline/epinephrine p. 196 (which has both alpha- and beta-$\alpha$-adrenoceptor agonist properties) is used in the emergency management of acute allergic and anaphylactic reactions, in angioedema, in cardiopulmonary resuscitation, and in the management of severe croup.

**Short-acting $\beta_2$ agonists**

Mild to moderate symptoms of asthma respond rapidly to the inhalation of a selective short-acting $\beta_2$ agonist such as salbutamol or terbutaline sulfate. If $\beta_2$ agonist inhalation is needed more often than twice a week, or if night-time symptoms occur at least once a week, or if the patient has suffered an exacerbation in the last year, then prophylactic treatment should be considered using a stepped approach.

A short-acting $\beta_2$ agonist inhaled immediately before exertion reduces exercise-induced asthma; however, frequent exercise-induced asthma probably reflects poor overall control and calls for reassessment of asthma treatment.

**Long-acting $\beta_2$ agonists**

Formoterol fumarate p. 220 (eformoterol) and salmeterol p. 222 are longer-acting $\beta_2$ agonists which are administered by inhalation. They should be used for asthma only in patients who regularly use an inhaled corticosteroid. They have a role in the long-term management of chronic asthma and can be useful in nocturnal asthma.

Salmeterol should not be used for the relief of an asthma attack; it has a slower onset of action than salbutamol or terbutaline sulfate. Formoterol fumarate is licensed for short-term symptom relief and for the prevention of exercise-induced bronchospasm; its speed of onset of action is similar to that of salbutamol.

Combination inhalers that contain a long-acting $\beta_2$ agonist and a corticosteroid ensure that long-acting $\beta_2$ agonists are not used without concomitant corticosteroids, but reduce the flexibility to adjust the dose of each component.

Indacaterol p. 221 and olodaterol p. 222 are long-acting $\beta_2$ agonists licensed for chronic obstructive pulmonary disease in adults; they are not indicated for the relief of acute bronchospasm.

Vilanterol is a long-acting $\beta_2$ agonist available only in a combination inhaler with fluticasone furoate or with umectidinum p. 219.

**Oral**

Oral preparations of $\beta_2$ agonists may be used by patients who cannot manage the inhaled route. They are sometimes used for children and the elderly, but inhaled $\beta_2$ agonists are more effective and have fewer side-effects. The long-acting oral preparations, including bambuterol hydrochloride p. 220, may be of value in nocturnal asthma but they have a limited role and inhaled long-acting $\beta_2$ agonists are usually preferred.

**Parenteral**

Salbutamol or terbutaline sulfate can be given intravenously for severe or life-threatening acute asthma; patients should be carefully monitored and the dose adjusted according to response and heart rate. The regular use of $\beta_2$ agonists by the subcutaneous route is not recommended since the evidence of benefit is uncertain and it may be difficult to withdraw such treatment once started. In adults, $\beta_2$ agonists may also be given by intramuscular injection.

**Children**

Selective $\beta_2$ agonists are useful even in children under the age of 18 months. They are most effective by the inhaled route; a pressurised metered-dose inhaler should be used with a spacer device in children under 5 years. A $\beta_2$ agonist may also be given by mouth but administration by inhalation is preferred; a long-acting inhaled $\beta_2$ agonist may be used where appropriate. In severe attacks nebulisation using a selective $\beta_2$ agonist or ipratropium bromide is advisable.

**Antimuscarinic bronchodilators**

Ipratropium bromide p. 217 can provide short-term relief in chronic asthma, but short-acting $\beta_2$ agonists act more quickly and are preferred. Ipratropium bromide by nebulisation can be added to other standard treatment in life-threatening asthma or if acute asthma fails to improve with standard therapy.

The aerosol inhalation of ipratropium bromide can be used for short-term relief in mild chronic obstructive pulmonary disease in patients who are not using a long-acting antimuscarinic drug. Its maximal effect occurs 30–60 minutes after use; its duration of action is 3 to 6 hours and bronchodilation can usually be maintained with treatment 3 times a day.

Aclidinium bromide p. 217, glycopyronium bromide p. 217, tiotropium p. 218, and umecldinum p. 219 are licensed for the treatment of adults with chronic obstructive pulmonary disease. They are not suitable for the relief of acute bronchospasm. Tiotropium p. 218 (via Respimat® device) is also licensed as an adjunct to inhaled corticosteroids and long-acting $\beta_2$ agonists for the maintenance treatment of patients with asthma who have suffered one or more severe exacerbations in the last year.

**Theophylline**

Theophylline p. 238 is a xanthine used as a bronchodilator in asthma and stable chronic obstructive pulmonary disease; it
is not generally effective in exacerbations of chronic obstructive pulmonary disease. Theophylline may have an additive effect when used in conjunction with small doses of beta-agonists; the combination may increase the risk of side-effects, including hypokalaemia.

Theophylline is given by injection as aminophylline p. 227, a mixture of theophylline with ethylenediamine, which is 20 times more soluble than theophylline alone. Aminophylline injection is needed rarely for severe acute asthma.

**Compound bronchodilator preparations**

In general, patients are best treated with single-ingredient preparations, such as a selective beta-2 agonist or ipratropium bromide p. 217, so that the dose of each drug can be adjusted. This flexibility is lost with compound bronchodilator preparations. However, a combination product may be appropriate for patients stabilised on individual components in the same proportion.

**Chronic obstructive pulmonary disease**

Smoking cessation reduces the progressive decline in lung function in chronic obstructive pulmonary disease (COPD, chronic bronchitis, or emphysema). Infection can complicate chronic obstructive pulmonary disease and may be prevented by vaccination (pneumococcal vaccine p. 1089 and influenza vaccine p. 1085).

A trial of a high-dose inhaled corticosteroid or an oral corticosteroid is recommended for patients with moderate or severe airflow obstruction if the diagnosis is in doubt.

Symptoms of chronic obstructive pulmonary disease may be alleviated by an inhaled short-acting beta-2 agonist or a short-acting antimuscarinic bronchodilator used as required.

When the airways obstruction is more severe, regular inhaled therapy should be used. It is important to check compliance and inhaler technique before initiating a new drug.

If the Forced Expiratory Volume in 1 second (FEV1) is 50% of predicted or more, *either* a long-acting antimuscarinic bronchodilator or a long-acting beta-2 agonist should be used. Short-acting antimuscarinic bronchodilators should be discontinued when a long-acting antimuscarinic bronchodilator is started. A long-acting beta-2 agonist with a corticosteroid in a combination inhaler can be used for patients who remain symptomatic despite regular treatment with a long-acting beta-2 agonist.

If FEV1 is less than 50% of predicted, *either* a long-acting antimuscarinic bronchodilator or a long-acting beta-2 agonist with a corticosteroid in a combination inhaler should be used.

In any patient who remains breathless or continues to have exacerbations, triple therapy with a long-acting beta-2 agonist and a corticosteroid in a combination inhaler plus a long-acting antimuscarinic bronchodilator should be used.

If an inhaled corticosteroid is not appropriate, a long-acting antimuscarinic bronchodilator can be used with a long-acting beta-2 agonist (see Use of inhaled therapies in chronic obstructive pulmonary disease algorithm, p. 215).

If symptoms persist or if the patient is unable to use an inhaler, oral modified-release aminophylline p. 237 or theophylline p. 238 can be used.

Indacaterol p. 221 is a long-acting beta-2 agonist licensed for the maintenance treatment of chronic obstructive pulmonary disease.

In patients with severe chronic obstructive pulmonary disease associated with chronic bronchitis and a history of frequent exacerbations, roflumilast p. 236 is licensed as an adjunct to existing bronchodilator treatment.

A mucolytic drug may be considered for a patient with a chronic productive cough.

Long-term oxygen therapy prolongs survival in patients with severe chronic obstructive pulmonary disease and hypoxaemia.

During an exacerbation of chronic obstructive pulmonary disease, bronchodilator therapy can be administered through a nebuliser if necessary and oxygen given if appropriate. Aminophylline can be given intravenously if response to nebulised bronchodilators is poor. A short course of oral corticosteroid, such as prednisolone for 7–14 days, should be given if increased breathlessness interferes with daily activities. Antibacterial treatment is required if sputum becomes more purulent than usual, or if there are other signs of infection.

Patients who have had an episode of hypercapnic respiratory failure should be given a 24% or 28% Venturi mask and an oxygen alert card endorsed with the oxygen saturations required during previous exacerbations. Patients and their carers should be instructed to show the card to emergency healthcare providers in the event of an exacerbation.

**Oxygen alert card based on British Thoracic Society guideline for emergency oxygen use in adult patients (October 2008)**

**Oxygen**

Oxygen should be regarded as a drug. It is prescribed for hypoxaemic patients to increase alveolar oxygen tension and decrease the work of breathing. The concentration of oxygen required depends on the condition being treated; the administration of an inappropriate concentration of oxygen can have serious or even fatal consequences.

Oxygen is probably the most common drug used in medical emergencies. It should be prescribed initially to achieve a normal or near-normal oxygen saturation; in most acutely ill patients with a normal or low arterial carbon dioxide (Paco2), oxygen saturation should be 94–98% oxygen saturation. However, in some clinical situations such as cardiac arrest and carbon monoxide poisoning it is more appropriate to aim for the highest possible oxygen saturation until the patient is stable. A lower target of 88–92% oxygen saturation is indicated for patients at risk of hypercapnic respiratory failure.

High concentration oxygen therapy is safe in uncomplicated cases of conditions such as pneumonia, pulmonary thromboembolism, pulmonary fibrosis, shock, severe trauma, sepsis, or anaphylaxis. In such conditions low arterial oxygen (Pao2) is usually associated with low or
normal arterial carbon dioxide ($P_{aCO_2}$), and therefore there is little risk of hypoventilation and carbon dioxide retention.

In acute severe asthma, the arterial carbon dioxide ($P_{aCO_2}$) is usually subnormal but as asthma deteriorates it may rise steeply (particularly in children). These patients usually require high concentrations of oxygen and if the arterial carbon dioxide ($P_{aCO_2}$) remains high despite other treatment, intermittent positive-pressure ventilation needs to be considered urgently.

Low concentration oxygen therapy (controlled oxygen therapy) is reserved for patients at risk of hypercapnic respiratory failure, which is more likely in those with:
- chronic obstructive pulmonary disease;
- advanced cystic fibrosis;
- severe non-cystic fibrosis bronchiectasis;
- severe kyphoscoliosis or severe ankylosing spondylitis;
- severe lung scarring caused by tuberculosis;
- musculoskeletal disorders with respiratory weakness, especially if on home ventilation;
- an overdose of opioids, benzodiazepines, or other drugs causing respiratory depression.

Until blood gases can be measured, initial oxygen should be given using a controlled concentration of 28% or less, titrated towards a target oxygen saturation of 88–92%. The aim is to provide the patient with enough oxygen to achieve an acceptable arterial oxygen tension without worsening carbon dioxide retention and respiratory acidosis. Patients may carry an oxygen alert card.

Domiciliary oxygen
Oxygen should only be prescribed for use in the home after careful evaluation in hospital by respiratory experts. Patients should be advised of the risks of continuing to smoke when receiving oxygen therapy, including the risk of fire. Smoking cessation therapy should be recommended before home oxygen prescription.

Air travel
Some patients with arterial hypoxaemia require supplementary oxygen for air travel. The patient’s requirement should be discussed with the airline before travel.
Long-term oxygen therapy

Long-term administration of oxygen (usually at least 15 hours/day) prolongs survival in some patients with chronic obstructive pulmonary disease.

Assessment for long-term oxygen therapy requires measurement of arterial blood gas tensions. Measurements should be taken on 2 occasions at least 3 weeks apart to demonstrate clinical stability, and not sooner than 4 weeks after an acute exacerbation of the disease. Long-term oxygen therapy should be considered for patients with:
- chronic obstructive pulmonary disease with $P_{aO_2} < 7.3$ kPa when breathing air during a period of clinical stability;
- chronic obstructive pulmonary disease with $P_{aO_2} 7.3–8$ kPa in the presence of secondary polycythaemia, nocturnal hypoxaemia, peripheral oedema, or evidence of pulmonary hypertension;
- severe chronic asthma with $P_{aO_2}<7.3$ kPa or persistent disabling breathlessness;
- interstitial lung disease with $P_{aO_2}<8$ kPa and in patients with $P_{aD<8}$ kPa with disabling dyspnoea;
- cystic fibrosis when $P_{aO_2}<7.3$ kPa or if $P_{aO_2} 7.3–8$ kPa in the presence of secondary polycythaemia, nocturnal hypoxaemia, pulmonary hypertension, or peripheral oedema;
- pulmonary hypertension, without parenchymal lung involvement when $P_{aO_2}<8$ kPa;
- neuromuscular or skeletal disorders, after specialist assessment;
- obstructive sleep apnoea despite continuous positive airways pressure therapy, after specialist assessment;
- pulmonary malignancy or other terminal disease with disabling dyspnoea;
- heart failure with daytime $P_{aO_2}<7.3$ kPa when breathing air or with nocturnal hypoxaemia;
- paediatric respiratory disease, after specialist assessment.

Increased respiratory depression is seldom a problem in patients with stable respiratory failure treated with low concentrations of oxygen although it may occur during exacerbations; patients and relatives should be warned to call for medical help if drowsiness or confusion occurs.

Short-burst oxygen therapy

Oxygen is occasionally prescribed for short-burst (intermittent) use for episodes of breathlessness not relieved by other treatment in patients with severe chronic obstructive pulmonary disease, interstitial lung disease, heart failure, and in palliative care. It is important, however, that the patient does not rely on oxygen instead of obtaining medical help or taking more specific treatment. Short-burst oxygen therapy can be used to improve exercise capacity and recovery; it should only be continued if there is proven improvement in breathlessness or exercise tolerance.

Ambulatory oxygen therapy

Ambulatory oxygen is prescribed for patients on long-term oxygen therapy who need to be away from home on a regular basis. Patients who are not on long-term oxygen therapy can be considered for ambulatory oxygen therapy if there is evidence of exercise-induced oxygen desaturation and of improvement in blood oxygen saturation and exercise capacity with oxygen. Ambulatory oxygen therapy is not recommended for patients with heart failure or those who smoke.

Oxygen therapy equipment

Under the NHS oxygen may be supplied as oxygen cylinders. Oxygen flow can be adjusted as the cylinders are equipped with an oxygen flow meter with ‘medium’ (2 litres/minute) and ‘high’ (4 litres/minute) settings.

Oxygen delivered from a cylinder should be passed through a humidifier if used for long periods.

Oxygen concentrators are more economical for patients who require oxygen for long periods, and in England and Wales can be ordered on the NHS on a regional tendering basis. A concentrator is recommended for a patient who requires oxygen for more than 8 hours a day (or 21 cylinders per month). Exceptionally, if a higher concentration of oxygen is required the output of 2 oxygen concentrators can be combined using a ‘Y’ connection.

A nasal cannula is usually preferred for long-term oxygen therapy from an oxygen concentrator. It can, however, produce dermatitis and mucosal drying in sensitive individuals.

Giving oxygen by nasal cannula allows the patient to talk, eat, and drink, but the concentration of oxygen is not controlled; this may not be appropriate for acute respiratory failure. When oxygen is given through a nasal cannula at a rate of 1–2 litres/minute the inspiratory oxygen concentration is usually low, but it varies with ventilation and can be high if the patient is underventilating.

Arrangements for supplying oxygen

The following oxygen services may be ordered in England and Wales:
- emergency oxygen;
- short-burst (intermittent) oxygen therapy;
- long-term oxygen therapy;
- ambulatory oxygen.

The type of oxygen service (or combination of services) should be ordered on a Home Oxygen Order Form (HOOF); the amount of oxygen required (hours per day) and flow rate should be specified. The clinician will determine the appropriate equipment to be provided. Special needs or preferences should be specified on the HOOF.

The clinician should obtain the patient or carers consent, to pass on the patient’s details to the supplier, the fire brigade, and other relevant organisations. The supplier will contact the patient to make arrangements for delivery, installation, and maintenance of the equipment. The supplier will also train the patient or carer to use the equipment.

The clinician should send the HOOF to the supplier who will continue to provide the service until a revised HOOF is received, or until notified that the patient no longer requires the home oxygen service.

- East of England, North East: BOC Medical: Tel: 0800 136 603 Fax: 0800 169 9989
- South West: Air Liquide: Tel: 0808 202 2229 Fax: 0191 497 4340
- London, East Midlands, North West: Air Liquide: Tel: 0500 823 773 Fax: 0800 781 4610
- Yorkshire and Humberside, West Midlands, Wales: Air Products: Tel: 0800 373 580 Fax: 0800 214 709
- South East Coast, South Central: Dolby Vivisol: Tel: 08443 814 402 Fax: 0800 781 4610

In Scotland refer the patient for assessment by a respiratory consultant. If the need for a concentrator is confirmed the consultant will arrange for the provision of a concentrator through the Common Services Agency. In Northern Ireland oxygen concentrators and cylinders should be prescribed on form HS21; oxygen concentrators are supplied by a local contractor. In Scotland and Northern Ireland prescriptions for oxygen cylinders and accessories can be dispensed by pharmacists contracted to provide domiciliary oxygen services.
### Antimuscarinics (inhaled)

**Antimuscarinics**

- **CAUTIONS**
  - Bladder outflow obstruction - prostatic hyperplasia - susceptibility to angle-closure glaucoma
  - **INTERACTIONS**
    - See Appendix 1 (antimuscarinics).
    - However, note that interactions do not **generally** apply to antimuscarinics used by inhalation.

- **SIDE-EFFECTS**
  - **Common or very common**
    - Constipation - cough - diarrhoea - dry mouth - gastro-intestinal motility disorder - headache
  - **Uncommon**
  - **Rare**
    - Dental caries - dry skin

#### Glycopyrronium bromide

**INDICATIONS AND DOSE**

Maintenance treatment of chronic obstructive pulmonary disease

**BY INHALATION OF POWDER**

- **Child 1 month**
  - Adult: 375 micrograms twice daily

**Dose equivalence and conversion**

Each 375 microgram inhalation of glycopyrronium bromide delivers 322 micrograms of acilinium bromide.

**CAUTIONS**

- Hospitalisation with moderate or severe heart failure within last 6 months - myocardial infarction within last 6 months - newly diagnosed arrhythmia within last 3 months - unstable angina

**SIDE-EFFECTS**

- Sinusitis

**PREGNANCY**

Manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING**

Manufacturer advises use only if potential benefit outweighs risk.

**RENAL IMPAIRMENT**

Use with caution eGFR less than 30 mL/minute/1.73 m².

**PATIENT AND CARER ADVICE**

Patients or carers should be given advice on how to administer glycopyrronium for inhalation.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Inhalation powder**
  - Seebri Breezhaler (Novartis Pharmaceuticals UK Ltd)
  - Glycopyrronium bromide 55 microgram
  - Seebri Breezhaler 44 microgram inhalation powder capsules with device

- **Capsule**
  - 6 capsule 55 microgram £1.50 | 30 capsule 55 microgram £27.50

#### Aclidinium bromide

**INDICATIONS AND DOSE**

Maintenance treatment of chronic obstructive pulmonary disease

**BY INHALATION OF NEBULISED SOLUTION**

- **Child 1 month**
  - Adult: 50 micrograms every 6 hours as required

**INDICATIONS AND DOSE**

Reversible airways obstruction, particularly in chronic obstructive pulmonary disease

**BY INHALATION OF AEROSOL**

- **Child 1 month**
  - Adult: 20–40 micrograms 3–4 times a day

**Dose equivalence and conversion**

Each 1 microgram of aclidinium bromide delivers 0.6 microgram of glycopyrronium bromide.

**CAUTIONS**

- Asthma - allergic rhinitis - angioedema - bronchospasm - diarrhoea - gastro-oesophageal reflux disease - mydriasis - nasopharyngitis - nausea - palpitation - paradoxical bronchospasm - pharyngitis - tachycardia - throat irritation - urinary retention

**SIDE-EFFECTS**

- **Common or very common**
  - Constipation - cough - diarrhoea - dry mouth - gastro-intestinal motility disorder - headache

- **Uncommon**

- **Rare**
  - Dental caries - dry skin

#### Ipratropium bromide

**INDICATIONS AND DOSE**

Reversible airways obstruction

**BY INHALATION OF AEROSOL**

- **Child 1 month**
  - Adult: 500 micrograms 3–4 times a day

**Dose equivalence and conversion**

Each 1 microgram of aclidinium bromide delivers 0.6 microgram of glycopyrronium bromide.

**CAUTIONS**

- Cystic fibrosis

**INTERACTIONS**

**Glaucoma**

Acute angle-closure glaucoma has been reported with nebulised ipratropium, particularly when given with nebulised salbutamol (and possibly other beta₂ agonists); care needed to protect the patient’s eyes from nebulised drug or from drug powder.

**SIDE-EFFECTS**

- **Common or very common**
  - Dizziness - headache - nasal congestion

- **Uncommon**
  - Atrial fibrillation

- **Rare**
  - Atrial fibrillation - ocular accommodation disorder

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Inhalation powder**
  - Eklira (AstraZeneca UK Ltd)
  - Aclidinium bromide 375 microgram per 1 dose Eklira

- **Capsule**
  - 6 capsule 375 microgram £2.75 | 30 capsule 375 microgram £27.50

**Pharmacokinetics**

The maximal effect of inhaled ipratropium occurs 30–60 minutes after use; its duration of action is 3 to 6 hours and bronchodilation can usually be maintained with treatment 3 times a day.
**218 Airways disease, obstructive**

- **PREGNANCY** Inhaled drugs for asthma can be taken as normal during pregnancy.
- **BREAST FEEDING** Inhaled drugs for asthma can be taken as normal during breast-feeding.
- **DIRECTIONS FOR ADMINISTRATION** If dilution of ipratropium bromide nebuliser solution is necessary use only sterile sodium chloride 0.9%.
- **PATIENT AND CARER ADVICE** Advise patient not to exceed prescribed dose and to follow manufacturer’s directions.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Pressurised inhalation**

- **IPRATROPNIUM BROMIDE (Non-proprietary)**
  - Ipratropium bromide 20 microgram per 1 dose **Combivent** (Boehringer Ingelheim Ltd)
  - Atrovent (Boehringer Ingelheim Ltd)
  - Ipratropium bromide 20 microgram per 1 dose Atrovent
  - Salbutamol sulfate) 1 mg per 1 ml Salbutamol 2.5mg/2.5ml

- **IPRATROPNIUM BROMIDE (Non-proprietary)**
  - Ipratropium bromide 200 microgram per 1 ml, Salbutamol (as Salbutamol sulfate) 1 mg per 1 ml Combivent nebuliser liquid

- **IPRATROPIUM WITH SALBUTAMOL (Non-proprietary)**
  - Ipratropium bromide 20 microgram per 1 ml, Salbutamol (as Salbutamol sulfate) 1 mg per 1 ml Combivent nebuliser liquid

**Indications and dose**

**Maintenance treatment of chronic obstructive pulmonary disease**

BY INHALATION OF POWDER

- Adult: 18 micrograms once daily

SPIRIVA RESPIMAT®

Maintenance treatment of chronic obstructive pulmonary disease | Adjunct to inhaled corticosteroids and long-acting beta; agonists for the maintenance treatment of patients with asthma who have suffered one or more severe exacerbations in the last year

BY INHALATION OF AEROSOL

- Adult: 5 micrograms once daily

- **CAUTIONS** Cardiac arrhythmia requiring intervention in the previous 12 months - hospitalisation for moderate to severe heart failure in the previous 12 months - life-threatening cardiac arrhythmia - myocardial infarction in the previous 6 months - unstable cardiac arrhythmia

- **SIDE-EFFECTS**
  - Common or very common Dizziness - epistaxis - oropharyngeal candidiasis - pruritus - taste disturbance
  - Rare Gingivitis - glossitis - insomnia - gastrointestinal obstruction - paralytic ileus - sinusitis - stomatitis
  - Frequency not known Dehydration - joint swelling
  - **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **RENAL IMPAIRMENT** Plasma-tiotropium concentration raised. Manufacturer advises use only if potential benefit outweighs risk if eGFR less than 50 mL/ minute/1.73 m².

- **PATIENT AND CARER ADVICE** Counselling Advise patients to report any worsening of cardiac symptoms during treatment. Patients or carers should be given advice on how to administer tiotropium powder inhalation and pressurised inhalation.

**National funding/access decisions**

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (November 2007) that Spiriva Respimat® is restricted for use in chronic obstructive pulmonary disease in patients who have poor manual dexterity and difficulty using the Handihaler® device.

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug.

**Pressurised inhalation**

- **TIOTROPIUM (Non-proprietary)**
  - Tiotropium (as Tiotropium bromide) 2.5 microgram per 1 dose Tiotropium bromide 2.5micrograms/dose solution for inhalation with device CFC free | 60 unit dose (£94) no price available DT price = £34.00

- **SPIRIVA RESPIMAT®**
  - Tiotropium bromide 2.5 microgram per 1 dose Tiotropium Respimat 2.5micrograms/dose solution for inhalation with device | 60 dose (£50) £33.50 DT price = £33.50

**Ipratropium with salbutamol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, salbutamol p. 222, ipratropium bromide p. 217.

**INDICATIONS AND DOSE**

Bronchospasm in chronic obstructive pulmonary disease

- Adult: 0.5/2.5 mg 3–4 times a day

**Prescribing and dispensing information**

A mixture of ipratropium bromide and salbutamol (as sulphate); the proportions are expressed in the form x/y where x and y are the strengths in milligrams of ipratropium and salbutamol respectively.

**Less suitable for prescribing** Ipratropium bromide with salbutamol nebuliser solution is considered less suitable for prescribing.

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug.

**Nebuliser liquid**

- **IPRATROPIUM WITH SALBUTAMOL (Non-proprietary)**
  - Ipratropium bromide 200 microgram per 1 ml, Salbutamol (as Salbutamol sulphate) 1 mg per 1 ml Salbutamol 2.5mg/2.5ml

- **Ipratropium bromide 200 microgram per 1 ml, Salbutamol (as Salbutamol sulphate) 1 mg per 1 ml**

- **IPRATROPIUM BROMIDE (Non-proprietary)**
  - Ipratropium bromide 250 microgram per 1 ml Ipratropium 250micrograms/1ml nebuleiser liquid Steri-Neb unit dose vials | 20 unit dose (£6.60) DT price = £5.23
  - Ipratropium bromide 50micrograms/1ml nebuleiser liquid unit dose Steripoule vials | 20 unit dose (£6.00) DT price = £3.94
  - Ipratropium bromide 25micrograms/1ml nebuleiser liquid unit dose Steripoule vials | 20 unit dose (£2.39) DT price = £1.56

**Brands may include Respontin**
Umeclidinium with vilanterol

**INDICATIONS AND DOSE**

**Maintenance treatment of chronic obstructive pulmonary disease**

**BY INHALATION OF POWDER**

- **Adults**: 55 micrograms once daily

**SIDE-EFFECTS**

- **Uncommon**: Arrhythmias, rash, sinusitis, urinary tract infection

**PREGNANCY**

Manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING**

Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT**

Use with caution in severe impairment.

**PATIENT AND CARER ADVICE**

Patient or carers should be given advice on how to administer umeclidinium inhalation powder.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Inhalation powder**

- **Anoro Ellipta** (GSK) 55 micrograms per dose (single dose)

**Uncommon** Atrial fibrillation, rash, rhythm idioventricular, supraventricular extrasystoles, supraventricular tachycardia, tachycardia

**Frequency not known**

- Angle-closure glaucoma
- Arrhythmias
- Fine tremor (particularly in the hands)
- Hyperglycaemia
- Hypokalaemia
- Paradoxical bronchospasm
- Urinary retention

**SIDE-EFFECTS, FURTHER INFORMATION**

**Hypokalaemia**

Potentially serious hypokalaemia may result from beta agonist therapy.

**PREGNANCY**

Manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING**

Manufacturer advises avoid—no information available.

**PATIENT AND CARER ADVICE**

Patient or carers should be given advice on how to administer umeclidinium with vilanterol dry powder inhaler.

**BETA₂ AGONISTS (LONG-ACTING)**

**Selective beta₂ agonists**

**CONTRA-INDICATIONS**

Severe pre-eclampsia

**CAUTIONS**

- Arrhythmias
- Cardiovascular disease
- Diabetes (risk of hyperglycaemia and ketoacidosis, especially with intravenous use)
- Hypertension
- Hyperthyroidism
- Hypokalaemia
- Susceptibility to QT-interval prolongation

**CAUTIONS, FURTHER INFORMATION**

**Hypokalaemia**

Potentially serious hypokalaemia may result from beta, agonist therapy. Particular caution is required in severe asthma, because this effect may be potentiated by concomitant treatment with theophylline and its derivatives, corticosteroids, diuretics, and by hypoxia.

**INTERACTIONS**

Appendix 1 (sympathomimetics, beta₂). Hypokalaemia may be potentiated by concomitant treatment with theophylline and its derivatives, corticosteroids, and diuretics.

**SIDE-EFFECTS**

- Angioedema
- Arrhythmias
- Behavioural disturbances
- Collapse
- Fine tremor (particularly in the hands)
- Headache
- Hyperglycaemia (especially when given intravenously)
- Hypersensitivity reactions
- Hypokalaemia (with high doses)
- Hypotension
- Ketoacidosis (especially when given intravenously)
- Muscle cramps
- Myocardial ischaemia
- Nervous tension
- Palpitation
- Paradoxical bronchospasm (occasionally severe)
- Peripheral vasodilation
- Rash
- Sleep disturbances
- Tachycardia
- Urticaria

**PREGNANCY**

Women planning to become pregnant should be counselled about the importance of taking their asthma medication regularly to maintain good control.

**MONITORING REQUIREMENTS**

- In severe asthma, plasma-potassium concentration should be monitored (risk of hypokalaemia).
- In patients with diabetes, monitor blood glucose (risk of hyperglycaemia and ketoacidosis, especially when beta₂ agonist given intravenously).

**PATIENT AND CARER ADVICE**

- When used by inhalation, the dose, the frequency, and the maximum number of inhalations in 24 hours of the beta₂
agostin should be stated explicitly to the patient or their carer. The patient or their carer should be advised to seek medical advice when the prescribed dose of β₂-agonist fails to provide the usual degree of symptomatic relief because this usually indicates a worsening of the asthma and the patient may require a prophylactic drug. Patients or their carers should be advised to follow manufacturers’ instructions on the care and cleansing of inhaler devices.

### Bambuterol hydrochloride

**DRUG ACTION** Bambuterol is a pro-drug of terbutaline.

**INDICATIONS AND DOSE**
- Asthma (patients who have previously tolerated β₂-agonists) OR Other conditions associated with reversible airways obstruction (patients who have previously tolerated β₂-agonists)

**BY MOUTH**
- Adult: 20 mg once daily, dose to be taken at bedtime
- Asthma (patients who have not previously tolerated β₂-agonists) OR Other conditions associated with reversible airways obstruction (patients who have not previously tolerated β₂-agonists)

**PREGNANCY** Manufacturer advises avoid—no information available.

**BREAST FEEDING** Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT** Avoid in severe impairment.

**RENAI IMPAIRMENT** Reduce initial dose by half if eGFR less than 50 ml/minute/1.73 m².

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- Bambec (AstraZeneca UK Ltd)
  - Bambuterol hydrochloride 10 mg: Bambec 10mg tablets
    - 28 tablet pack £14.46 DT price = £14.46
  - Bambuterol hydrochloride 20 mg: Bambec 20mg tablets
    - 28 tablet pack £15.77 DT price = £15.77

### Formoterol fumarate

(Eformoterol fumarate)

**INDICATIONS AND DOSE**
- Reversible airways obstruction in patients requiring long-term regular bronchodilator therapy
- Nocturnal asthma in patients requiring long-term regular bronchodilator therapy
- Prophylaxis of exercise-induced bronchospasm in patients requiring long-term regular bronchodilator therapy
- Chronic asthma in patients who regularly use an inhaled corticosteroid

**BY INHALATION OF POWDER**
- Adult: 20 micrograms twice daily, dose to be increased in more severe airway obstruction; increased to 24 micrograms twice daily

**BY INHALATION OF AEROSOL**
- Child 12–17 years: 12 micrograms twice daily, dose may be increased in more severe airway obstruction; increased to 24 micrograms twice daily

**Oxis**

**Chronic asthma**

**BY INHALATION OF POWDER**
- Child 6–17 years: 6–12 micrograms 1–2 times a day (max. per dose 12 micrograms), occasionally doses up to the maximum daily may be needed, reassess treatment if additional doses required on more than 2 days a week; maximum 48 micrograms per day
- Adult: 12 micrograms twice daily, dose may be increased in more severe airway obstruction; increased to 24 micrograms twice daily

**Chronic obstructive pulmonary disease**

**BY INHALATION OF POWDER**
- Adult: 12 micrograms twice daily

**Prophylaxis of exercise-induced bronchospasm**

**BY INHALATION OF POWDER**
- Child 6–17 years: 6–12 micrograms, dose to be taken before exercise
- Adult: 12 micrograms, dose to be taken before exercise

**Chronic obstructive pulmonary disease**

**BY INHALATION OF POWDER**
- Adult: 12 micrograms 1–2 times a day (max. per dose 24 micrograms), for symptom relief additional doses up to maximum daily dose can be taken; maximum 48 micrograms per day

**PHARMACOKINETICS**
At recommended inhaled doses, the duration of action of formoterol is about 12 hours.

**Important safety information**

**CHM ADVICE**
To ensure safe use, the CHM has advised that for the management of chronic asthma, long-acting β₂-agonist (formoterol) should:
- be added only if regular use of standard-dose inhaled corticosteroids has failed to control asthma adequately;
- not be initiated in patients with rapidly deteriorating asthma;
- be introduced at a low dose and the effect properly monitored before considering dose increase;
- be discontinued in the absence of benefit;
Beclometasone with formoterol

The properties listed below are those particular to the combination only. For the properties of the components please consider, beclometasone dipropionate p. 227, formoterol fumarate p. 220.

INDICATIONS AND DOSE

Asthma maintenance therapy
BY INHALATION OF AEROSOL OR BY INHALATION OF POWDER
Adult: 100/6–200/12 micrograms twice daily; maximum 400/24 micrograms per day

Asthma, maintenance and reliever therapy
BY INHALATION OF AEROSOL
Adult: Maintenance 100/6 micrograms twice daily; 100/6 micrograms as required for relief of symptoms; maximum 800/48 micrograms per day

Chronic obstructive pulmonary disease with forced expiratory volume in 1 second < 50% of predicted
BY INHALATION OF AEROSOL
Adult: 200/12 micrograms twice daily

Dose equivalence and conversion
For inhalation of aerosol, when switching patients from other beclometasone dipropionate and formoterol fumarate inhalers, Fostair® 100/6 can be prescribed for patients already using beclometasone dipropionate 250 micrograms in another CFC-free inhaler; the dose of Fostair® should be adjusted according to response. For inhalation of powder, when switching patients from other beclometasone dipropionate formulations with non-extrafine particle size distribution, the dose should be adjusted according to response. 1 puff is equivalent to 100 micrograms beclometasone dipropionate and 6 micrograms formoterol fumarate.

PATIENT AND CARER ADVICE
With high doses, a steroid card should be supplied. Patients or carers should be given advice on how to administer beclometasone with formoterol inhalation.

MEDICAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Pressurised inhalation
CAUTIONARY AND ADVISORY LABELS 8, 10
† Fostair (Chiesi Ltd)
Beclometasone dipropionate 100 microgram per 1 dose, Formoterol fumarate dihydrate 6 microgram per 1 dose Fostair 100micrograms/dose / 6micrograms/dose inhaler | 120 dose (POT) £29.32 DT price = £29.32

Inhalation powder
CAUTIONARY AND ADVISORY LABELS 8, 10
† Fostair NEXThaler (Chiesi Ltd)
Beclometasone dipropionate 100 microgram per 1 dose, Formoterol fumarate dihydrate 6 microgram per 1 dose Fostair NEXThaler 100micrograms/dose / 6micrograms/dose dry powder inhaler | 120 dose (POT) £29.32

Indacaterol

INDICATIONS AND DOSE
Maintenance treatment of chronic obstructive pulmonary disease
BY INHALATION OF POWDER
Adult: 150 micrograms once daily, then increased to 300 micrograms once daily

CAUTIONS
Convulsive disorders
SIDE-EFFECTS
Common or very common Cough · dizziness · nasopharyngitis · oropharyngeal pain · peripheral oedema · rhinorrhea · sinusitis
Uncommon Atrial fibrillation · chest pain · paraesthesia · pruritus
PREGNANCY
Manufacturer advises use only if potential benefit outweighs risk.

BREAST FEEDING
Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT
Use with caution in severe impairment—no information available.

BREAST FEEDING
Manufacturer advises only if potential benefit outweighs risk.

MEDICAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Inhalation powder
† Onbrez Breezhaler (Novartis Pharmaceuticals UK Ltd)
Indacaterol (as Indacaterol maleate) 150 microgram Onbrez Breezhaler 150microgram inhalation powder capsules with device | 30 capsule (POT) £29.26 DT price = £29.26
Indacaterol (as Indacaterol maleate) 300 microgram Onbrez Breezhaler 300microgram inhalation powder capsules with device | 30 capsule (POT) £29.26 DT price = £29.26
Olodaterol

INDICATIONS AND DOSE
Maintenance treatment of chronic obstructive pulmonary disease

BY INHALATION
- Adult: 5 micrograms once daily

Dose equivalence and conversion
2 puffs is equivalent to 5 micrograms.

SIDE-EFFECTS
- Uncommon: Dizziness, nasopharyngitis
- Rare: Arthralgia, hypertension

PREGNANCY
Manufacturer advises avoid—no information available.

BREAST FEEDING
Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT
Use with caution in severe hepatic impairment—no information available.

PATIENT AND CARER ADVICE
Patients or carers should be given advice on how to administer olodaterol solution for inhalation.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Pressurised inhalation
- Striverdi Respimat (Boehringer Ingelheim Ltd)
  Olodaterol (as Olodaterol hydrochloride) 2.5 microgram per 1 dose
  Striverdi Respimat 2.5 micrograms/dose solution for inhalation cartridge with device | 60 dose [POT] £26.35 DT price = £26.35

Salmeterol

INDICATIONS AND DOSE
Reversible airways obstruction in patients requiring long-term regular bronchodilator therapy | Nocturnal asthma in patients requiring long-term regular bronchodilator therapy | Prevention of exercise-induced bronchospasm in patients requiring long-term regular bronchodilator therapy | Chronic asthma only in patients who regularly use an inhaled corticosteroid (not for immediate relief of acute asthma)

BY INHALATION OF AEROSOL OR BY INHALATION OF POWDER
- Child 5–11 years: 50 micrograms twice daily
- Child 12–17 years: 50 micrograms twice daily, dose may be increased in more severe airway obstruction; increased to 100 micrograms twice daily
- Adult: 50 micrograms twice daily, dose may be increased in more severe airway obstruction; increased to 100 micrograms twice daily

Chronic obstructive pulmonary disease
BY INHALATION OF AEROSOL OR BY INHALATION OF POWDER
- Adult: 50 micrograms twice daily

PHARMACOKINETICS
At recommended inhaled doses, the duration of action of salmeterol is about 12 hours.

UNLICENSED USE
- Neovent® not licensed for use in children under 12 years.

Important safety information
CHM ADVICE
To ensure safe use, the CHM has advised that for the management of chronic asthma, long-acting beta_2_ agonist (salmeterol) should:
- be added only if regular use of standard-dose inhaled corticosteroids has failed to control asthma adequately;
- not be initiated in patients with rapidly deteriorating asthma;
- be introduced at a low dose and the effect properly monitored before considering dose increase;
- be discontinued in the absence of benefit;
- not be used for the relief of exercise-induced asthma symptoms unless regular inhaled corticosteroids are also used;
- be reviewed as clinically appropriate: stepping down therapy should be considered when good long-term asthma control has been achieved.

SIDE-EFFECTS
- Arthralgia, dizziness, nausea

PREGNANCY
Inhaled drugs for asthma can be taken as normal during pregnancy.

BREAST FEEDING
Inhaled drugs for asthma can be taken as normal during breast-feeding.

PATIENT AND CARER ADVICE
Medicines for Children leaflet: Salmeterol inhaler for asthma prevention (prophylaxis) www.medicinesforchildren.org.uk/salmeterol-inhaler-for-asthma-prevention

Advise patients that salmeterol should not be used for relief of acute attacks, not to exceed prescribed dose, and to follow manufacturer’s directions; if a previously effective dose of inhaled salmeterol fails to provide adequate relief, a doctor’s advice should be obtained as soon as possible.

Patients should be advised to report any deterioration in symptoms following initiation of treatment with a long-acting beta_2_ agonist.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Pressurised inhalation
- SALMETEROL (Non-proprietary)
  Salmeterol (as Salmeterol xinafoate) 25 microgram per 1 dose
  Salmeterol 25 micrograms/dose inhaler CFC free | 120 dose [POT] £29.26 DT price = £29.26
  Serevent Evohaler (GlaxoSmithKline UK Ltd)
  Salmeterol (as Salmeterol xinafoate) 25 microgram per 1 dose
  Serevent 25 micrograms/dose Evohaler | 120 dose [POT] £29.26 DT price = £29.26
  Brands may include Neovent, Vertine

Inhalation powder
- Serevent Accuhaler (GlaxoSmithKline UK Ltd)
  Salmeterol (as Salmeterol xinafoate) 50 microgram per 1 dose
  Serevent 50 micrograms/dose Accuhaler | 60 dose [POT] £29.26 DT price = £29.26

Also available in combination with fluticasone, p. 231

BET_2_ AGONISTS (SHORT-ACTING)

Salbutamol
(Albuterol)

INDICATIONS AND DOSE
Asthma | Other conditions associated with reversible airways obstruction

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
- Adult: 4 mg 3–4 times a day, maximum single dose 8 mg (but unlikely to provide much extra benefit or to be tolerated), inhalation route preferred over oral route, use elderly dose for sensitive patients
- Elderly: Initially 2 mg 3–4 times a day, maximum single dose 8 mg (but unlikely to provide much extra benefit or to be tolerated), inhalation route preferred over oral route

BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION
- Adult: 500 micrograms every 4 hours if required
Uncomplicated premature labour (between 22 and 37 weeks of gestation) (specialist use only)

**BY INTRAVENOUS INFUSION**
- Adult: Initially 10 micrograms/minute, rate increased gradually according to response to 10-minute intervals until contractions diminish then increase rate slowly until contractions cease (maximum rate 45 micrograms/minute), maintain rate for 1 hour after contractions have stopped, then gradually reduce by 50% every 6 hours, maximum duration 48 hours

**VENTOLIN ACCUHALER**

**Acute bronchospasm**
- **BY INHALATION OF POWDER**
  - Adult: Initially 200 micrograms, up to 4 times daily for persistent symptoms

**Prophylaxis of allergen- or exercise-induced bronchospasm**
- **BY INHALATION OF POWDER**
  - Adult: 200 micrograms

**SALBUTAMOL**

**Acute bronchospasm**
- **BY INHALATION OF POWDER**
  - Adult: Initially 200 micrograms, up to 800 micrograms daily for persistent symptoms

**Prophylaxis of allergen- or exercise-induced bronchospasm**
- **BY INHALATION OF POWDER**
  - Adult: 200 micrograms

**EASYHALER**

**Acute bronchospasm**
- **BY INHALATION OF POWDER**
  - Adult: Initially 200 micrograms, up to 800 micrograms for persistent symptoms

**Prophylaxis of allergen- or exercise-induced bronchospasm**
- **BY INHALATION OF POWDER**
  - Adult: 200 micrograms

**ASMASAL CLICKHALER**

**Acute bronchospasm**
- **BY INHALATION OF POWDER**
  - Adult: 1–2 puffs, up to 4 times daily for persistent symptoms

**Prophylaxis of allergen- or exercise-induced bronchospasm**
- **BY INHALATION OF POWDER**
  - Adult: 1–2 puffs

**PHARMACOKINETICS**

At recommended inhaled doses, the duration of action of salbutamol is about 3 to 5 hours.

**UNLICENSED USE**
- With oral use: Syrup and tablets not licensed for use in children under 2 years.
- With intravenous use: Administration of undiluted salbutamol injection through a central venous catheter is not licensed.

**CONTRA-INDICATIONS**
- When used for uncomplicated premature labour under specialist supervision: abruptio placenta, antepartum haemorrhage, cord compression, eclampsia, history of cardiac disease, intra-uterine fetal death, intra-uterine infection, placenta praevia, pulmonary hypertension, severe pre-eclampsia.
significant risk factors for myocardial ischaemia • threatened miscarriage

**CAUTIONS**

- With intravenous use mild to moderate pre-eclampsia (when used for uncomplicated premature labour) • suspected cardiovascular disease (should be assessed by a cardiologist before initiating therapy for uncomplicated premature labour)

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**
Lactic acidosis (with high doses) • nausea

**SPECIFIC SIDE-EFFECTS**
- When used for uncomplicated premature labour bronchospasm • muscle tension • pulmonary oedema • vomiting

**BREATFEEDING**
Inhaled drugs for asthma can be taken as normal during breast-feeding.

**MONITORING REQUIREMENTS**
In uncomplicated premature labour it is important to monitor blood pressure, pulse rate (should not exceed 120 beats per minute), ECG (discontinue treatment if signs of myocardial ischaemia develop), blood glucose and lactate concentrations, and the patient’s fluid and electrolyte status (avoid over-hydration—discontinue drug immediately and initiate diuretic therapy if pulmonary oedema occurs).

**DIRECTIONS FOR ADMINISTRATION**
- When used by inhalation For nebulisation, dilute nebuliser solution with a suitable volume of sterile Sodium Chloride 0.9% solution according to nebuliser type and duration of administration; salbutamol and ipratropium bromide solutions are compatible and can be mixed for nebulisation.
- When used by continuous intravenous infusion For bronchodilation, dilute to a concentration of 200 micrograms/mL with Glucose 5% or Sodium Chloride 0.9%. For premature labour, dilute with Glucose 5% to a concentration of 200 micrograms/mL for use in a syringe pump or for other infusion methods (preferably via controlled infusion device), dilute to a concentration of 20 micrograms/mL; close attention to patient’s fluid and electrolyte status essential.

**PATIENT AND CARER ADVICE**
Medicines for Children leaflet: Salbutamol inhaler for asthma and wheeze [www.medicinesforchildren.org.uk/salbutamol-inhaler-for-asthma-and-wheeze](http://www.medicinesforchildren.org.uk/salbutamol-inhaler-for-asthma-and-wheeze)
For inhalation by aerosol or dry powder, advise patients and carers not to exceed prescribed dose and to follow manufacturer’s directions; if a previously effective dose of inhaled salbutamol fails to provide at least 3 hours relief, a doctor’s advice should be obtained as soon as possible.
For inhalation by nebuliser, the dose given by nebuliser is substantially higher than that given by inhaler. Patients should therefore be warned that it is dangerous to exceed the prescribed dose and they should seek medical advice if they fail to respond to the usual dose of the respirator solution.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **SALBUTAMOL (Non-proprietary)**
  - Salbutamol (as Salbutamol sulfate) 2 mg Salbutamol 2mg tablets | 28 tablet [PSt] £113.05 DT price = £104.95
  - Salbutamol (as Salbutamol sulfate) 4 mg Salbutamol 4mg tablets | 28 tablet [PSt] £115.76 DT price = £107.43

**Modified-release capsule**
CAUTIONARY AND ADVISORY LABELS 25
- Ventmax SR (Chiesi Ltd)
  - Salbutamol (as Salbutamol sulfate) 4 mg Ventmax SR 4mg capsules | 56 capsule [PSt] £8.08 DT price = £8.08

**Salbutamol (as Salbutamol sulfate) 8 mg** Ventmax SR 8mg capsules | 56 capsule [PSt] £9.69 DT price = £9.69

**Oral solution**
- **SALBUTAMOL (Non-proprietary)**
  - Salbutamol (as Salbutamol sulfate) 400 microgram per 1 ml Salbutamol 2mg/5ml oral solution sugar free (sugar-free) | 150 ml [PSt] no price available DT price = £0.72
  - Ventolin (GlaxoSmithKline UK Ltd)
  - Salbutamol (as Salbutamol sulfate) 400 microgram per 1 ml Ventolin 2mg/5ml syrup (sugar-free) | 150 ml [PSt] £0.72 DT price = £0.72

**Solution for injection**
- Ventolin (GlaxoSmithKline UK Ltd)
- Salbutamol (as Salbutamol sulfate) 500 microgram per 1 ml Ventolin 500micrograms/1ml solution for injection ampoules | 5 ampoule [PSt] £1.91

**Solution for infusion**
- Ventolin (GlaxoSmithKline UK Ltd)
- Salbutamol (as Salbutamol sulfate) 1 mg per 1 ml Ventolin 5mg/5ml solution for infusion ampoules | 10 ampoule [PSt] £24.81

**Pressurised inhalation**
- **SALBUTAMOL (Non-proprietary)**
  - Salbutamol 100 microgram per 1 dose Easyhaler Salbutamol sulfate 100micrograms/dose dry powder inhaler | 200 dose [PSt] £3.31 DT price = £3.31
  - Salbutamol 200 microgram per 1 dose Easyhaler Salbutamol sulfate 200micrograms/dose dry powder inhaler | 200 dose [PSt] £6.63
  - Asmusal Clickhaler (Focus Pharmaceuticals Ltd)
  - Salbutamol (as Salbutamol sulfate) 95 microgram per 1 dose Asmusal 95micrograms/dose Clickhaler | 200 dose [PSt] £5.65 DT price = £5.65
  - Pulvinal (salbutamol) (Chiesi Ltd)
  - Salbutamol 200 microgram per 1 dose Pulvinal Salbutamol 200micrograms/dose dry powder inhaler | 100 dose [PSt] £4.85 DT price = £4.85
  - Salbutamol Novologizer (Meda Pharmaceuticals Ltd)
  - Salbutamol (as Salbutamol sulfate) 100 microgram per 1 dose Salbutamol Novologizer 100micrograms/dose inhalation powder | 200 dose [PSt] £4.95
  - Salbutamol Novologizer 100micrograms/dose inhalation powder refill | 200 dose [PSt] £2.75
  - Ventolin Accuhaler (GlaxoSmithKline UK Ltd)
  - Salbutamol 200 microgram per 1 dose Ventolin 200micrograms/dose Accuhaler | 60 dose [PSt] £3.00 DT price = £3.00

**Nebuliser liquid**
- **SALBUTAMOL (Non-proprietary)**
  - Salbutamol 2.5mg/2.5ml nebuliser liquid unit dose Steripoule vials | 20 unit dose [PSt] £2.87 DT price = £1.91
  - Salbutamol 2.5mg/2.5ml nebuliser liquid unit dose vials | 20 unit dose [PSt] £1.00 DT price = £1.00
  - Salbutamol (as Salbutamol sulfate) 2 mg per 1 ml Salbutamol 5mg/2.5ml nebuliser liquid unit dose vials | 20 unit dose [PSt] £7.35 DT price = £3.82
  - Salbutamol 5mg/2.5ml nebuliser liquid unit dose Steripoule vials | 20 unit dose [PSt] £6.08 DT price = £3.82
  - Ventolin (GlaxoSmithKline UK Ltd)
  - Salbutamol (as Salbutamol sulfate) 5 mg per 1 ml Ventolin 5mg/ml respirator solution | 20 ml [PSt] £2.18 DT price = £2.18
  - Ventolin Nebules (GlaxoSmithKline UK Ltd)
  - Salbutamol (as Salbutamol sulfate) 1 mg per 1 ml Ventolin 2.5mg Nebules | 20 unit dose [PSt] £1.65 DT price = £1.91
  - Salbutamol (as Salbutamol sulfate) 2 mg per 1 ml Ventolin 5mg Nebules | 20 unit dose [PSt] £2.78 DT price = £3.82

Brands may include [Salamol Steri-Neb](http://www.medicinesforchildren.org.uk/salbutamol-inhaler-for-aerosol)

Also available in combination with [Ipratropium](http://www.medicinesforchildren.org.uk/salbutamol-inhaler-for-aerosol), p. 218
Terbutaline sulfate

**INDICATIONS AND DOSE**

**Asthma | Other conditions associated with reversible airways obstruction**

**BY MOUTH**

- **Adult:** Initially 2.5 mg 3 times a day for 1–2 weeks, then increased to up to 5 mg 3 times a day, use by inhalation preferred over by mouth

**BY SUBCUTANEOUS INJECTION OR BY SLOW INTRAVENOUS INJECTION**

- **Adult:** 250–500 micrograms up to 4 times a day, reserve intravenous beta, agonists for those in whom inhaled therapy cannot be used reliably or there is no current effect

**BY CONTINUOUS INTRAVENOUS INFUSION**

- **Adult:** 90–300 micrograms/hour for 8–10 hours, to be administered as a solution containing 3–5 micrograms/mL, high doses require close monitoring, reserve intravenous beta, agonists for those in whom inhaled therapy cannot be used reliably or there is no current effect

**BY INHALATION OF POWDER**

- **Adult:** 500 micrograms up to 4 times a day, for persistent symptoms

**BY INHALATION OF NEBULISED SOLUTION**

- **Adult:** 5–10 mg 2–4 times a day, additional doses may be necessary in severe acute asthma

**Acute asthma**

**BY SUBCUTANEOUS INJECTION OR BY SLOW INTRAVENOUS INJECTION**

- **Child 2–4 years:** 10 micrograms/kg up to 4 times a day (max. per dose 300 micrograms), reserve intravenous beta, agonists for those in whom inhaled therapy cannot be used reliably or there is no current effect

- **Child 5–17 years:** 250–500 micrograms up to 4 times a day, reserve intravenous beta, agonists for those in whom inhaled therapy cannot be used reliably or there is no current effect

**BY CONTINUOUS INTRAVENOUS INFUSION**

- **Child:** Loading dose 2–4 micrograms/kg, then 1–10 micrograms/kg/hour, dose to be adjusted according to response and heart rate, close monitoring is required for doses above 10 micrograms/kg/hour, reserve intravenous beta, agonists for those in whom inhaled therapy cannot be used reliably or there is no current effect

**Moderate, severe, or life-threatening acute asthma**

**BY INHALATION OF NEBULISED SOLUTION**

- **Child 1 month–4 years:** Initially 5 mg, then 5 mg every 20–30 minutes or when required, give via oxygen-driven nebuliser if available

- **Child 5–11 years:** Initially 5–10 mg, then 5–10 mg every 20–30 minutes or when required, give via oxygen-driven nebuliser if available

- **Child 12–17 years:** Initially 10 mg, then 10 mg every 20–30 minutes or when required, give via oxygen-driven nebuliser if available

- **Adult:** Initially 10 mg, then 10 mg every 20–30 minutes or when required, give via oxygen-driven nebuliser if available

**Exacerbation of reversible airways obstruction (including nocturnal asthma) | Prevention of exercise-induced bronchospasm**

**BY INHALATION OF POWDER**

- **Child 5–17 years:** 500 micrograms up to 4 times a day, for occasional use only

**BY MOUTH**

- **Child 1 month–6 years:** 75 micrograms/kg 3 times a day (max. per dose 2.5 mg)

**Airways disease, obstructive**

- **Child 7–14 years:** 2.5 mg 2–3 times a day

- **Child 15–17 years:** Initially 2.5 mg 3 times a day, then increased if necessary to 5 mg 3 times a day

**Uncomplicated premature labour (between 22 and 37 weeks of gestation) (specialist supervision in hospital)**

**BY INTRAVENOUS INFUSION**

- **Adult:** Initially 5 micrograms/minute for 20 minutes, then increased in steps of 2.5 micrograms/minute every 20 minutes until contractions have ceased (more than 10 micrograms/minute should seldom be given—20 micrograms/minute should not be exceeded), continue for 1 hour, then reduced in steps of 2.5 micrograms/minute every 20 minutes to lowest dose that maintains suppression (maximum total duration 48 hours)

**PHARMACOKINETICS**

At recommended inhaled doses, the duration of action of terbutaline is about 3 to 5 hours.

**UNLICENSED USE** Tablets not licensed for use in children under 7 years. Injection not licensed for use in children under 2 years.

**CONTRA-INDICATIONS**

- **When used for uncomplicated premature labour** abruptio placenta · antepartum haemorrhage · cord compression · eclampsia · history of cardiac disease · intra-uterine fetal death · intra-uterine infection · placenta praevia · pulmonary hypertension · severe pre-eclampsia · significant risk factors for myocardial ischaemia · threatened miscarriage

**CAUTIONS** Mild to moderate pre-eclampsia (when used for uncomplicated premature labour) · suspected cardiovascular disease (should be assessed by a cardiologist before initiating therapy for uncomplicated premature labour)

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

Nausea

**SPECIFIC SIDE-EFFECTS**

**Respiratory system**

- **Bronchial spasm**

- **Intrigluconic effects**

- **Muscle relaxation**

- **Nausea**

- **Vomiting**

**PREGNANCY**

Inhaled drugs for asthma can be taken as normal during pregnancy.

**BREAST FEEDING**

Inhaled drugs for asthma can be taken as normal during breast-feeding.

**MONITORING REQUIREMENTS**

In uncomplicated premature labour it is important to monitor blood pressure, pulse rate (should not exceed 120 beats per minute), ECG (discontinue treatment if signs of myocardial ischaemia develop), blood glucose and lactate concentrations, and the patient’s fluid and electrolyte status (avoid over-hydration—discontinue drug immediately and initiate diuretic therapy if pulmonary oedema occurs).

**DIRECTIONS FOR ADMINISTRATION**

- **When used by inhalation** For nebulisation, dilute nebuliser solution with sterile Sodium Chloride 0.9% solution according to nebuliser type and duration of administration; terbutaline and ipratropium bromide solutions are compatible and may be mixed for nebulisation.

- **With intravenous use in children** For continuous intravenous infusion, dilute to a concentration of 5 micrograms/mL with Glucose 5% or Sodium Chloride 0.9%; if fluid-restricted, dilute to a concentration of 100 micrograms/mL.

- **With intravenous use in adults** For bronchodilation by continuous intravenous infusion, dilute 1.5–2.5 mg with 500 mL glucose 5% or sodium chloride 0.9% and give over 8–10 hours. For premature labour by continuous intravenous infusion, dilute in glucose 5% and give via controlled infusion device preferably a syringe pump; if
Airways disease, use of corticosteroids

Corticosteroids are used for the management of reversible and irreversible airway disease.

Asthma

Inhaled corticosteroids

An inhaled corticosteroid used for 3–4 weeks may help to distinguish asthma from chronic obstructive pulmonary disease; clear improvement over 3–4 weeks suggests asthma.

Corticosteroids are effective in asthma; they reduce airway inflammation (and hence reduce oedema and secretion of mucus into the airway). An inhaled corticosteroid is used regularly for prophylaxis of asthma when patients require a beta, agonist more than twice a week, or if symptoms disturb sleep at least once a week, or if the patient has suffered an exacerbation in the last 2 years requiring a systemic corticosteroid. Regular use of inhaled corticosteroids reduces the risk of exacerbation of asthma.

Current and previous smoking reduces the effectiveness of inhaled corticosteroids and higher doses may be necessary. Corticosteroid inhalers must be used regularly for maximum benefit; alleviation of symptoms usually occurs 3 to 7 days after initiation. Beclometasone dipropionate p. 227, budesonide p. 228, fluticasone p. 230, and mometasone furoate p. 222 appear to be equally effective. Preparations that combine a corticosteroid with a long-acting beta<sub>2</sub> agonist may be helpful for patients stabilised on the individual components in the same proportion.

In adults using an inhaled corticosteroid and a long-acting beta<sub>2</sub> agonist for the prophylaxis of asthma, but who are poorly controlled, Symbicort<sup>®</sup> or DuoResp Spiramas<sup>®</sup> (both containing budesonide with formoterol p. 229) can be used as relievers (instead of a short-acting beta<sub>2</sub> agonist), in addition to their regular use for the prophylaxis of asthma. Symbicort<sup>®</sup> can also be used in this way in adults using an inhaled corticosteroid with a dose greater than beclometasone dipropionate 400 micrograms daily, but who are poorly controlled (standard doses of other inhaled corticosteroids can be used). When starting this treatment, the total regular daily dose of inhaled corticosteroid should not be reduced. Patients must be carefully instructed on the appropriate dose and management of exacerbations before initiating this therapy. Patients using budesonide with formoterol as a reliever once a day or more should have their treatment reviewed regularly. The use of Symbicort<sup>®</sup> for both reliever and maintenance therapy is also used by some specialists in children 12–18 years [unlicensed].

Fostair<sup>®</sup> can also be used in adults as a reliever (instead of a short-acting beta<sub>2</sub> agonist) in addition to its regular use for the prophylaxis of asthma. It may be particularly useful for patients with poorly controlled asthma requiring reliever therapy, or for those who have had previous exacerbations of asthma which needed medical intervention. Patients requiring frequent daily use of Fostair<sup>®</sup> as a reliever should have their maintenance treatment reviewed. This approach has not been investigated with combination inhalers containing other corticosteroids and long-acting beta<sub>2</sub> agonists.

High doses of inhaled corticosteroid can be prescribed for patients who respond only partially to standard doses with a long-acting beta<sub>2</sub> agonist or another long-acting bronchodilator. High doses should be continued only if there is clear benefit over the lower dose. The recommended maximum dose of an inhaled corticosteroid should not generally be exceeded. However, if a higher dose is required, then it should be initiated and supervised by a specialist. The use of high doses of inhaled corticosteroid can minimise the requirement for an oral corticosteroid.

Oral corticosteroids

Systemic corticosteroid therapy may be necessary during episodes of stress, such as severe infection, or if the asthma is worsening, when higher doses are needed and access of inhaled drug to small airways may be reduced; patients may need a reserve supply of corticosteroid tablets.

In chronic asthma, when the response to other drugs has been inadequate, longer term administration of an oral corticosteroid may be necessary; in such cases high doses of an inhaled corticosteroid should be continued to minimise oral corticosteroid requirements. Patients taking long-term oral corticosteroids for asthma can often be transferred to an inhaled corticosteroid but the transfer must be slow, with gradual reduction in the dose of the oral corticosteroid, and at a time when the asthma is well controlled.

An acute attack of asthma should be treated with a short course of an oral corticosteroid starting with a high dose. Patients whose asthma has deteriorated rapidly usually respond quickly to corticosteroids. The dose can usually be stopped abruptly; tapering is not needed provided that the patient receives an inhaled corticosteroid in an adequate dose (apart from those on maintenance oral corticosteroid
treatment or where oral corticosteroids are required for 3 or more weeks). In patients who have needed several courses of oral corticosteroids and in whom the possibility of a period on maintenance corticosteroids is being considered, it may be useful to taper the corticosteroid dose gradually to identify a threshold dose for asthma control. This should only be done after other standard options for controlling asthma have been tried.

An oral corticosteroid should normally be taken as a single dose in the morning to reduce the disturbance to circadian cortisol secretion. Dosage should always be titrated to the lowest dose that controls symptoms. Regular peak-flow measurements help to optimise the dose.

Parenteral corticosteroids

Hydrocortisone p. 583 injection has a role in the emergency treatment of acute severe asthma.

Chronic obstructive pulmonary disease

Inhaled corticosteroids

In chronic obstructive pulmonary disease inhaled corticosteroid therapy may reduce exacerbations when given in combination with an inhaled long-acting beta2 agonist.

Oral corticosteroids

During an acute exacerbation of chronic obstructive pulmonary disease, prednisolone p. 585 should be given; treatment can be stopped abruptly. Prolonged treatment with oral prednisolone p. 585 is of no benefit and maintenance treatment is not normally recommended.

Corticosteroids (inhaled)

- **INTERACTIONS**  
  Appendix 1 (corticosteroids). Interactions do not generally apply to corticosteroids used for inhalation unless specified.

- **SIDE-EFFECTS**
  - Very rare  
    - Paradoxical bronchospasm
  - Frequency not known  
    - Adrenal crisis (with prolonged high doses)  
    - Adrenal suppression (with prolonged high doses)  
    - Aggression (particularly in children)  
    - Anxiety  
    - Behavioural changes (particularly in children)  
    - Bruising  
    - Candidiasis of the mouth  
    - Candidiasis of the throat  
    - Catarracts  
    - Coma (with prolonged high doses)  
    - Cushing’s syndrome (with moon face, striae and acne)  
    - Depression  
    - Dysphonia  
    - Glaucoma (with prolonged high doses)  
    - Hoarseness  
    - Hyperactivity (particularly in children)  
    - Hyperglycaemia (usually only with high doses)  
    - Irritability (particularly in children)  
    - Lower respiratory tract infections in older patients with chronic obstructive pulmonary disease (with high doses)  
    - Pneumonia in older patients with chronic obstructive pulmonary disease (with high doses)  
    - Reduced mineral bone density (with long-term treatment of high doses)
  - Side-effects applicable to systemic corticosteroids may also apply if absorption occurs following inhaled use
  - Sleep disturbances  
  - Throat irritation

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Candidiasis
    - The risk of oral candidiasis can be reduced by using a spacer device with the corticosteroid inhaler; rinsing the mouth with water after inhalation of a dose may also be helpful. An anti-fungal oral suspension or oral gel can be used to treat oral candidiasis without discontinuing corticosteroid therapy.
  - Paradoxical bronchospasm
    - The potential for paradoxical bronchospasm (calling for discontinuation and alternative therapy) should be borne in mind—mild bronchospasm may be prevented by inhalation of a short-acting beta2 agonist beforehand (or by transfer from an aerosol inhalation to a dry powder inhalation).
  - Pregnancy
    - Inhaled drugs for asthma can be taken as normal during pregnancy.
Pressurised inhalation

**INDICATIONS AND DOSE**

**Prophylaxis of asthma**

**By inhalation of powder**

- **Child 6-11 years**: 100–400 micrograms twice daily, dose to be adjusted as necessary
- **Child 12-17 years**: 100–800 micrograms twice daily, dose to be adjusted as necessary
- **Adult**: 100–800 micrograms twice daily, dose to be adjusted as necessary

**By inhalation of nebulised suspension**

- **Child 6 months-11 years**: 125–500 micrograms twice daily, adjusted according to response; maximum 2 mg per day
- **Child 12-17 years**: Initially 0.25–1 mg twice daily, adjusted according to response, doses higher than recommended max. may be used in severe disease; maximum 2 mg per day
- **Adult**: Initially 0.25–1 mg twice daily, adjusted according to response, doses higher than recommended max. may be used in severe disease; maximum 2 mg per day

**Prophylaxis of mild to moderate asthma (in patients stabilised on twice daily dose)**

**By inhalation of powder**

- **Child 6-11 years**: 200–400 micrograms once daily, dose to be given in the evening
- **Child 12-17 years**: 200–400 micrograms once daily (max. per dose 800 micrograms), dose to be given in the evening
- **Adult**: 200–400 micrograms once daily (max. per dose 800 micrograms), dose to be given in the evening

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**Budesonide**

**INDICATIONS AND DOSE**

**Prophylaxis of asthma**

**By inhalation of powder**

- **Child 6-11 years**: 100–400 micrograms twice daily, dose to be adjusted as necessary
- **Child 12-17 years**: 100–800 micrograms twice daily, dose to be adjusted as necessary
- **Adult**: 100–800 micrograms twice daily, dose to be adjusted as necessary

**By inhalation of nebulised suspension**

- **Child 6 months-11 years**: 125–500 micrograms twice daily, adjusted according to response; maximum 2 mg per day
- **Child 12-17 years**: Initially 0.25–1 mg twice daily, adjusted according to response, doses higher than recommended max. may be used in severe disease; maximum 2 mg per day
- **Adult**: Initially 0.25–1 mg twice daily, adjusted according to response, doses higher than recommended max. may be used in severe disease; maximum 2 mg per day

**Prophylaxis of mild to moderate asthma (in patients stabilised on twice daily dose)**

**By inhalation of powder**

- **Child 6-11 years**: 200–400 micrograms once daily, dose to be given in the evening
- **Child 12-17 years**: 200–400 micrograms once daily (max. per dose 800 micrograms), dose to be given in the evening
- **Adult**: 200–400 micrograms once daily (max. per dose 800 micrograms), dose to be given in the evening
Airways disease, obstructive 229

PULMICORT® RESPULES
Prophylaxis of asthma
BY INHALATION OF NEBULISED SUSPENSION
- Child 3 months-11 years: Initially 0.5–1 mg twice daily, reduced to 250–500 micrograms twice daily
- Child 12-17 years: Initially 1–2 mg twice daily, reduced to 0.5–1 mg twice daily
- Adult: Initially 1–2 mg twice daily, reduced to 0.5–1 mg twice daily

BUDESONIDE (Non-proprietary)
Prophylaxis of asthma
BY INHALATION OF POWDER
- Adult: 200–800 micrograms twice daily, dose is adjusted as necessary

Alternative in mild to moderate asthma, for patients previously stabilised on a twice daily dose
BY INHALATION OF POWDER
- Adult: 200–400 micrograms once daily (max. per dose 800 micrograms), to be taken in the evening

PULMICORT® TURBOHALER
Prophylaxis of asthma
BY INHALATION OF POWDER
- Adult: 100–800 micrograms twice daily, dose to be adjusted as necessary

Alternative in mild to moderate asthma, for patients previously stabilised on a twice daily dose
BY INHALATION OF POWDER
- Adult: 200–400 micrograms once daily (max. per dose 800 micrograms), to be taken in the evening

Potency
Dose adjustments may be required for some inhaler devices, see under individual preparations.

Pulmicort® Turbhaler (AstraZeneca UK Ltd)
Budesonide 100 microgram per 1 dose (Rebameron 11.82 lb) £3.64
Budesonide 200 microgram per 1 dose (Rebameron 12.00 lb) £5.96
Budesonide 400 microgram per 1 dose (Rebameron 12.18 lb) £11.84

Pulmicort® Turbohaler (AstraZeneca UK Ltd)
Budesonide 100 microgram per 1 dose Pulmicort 100 Turbohaler | 200 dose (Pst) £11.84 DT price = £11.84
Budesonide 200 microgram per 1 dose Pulmicort 200 Turbohaler | 100 dose (Pst) £11.84 DT price = £11.84
Budesonide 400 microgram per 1 dose Pulmicort 400 Turbohaler | 50 dose (Pst) £13.86 DT price = £13.86

Budesonide with formoterol

The properties listed below are those particular to the combination only. For the properties of the components please consider, budesonide p. 228, formoterol fumarate p. 220.

INDICATIONS AND DOSE
SYMBICORT 100/6 TURBOHALER®
Asthma, maintenance therapy
BY INHALATION OF POWDER
- Child 6-17 years: Initially 1–2 puffs twice daily; reduced to 1 puff daily, dose reduced only if control is maintained
- Adult: Initially 1–2 puffs twice daily, increased if necessary up to 4 puffs twice daily; reduced to 1 puff daily, dose reduced only if control is maintained

Asthma, maintenance and reliever therapy
BY INHALATION OF POWDER
- Adult: Maintenance 2 puffs daily in 1–2 divided doses; 1 puff as required for relief of symptoms, increased if necessary up to 6 puffs as required; max. 8 per day; up to 12 puffs daily can be used for a limited time but medical assessment should be considered

SYMBICORT 200/6 TURBOHALER®
Asthma maintenance therapy
BY INHALATION OF POWDER
- Child 12-17 years: Initially 1–2 puffs twice daily; reduced to 1 puff daily, dose reduced only if control is maintained
- Adult: Initially 1–2 puffs twice daily, increased if necessary up to 4 puffs twice daily; reduced to 1 puff daily, dose reduced only if control is maintained

Asthma, maintenance and reliever therapy
BY INHALATION OF POWDER
- Adult: Maintenance 2 puffs daily in 1–2 divided doses, increased if necessary to 2 puffs twice daily; 1 puff as required for relief of symptoms, increased if necessary up to 6 puffs as required; max. 8 puffs per day; up to 12 puffs daily can be used for a limited time but medical assessment should be considered

Chronic obstructive pulmonary disease with forced expiratory volume in 1 second &lt;50% of predicted
BY INHALATION OF POWDER
- Adult: 2 puffs twice daily

SYMBICORT 400/12 TURBOHALER®
Asthma, maintenance therapy
BY INHALATION OF POWDER
- Child 12-17 years: Initially 1 puff twice daily; reduced to 1 puff daily, dose reduced only if control is maintained
- Adult: Initially 1 puff twice daily, increased if necessary up to 2 puffs twice daily; reduced to 1 puff daily, dose reduced only if control is maintained

Chronic obstructive pulmonary disease with forced expiratory volume in 1 second &lt;50% of predicted
BY INHALATION OF POWDER
- Adult: 1 puff twice daily

continue →
Respiratory system

Ciclesonide

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Pressurised inhalation**

**CAUTIONARY AND ADVISORY LABELS 8**

- Alvesco (Takeda UK Ltd)
  - Ciclesonide 80 microgram per 1 dose
    - Alvesco 80 inhaler | £32.83 DT price = £32.83
  - Ciclesonide 160 microgram per 1 dose
    - Alvesco 160 inhaler | £38.62 DT price = £38.62

Fluticasone

**INDICATIONS AND DOSE**

Prophylaxis of asthma

**BY INHALATION OF POWDER**

- Child 5–15 years: Initially 50–100 micrograms twice daily (max. per dose 200 micrograms twice daily), dose to be adjusted as necessary
- Child 16–17 years: Initially 100–500 micrograms twice daily (max. per dose 1 mg twice daily), dose may be increased according to severity of asthma. Doses above 500 micrograms twice daily initiated by a specialist
- Adult: Initially 100–500 micrograms twice daily (max. per dose 1 mg twice daily), dose may be increased according to severity of asthma. Doses above 500 micrograms twice daily initiated by a specialist

**BY INHALATION OF AEROSOL**

- Child 4–15 years: Initially 50–100 micrograms twice daily (max. per dose 200 micrograms twice daily), dose to be adjusted as necessary
- Child 16–17 years: Initially 100–500 micrograms twice daily (max. per dose 1 mg twice daily), dose may be increased according to severity of asthma. Doses above 500 micrograms twice daily initiated by a specialist
- Adult: Initially 100–500 micrograms twice daily (max. per dose 1 mg twice daily), dose may be increased according to severity of asthma. Doses above 500 micrograms twice daily initiated by a specialist

**SIDE-EFFECTS**

- arthralgia
- dyspepsia

**DIRECTIONS FOR ADMINISTRATION**

Fluticasone nebuliser liquid may be diluted with sterile sodium chloride 0.9%. It is not suitable for use in ultrasonic nebulisers.

**PATIENT AND CARER ADVICE**

With high doses, a steroid card should be supplied. Patient counselling is advised for budesonide with formoterol dry powder inhalation (administration).

Ciclesonide

**INDICATIONS AND DOSE**

Prophylaxis of asthma

**BY INHALATION OF AEROSOL**

- Child 12–17 years: 160 micrograms once daily; reduced to 80 micrograms daily, if control maintained
- Adult: Initially 160 micrograms once daily; reduced to 80 micrograms once daily, if control maintained; increased if necessary up to 320 micrograms twice daily, in severe asthma

**SIDE-EFFECTS**

- Nausea
- Taste disturbance

**PATIENT AND CARER ADVICE**

Patients or carers should be given advice on how to administer ciclesonide aerosol inhaler.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Pressurised inhalation**

**CAUTIONARY AND ADVISORY LABELS 8**

- Flixotide (GlaxoSmithKline UK Ltd)
  - Fluticasone propionate 50 microgram per 1 dose
    - Flixotide 50micrograms/dose Evohaler | £5.44 DT price = £5.44
**Fluticasone with formoterol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, fluticasone p. 220, formoterol fumarate p. 220.

**INDICATIONS AND DOSE**

**FLUTICOSONE PROPAionate 125 microgram per 1 dose Flutiform® 125 microgram/dose EVOHALER | 120 dose PPT £12.26 DT price = £21.26**

**Fluticasone propionate 250 microgram per 1 dose Flutiform® 250 microgram/dose EVOHALER | 120 dose PPT £36.14 DT price = £63.14**

**Inhalation powder**

**CAUTIONARY AND ADVISORY LABELS 8, 10**

- **Flixotide Accuhaler (GlaxoSmithKline UK Ltd)**
  - Fluticasone propionate 100 microgram per 1 dose Flutiform® 100micrograms/dose Accuhaler | 60 dose PPT £8.93 DT price = £8.93
  - Fluticasone propionate 250 microgram per 1 dose Flutiform® 250micrograms/dose Accuhaler | 60 dose PPT £21.26 DT price = £21.26

**Nebuliser liquid**

**CAUTIONARY AND ADVISORY LABELS 8, 10**

- **Flixotide Nebule (GlaxoSmithKline UK Ltd)**
  - Fluticasone propionate 125 microgram per 1 ml Flixotide 125microgram/2ml Nebules | 10 unit dose PPT £3.34
  - Fluticasone propionate 1 microgram per 1 ml Flixotide 2mg/2ml **Nebules | 10 unit dose PPT £37.35**

**Patient and Carer Advice** With high doses, a steroid card should be provided. Patients or carers should be given advice on how to administer fluticasone with formoterol aerosol inhalation.

**Medicinal Forms**

- **Flutiform® 50 micrograms/5 micrograms**
  - **Prophylaxis of asthma**
    - **BY INHALATION OF AEROSOL**
      - Child 5-17 years: 2 puffs twice daily
      - Adult: 2 puffs twice daily
  - **Flutiform® 125 micrograms/5 micrograms**
    - **Prophylaxis of asthma**
      - **BY INHALATION OF AEROSOL**
        - Child 12-17 years: 2 puffs twice daily
        - Adult: 2 puffs twice daily
  - **Flutiform® 250 micrograms/10 micrograms**
    - **Prophylaxis of asthma**
      - **BY INHALATION OF AEROSOL**
        - Adult: 2 puffs twice daily

**Fluticasone with salmeterol**

**INDICATIONS AND DOSE**

**SERETIDE 500 EVOHALER®**

- **Fluticasone propionate 125 microgram per 1 dose, Salmeterol fumarate dihydrate 5 microgram per 1 dose**
  - **Prophylaxis of asthma**
    - **BY INHALATION**
      - Child 5-17 years: 2 puffs twice daily, reduced to 2 puffs once daily, reduce dose if control maintained
      - Adult: 2 puffs twice daily, reduced to 2 puffs once daily, reduce dose if control maintained

**SERETIDE 125 EVOHALER®**

- **Fluticasone propionate 50 microgram per 1 dose, Salmeterol fumarate dihydrate 2.5 microgram per 1 dose**
  - **Prophylaxis of asthma**
    - **BY INHALATION**
      - Child 5-17 years: 2 puffs twice daily
      - Adult: 2 puffs twice daily

**SERETIDE 250 ACCUHALER®**

- **Fluticasone propionate 100 microgram per 1 dose, Salmeterol fumarate dihydrate 5 microgram per 1 dose**
  - **Prophylaxis of asthma**
    - **BY INHALATION**
      - Child 5-17 years: 1 inhalation twice daily, reduced to 1 inhalation daily, reduce dose if control maintained
      - Adult: 1 inhalation twice daily, reduced to 1 inhalation daily, reduce dose if control maintained

**SERETIDE 500 ACCUHALER®**

- **Fluticasone propionate 250 microgram per 1 dose, Salmeterol fumarate dihydrate 12.5 microgram per 1 dose**
  - **Prophylaxis of asthma**
    - **BY INHALATION OF POWDER**
      - Child 5-17 years: 1 inhalation twice daily, reduced to 1 inhalation daily, reduce dose if control maintained
      - Adult: 1 inhalation twice daily, reduced to 1 inhalation daily, reduce dose if control maintained

**Patient and Carer Advice** With preparations containing greater than 100 micrograms fluticasone, a steroid card should be provided. Patients or carers should be given advice on how to administer fluticasone with salmeterol dry powder inhalation and aerosol inhalation.

**National Funding/Access Decisions**

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (December 2008) that Seretide 500 Accuhaler® is **not** recommended for use within NHS Scotland for chronic obstructive pulmonary disease in patients with a forced expiratory volume in 1 second (FEV1) less than 60% and greater than 50% of the predicted normal value, with significant symptoms despite regular bronchodilator therapy, and a history of repeated exacerbations.

**Medicinal Forms**

- **Fluticasone WITH SALMETEROL (Non-proprietary)**
  - Fluticasone propionate 125 microgram per 1 dose, Salmeterol (as Salmeterol xinafoate) 25 microgram per 1 dose **Sirdupla**

**BNF 70 Airways disease, obstructive 231**
Fluticasone with vilanterol

The properties listed below are those particular to the combination only. For the properties of the components please consider, fluticasone p. 230.

INDICATIONS AND DOSE RELVAR ELLIPTA® 92 MICROGRAMS/22 MICROGRAMS Prophylaxis of asthma BY INHALATION OF POWDER

- Adult: 1 inhalation once daily

Chronic obstructive pulmonary disease with forced expiratory volume in 1 second < 70% of predicted BY INHALATION OF POWDER

- Adult: 1 inhalation once daily RELVAR ELLIPTA® 184 MICROGRAMS/22 MICROGRAMS Prophylaxis of asthma BY INHALATION OF POWDER

- Child 12-17 years: 1 inhalation once daily
- Adult: 1 inhalation once daily

Dose equivalence and conversion

1 inhalation (delivered dose) of fluticasone furoate 92 micrograms once daily is approximately equivalent to fluticasone propionate 250 micrograms twice daily, 1 inhalation (delivered dose) of fluticasone furoate 184 micrograms once daily is approximately equivalent to fluticasone propionate 500 micrograms twice daily.

SIDE-EFFECTS Abdominal pain · back pain

PREGNANCY Manufacturer advises use only if potential benefit outweighs risk.

BREAST FEEDING Manufacturer advises avoid—no information available.

HEPATIC IMPAIRMENT Max. dose fluticasone furoate 92 micrograms, vilanterol 22 micrograms.

RELVAR ELLIPTA® 184 MICROGRAMS/22 MICROGRAMS Avoid in moderate to severe impairment.

PATIENT AND CARER ADVICE A steroid card should be provided. Patients or carers should be given advice on how to administer fluticasone with vilanterol powder for inhalation.

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (March 2014) that fluticasone furoate/vilanterol (Relvar Ellipta®) is accepted for restricted use within NHS Scotland in patients with severe chronic obstructive pulmonary disease with a forced expiratory volume in 1 second (FEV₁) less than 50% of the predicted normal value.

MEDIcularna FORMS

There can be variation in the licensing of different medicines containing the same drug.

Inhalation powder

CAUTIONARY AND ADVISORY LABELS 8, 10

- Relvar Ellipta (GlaxoSmithKline UK Ltd)
- Fluticasone furoate 92 micrograms per 1 dose, Vilanterol 22 micrograms per 1 dose Relvar Ellipta 92 micrograms/dose / 22 micrograms/dose dry powder inhaler | 30 dose (P&G) £27.80
- Fluticasone furoate 184 micrograms per 1 dose, Vilanterol 22 micrograms per 1 dose Relvar Ellipta 184 micrograms/dose / 22 micrograms/dose dry powder inhaler | 30 dose (P&G) £38.87

Mometasone furoate

INDICATIONS AND DOSE Prophylaxis of asthma BY INHALATION OF POWDER

- Child 12-17 years: Initially 400 micrograms daily in 1–2 divided doses, single dose to be inhaled in the evening, reduced to 200 micrograms once daily, if control maintained
- Adult: Initially 400 micrograms daily in 1–2 divided doses, single dose to be inhaled in the evening, reduced to 200 micrograms once daily, if control maintained

Prophylaxis of severe asthma BY INHALATION OF POWDER

- Child 12-17 years: Increased if necessary up to 400 micrograms twice daily
- Adult: Increased if necessary up to 400 micrograms twice daily

SIDE-EFFECTS Common or very common Headache

Uncommon Dyspepsia · palpitation · weight gain

PATIENT AND CARER ADVICE

Medicines for Children leaflet: Mometasone furoate inhaler for asthma prevention (prophylaxis) www.medicinesforchildren.org.uk/mometasone-furoate-inhaler-for-asthma-prevention-prophylaxis

Patients or carers should be given advice on how to administer mometasone by inhaler. With high doses, a steroid card should be supplied.

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (November 2003) that Asmanex® is restricted for use following failure of first-line inhaled corticosteroids.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Inhalation powder

CAUTIONARY AND ADVISORY LABELS 8, 10

- Asmanex Twisthaler (Merck Sharp & Dohme Ltd)
  - Mometasone furoate 200 micrograms per 1 dose Asmanex 200 micrograms/dose Twisthaler | 30 dose (P&G) £15.70 DT price = £15.70 | 60 dose (P&G) £23.54 DT price = £23.54
  - Mometasone furoate 400 micrograms per 1 dose Asmanex 400 micrograms/dose Twisthaler | 30 dose (P&G) £21.78 DT price = £21.78 | 60 dose (P&G) £36.05 DT price = £36.05
LEUKOTRIENE RECEPTOR ANTAGONISTS

Leukotriene receptor antagonist
The leukotriene receptor antagonists, montelukast below and zafirlukast below, block the effects of cysteinyl leukotrienes in the airways. They are effective in asthma when used alone or with an inhaled corticosteroid. Montelukast below has not been shown to be more effective than a standard dose of inhaled corticosteroid, but the two drugs appear to have an additive effect. The leukotriene receptor antagonists may be of benefit in exercise-induced asthma and in those with concomitant rhinitis, but they are less effective in those with severe asthma who are also receiving high doses of other drugs.

Montelukast

INDICATIONS AND DOSE
Prophylaxis of asthma
BY MOUTH
- Child 6 months-5 years: 4 mg once daily, dose to be taken in the evening
- Child 6-14 years: 5 mg once daily, dose to be taken in the evening
- Child 15-17 years: 10 mg once daily, dose to be taken in the evening
- Adult: 10 mg once daily, dose to be taken in the evening
Symptomatic relief of seasonal allergic rhinitis in patients with asthma.
BY MOUTH
- Child 15-17 years: 10 mg once daily, dose to be taken in the evening
- Adult: 10 mg once daily, dose to be taken in the evening

INTERACTIONS → Appendix 1 (leukotriene receptor antagonists).

SIDE-EFFECTS
- Common or very common Abdominal pain - headache - hyperkinesia (in young children) - thirst
- Rare Disturbance in attention - increased bleeding tendency - memory impairment - palpitation - tremor
- Very rare Churg-Strauss syndrome - disorientation - erythema multiforme - erythema nodosum - hallucinations - hepatic disorders - hepatic eosinophilic infiltration - suicidal behaviour - suicidal thoughts

SIDE-EFFECTS, FURTHER INFORMATION
Churg-Strauss syndrome has occurred very rarely in association with the use of montelukast; in many of the reported cases the reaction followed the reduction or withdrawal of oral corticosteroid therapy. Prescribers should be alert to the development of eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, or peripheral neuropathy.

PREGNANCY
Manufacturer advises avoid unless essential.
There is limited evidence for the safe use of montelukast during pregnancy; however, it can be taken as normal in women who have shown a significant improvement in asthma not achievable with other drugs before becoming pregnant.

Bronchial asthma who are also receiving high doses of other drugs.

BREAST FEEDING
Manufacturer advises avoid unless essential.

DIRECTIONS FOR ADMINISTRATION
Granules may be swallowed or mixed with cold, soft food (not liquid) and taken immediately.

PRESCRIBING AND DISPENSING INFORMATION
Flavours of chewable tablet formulations may include cherry.

PATIENT AND CARER ADVICE
Medicines for Children leaflet: Montelukast for asthma www.medicinesforchildren.org.uk/montelukast-for-asthma Patients or carers should be given advice on how to administer montelukast granules.

NATIONAL FUNDING/ACCESS DECISIONS
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (June 2007) that Singulair® chewable tablets are restricted for use as an alternative to low-dose inhaled corticosteroids for children 2–14 years with mild persistent asthma who have not recently had serious asthma attacks that required oral corticosteroid use and who are not capable of using inhaled corticosteroids; Singulair® chewable tablets should be initiated by a specialist in paediatric asthma.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
- MONTELUKAST (Non-proprietary)
  Montelukast (as Montelukast sodium) 10 mg Montelukast 10 mg tablets | 28 tablet £26.97 DT price = £2.20
  Singulair (Merck Sharp & Dohme Ltd) Montelukast (as Montelukast sodium) 10 mg Singulair 10 mg tablets | 28 tablet £26.97 DT price = £2.20

Chewable tablet
CAUTIONARY AND ADVISORY LABELS 23, 24 EXCipients: May contain Aspartame
- MONTELUKAST (Non-proprietary)
  Montelukast (as Montelukast sodium) 4 mg Montelukast 4 mg chewable tablets sugar free (sugar-free) | 28 tablet £25.69 DT price = £1.90
  Montelukast (as Montelukast sodium) 5 mg Montelukast 5 mg chewable tablets sugar free (sugar-free) | 28 tablet £25.69 DT price = £2.18
  Singulair (Merck Sharp & Dohme Ltd) Montelukast (as Montelukast sodium) 4 mg Singulair Paediatric 4 mg chewable tablets (sugar-free) | 28 tablet £25.69 DT price = £1.90
  Montelukast (as Montelukast sodium) 5 mg Singulair Paediatric 5 mg chewable tablets (sugar-free) | 28 tablet £25.69 DT price = £2.18

Granules
- MONTELUKAST (Non-proprietary)
  Montelukast (as Montelukast sodium) 4 mg Montelukast 4 mg granules sachets sugar free (sugar-free) | 28 sachet £4.25–£24.41 DT price = £4.25
  Singulair (Merck Sharp & Dohme Ltd) Montelukast (as Montelukast sodium) 4 mg Singulair Paediatric 4 mg granules sachets (sugar-free) | 28 sachet £25.69 DT price = £4.25

Zafirlukast

INDICATIONS AND DOSE
Prophylaxis of asthma
BY MOUTH
- Child 12-17 years: 20 mg twice daily
- Adult: 20 mg twice daily

CAUTIONS
Elderly

INTERACTIONS → Appendix 1 (leukotriene receptor antagonists).
**Respiratory system**

**Dose frequency is adjusted according to response but is in practice, it is difficult to predict who will benefit; they may be of value in asthma with an allergic basis, but, nedocromil sodium below is not completely understood.**

**The mode of action of sodium cromoglicate below and nedocromil sodium below is not completely understood.**

**Respiratory system**

**Side-effects, further information**

**Hepatic disorder** Patients or their carers should be told how to recognise development of liver disorder and advised to seek medical attention if symptoms or signs such as persistent nausea, vomiting, malaise, or jaundice develop.

**Churg-Strauss syndrome** has occurred very rarely in association with the use of zafirlukast; in many of the reported cases the reaction followed the reduction or withdrawal of oral corticosteroid therapy. Prescribers should be alert to the development of eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, or peripheral neuropathy.

**Pregnancy** Manufacturer advises use only if potential benefit outweighs risk. There is limited evidence for the safe use of zafirlukast during pregnancy; however, it can be taken as normal in women who have shown a significant improvement in asthma not achievable with other drugs before becoming pregnant.

**Breast feeding** Present in milk—manufacturer advises avoid.

**Hepatic impairment** Manufacturer advises avoid.

**Renal impairment** Manufacturer advises caution in moderate to severe impairment.

**Patient and carer advice**


**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Aurocote** (AstraZeneca UK Ltd)
  - Zafirlukast 20 mg: Accolate 20mg tablets. Price £17.75
  - DT price = £94.94

**MAST CELL STABILISERS**

**Cromoglicate and related therapy**

The mode of action of sodium cromoglicate below and nedocromil sodium below is not completely understood. They may be of value in asthma with an allergic basis, but, in practice, it is difficult to predict who will benefit; they could probably be given for 4 to 6 weeks to assess response. Dose frequency is adjusted according to response but is usually 3 to 4 times a day initially; this may subsequently be reduced.

In general, prophylaxis with sodium cromoglicate is less effective than prophylaxis with corticosteroid inhalations. There is evidence of efficacy of nedocromil sodium in children aged 5–12 years. Sodium cromoglicate and nedocromil sodium are of no value in the treatment of acute attacks of asthma.

Sodium cromoglicate can prevent exercise-induced asthma. However, exercise-induced asthma may reflect poor overall control and the patient should be reassessed.

Sodium cromoglicate below and nedocromil sodium below may also have a role in allergic conjunctivitis; sodium cromoglicate is used also in allergic rhinitis and allergy-related diarrhoea.

**Nedocromil sodium**

**Indications and dose**

**Prophylaxis of asthma**

- **By inhalation of aerosol**
  - Child 5–17 years: Initially 4 mg 4 times a day, when control achieved may be possible to reduce to twice daily
  - Adult: Initially 4 mg 4 times a day, when control achieved may be possible to reduce to twice daily

**Dose equivalence and conversion**

- 2 puffs = 4 mg

**Unlicensed use**

Not licensed for use in children under 6 years.

**Side-effects**

- **Common or very common** Abdominal pain · dyspepsia · nausea · pharyngitis · vomiting
  - Rare: Taste disturbances
  - Frequency not known: Bronchospasm · cough · nausea · pharyngitis · vomiting

**Side-effects, further information**

**Paradoxical bronchospasm** If paradoxical bronchospasm occurs, a short-acting beta agonist such as salbutamol or terbutaline should be used to control symptoms; treatment with nedocromil should be discontinued.

**Pregnancy** Inhaled drugs can be taken as normal during pregnancy.

**Breast feeding** Inhaled drugs can be taken as normal during breast-feeding.

**Treatment cessation** Withdrawal should be done gradually over a period of one week—symptoms of asthma may recur.

**Prescribing and dispensing information**

Flavours of inhalers may include mint.

**Patient and carer advice**

Patient counselling is advised for Nedocromil aerosol for inhalation (administration).

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug.

**Pressurised inhalation**

- **Tilade** (Sanofi)
  - Nedocromil sodium 2 mg per 1 dose
  - Tilade 2mg/dose inhaler CFC free | 112 dose £39.94

**Sodium cromoglicate**

(Sodium cromoglicate)

**Indications and dose**

**Prophylaxis of asthma**

- **By inhalation of aerosol**
  - Child 5–17 years: Initially 10 mg 4 times a day, additional dose may also be taken before exercise, increased if necessary to 10 mg 6–8 times a day; maintenance 5 mg 4 times a day, 5 mg is equivalent to 1 puff
  - Adult: Initially 10 mg 4 times a day, additional dose may also be taken before exercise, increased if necessary to 10 mg 6–8 times a day; maintenance 5 mg 4 times a day, 5 mg is equivalent to 1 puff
Food allergy (in conjunction with dietary restriction)

**BY MOUTH**
- Child 2-13 years: Initially 100 mg 4 times a day for 2–3 weeks, then increased if necessary up to 40 mg/kg daily, then reduced according to response, to be taken before meals
- Child 14-17 years: Initially 200 mg 4 times a day for 2–3 weeks, then increased if necessary up to 40 mg/kg daily, then reduced according to response, to be taken before meals
- Adult: Initially 200 mg 4 times a day for 2–3 weeks, then increased if necessary up to 40 mg/kg daily, then reduced according to response, to be taken before meals

**DIRECTIONS FOR ADMINISTRATION**

**TREATMENT CESSATION**

When used by inhalation Withdrawal of sodium cromoglicate should be done gradually over a period of one week—symptoms of asthma may recur.

**BREAST FEEDING**

- Not known to be harmful. Inhaled drugs can be taken as normal during pregnancy.
- Not known to be harmful. Inhaled drugs can be taken as normal during breast-feeding.

**SIDE-EFFECTS, FURTHER INFORMATION**

- Common or very common Abdominal pain · arthralgia · headache · injection-site reactions · pruritis · sinusitis · upper respiratory tract infection
- Uncommon Bronchospasm · cough · diarrhoea · dizziness · drowsiness · dyspepsia · flushing · influenza-like illness · malaise · nausea · paraesthesia · pharyngitis · photosensitivity · postural hypotension · pruritus · rash · syncope · urticaria · weight gain
- Rare Angioedema · antibody formation · laryngoedema · parasitic infection

**SIDE-EFFECTS**

- Autoimmune disease · susceptibility to helminth infection—discontinue if infection does not respond to anthelmintic

**INDICATIONS AND DOSE**

**Prophylaxis of severe persistent allergic asthma**

**BY SUBCUTANEOUS INJECTION**

- Adult: Dose according to immunoglobulin E concentration and body-weight (consult product literature)

**Add-on therapy for chronic spontaneous urticaria in patients who have had an inadequate response to H1 antihistamine treatment**

**BY SUBCUTANEOUS INJECTION**

- Adult: 300 mg every 4 weeks

**CAUTIONS**

- Autoimmune disease · susceptibility to helminth infection—discontinue if infection does not respond to anthelmintic

**MEDICINAL FORMS**

- Inhaled: 200 mg pressurized inhalation

**CAUTIONARY AND ADVISORY LABELS 22**

- Nalcrom (Sanofi)
  - Sodium cromoglicate 100 mg Nalcrom 100mg capsules | 100 capsule pack £41.14 OT price = £41.14

- Intal (Sanofi)
  - Sodium cromoglicate 5 mg per 1 dose Intal 5mg/dose inhaler CFC free | 122 dose pack £18.33

**MONOCLONAL ANTIBODIES**

**Omalizumab**

**INDICATIONS AND DOSE**

**Prophylaxis of severe persistent allergic asthma**

**BY SUBCUTANEOUS INJECTION**

- Adult: Dose according to immunoglobulin E concentration and body-weight (consult product literature)

**Add-on therapy for chronic spontaneous urticaria in patients who have had an inadequate response to H1 antihistamine treatment**

**BY SUBCUTANEOUS INJECTION**

- Adult: 300 mg every 4 weeks

**CAUTIONS**

- Autoimmune disease · susceptibility to helminth infection—discontinue if infection does not respond to anthelmintic

**SIDE-EFFECTS**

- Common or very common Abdominal pain · arthralgia · headache · injection-site reactions · pruritis · sinusitis · upper respiratory tract infection
- Uncommon Bronchospasm · cough · diarrhoea · dizziness · drowsiness · dyspepsia · flushing · influenza-like illness · malaise · nausea · paraesthesia · pharyngitis · photosensitivity · postural hypotension · pruritus · rash · syncope · urticaria · weight gain
- Rare Angioedema · antibody formation · laryngoedema · parasitic infection

**SIDE-EFFECTS, FURTHER INFORMATION**

**Churg-Strauss syndrome**

Churg-Strauss syndrome has occurred rarely in patients given omalizumab; the reaction is usually associated with the reduction of oral corticosteroid therapy. Churg-Strauss syndrome can present as eosinophilia, vasculitic rash, cardiac complications, worsening pulmonary symptoms, or peripheral neuropathy.

**Hypersensitivity reactions**

Hypersensitivity reactions can also occur immediately following treatment with omalizumab or sometimes more than 24 hours after the first injection.

**PREGNANCY**

- Manufacturer advises avoid unless essential—crosses the placenta.

**BREAST FEEDING**

- Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**

- Manufacturer advises caution—no information available.

**RENAL IMPAIRMENT**

- Manufacturer advises caution—no information available.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Omalizumab for previously treated chronic spontaneous urticaria (June 2015) NICE TA339

- Omalizumab is an option as add-on therapy for the treatment of severe chronic spontaneous urticaria in patients 12 years and over, only if:
  - the severity of the condition is assessed objectively, for example, using a weekly urticaria activity score of 28 or more,
  - the patient’s condition has not responded to standard treatment with H1-antihistamines and leukotriene receptor antagonists,
  - omalizumab is stopped at or before the fourth dose if the condition has not responded,
Respiratory system

CONTRA-INDICATIONS

- Roflumilast
- **PHOSPHODIESTERASE TYPE-4 INHIBITORS**

Omalizumab for severe persistent allergic asthma (April 2013) NICE TA278

Omalizumab is recommended as an option for treating severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimised standard therapy in patients aged 12 years or older.

- who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year), and
- only if the manufacturer makes omalizumab available with the discount agreed in the patient access scheme.

Optimised standard therapy is defined as a full trial of and, if tolerated, documented compliance with inhaled high-dose corticosteroids, long-acting beta agonists, leukotriene receptor antagonists, theophyllines, oral corticosteroids, and smoking cessation if clinically appropriate.

Patients currently receiving omalizumab whose disease does not meet the criteria should be able to continue treatment until they and their clinician consider it appropriate to stop. www.nice.org.uk/TA278

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (December 2014) that omalizumab (Xolair®) is accepted for restricted use within NHS Scotland for the treatment of chronic spontaneous urticaria in patients aged 12 years and over, who have had an inadequate response to combination therapy with H1-antihistamines, leukotriene receptor antagonists and H2-antihistamines, used according to current treatment guidelines.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Solution for injection**
    - **Xolair** (Novartis Pharmaceuticals UK Ltd)
      - Omalizumab 150 mg per 1 ml Xolair 150mg/1ml solution for injection pre-filled syringes | 1 pre-filled disposable injection POM £256.15
      - Xolair 75mg/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection POM £128.07

PHOSPHODIESTERASE TYPE-4 INHIBITORS

Roflumilast

- **DRUG ACTION**
  - Roflumilast is a phosphodiesterase type-4 inhibitor with anti-inflammatory properties.

INDICATIONS AND DOSE

Adjuvant to bronchodilators for the maintenance treatment of patients with severe chronic obstructive pulmonary disease associated with chronic bronchitis and a history of frequent exacerbations

BY MOUTH

- Adult: 500 micrograms once daily

CONTRA-INDICATIONS

- Cancer (except basal cell carcinoma) - concomitant treatment with immunosuppressive drugs (except short-term systemic corticosteroids) - history of depression associated with suicidal ideation or behaviour - moderate to severe cardiac failure - severe acute infectious disease - severe immunological disease

- **CAUTIONS**
  - History of psychiatric illness (discontinue if new or worsening psychiatric symptoms occur) - latent infection (such as tuberculosis, viral hepatitis, herpes infection)

- **INTERACTIONS**
  - Caution with concomitant use of drugs likely to cause psychiatric events (discontinue if new or worsening psychiatric symptoms occur).

Appendix 1 (roflumilast).

- **SIDE-EFFECTS**
  - **Common or very common** Abdominal pain - decreased appetite - diarrhoea - headache - insomnia - nausea - weight loss
  - **Uncommon** Anxiety - back pain - dizziness - dyspepsia - gastritis - gastro-oesophageal reflux - malaise - muscle spasm - myalgia - palpititation - rash - tremor - vertigo - vomiting
  - **Rare** Constipation - depression - gynaecomastia - haematochezia - nervousness - raised creatine kinase - respiratory tract infections - suicidal behaviour - suicidal ideation - taste disturbances - urticaria

- **CONCEPTION AND CONTRACEPTION**
  - Women of child-bearing age should use effective contraception.

- **PREGNANCY**
  - Manufacturer advises avoidance—毒性 in animal studies.

- **BREAST FEEDING**
  - Manufacturer advises avoidance—present in milk in animal studies.

- **HEPATIC IMPAIRMENT**
  - Caution in mild impairment. Avoid in moderate to severe impairment.

- **MONITORING REQUIREMENTS**
  - Monitor body-weight.

- **PATIENT AND CARER ADVICE**
  - Patients should be given a patient card before starting treatment and advised to record body-weight at regular intervals.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE technology appraisals (TAs)**
    - Roflumilast for the management of severe chronic obstructive pulmonary disease (January 2012) NICE TA244
      - Roflumilast is recommended only in the context of research as part of a clinical trial for adults with severe chronic obstructive pulmonary disease associated with chronic bronchitis with a history of frequent exacerbations as an add-on to bronchodilator treatment.
      - Patients receiving roflumilast should have the option to continue treatment until they and their clinicians consider it appropriate to stop. www.nice.org.uk/TA244

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - **Daxas** (Takeda UK Ltd)
      - Roflumilast 500 microgram Daxas 500microgram tablets | 30 tablet (POM) £37.71 07 price = £37.71

SYMPATHOMIMETICS (VASOCONSTRICTOR)

Ephedrine hydrochloride

- **INDICATIONS AND DOSE**
  - Reversible airways obstruction
    - **BY MOUTH**
      - Adult: 15–60 mg 3 times a day
      - Neuropathic oedema
        - **BY MOUTH**
          - Adult: 30–60 mg 3 times a day
Reversal of hypotension from spinal or epidural anaesthesia by slow intravenous injection
- Adult: 3–6 mg every 3–4 minutes (max. per dose 9 mg), adjusted according to response, injection solution to contain ephedrine hydrochloride 3 mg/mL; maximum 30 mg per course

- **UNLICENSED USE** Not licensed for neuropathic oedema.

- **CAUTIONS**
  - **GENERAL CAUTIONS** Diabetes mellitus - elderly - hypertension - hyperthyroidism - ischaemic heart disease - prostatic hypertrophy (risk of acute urinary retention)
  - **SPECIFIC CAUTIONS**
    - With intravenous use: susceptibility to angle-closure glaucoma
    - **INTERACTIONS** Appendix 1 (sympathomimetcs).
  - **SIDE-EFFECTS**
    - **Common or very common**
    - With oral use: anxiety - arrhythmias - insomnia - restlessness - tachycardia - tremor
  - **Very rare**
    - With intravenous use: angle-closure glaucoma
    - Frequency not known
    - With intravenous use: bradycardia
    - With oral use: cold extremities - dry mouth
    - With systemic use: increased lacrimation (can have adverse effects on contact lens wear)

- **PREGNANCY** Increased fetal heart rate reported with parenteral ephedrine.
  - With oral use: Manufacturer advises avoid
  - **BREAST FEEDING** Present in milk; manufacturer advises avoid—irritability and disturbed sleep reported.
  - **RENAL IMPAIRMENT** Use with caution.
  - **LESS SUITABLE FOR PRESCRIBING** Ephedrine tablets are less suitable and less safe for use as a bronchodilator than the selective beta2 agonists.
  - **EXCEPTIONS TO LEGAL CATEGORY** For exceptions relating to ephedrine tablets see Medicines, Ethics and Practice, London, Pharmaceutical Press (always consult latest edition).

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, oral suspension, oral solution

### Tablet
- **EPHEDRINE HYDROCHLORIDE** (Non-proprietary)
  - Ephedrine hydrochloride 15 mg Ephedrine hydrochloride 15 mg tablets | 28 tablet £15.86-£16.38 DT price = £15.86
  - Ephedrine hydrochloride 30 mg Ephedrine hydrochloride 30 mg tablets | 28 tablet £24.87-£25.43 DT price = £24.87

### Solution for injection
- **EPHEDRINE HYDROCHLORIDE** (Non-proprietary)
  - Ephedrine hydrochloride 3 mg per 1 mL Ephedrine hydrochloride 3 mg/10 mL solution for injection ampoules | 10 ampoule £63.38
  - Ephedrine 30 mg/10 mL solution for injection pre-filled syringes | 1 pre-filled disposable injection £7.59 | 12 pre-filled disposable injection £8.86 no price available
  - Ephedrine hydrochloride 30 mg per 1 mL Ephedrine 30 mg/1 mL solution for injection ampoules | 10 ampoule £4.10

### XANTHINES

#### Aminophylline

### INDICATIONS AND DOSE

#### Severe acute asthma by intravenous infusion
- Child: 5 mg/kg/hour, adjusted according to plasma-theophylline concentration
- Elderly: 500–700 micrograms/kg/hour, adjusted according to plasma-theophylline concentration
- Adult: 250–500 mg (max. per dose 5 mg/kg), to be followed by intravenous infusion

#### Severe acute exacerbation of chronic obstructive pulmonary disease by intravenous infusion
- Adult: 500–700 micrograms/kg/hour, adjusted according to plasma-theophylline concentration
- Elderly: 300 micrograms/kg/hour, adjusted according to plasma-theophylline concentration

#### Severe acute exacerbation of chronic obstructive pulmonary disease in patients not previously treated with theophylline by slow intravenous injection
- Adult: 5 mg/kg (max. per dose 500 mg), to be followed by intravenous infusion
- Adult: 250–500 mg (max. per dose 5 mg/kg), to be followed by intravenous infusion

#### Chronic asthma by mouth using modified-release medicines
- Child (body-weight 40 kg and above): Initially 225 mg twice daily for 1 week, then increased if necessary to 450 mg twice daily, adjusted according to plasma-theophylline concentration

#### Reversible airway obstruction by mouth using modified-release medicines
- Adult (body-weight 40 kg and above): Initially 225 mg twice daily for 1 week, then increased if necessary to 450 mg twice daily, adjusted according to plasma-theophylline concentration

#### PHYLLOCONTIN CONTINUS® FORTE

#### Reversible airways obstruction | Severe acute asthma by mouth using modified-release medicines
- Adult: Initially 350 mg twice daily for 1 week, then increased if necessary to 700 mg twice daily, increase dose according to plasma-theophylline concentration

### Dose adjustments due to interactions
Dose adjustment may be necessary if smoking started or stopped during treatment.

### Doses at extremes of body-weight
To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal weight for height.

#### Pharmacokinetics
Aminophylline is a stable mixture or combination of theophylline and ethylenediamine; the ethylenediamine confers greater solubility in water.

Theophylline is metabolised in the liver. The plasma-theophylline concentration is increased in heart failure, hepatic impairment, and in viral infections. The plasma-theophylline concentration is decreased in smokers, and by alcohol consumption. Differences in the continued
Airways disease, obstructive

Half-life of aminophylline is important because the toxic dose is close to the therapeutic dose.

- **UNLICENSED USE** Aminophylline injection not licensed for use in children under 6 months.
- **CAUTIONS** Arrhythmias following rapid intravenous injection - cardiac arrhythmias or other cardiac disease - elderly (increased plasma-theophylline concentration) - epilepsy - fever - hypertension - hyperthyroidism - peptic ulcer - risk of hypokalaemia
- **INTERACTIONS** → Appendix 1 (aminophylline).
- **SIDE-EFFECTS** Arrhythmias (especially if given rapidly by intravenous injection) - CNS stimulation - convulsions (especially if given rapidly by intravenous injection) - diarrhoea - gastric irritation - headache - hypotension (especially if given rapidly by intravenous injection) - insomnia - nausea - palpitation - tachycardia - vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

**Hypokalaemia** Potentially serious hypokalaemia may result from beta agonist therapy. Particular caution is required in severe asthma, because this effect may be potentiated by concomitant treatment with theophylline and its derivatives, corticosteroids, and diuretics, and by hypoxia. Plasma-potassium concentration should therefore be monitored in severe asthma.

**Overdose** Theophylline and related drugs are often prescribed as modified-release formulations and toxicity can therefore be delayed. They cause vomiting (which may be severe and intractable), agitation, restlessness, dilated pupils, sinus tachycardia, and hyperglycaemia. More serious effects are haematemesis, convulsions, and supraventricular and ventricular arrhythmias. Severe hypokalaemia may develop rapidly.

For specific details on the management of poisoning, see Theophylline, under Emergency treatment of poisoning p. 1123.

- **ALLERGY AND CROSS-SENSITIVITY** Allergy to ethylenediamine can cause urticaria, erythema, and exfoliative dermatitis
- **PREGNANCY** Neonatal irritability and apnoea have been reported. Theophylline can be taken as normal during pregnancy as it is particularly important that asthma should be well controlled during pregnancy.
- **BREAST FEEDING** Present in milk—irritability in infant reported; modified-release preparations preferable. Theophylline can be taken as normal during breast-feeding.
- **HEPATIC IMPAIRMENT** Reduce dose.
- **MONITORING REQUIREMENTS**
  - Aminophylline is monitored therapeutically in terms of plasma-theophylline concentrations. Measurement of plasma-theophylline concentration may be helpful and is essential if a loading dose of intravenous aminophylline is to be given to children who are already taking theophylline, because serious side-effects such as convulsions and arrhythmias can occasionally precede other symptoms of toxicity. In most individuals, a plasma-theophylline concentration of 5–10 mg/litre is required for satisfactory bronchodilation, although a lower plasma-theophylline concentration of 5–15 mg/litre may be effective. Adverse effects can occur within the range 10–20 mg/litre and both the frequency and severity increase at concentrations above 20 mg/litre.
  - If aminophylline is given intravenously, a blood sample should be taken 4–6 hours after starting treatment.
  - Plasma-theophylline concentration is measured 5 days after starting oral treatment and at least 3 days after any dose adjustment. A blood sample should usually be taken 4–6 hours after an oral dose of a modified-release preparation (sampling times may vary—consult local guidelines).
- **DIRECTIONS FOR ADMINISTRATION**
  - With intravenous use in children For intravenous infusion, dilute to a concentration of 1 mg/ml with Glucose 5% or Sodium Chloride 0.9%.
  - With intravenous use in adults For intravenous infusion, give continuously in Glucose 5% or Sodium Chloride 0.9%. For intravenous injection, give very slowly over at least 20 minutes (with close monitoring).
  - With intramuscular use Aminophylline is too irritant for intramuscular use.
- **PRESCRIBING AND DISPENSING INFORMATION**
  - Patients taking oral theophylline or aminophylline should not normally receive a loading dose of intravenous aminophylline.
  - Consider intravenous aminophylline for treatment of severe and life-threatening acute asthma only after consultation with senior medical staff.
  - Modified release The rate of absorption from modified-release preparations can vary between brands. If a prescription for a modified-release oral aminophylline preparation does not specify a brand name, the pharmacist should contact the prescriber and agree the brand to be dispensed. Additionally, it is essential that a patient discharged from hospital should be maintained on the brand on which that patient was stabilised as an in-patient.
  - **Phylocontin Continus®** Forte tablets are for smokers and other patients where theophylline half-life is shorter.
- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for infusion, suppository
  - **Modified-release tablet**
  - **CAUTIONARY AND ADVISORY LABELS** 25
  - **AMINOPHYLLINE (Non-proprietary)**
    - Aminophylline hydrate 225 mg
    - Aminophylline hydrate 225mg modified-release tablets | 56 tablet | no price available
    - **Phylocontin Continus (Napp Pharmaceuticals Ltd)**
      - Aminophylline hydrate 225 mg
      - Phyllocontin Continus 225mg tablets | 56 tablet | £2.40
    - **Aminophylline hydrate 350 mg**
      - Phyllocontin Forte Continus 350mg tablets | 56 tablet | £4.22
  - **Solution for injection**
    - **AMINOPHYLLINE (Non-proprietary)**
      - Aminophylline 25 mg per 1 ml
      - Aminophylline 250mg/10ml solution for injection ampoules | 10 ampoule (PMD) £6.51 OT price = £6.51

**Theophylline**

**INDICATIONS AND DOSE**

**NUELIN SA® 175MG TABLETS**

**Chronic asthma**

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Child 6–11 years: 175 mg every 12 hours
  - Child 12–17 years: 175–350 mg every 12 hours

**Reversible airways obstruction | Chronic asthma**

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Adult: 175–350 mg every 12 hours

**NUELIN SA® 250 TABLETS**

**Chronic asthma**

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Child 6–11 years: 125–250 mg every 12 hours
  - Child 12–17 years: 250–500 mg every 12 hours

**Reversible airways obstruction | Chronic asthma**

- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Adult: 250–500 mg every 12 hours
**UNIPHYSLLIN CONTINUS®**

**Chronic asthma**

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

- **Child 2-11 years:** 9 mg/kg every 12 hours (max. per dose 200 mg), dose may be increased in some children with chronic asthma to 10–16 mg/kg every 12 hours (max. per dose 400 mg), may be appropriate to give larger evening or morning dose to achieve optimum therapeutic effect when symptoms most severe; in patients whose night or daytime symptoms persist despite other therapy, who are not currently receiving theophylline, total daily requirement may be added as single evening or morning dose
- **Child 12-17 years:** 200 mg every 12 hours, adjusted according to response to 400 mg every 12 hours, may be appropriate to give larger evening or morning dose to achieve optimum therapeutic effect when symptoms most severe; in patients whose night or daytime symptoms persist despite other therapy, who are not currently receiving theophylline, total daily requirement may be added as single evening or morning dose

**Reversible airways obstruction | Chronic asthma**

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

- **Adult:** 200 mg every 12 hours, adjusted according to response to 400 mg every 12 hours, may be appropriate to give larger evening or morning dose to achieve optimum therapeutic effect when symptoms most severe; in patients whose night or daytime symptoms persist despite other therapy, who are not currently receiving theophylline, total daily requirement may be added as single evening or morning dose

**SLO-PHYLLIN®**

**Chronic asthma**

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

- **Child 2-5 years:** 60–120 mg every 12 hours
- **Child 6-11 years:** 125–250 mg every 12 hours
- **Child 12-17 years:** 250–500 mg every 12 hours

**Reversible airways obstruction | Chronic asthma**

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

- **Adult:** 250–500 mg every 12 hours

**PHARMACOKINETICS**

Theophylline is metabolised in the liver. The plasma-theophylline concentration is increased in heart failure, hepatic impairment, and in viral infections. The plasma-theophylline concentration is decreased in smokers, and by alcohol consumption. Differences in the half-life of theophylline are important because the toxic dose is close to the therapeutic dose.

- **CAUTIONS** Cardiac arrhythmias or other cardiac disease • elderly (increased plasma-theophylline concentration) • epilepsy • fever • hypertension • hyperthyroidism • peptic ulcer - risk of hypokalaemia
- **INTERACTIONS** Appendix 1 (theophylline).
- **SIDE-EFFECTS** Arrhythmias • CNS stimulation • convulsions • diarrhoea • gastric irritation • headache • insomnia • nauseae • palpitation • tachycardia • vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

**Hypokalaemia** Potentially serious hypokalaemia may result from beta, agonist therapy. Particular caution is required in severe asthma, because this effect may be potentiated by concomitant treatment with theophylline and its derivatives, corticosteroids, and diuretics, and by hypoxia. Plasma-potassium concentration should therefore be monitored in severe asthma.

**Overdose** Theophylline in overdose can cause vomiting (which may be severe and intractable), agitation, restlessness, dilated pupils, sinus tachycardia, and hyperglycaemia. More serious effects are haematemeses, convulsions, and supraventricular and ventricular arrhythmias. Severe hypokalaemia may develop rapidly. For details on the management of poisoning, see Theophylline, under Emergency treatment of poisoning p. 1123.

- **PREGNANCY** Neonatal irritability and apnoea have been reported. Theophylline can be taken as normal during pregnancy as it is particularly important that asthma should be well controlled during pregnancy.
- **BREAST FEEDING** Present in milk—irritability in infant reported; modified-release preparations preferable. Theophylline can be taken as normal during breast-feeding.
- **HEPATIC IMPAIRMENT** Reduce dose.
- **MONITORING REQUIREMENTS**
  - In most individuals, a plasma-theophylline concentration of 10–20 mg/litre (55–110 micromol/litre) is required for satisfactory bronchodilation, although a lower plasma-theophylline concentration of 5–15 mg/litre may be effective. Adverse effects can occur within the range 10-20 mg/litre and both the frequency and severity increase at concentrations above 20 mg/litre.
  - Plasma-theophylline concentration is measured 5 days after starting oral treatment and at least 3 days after any dose adjustment. A blood sample should usually be taken 4–6 hours after an oral dose of a modified-release preparation (sampling times may vary—consult local guidelines).

**DIRECTIONS FOR ADMINISTRATION**

**SLO-PHYLLIN®** Swallow whole with fluid or swallow enclosed granules with soft food (e.g. yoghurt). Contents of the capsule (enteric-coated granules) may be sprinkled on to a spoonful of soft food (e.g. yoghurt) and swallowed without chewing.

- **PRESCRIBING AND DISPENSING INFORMATION** The rate of absorption from modified-release preparations can vary between brands. If a prescription for a modified-release oral theophylline preparation does not specify a brand name, the pharmacist should contact the prescriber and agree the brand to be dispensed. Additionally, it is essential that a patient discharged from hospital should be maintained on the brand on which that patient was stabilised as an in-patient.

**PATIENT AND CARER ADVICE**

**SLO-PHYLLIN®** Patient or carer should be given advice on how to administer theophylline modified release capsules.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Modified-release tablet**

- **CAUTIONARY AND ADVISORY LABELS 21, 25**
- **Nuelin SA (Meda Pharmaceuticals Ltd)**
  - Theophylline 175 mg Nuelin SA 175mg tablets | 60 tablet [p] £6.38
  - DT price = £6.38
- **Theophylline 250 mg** Nuelin SA 250 tablets | 60 tablet [p] £8.92 DT price = £8.92
- **Uniphyllin Continus (Napp Pharmaceuticals Ltd)**
  - Theophylline 200 mg Uniphyllin Continus 200mg tablets | 56 tablet [p] £2.96
  - Theophylline 300 mg Uniphyllin Continus 300mg tablets | 56 tablet [p] £4.77
- **Theophylline 400 mg** Uniphyllin Continus 400mg tablets | 56 tablet [p] £5.65 DT price = £5.65

**Modified-release capsule**

- **CAUTIONARY AND ADVISORY LABELS 25**
- **Slo-Phyllin (Merck Serono Ltd)**
  - Theophylline 60 mg Slo-Phyllin 60mg capsules | 56 capsule [p] £2.76 DT price = £2.76
Nebuliser solutions
Also see sodium chloride p. 851

● HYPERTONIC SODIUM CHLORIDE SOLUTIONS

INDICATIONS AND DOSE
MUCOCLEAR® 3%
Mobilise lower respiratory tract secretions in mucous consolidation (e.g. cystic fibrosis)
BY INHALATION OF NEBULISED SOLUTION

Adult: 4 ml 2–4 times a day, temporary irritation, such as coughing, hoarseness, or reversible bronchoconstriction may occur; an inhaled bronchodilator can be used before treatment to reduce the risk of these adverse effects

Mucoclear 3% inhalation solution 4ml ampoules (Pari Medical Ltd) | 20 ampoule • NHS indicative price = £12.98 • Drug Tariff (Part IXa) | 60 ampoule • NHS indicative price = £27.00 • Drug Tariff (Part IXa)

INDICATIONS AND DOSE
MUCOCLEAR® 6%
Mobilise lower respiratory tract secretions in mucous consolidation (e.g. cystic fibrosis)
BY INHALATION OF NEBULISED SOLUTION

Adult: 4 ml twice daily, temporary irritation, such as coughing, hoarseness, or reversible bronchoconstriction may occur; an inhaled bronchodilator can be used before treatment to reduce the risk of these adverse effects

Mucoclear 6% inhalation solution 4ml ampoules (Pari Medical Ltd) | 20 ampoule • NHS indicative price = £12.98 • Drug Tariff (Part IXa) | 60 ampoule • NHS indicative price = £27.00 • Drug Tariff (Part IXa)

INDICATIONS AND DOSE
NEBUSAL®
Mobilise lower respiratory tract secretions in mucous consolidation (e.g. cystic fibrosis)
BY INHALATION OF NEBULISED SOLUTION

Adult: up to twice daily, temporary irritation, such as coughing, hoarseness, or reversible bronchoconstriction may occur; an inhaled bronchodilator can be used before treatment to reduce the risk of these adverse effects

Nebusal 7% inhalation solution 4ml vials (Forest Laboratories UK Ltd) | 60 vial • NHS indicative price = £27.00 • Drug Tariff (Part IXa)

Peak flow meters

● LOW RANGE PEAK FLOW METERS
Compliant to standard EN ISO 23747:2007 except for scale range.

MEDI® LOW RANGE
Range 40–420 litres/minute.

Medi peak flow meter low range (Medicareplus International Ltd) | 1 device • NHS indicative price = £6.50 • Drug Tariff (Part IXa) price = £6.50

MINI-WRIGHT® LOW RANGE
Range 30–400 litres/minute.

Midi peak flow meter low range (Medicareplus International Ltd) | 1 device • NHS indicative price = £6.50 • Drug Tariff (Part IXa) price = £6.50

POCKETPEAK® LOW RANGE
Range 50–400 litres/minute.

nSPIRE Pocket Peak peak flow meter low range (nSPIRE Health Ltd) | 1 device • NHS indicative price = £6.53 • Drug Tariff (Part IXa) price = £6.50

STANDARD RANGE PEAK FLOW METERS

AIRZONE®
Range 60–720 litres/minute.

AirZone peak flow meter standard range (Clement Clarke International Ltd) | 1 device • NHS indicative price = £4.69 • Drug Tariff (Part IXa) price = £4.50

MEDI® STANDARD RANGE
Range 60–800 litres/minute.

Midi peak flow meter standard range (Medicareplus International Ltd) | 1 device • NHS indicative price = £4.50 • Drug Tariff (Part IXa) price = £4.50

MICROPEAK®
Range 60–900 litres/minute.

MicroPeak peak flow meter standard range (Micro Medical Ltd) | 1 device • NHS indicative price = £6.50 • Drug Tariff (Part IXa) price = £6.50

MINI-WRIGHT® STANDARD RANGE
Range 60–800 litres/minute.

Mini-Wright peak flow meter standard range (Clement Clarke International Ltd) | 1 device • NHS indicative price = £7.08 • Drug Tariff (Part IXa) price = £7.05

PIKO®
Range 15–999 litres/minute.

nSPIRE Piko-1 peak flow meter standard range (nSPIRE Health Ltd) | 1 device • NHS indicative price = £9.50 • Drug Tariff (Part IXa) price = £9.45

PINNACLE®
Range 60–900 litres/minute.

Fyne Dynamics Pinnacle peak flow meter standard range (Fyne Dynamics Ltd) | 1 device • NHS indicative price = £6.50 • Drug Tariff (Part IXa) price = £6.45

POCKETPEAK® STANDARD RANGE
Range 60–800 litres/minute.

nSPIRE Pocket Peak peak flow meter standard range (nSPIRE Health Ltd) | 1 device • NHS indicative price = £6.53 • Drug Tariff (Part IXa) price = £6.50

VITALOGRAPH®
Range 50–800 litres/minute.

Vitalograph peak flow meter standard range (Vitalograph Ltd) | 1 device • NHS indicative price = £4.83 • Drug Tariff (Part IXa) price = £4.80

Spacers

● SPACERS

A2A SPACER®
For use with all pressurised (aerosol) inhalers.

A2A Spacer (Clement Clarke International Ltd) | 1 device • NHS indicative price = £4.15 • Drug Tariff (Part IXa)

A2A Spacer with medium mask (Clement Clarke International Ltd) | 1 device • NHS indicative price = £6.68 • Drug Tariff (Part IXa)

A2A Spacer with small mask (Clement Clarke International Ltd) | 1 device • NHS indicative price = £6.68 • Drug Tariff (Part IXa)

ABLE SPACER®
Small-volume device. For use with all pressurised (aerosol) inhalers.

Able Spacer (Clement Clarke International Ltd) | 1 device • NHS indicative price = £4.39 • Drug Tariff (Part IXa)

Able Spacer with medium mask (Clement Clarke International Ltd) | 1 device • NHS indicative price = £7.16 • Drug Tariff (Part IXa)

Able Spacer with small mask (Clement Clarke International Ltd) | 1 device • NHS indicative price = £7.16 • Drug Tariff (Part IXa)

AEROCAMBER PLUS®
Medium-volume device. For use with all pressurised (aerosol) inhalers.

AeroChamber Plus (GlaxoSmithKline UK Ltd) | 1 device • NHS indicative price = £4.79 • Drug Tariff (Part IXa)

AeroChamber Plus with adult mask (GlaxoSmithKline UK Ltd) | 1 device • NHS indicative price = £7.99 • Drug Tariff (Part IXa)

AeroChamber Plus with child mask (GlaxoSmithKline UK Ltd) | 1 device • NHS indicative price = £7.99 • Drug Tariff (Part IXa)
2 Allergic conditions

**Antihistamines, allergen immunotherapy and allergic emergencies**

**Antihistamines**

All antihistamines are of potential value in the treatment of nasal allergies, particularly seasonal allergic rhinitis (hayfever), and they may be of some value in vasomotor rhinitis. They reduce rhinorrhea and sneezing but are usually less effective for nasal congestion. Antihistamines are used topically in the eye, in the nose, and on the skin. Oral antihistamines are also of some value in preventing urticaria and are used to treat urticarial rashes, pruritus, and insect bites and stings; they are also used in drug allergies. Injections of chlorphenamine maleate p. 245 or promethazine hydrochloride p. 251 are used as an adjunct to adrenaline/epinephrine p. 136 in the emergency treatment of anaphylaxis and angioedema. Antihistamines (including cinnarizine p. 342, cyclizine p. 343, and promethazine teoclolate p. 252) may also have a role in nausea and vomiting. Buclizine is included as an anti-emetic in a preparation for migraine. Antihistamines may also have a role in occasional insomnia.

All older antihistamines cause sedation but alimemazine tartrate p. 243 and promethazine may be more sedating whereas chlorphenamine maleate and cyclizine may be less so. This sedating activity is sometimes used to manage the pruritus associated with some allergies. There is little evidence that any one of the older, 'sedating' antihistamines is superior to another and patients vary widely in their response.

Non-sedating antihistamines such as acrivastine p. 243, bilastine p. 244, cetirizine hydrochloride p. 244, desloratadine p. 247 (an active metabolite of loratadine p. 250), fexofenadine hydrochloride p. 247 (an active metabolite of terfenadine), levocetirizine hydrochloride p. 249 (an isomer of cetirizine hydrochloride), loratadine, and mizolastine cause less sedation and psychomotor impairment than the older antihistamines because they penetrate the blood brain barrier only to a slight extent.

**Allergen immunotherapy**

Immunotherapy using allergen vaccines containing house dust mite, animal dander (cat or dog), or extracts of grass and tree pollen can reduce symptoms of asthma and allergic rhinoconjunctivitis. A vaccine containing extracts of wasp and bee venom is used to reduce the risk of severe anaphylaxis and systemic reactions in individuals with hypersensitivity to wasp and bee stings. An oral preparation of grass pollen extract (Grazax\textsuperscript{®}) is also licensed for disease-modifying treatment of grass pollen–induced rhinitis and conjunctivitis. Those requiring immunotherapy must be referred to a hospital specialist for accurate diagnosis, assessment, and treatment.

Omalizumab p. 235 is a monoclonal antibody that binds to immunoglobulin E (IgE). It is used as additional therapy in individuals with proven IgE-mediated sensitivity to inhaled allergens, whose severe persistent allergic asthma cannot be controlled adequately with high dose inhaled corticosteroid together with a long-acting beta, agonist. Omalizumab should be initiated by physicians in specialist centres experienced in the treatment of severe persistent asthma. Omalizumab is also indicated as add-on therapy for the treatment of chronic spontaneous urticaria in patients who have had an inadequate response to H\textsubscript{1} antihistamine treatment.
Allergic emergencies

Anaphylaxis

Anaphylaxis is a severe, life-threatening, generalised or systemic hypersensitivity reaction. It is characterised by the rapid onset of respiratory and/or circulatory problems and is usually associated with skin and mucosal changes; prompt treatment is required. Patients with pre-existing asthma, especially poorly controlled asthma, are at particular risk of life-threatening reactions. Insect stings are a recognised risk (in particular wasp and bee stings). Latex and certain foods, including eggs, fish, cow’s milk protein, peanuts, sesame, shellfish, soy, and tree nuts may also precipitate anaphylaxis. Medicinal products particularly associated with anaphylaxis include blood products, vaccines, hyposensitising (allergen) preparations, antibacterials, aspirin and other NSAIDs, and neuromuscular blocking drugs. In the case of drugs, anaphylaxis is more likely after parenteral administration; resuscitation facilities must always be available for injections associated with special risk. Anaphylactic reactions may also be associated with additives and excipients in foods and medicines. Refined arachis (peanut) oil, which may be present in some medicinal products, is unlikely to cause an allergic reaction—nevertheless it is wise to check the full formula of preparations which may contain allergens.

Treatment of anaphylaxis

Adrenaline/epinephrine p. 196 provides physiological reversal of the immediate symptoms associated with hypersensitivity reactions such as anaphylaxis and angioedema.

First-line treatment includes:
- securing the airway, restoration of blood pressure (laying the patient flat and raising the legs, or in the recovery position if unconscious or nauseous and at risk of vomiting);
- administering adrenaline/epinephrine (by intramuscular injection in a dose of 500 micrograms (a dose of 300 micrograms may be appropriate for immediate self-administration); the dose should be repeated if necessary at 5-minute intervals according to blood pressure, pulse, and respiratory function. Patients receiving beta-blockers require special consideration;
- administering high-flow oxygen and intravenous fluids is also of primary importance;
- administering an antihistamine, such as chlorphenamine maleate, by slow intravenous injection or intramuscular injection is a useful adjunctive treatment, given after adrenaline.
- Administering an intravenous corticosteroid such as hydrocortisone p. 583 (preferably as sodium succinate) is of secondary value in the initial management of anaphylaxis because the onset of action is delayed for several hours, but should be given to prevent further deterioration in severely affected patients.

Continuing respiratory deterioration requires further treatment with bronchodilators including inhaled or intravenous salbutamol p. 222, inhaled ipratropium bromide p. 217, intravenous aminophylline p. 237, or intravenous magnesium sulfate p. 858 [unlicensed indication] (as for acute severe asthma); in addition to oxygen, assisted respiration and possibly emergency tracheotomy may be necessary.

When a patient is so ill that there is doubt about the adequacy of the circulation, the initial injection of adrenaline/epinephrine may need to be given as a dilute solution by the intravenous route.

Cardiopulmonary arrest may follow an anaphylactic reaction; resuscitation should be started immediately.

On discharge, patients should be considered for further treatment with an oral antihistamine and an oral corticosteroid for up to 3 days to reduce the risk of further reaction. Patients should be instructed to return to hospital if symptoms recur and to contact their general practitioner for follow-up.

Patients who are suspected of having had an anaphylactic reaction should be referred to a specialist for specific allergy diagnosis. Avoidance of the allergen is the principal treatment; if appropriate, an adrenaline/epinephrine auto-injector should be given for self-administration or a replacement supplied.

Intramuscular adrenaline (epinephrine)

The intramuscular route is the first choice route for the administration of adrenaline/epinephrine in the management of anaphylaxis. Adrenaline/epinephrine is best given as an intramuscular injection into the anterolateral aspect of the middle third of the thigh; it has a rapid onset of action after intramuscular administration and in the shocked patient its absorption from the intramuscular site is faster and more reliable than from the subcutaneous site.

Patients with severe allergy should be instructed in the self-administration of adrenaline/epinephrine by intramuscular injection.

Prompt injection of adrenaline/epinephrine is of paramount importance. The adrenaline/epinephrine doses recommended for the emergency treatment of anaphylaxis by appropriately trained healthcare professionals are based on the revised recommendations of the Working Group of the Resuscitation Council (UK).

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Volume of adrenaline 1 in 1000 (1 mg/mL)</th>
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<tbody>
<tr>
<td>Child under 6 years</td>
<td>150 micrograms</td>
<td>0.15 mL¹</td>
</tr>
<tr>
<td>Child 6-11 years</td>
<td>300 micrograms</td>
<td>0.3 mL</td>
</tr>
<tr>
<td>Child 12-17 years</td>
<td>500 micrograms</td>
<td>0.5 mL²</td>
</tr>
<tr>
<td>Adult</td>
<td>500 micrograms</td>
<td>0.5 mL</td>
</tr>
</tbody>
</table>

ª These doses may be repeated several times if necessary at 5-minute intervals according to blood pressure, pulse, and respiratory function.

¹ Use suitable syringe for measuring small volume
² 300 micrograms (0.3 mL) if child is small or prepubertal

intravenous adrenaline (epinephrine)

Intravenous adrenaline/epinephrine p. 196 should be given only by those experienced in its use, in a setting where patients can be carefully monitored.

When the patient is severely ill and there is real doubt about the adequacy of the circulation and absorption after intramuscular injection, adrenaline/epinephrine can be given by slow intravenous injection repeated according to response; if multiple doses are required, adrenaline/epinephrine should be given as a slow intravenous infusion stopping when a response has been obtained.

It is important that, where intramuscular injection might still succeed, time should not be wasted seeking intravenous access.

The intravenous route is also used for cardiac resuscitation.

Angioedema

Angioedema is dangerous if laryngeal oedema is present. In this circumstance adrenaline/epinephrine injection and oxygen should be given as described under Anaphylaxis; antihistamines and corticosteroids should also be given. Tracheal intubation may be necessary.
Hereditary angioedema

The treatment of hereditary angioedema should be under specialist supervision. Unlike allergic angioedema, adrenaline/epinephrine, corticosteroids, and antihistamines should not be used for the treatment of acute attacks, including attacks involving laryngeal oedema, as they are ineffective and may delay appropriate treatment—intubation may be necessary. The administration of C1-esterase inhibitor p. 255, an endogenous complement blocker derived from human plasma, (in fresh frozen plasma or in partially purified form) can terminate acute attacks of hereditary angioedema; it can also be used for short-term prophylaxis before dental, medical or surgical procedures. Conestat alfa p. 255 and icatibant p. 255 are licensed for the treatment of acute attacks of hereditary angioedema in adults with C1-esterase inhibitor deficiency.

Tranexamic acid p. 95 and danazol p. 636 [unlicensed indication] are used for short-term and long-term prophylaxis of hereditary angioedema. Short-term prophylaxis with tranexamic acid or danazol is started several days before planned procedures (e.g. dental work) and continued for 2–5 days afterwards. Danazol should be avoided in children because of its androgenic effects.

ANTIHISTAMINES

Acrivastine

INDICATIONS AND DOSE

Symptomatic relief of allergy such as hayfever, chronic idiopathic urticaria

BY MOUTH

- Child 12–17 years: 8 mg 3 times a day
- Adult: 8 mg 3 times a day

- CONTRA-INDICATIONS Avoid in Acute porphyrias p. 864 (some antihistamines are thought to be safe) - elderly
- CAUTIONS Epididymitis
- INTERACTIONS - Appendix 1 (antihistamines). Sedative antihistamine interactions apply to a lesser extent to the non-sedating antihistamines.
- SIDE-EFFECTS
  - Uncommon Antimuscarinic effects - gastro-intestinal disturbances - headache - psychomotor impairment
  - Rare Anaphylaxis - angioedema - angle-closure glaucoma (in adults) - arrhythmias - blood disorders - bronchospasm - confusion - convulsions - depression - dizziness - extrapyramidal effects - hypersensitivity reactions - hypotension - liver dysfunction - palpitation - photosensitivity reactions - rashes - sleep disturbances - tremor - Frequency not known Blurred vision - drowsiness - dry mouth - urinary retention

SIDE-EFFECTS, FURTHER INFORMATION

Non-sedating antihistamines such as acrivastine cause less sedation and psychomotor impairment than the older antihistamines because they penetrate the blood brain barrier only to a slight extent. If drowsiness occurs, it may diminish after a few days of treatment. Children and the elderly are more susceptible to side-effects.

- ALLERGY AND CROSS-SENSITIVITY Contraindicated if history of hypersensitivity to triprolidine.
- PREGNANCY Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity.
- BREASTFEEDING Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

- RENAL IMPAIRMENT Avoid in severe impairment.
- PATIENT AND CARER ADVICE Although drowsiness is rare, nevertheless patients should be advised that it can occur and may affect performance of skilled tasks (e.g. cycling or driving); excess alcohol should be avoided.
- MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Capsule

- Benadryl Allergy Relief (McNeil Products Ltd)
  Acrivastine 8 mg Benadryl Allergy Relief 8mg capsules
  12 capsule £2.91 OT price £2.91 | 24 capsule £4.95

Alimemazine tartrate (Trimepazine tartrate)

INDICATIONS AND DOSE

Urticaria | Pruritus

BY MOUTH

- Child 2–4 years: 2.5 mg 3–4 times a day
- Child 5–11 years: 5 mg 3–4 times a day
- Child 12–17 years: 10 mg 2–3 times a day, in severe cases up to maximum daily dose has been used; maximum 100 mg per day
- Adult: 10 mg 2–3 times a day, in severe cases up to maximum daily dose has been used; maximum 100 mg per day
- Elderly: 10 mg 1–2 times a day

- CONTRA-INDICATIONS Epilepsy - hepatic dysfunction - history of narrow angle glaucoma - hypothyroidism - many antihistamines should be avoided in Acute porphyrias p. 864 but alimemazine is thought to be safe - myasthenia gravis - parkinson’s disease - phaeochromocytoma - prostatic hypertrophy - renal dysfunction
- CAUTIONS Cardiovascular diseases (due to tachycardia-inducing and hypotensive effects of phenothiazines) - elderly - exposure to sunlight should be avoided during treatment with high doses - pyloroduodenal obstruction - urinary retention - volume depleted patients who are more susceptible to orthostatic hypotension

- INTERACTIONS - Appendix 1 (antihistamines).
- SIDE-EFFECTS
  - Rare Anaphylaxis - angioedema - bronchospasm - hypersensitivity reactions
  - Frequency not known Acute dystonia - agitation - agranulocytosis - akathisia - akinesia - angle-closure glaucoma - anti-muscarinic effects - arrhythmias (may be predisposed by hypokalaemia and cardiac disease) - blurred vision - contact sensitisation - convulsions - drowsiness - dry mouth - dyskinesia - gastro-intestinal disturbances - headache - hyperprolactinamia - hypotension - insomnia - jaundice - leukopenia (on prolonged high dose) - nasal stuffiness - neuroleptic malignant syndrome - ocular changes - paller (in children) - paradoxical excitement - parkinsonism - photosensitivity - postural hypotension (in elderly) - postural hypotension (in volume depletion) - rashes - respiratory depression - rigidity - tardive dyskinesia (usually after prolonged high doses) - tremor - urinary retention

SIDE-EFFECTS, FURTHER INFORMATION

Patients on high dosage may develop photosensitivity and should avoid exposure to direct sunlight. Children and the elderly are more susceptible to side-effects. Drowsiness is a significant side-effect with most of the older antihistamines although paradoxical stimulation may occur rarely, especially with high doses or in children and the elderly. Drowsiness may diminish after a few days.
of treatment and is considerably less of a problem with the newer antihistamines.

- **PREGNANCY** Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity. Use in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor.

- **BREAST FEEDING** Avoid in severe liver disease—increased risk of coma.

- **INTERACTIONS** Avoid in Acute porphyrias.

- **CAUTIONS** Avoid in severe liver disease.

### Bilastine

**INDICATIONS AND DOSE**
Symptomatic relief of allergic rhinoconjunctivitis and urticaria

**BY MOUTH**
- Child 12–17 years: 20 mg once daily
- Adult: 20 mg once daily

**CONTRA-INDICATIONS** Avoid in Acute porphyrias p. 864 (some antihistamines are thought to be safe)

**CAUTIONS** Epilepsy

**INTERACTIONS** → Appendix 1 (antihistamines). Sedative antihistamine interactions apply to a lesser extent to the non-sedating antihistamines.

**SIDE-EFFECTS**
- **Common or very common** Headache - malaise
- **Uncommon** Abdominal pain - anxiety - diarrhoea - dizziness - dyspnoea - gastritis - increased appetite - insomnia - oral herpes - prolongation of the QT interval - pyrexia - thirst - tinnitus - vertigo - weight gain

**SIDE-EFFECTS, FURTHER INFORMATION**
Children and the elderly are more susceptible to side-effects. Non-sedating antihistamines such as bilastine cause less sedation and psychomotor impairment than the older antihistamines because they penetrate the blood brain barrier only to a slight extent.

- **PREGNANCY** Avoid—limited information available. Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity.

- **BREAST FEEDING** Avoid—no information available. Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

**DIRECTIONS FOR ADMINISTRATION** Take tablet 1 hour before or 2 hours after food or fruit juice.

**PATIENT AND CARER ADVICE** Although drowsiness is rare, nevertheless patients should be advised that it can occur and may affect performance of skilled tasks (e.g. cycling or driving); alcohol should be avoided. Patients or carers should be given advice on how to administer bilastine tablets.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

<table>
<thead>
<tr>
<th><strong>ALIMEZINE TARTRATE (Non-proprietary)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alimemazine tartrate 10 mg</strong> Alimemazine 10mg tablets</td>
</tr>
</tbody>
</table>

**Oral solution**

<table>
<thead>
<tr>
<th><strong>ALIMEZINE TARTRATE (Non-proprietary)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alimemazine tartrate 1.5 mg per 1 ml</strong> Alimemazine 7.5mg/5ml oral solution</td>
</tr>
<tr>
<td><strong>Alimemazine tartrate 6 mg per 1 ml</strong> Alimemazine 30mg/5ml oral solution</td>
</tr>
</tbody>
</table>

**Cetirizine hydrochloride**

**INDICATIONS AND DOSE**
Symptomatic relief of allergy such as hay fever, chronic idiopathic urticaria, atopic dermatitis

**BY MOUTH**
- Child 2–5 years: 2.5 mg twice daily
- Child 6–11 years: 5 mg twice daily
- Child 12–17 years: 10 mg once daily
- Adult: 10 mg once daily

**CONTRA-INDICATIONS** Avoid in Acute porphyrias p. 864 (some antihistamines are thought to be safe)

**CAUTIONS** Epilepsy

**INTERACTIONS** → Appendix 1 (antihistamines). Sedative antihistamine interactions apply to a lesser extent to the non-sedating antihistamines.

**SIDE-EFFECTS**
- **Uncommon** Antimuscarinic effects - blurred vision - dry mouth - gastro-intestinal disturbances - headache - psychomotor impairment - urinary retention - photosensitivity reactions
- **Rare** Anaphylaxis - angioedema - angle-closure glaucoma (in adults) - arrhythmias - blood disorders - bronchospasm - confusion - convulsions - depression - dizziness - extrapyramidal effects - hypersensitivity reactions - hypotension - liver dysfunction - palpitation - palpitations - photosensitivity reactions - rashes - sleep disturbances - tremor
- **Frequency not known** Drowsiness

**SIDE-EFFECTS, FURTHER INFORMATION**
Non-sedating antihistamines such as cetirizine cause less sedation and psychomotor impairment than the older antihistamines because they penetrate the blood brain barrier only to a slight extent. If drowsiness occurs, it may diminish after a few days of treatment. Children and the elderly are more susceptible to side-effects.

- **PREGNANCY** Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity.

- **BREAST FEEDING** Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.
**Chlorphenamine maleate (Chlorpheniramine maleate)**

**INDICATIONS AND DOSE**

Symptomatic relief of allergy such as hay fever, urticaria, food allergy, drug reactions / Relief of itch associated with chickenpox

**BY MOUTH**

- **Child 12–23 months:** 1 mg twice daily
- **Child 2–5 years:** 1 mg every 4–6 hours; maximum 6 mg per day
- **Child 6–11 years:** 2 mg every 4–6 hours; maximum 12 mg per day
- **Child 12–17 years:** 4 mg every 4–6 hours; maximum 24 mg per day
- **Adult:** 4 mg every 4–6 hours; maximum 24 mg per day
- **Elderly:** 4 mg every 4–6 hours; maximum 12 mg per day

**BY INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INJECTION**

- **Child 1–5 years:** 250 micrograms/kg (max. per dose 2.5 mg), repeated if necessary; maximum 4 doses per day
- **Child 6 months–5 years:** 2.5 mg, repeated if necessary; maximum 4 doses per day
- **Child 6–11 years:** 5 mg, repeated if necessary; maximum 4 doses per day

**PROFESSION SPECIFIC INFORMATION**

**Dental practitioners’ formulary**

Cetirizine Tablets 10 mg may be prescribed. Cetirizine Oral Solution 5 mg/5 mL may be prescribed.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **CETIRIZINE HYDROCHLORIDE (Non-proprietary)**
  - Cetirizine hydrochloride 10 mg: Cetirizine 10mg tablets
  - 30 tablet [P] £1.40 | 30 tablet [PS] £1.07 DT price = £1.07
  - 30 tablet [P]: £8.29 DT price = £1.07
  - Brands may include Pollenshield, Zirtek

**Capsule**

- **Benadryl Allergy (McNeil Products Ltd)**
  - Cetirizine hydrochloride 10 mg: Benadryl Allergy Liquid Release 10mg capsules
  - 7 capsule [PS] £2.91 DT price = £2.91

**Oral solution**

**EXCIPIENTS:** may contain Propylene glycol

- **CETIRIZINE HYDROCHLORIDE (Non-proprietary)**
  - Cetirizine hydrochloride 1 mg per 1 ml: Cetirizine 1mg/ml oral solution sugar free (sugar-free)
  - 200 ml [P]: no price available DT price = £1.79 (sugar-free)
  - 200 ml [PS]: £3.50 DT price = £1.79
  - Brands may include Benadryl Allergy; Zirtek

**CONTRA-INDICATIONS**

Many antihistamines should be avoided in Acute porphyrias p. 864 but chlorphenamine is thought to be safe

**CAUTIONS**

- Epilepsy; prostatic hypertrophy; pyloro-duodenal obstruction; susceptibility to angle-closure glaucoma; urinary retention

**INTERACTIONS**

- Appendix 1 (antihistamines).

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- Common or very common: Blurred vision; dry mouth; gastro-intestinal disturbances; headache; psychomotor impairment; urinary retention

- Rare: Anaphylaxis; angioedema; angle-closure glaucoma (in adults) - arrhythmias; bronchospasm; confusion; convulsions; depression; dizziness; extrapyramidal effects; hypersensitivity reactions; hypotension; liver dysfunction; palpitation; photosensitivity reactions; sleep disturbances; tremor

- Frequency not known: Antimuscarinic effects; blood disorders; exfoliative dermatitis; rash; tinnitus

**SPECIFIC SIDE-EFFECTS**

- **With intramuscular use** CNS stimulation - irritant effects - transient hypotension

- **With intravenous use** CNS stimulation - irritant effects - transient hypotension

**SIDE-EFFECTS, FURTHER INFORMATION**

Children and the elderly are more susceptible to side-effects.

Drowsiness is a significant side-effect with most of the older antihistamines although paradoxical stimulation may occur rarely, especially with high doses or in children and the elderly. Drowsiness may diminish after a few days of treatment and is considerably less of a problem with the newer antihistamines.

**PREGNANCY**

Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity. Use in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor.

**BREAST FEEDING**

Most antihistamines are present in breast milk in varying amounts; although not known to be

**UNLICENSED USE**

Tablets not licensed for use in children under 6 years.

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**Chlorphenamine maleate**

**MEDICINAL FORMS**

- **In adults** Use half normal dose if eGFR 30–50 mL/minute/1.73 m². Use half normal dose and reduce dose frequency to alternate days if eGFR 10–30 mL/minute/1.73 m². Avoid if eGFR less than 10 mL/minute/1.73 m².
- In children Use half normal dose if estimated glomerular filtration rate 30–50 mL/minute/1.73 m². Use half normal dose and reduce dose frequency to alternate days if estimated glomerular filtration rate 10–30 mL/minute/1.73 m². Avoid if estimated glomerular filtration rate less than 10 mL/minute/1.73 m².

**PATIENT AND CARER ADVICE**

Although drowsiness is rare, nevertheless patients should be advised that it can occur and may affect performance of skilled tasks (e.g. cycling or driving); alcohol should be avoided.

Medicines for Children leaflet: Cetirizine hydrochloride for hay fever www.medicinesforchildren.org.uk/cetirizine-hay-fever-0

**CONTRA-INDICATIONS**

- For children under 6 years:
- Chlorphenamine maleate may cause drowsiness and is considerably less of a problem with the newer antihistamines.

**CAUTIONS**

- For children under 6 years:
- Avoid if estimated glomerular filtration rate less than 10 mL/minute/1.73 m².
- Use half normal dose and reduce dose frequency to alternate days if estimated glomerular filtration rate less than 10 mL/minute/1.73 m².

**INTERACTIONS**

- Appendix 1 (antihistamines).

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- Common or very common: Blurred vision; dry mouth; gastro-intestinal disturbances; headache; psychomotor impairment; urinary retention

- Rare: Anaphylaxis; angioedema; angle-closure glaucoma (in adults) - arrhythmias; bronchospasm; confusion; convulsions; depression; dizziness; extrapyramidal effects; hypersensitivity reactions; hypotension; liver dysfunction; palpitation; photosensitivity reactions; sleep disturbances; tremor

- Frequency not known: Antimuscarinic effects; blood disorders; exfoliative dermatitis; rash; tinnitus

**SPECIFIC SIDE-EFFECTS**

- **With intramuscular use** CNS stimulation - irritant effects - transient hypotension

- **With intravenous use** CNS stimulation - irritant effects - transient hypotension

**SIDE-EFFECTS, FURTHER INFORMATION**

Children and the elderly are more susceptible to side-effects.

Drowsiness is a significant side-effect with most of the older antihistamines although paradoxical stimulation may occur rarely, especially with high doses or in children and the elderly. Drowsiness may diminish after a few days of treatment and is considerably less of a problem with the newer antihistamines.

**PREGNANCY**

Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity. Use in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor.

**BREAST FEEDING**

Most antihistamines are present in breast milk in varying amounts; although not known to be
harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

- **HEPATIC IMPAIRMENT** Avoid in severe liver disease—increased risk of coma.

- **DIRECTIONS FOR ADMINISTRATION**
  - In children, for intravenous injection, give over 1 minute; if small dose required, dilute with Sodium Chloride 0.9%.

- **PATIENT AND CARER ADVICE** Drowsiness may affect performance of skilled tasks (e.g. cycling or driving); sedating effects enhanced by alcohol.

  - **Cautions**
    - Medicines for Children leaflet: Chlorphenamine maleate for allergy symptoms www.medicinesforchildren.org.uk/chlorphenamine-maleate-allergy-symptoms-0

- **PROFESSIONAL SPECIFIC INFORMATION**
  - Dental practitioners’ formulary
  - Chlorphenamine tablets may be prescribed. Chlorphenamine oral solution may be prescribed.

- **EXCEPTIONS TO LEGAL CATEGORY** Prescription only

  - **Contra-Indications** Avoid in Acute porphyrias.

  - **Pregnancy** Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity. Use in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor.

  - **Breast Feeding** Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

  - **Hepatic Impairment** Avoid in severe liver disease—increased risk of coma.

- **PATIENT AND CARER ADVICE** Drowsiness may affect performance of skilled tasks (e.g. driving); sedating effects enhanced by alcohol.

- **MEDICINAL FORMS**

  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

  - **Tablet**
    - CAUTIONARY AND ADVISORY LABELS 2
    - CHLORPHENAMINE MALEATE (Non-proprietary)
      - Chlorphenamine maleate 4 mg
      - 28 tablet [£1.38 DT price = £0.96] 30 tablet [no price available]
      - Brands may include Hayfev; Piriton; Pollenase (Chlorphenamine).

  - **Oral solution**
    - CAUTIONARY AND ADVISORY LABELS 2
    - CHLORPHENAMINE MALEATE (Non-proprietary)
      - Chlorphenamine maleate 400 microgram per l ml
      - Chlorphenamine 2mg/5ml oral solution sugar free (sugar-free) 150 ml [£2.85 DT price = £1.87]
      - Brands may include Hayfev; Piriton

  - **Solution for injection**
    - **CHLORPHENAMINE MALEATE (Non-proprietary)**
      - Chlorphenamine maleate 10 mg per l ml
      - Chlorphenamine 10mg/1ml solution for injection ampoules 5 ampoule [no price available] £22.42-22.50 DT price = £22.42

- **MEDICINAL FORMS**

  - There can be variation in the licensing of different medicines containing the same drug.

  - **Tablet**
    - CAUTIONARY AND ADVISORY LABELS 2
    - Tavegil (Novartis Consumer Health UK Ltd)
      - Clemastine (as Clemastine hydrofumarate) 1 mg
      - Tavegil 1mg tablets 60 tablet [£5.00 DT price = £5.00]

- **Clemastine**

  - **INDICATIONS AND DOSE** Symptomatic relief of allergy such as hay fever, urticaria Pruritus

  - **By mouth**
    - Adult: 4 mg 3 times a day, usual dose 4–20 mg daily; maximum 32 mg per day

  - **Contra-Indications** Avoid in Acute porphyrias p. 864 (some antihistamines are thought to be safe)

  - **Caution** Epilepsy, prostatic hypertrophy, pyloroduodenal obstruction, susceptibility to angle-closure glaucoma, urinary retention

  - **Interactions** → Appendix 1 (antihistamines).

  - **Side-Effects**
    - **Rare** Anaphylaxis, angioedema, angle-closure glaucoma, arrhythmias, blood disorders, bronchospasm, confusion, convulsions, depression, dizziness, extrapyramidal effects, hypersensitivity reactions, hypotension, liver dysfunction, palpitation, photosensitivity reactions, rash, sleep disturbances, tremor

  - **Frequency not known** Antimuscarinic effects, blurred vision, drowsiness, dry mouth, gastro-intestinal disturbances, headache, psychomotor impairment, urinary retention

  - **Side-Effects, Further Information** Elderly are more susceptible to side-effects.

  - **Pregnancy** Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity. Use in the latter part of the

- **Cyproheptadine hydrochloride**

  - **INDICATIONS AND DOSE** Symptomatic relief of allergy such as hay fever, urticaria Pruritus

  - **By mouth**
    - Adult: 1 mg twice daily, increased if necessary up to 6 mg daily

  - **Contra-Indications** Avoid in Acute porphyrias p. 864 (some antihistamines are thought to be safe)

  - **Caution** Epilepsy, prostatic hypertrophy, pyloroduodenal obstruction, susceptibility to angle-closure glaucoma, urinary retention

  - **Interactions** → Appendix 1 (antihistamines).

  - **Side-Effects**
    - **Rare** Anaphylaxis, angioedema, angle-closure glaucoma, arrhythmias, blood disorders, bronchospasm, confusion, convulsions, depression, dizziness, extrapyramidal effects, hypersensitivity reactions, hypotension, liver dysfunction, palpitation, photosensitivity reactions, rash, sleep disturbances, tremor

  - **Frequency not known** Antimuscarinic effects, blurred vision, drowsiness, dry mouth, gastro-intestinal disturbances, headache, psychomotor impairment, urinary retention

  - **Side-Effects, Further Information** Elderly are more susceptible to side-effects.

  - **Pregnancy** Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity. Use in the latter part of the
third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor.  

- **BREAST FEEDING** Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.  

- **HEPATIC IMPAIRMENT** Avoid in severe liver disease—increased risk of coma.  

- **PATIENT AND CARER ADVICE** Drowsiness may affect performance of skilled tasks (e.g. driving); sedating effects enhanced by alcohol.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension  

**Tablet**  
- **CAUTIONARY AND ADVISORY LABELS**  
  - Periactin (Auden McKenzie (Pharma Division) Ltd)  
  - Cypheptadine hydrochloride 4 mg Periactin 4mg tablets  
  - 30 tablet [P] £5.99 DT price + £5.99

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**Desloratadine**

**INDICATIONS AND DOSE**  
Symptomatic relief of allergy such as allergic rhinitis, urticaria, chronic idiopathic urticaria

**BY MOUTH**  
- Child 1-5 years: 1.25 mg once daily  
- Child 6-11 years: 2.5 mg once daily  
- Child 12-17 years: 5 mg once daily  
- Adult: 5 mg once daily

**PHARMACOKINETICS**  
Desloratadine is a metabolite of loratadine.

- **CAUTIONS** Acute porphyrias p. 864 - epilepsy
- **INTERACTIONS** → Appendix 1 (antihistamines).  
  Sedative antihistamine interactions apply to a lesser extent to the non-sedating antihistamines.

- **SIDE-EFFECTS**
  - **Uncommon** Antimuscarinic effects - blurred vision - dry mouth - gastro-intestinal disturbances - headache - psychomotor impairment - urinary retention
  - **Rare** Anaphylaxis - angioedema - angle-closure glaucoma (in adults) - arrhythmias - blood disorders - bronchospasm - confusion - convulsions - depression - dizziness - extrapyramidal effects - hypersensitivity reactions - hypotension - liver dysfunction - myalgia - palpitation - photosensitivity reactions - rashes - sleep disturbances - tremor
  - **Very rare** Hallucinations
  - **Frequency not known** Drowsiness

**SIDE-EFFECTS, FURTHER INFORMATION**  
Children and the elderly are more susceptible to side-effects.  
Non-sedating antihistamines such as desloratadine cause less sedation and psychomotor impairment than the older antihistamines because they penetrate the blood brain barrier only to a slight extent.  
If drowsiness occurs, it may diminish after a few days of treatment.

- **ALLERGY AND CROSS-SENSITIVITY** Contraindicated if history of hypersensitivity to loratadine.
- **PREGNANCY** Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity.
- **BREAST FEEDING** Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

- **RENAL IMPAIRMENT** Use with caution in severe impairment.
- **PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid formulations may include bubblegum.
- **PATIENT AND CARER ADVICE** Although drowsiness is rare, nevertheless patients should be advised that it can occur and may affect performance of skilled tasks (e.g. driving or cycling); excess alcohol should be avoided.
- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.  

**Tablet**

- **DESLORATADINE (Non-proprietary)**
  - Desloratadine 5 mg Desloratadine 5mg tablets | 30 tablet [P] £6.77 DT price + £6.77
  - Neoclarityn (Merck Sharp & Dohme Ltd)
  - Desloratadine 5 mg Neoclarityn 5mg tablets | 30 tablet [P] £6.77 DT price + £6.77

**Oral solution**

- **EXCIPIENTS:** May contain Propylene glycol, sorbitol  
- **DESLORATADINE (Non-proprietary)**
  - Desloratadine 500 microgram per 1 ml Desloratadine 2.5mg/5ml oral solution sugar free (sugar-free) | 100 ml [P] no price available
  - Neoclarityn (Merck Sharp & Dohme Ltd)
  - Desloratadine 500 microgram per 1 ml Neoclarityn 2.5mg/5ml oral solution (sugar-free) | 100 ml [P] £6.77 (sugar-free) | 150 ml [P] £10.15 DT price + £10.15

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**Fexofenadine hydrochloride**

**INDICATIONS AND DOSE**  
Symptomatic relief of seasonal allergic rhinitis

**BY MOUTH**  
- Child 6-11 years: 30 mg twice daily  
- Child 12-17 years: 120 mg once daily  
- Adult: 120 mg once daily

**Symptomatic relief of chronic idiopathic urticaria**

**BY MOUTH**  
- Child 12-17 years: 180 mg once daily  
- Adult: 180 mg once daily

**PHARMACOKINETICS**  
Fexofenadine is a metabolite of terfenadine.

- **CAUTIONS** Epilepsy
- **INTERACTIONS** → Appendix 1 (antihistamines).  
  Sedative antihistamine interactions apply to a lesser extent to the non-sedating antihistamines.

- **SIDE-EFFECTS**
  - **Uncommon** Antimuscarinic effects - blurred vision - dry mouth - gastro-intestinal disturbances - headache - psychomotor impairment - urinary retention
  - **Rare** Anaphylaxis - angioedema - angle-closure glaucoma (in adults) - arrhythmias - blood disorders - bronchospasm - confusion - convulsions - depression - dizziness - extrapyramidal effects - hypersensitivity reactions - hypotension - liver dysfunction - myalgia - palpitation - photosensitivity reactions - rashes - sleep disturbances - tremor
  - **Frequency not known** Drowsiness

**SIDE-EFFECTS, FURTHER INFORMATION**  
Children and the elderly are more susceptible to side-effects.  
Non-sedating antihistamines such as fexofenadine cause less sedation and psychomotor impairment than the older antihistamines because they penetrate the blood brain barrier only to a slight extent.  
If drowsiness occurs, it may diminish after a few days of treatment.

- **PREGNANCY** Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity.
Hydroxyzine hydrochloride

INDICATIONS AND DOSE
Pruritus
BY MOUTH
- Child 1-5 years: Initially 5–15 mg once daily, dose to be taken at night, increased if necessary to 50 mg daily in 3–4 divided doses
- Child 6-11 years: Initially 15–25 mg once daily, dose to be taken at night, increased if necessary to 50–100 mg daily in 3–4 divided doses
- Child 12-17 years: Initially 25 mg once daily, dose to be taken at night, increased if necessary to 100 mg daily in 3–4 divided doses
- Adult: Initially 25 mg daily, dose to be taken at night; increased if necessary to 25 mg 3–4 times a day

Important safety information
HYDROXYZINE: RISK OF QT-INTERVAL PROLONGATION AND TORSADE DE POINTE (APRIL 2015)
Following concerns of heart rhythm abnormalities, the safety and efficacy of hydroxyzine has been reviewed by the European Medicines Agency. The review concludes that hydroxyzine is associated with a small risk of QT-interval prolongation and Torsade de Pointes; these events are most likely to occur in patients who have risk factors for QT prolongation, e.g. concomitant use of drugs that prolong the QT interval, cardiovascular disease, family history of sudden cardiac death, significant electrolyte imbalance (low plasma-potassium or plasma-magnesium concentrations), or significant bradycardia.
To minimise the risk of such adverse effects, the following dose restrictions have been made and new cautions and contra-indications added:
- Hydroxyzine is contra-indicated in patients with prolonged QT-interval or who have risk factors for QT-interval prolongation;
- Avoid use in the elderly due to increased susceptibility to the side-effects of hydroxyzine;
- Consider the risks of QT-interval prolongation and Torsade de Pointes before prescribing to patients taking drugs that lower heart rate or plasma-potassium concentration;
- In adults, the maximum daily dose is 100 mg;
- In the elderly, the maximum daily dose is 50 mg (if use of hydroxyzine cannot be avoided);
- In children with body-weight up to 40 kg, the maximum daily dose is 2 mg/kg;
- The lowest effective dose for the shortest period of time should be prescribed.

CONTRA-INDICATIONS
Avoid in Acute porphyrias p. 864 (some antihistamines are thought to be safe)

CAUTIONS
Epilepsy - prostatic hypertrophy - pyloroduodenal obstruction - susceptibility to angle-closure glaucoma - susceptibility to QT interval prolongation - urination retention

INTERACTIONS • Appendix 1 (antihistamines).

SIDE-EFFECTS
> Rare Anaphylaxis - angioedema - angle-closure glaucoma - arrhythmias - blood disorders - bronchospasm - confusion - convulsions - depression - dizziness - extrapyramidal effects - hypersensitivity reactions - hypotension - liver dysfunction - palpitation - photosensitivity reactions - rashes - sleep disturbances - tremor
> Frequency not known Antimuscarinic effects - blurring vision - drowsiness - dry mouth - gastro-intestinal disturbances - headache - psychomotor impairment - urination retention

SIDE-EFFECTS, FURTHER INFORMATION
Children and the elderly are more susceptible to side-effects.
Drowsiness is a significant side-effect with most of the older antihistamines although paradoxical stimulation may occur rarely, especially with high doses or in children and the elderly. Drowsiness may diminish after a few days of treatment and is considerably less of a problem with the newer antihistamines.

PREGNANCY
Most manufacturers of antihistamines advise avoiding their use during pregnancy; toxicity in animal studies with higher doses. Use in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor.

BREAST FEEDING
Manufacturer advises avoid. Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

HEPATIC IMPAIRMENT
Reduce daily dose by one-third. Avoid in severe liver disease—increased risk of coma.

RENAL IMPAIRMENT
Reduce daily dose by half.

PATIENT AND CARER ADVICE
Drowsiness may affect performance of skilled tasks (e.g. cycling or driving); sedating effects enhanced by alcohol.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

Table

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Dose</th>
<th>Brand Name</th>
<th>Manufacturer</th>
</tr>
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<tbody>
<tr>
<td>Frequency not known</td>
<td>25 mg</td>
<td>Tab 30mg tablets</td>
<td>Fexofenadine (Non-proprietary)</td>
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<tr>
<td>Frequency not known</td>
<td>50 mg</td>
<td>Tab 50mg tablets</td>
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<td>100 mg</td>
<td>Tab 100mg tablets</td>
<td>Fexofenadine (Non-proprietary)</td>
</tr>
</tbody>
</table>

Tablet

| Frequency not known | 25 mg | Tab 25mg tablets | Fexofenadine (Non-proprietary) |
| Frequency not known | 50 mg | Tab 50mg tablets | Fexofenadine (Non-proprietary) |
| Frequency not known | 100 mg | Tab 100mg tablets | Fexofenadine (Non-proprietary) |

Syrup

| Frequency not known | 25 mg | 20 ml | Fexofenadine (Non-proprietary) |
| Frequency not known | 50 mg | 40 ml | Fexofenadine (Non-proprietary) |
| Frequency not known | 100 mg | 60 ml | Fexofenadine (Non-proprietary) |

**GLOBAL SERVICES**
Ketotifen

INDICATIONS AND DOSE
Allergic rhinitis
BY MOUTH
- Child 3-17 years: 1 mg twice daily
- Adult: 1 mg twice daily, increased if necessary to 2 mg twice daily, to be taken with food

Allergic rhinitis in readily sedated patients
BY MOUTH
- Adult: Initially 0.5–1 mg once daily, dose to be taken at night

CONTRA-INDICATIONS Avoid in Acute porphyrias p. 864 (some antihistamines are thought to be safe).

CAUTIONS Epilepsy - prostatic hypertrophy - pyloroduodenal obstruction - susceptibility to angle-closure glaucoma - urinary retention

INTERACTIONS Appendix 1 (antihistamines).
Sedative antihistamine interactions apply to a lesser extent to the non-sedating antihistamines.

SIDE-EFFECTS
- Common or very common Excitation (in adults) - irritability - nervousness
- Uncommon Cystitis
- Rare Weight gain
- Very rare Stevens-Johnson syndrome


SIDE-EFFECTS, FURTHER INFORMATION
Children and the elderly are even more susceptible to side effects.
Drowsiness is a significant side-effect with most of the older antihistamines although paradoxical stimulation may occur rarely, especially with high doses or in children and the elderly. Drowsiness may diminish after a few days of treatment and is considerably less of a problem with the newer antihistamines.

PREGNANCY Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity. Use in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitation, and tremor.

BREAST FEEDING Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

HEPATIC IMPAIRMENT Avoid in severe liver disease—increased risk of coma.

PATIENT AND CARER ADVICE Drowsiness may affect performance of skilled tasks (e.g. driving or cycling); sedating effects enhanced by alcohol.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
Tablet

Levocetirizine hydrochloride

INDICATIONS AND DOSE
Symptomatic relief of allergy such as hay fever, urticaria
BY MOUTH
- Child 6-17 years: 5 mg once daily
- Adult: 5 mg once daily

PHARMACOKINETICS
Levocetirizine is an isomer of cetirizine.

CONTRA-INDICATIONS Avoid in Acute porphyrias p. 864 (some antihistamines are thought to be safe).

CAUTIONS Epilepsy

INTERACTIONS Appendix 1 (antihistamines).
Sedative antihistamine interactions apply to a lesser extent to the non-sedating antihistamines.

SIDE-EFFECTS
- Uncommon Antimuscarinic effects - blurred vision - dry mouth - gastro-intestinal disturbances - headache - psychomotor impairment - urinary retention
- Rare Anaphylaxis - angioedema - angle-closure glaucoma (in adults) - arrhythmias - blood disorders - bronchospasm - confusion - convulsions - depression - dizziness - extrapyramidal effects - hypersensitivity reactions - hypotension - liver dysfunction - palpitation - photosensitivity reactions - rashes - sleep disturbances - tremor
- Very rare Weight gain
- Frequency not known Drowsiness

SIDE-EFFECTS, FURTHER INFORMATION
Children and the elderly are more susceptible to side-effects. Non-sedating antihistamines such as levocetirizine cause less sedation and psychomotor impairment than the older antihistamines because they penetrate the blood brain barrier only to a slight extent. If drowsiness occurs, it may diminish after a few days of treatment.

PREGNANCY Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity.

BREAST FEEDING Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

RENAL IMPAIRMENT
- In adults 5 mg on alternate days if eGFR 30–50 mL/minute/1.73 m². 5 mg every 3 days if eGFR 10–30 mL/minute/1.73 m². Avoid if eGFR less than 10 mL/minute/1.73 m².
- In children Reduce dose frequency to alternate days if estimated glomerular filtration rate 30–50 mL/minute/1.73 m². Reduce dose frequency to every 3 days if estimated glomerular filtration rate 10–30 mL/minute/1.73 m². Avoid if estimated glomerular filtration rate less than 10 mL/minute/1.73 m².

PATIENT AND CARER ADVICE Although drowsiness is rare, nevertheless patients should be advised that it can occur and may affect performance of skilled tasks (e.g. cycling or driving); alcohol should be avoided.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
**Loratadine**

**INDICATIONS AND DOSE**
Symptomatic relief of allergy such as hay fever, chronic idiopathic urticaria  
**BY MOUTH**  
- Child 2-11 years (body-weight up to 30 kg): 5 mg once daily  
- Child 2-11 years (body-weight 30 kg and above): 10 mg once daily  
- Child 12-17 years: 10 mg once daily  
- Adult: 10 mg once daily

- **CAUTIONS** Acute porphyria p. 864 • epilepsy
- **INTERACTIONS** → Appendix 1 (antihistamines). Sedative antihistamine interactions apply to a lesser extent to the non-sedating antihistamines used for topical action (including inhalation).
- **SIDE-EFFECTS**  
  - **Common** Antimuscarinic effects - blurred vision - dry mouth - gastro-intestinal disturbances - Headache - psychomotor impairment - urinary retention  
  - **Rare** Anaphylaxis - angioedema - angle-closure glaucoma (in adults) • arrhythmias • blood disorders • bronchospasm • confusion • convulsions • depression • dizziness • extrapyramidal effects • hypersensitivity reactions • hypotension • liver dysfunction • palpitation • photosensitivity reactions • rashes • sleep disturbances • tremor
- **Frequency not known** Drowsiness

SIDE-EFFECTS, FURTHER INFORMATION
Children and elderly are more susceptible to side-effects. Non-sedating antihistamines such as loratadine cause less sedation and psychomotor impairment than the older antihistamines because they penetrate the blood brain barrier only to a slight extent. If drowsiness occurs, it may diminish after a few days of treatment.

- **PREGNANCY** Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity.
- **BREAST FEEDING** Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.
- **HEPATIC IMPAIRMENT** Reduce dose frequency to alternate days in severe impairment.
- **PATIENT AND CARER ADVICE** Although drowsiness is rare, nevertheless patients and their carers should be advised that it can occur and may affect performance of skilled tasks (e.g. cycling or driving); alcohol should be avoided.
- **PROFESSIONAL INFORMATION**
  - **Preparations**  
    - **Clarityn (Loratadine)** (Bayer Plc)
      - Tablet: 10 mg (£8.65 DT price = £3.24)
      - Oral solution: £2.34 per ml
    - **Clarityn Rapide Allergy** (Bayer Plc)
      - Tablet: 10 mg (£3.24)
    - **Loratadine** (Non-proprietary)
      - Tablet: £8.24 | 120 ml £2.67-2.81 | 200 ml £2.34
    - **Loratadine syrup** (Bayer Plc)
      - Oral solution: £4.97 DT price = £1.11
- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Clarityn (Loratadine)** (Bayer Plc)
    - Tablet: 10 mg (£8.65 DT price = £3.24)
    - Oral solution: £2.34 per ml
  - **Clarityn Allergy** (Loratadine)  
    - Tablet: £4.85 DT price = £1.11
    - Oral solution: £8.65
  - **Loratadine** (Non-proprietary)
    - Tablet: £8.64
    - Oral solution: £2.34 per ml

**Mizolastine**

**INDICATIONS AND DOSE**
Symptomatic relief of allergy such as hay fever, urticaria  
**BY MOUTH**  
- Child 12-17 years: 10 mg once daily  
- Adult: 10 mg once daily

- **CONTRA-INDICATIONS** Avoid in Acute porphyrias p. 864 (some antihistamines are thought to be safe) • cardiac disease • hypokalaemia • susceptibility to QT-interval prolongation
- **CAUTIONS** Epilepsy
- **INTERACTIONS** → Appendix 1 (antihistamines). Sedative antihistamine interactions apply to a lesser extent to the non-sedating antihistamines.
- **SIDE-EFFECTS**  
  - **Common or very common** Anxiety • asthenia • weight gain  
  - **Uncommon** Antimuscarinic effects • arthralgia • blurred vision • dry mouth • gastro-intestinal disturbances • headache • myalgia • psychomotor impairment • urinary retention  
  - **Rare** Anaphylaxis • angioedema • angle-closure glaucoma (in adults) • arrhythmias • blood disorders • bronchospasm • confusion • convulsions • depression • dizziness • extrapyramidal effects • hypersensitivity reactions • hypotension • liver dysfunction • palpitation • photosensitivity reactions • rashes • sleep disturbances • tremor
- **Frequency not known** Drowsiness

SIDE-EFFECTS, FURTHER INFORMATION
Children and elderly are more susceptible to side-effects. Non-sedating antihistamines such as mizolastine cause less sedation and psychomotor impairment than the older antihistamines because they penetrate the blood brain barrier only to a slight extent. If drowsiness occurs, it may diminish after a few days of treatment.

- **PREGNANCY** Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity.
- **BREAST FEEDING** Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.
- **HEPATIC IMPAIRMENT** Manufacturer advises avoid in significant impairment.
- **PATIENT AND CARER ADVICE** Although drowsiness is rare, nevertheless patients and their carers should be advised...
that it can occur and may affect performance of skilled tasks (e.g. cycling or driving); alcohol should be avoided.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.

  Modified-release tablet
  CAUTIONARY AND ADVISORY LABELS 25
  > Mizolastine (Sanofi) Mizolastine 10 mg Mizolastine 10 mg modified-release tablets | 30 tablet [POD] £6.92 DT price + £6.92

Promethazine hydrochloride

INDICATIONS AND DOSE
Symptomatic relief of allergy such as hay fever and urticaria | Insomnia associated with urticaria and pruritus
BY MOUTH
> Child 2-4 years: 5 mg twice daily, alternatively 5–15 mg once daily, dose to be taken at night
> Child 5-9 years: 5–10 mg twice daily, alternatively 10–25 mg once daily, dose to be taken at night
> Child 10-17 years: 10–20 mg 2–3 times a day, alternatively 25 mg once daily, dose to be taken at night, increased if necessary to 25 mg twice daily
> Adult: 20–25 mg 2–3 times a day

BY DEEP INTRAMUSCULAR INJECTION
> Adult: 25–50 mg (max. per dose 100 mg)

Emergency treatment of anaphylactic reactions
BY SLOW INTRAVENOUS INJECTION
> Adult: 25–50 mg, to be administered as a solution containing 2.5 mg/mL in water for injections; maximum 100 mg per course

Sedation (short-term use)
BY MOUTH
> Child 2-4 years: 15–20 mg
> Child 5-9 years: 20–25 mg
> Child 10-17 years: 25–50 mg
> Adult: 25–50 mg

BY DEEP INTRAMUSCULAR INJECTION
> Adult: 25–50 mg

Nausea | Vomiting | Vertigo | Labyrinthine disorders | Motion sickness
BY MOUTH
> Child 2-4 years: 5 mg, to be taken at bedtime on night before travel, repeat following morning if necessary
> Child 5-9 years: 10 mg, to be taken at bedtime on night before travel, repeat following morning if necessary
> Child 10-17 years: 20–25 mg, to be taken at bedtime on night before travel, repeat following morning if necessary
> Adult: 20–25 mg, to be taken at bedtime on night before travel, repeat following morning if necessary

Important safety information
MHRA/CHM ADVICE (MARCH 2008 AND FEBRUARY 2009)
OVER-THE-COUNTER COUGH AND COLD MEDICINES FOR CHILDREN
Children under 6 years should not be given over-the-counter cough and cold medicines containing promethazine.

- CONTRA-INDICATIONS
  Many antihistamines should be avoided in Acute porphyrias p. 864 but promethazine is thought to be safe.

- CAUTIONS
  GENERAL CAUTIONS
  Epilepsy | prostatic hypertrophy | pyloroduodenal obstruction | severe coronary artery disease | susceptibility to angle-closure glaucoma | urinary retention

SPECIFIC CAUTIONS
> With intravenous use avoid extravasation with intravenous injection

- INTERACTIONS
  > Appendix 1 (antihistamines).

- SIDE-EFFECTS
  GENERAL SIDE-EFFECTS
  > Rare Anaphylaxis | angioedema | angle-closure glaucoma | arrhythmias | blood disorders | bronchospasm | confusion | convulsions | depression | dizziness | extrapyramidal effects | hypersensitivity reactions | hypotension | liver dysfunction | palpitation | photosensitivity reactions | rashes | sleep disturbances | tremor
  > Frequency not known Antimuscarinic effects | blurred vision | drowsiness | dry mouth | gastro-intestinal disturbances | headache | psychomotor impairment | restlessness | urinary retention

SPECIFIC SIDE-EFFECTS
> With intramuscular use injection pain
SIDE-EFFECTS, FURTHER INFORMATION
Children and elderly are more susceptible to side-effects. Drowsiness is a significant side-effect with most of the older antihistamines although paradoxical stimulation may occur rarely, especially with high doses or in children and the elderly. Drowsiness may diminish after a few days of treatment and is considerably less of a problem with the newer antihistamines.

PREGNANCY
  Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity. Use in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor.

BREAST FEEDING
  Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

HEPATIC IMPAIRMENT
  Avoid in severe liver disease—increased risk of coma.

RENAL IMPAIRMENT
  Use with caution.

PATIENT AND CARER ADVICE
Drowsiness may affect the performance of skilled tasks (e.g. cycling or driving); sedating effects enhanced by alcohol.

PROFESSION SPECIFIC INFORMATION
Dental practitioners’ formulary Promethazine Hydrochloride Tablets 10 mg or 25 mg may be prescribed. Promethazine Hydrochloride Oral Solution (elixir) 5 mg/5 mL may be prescribed.

LESS SUITABLE FOR PRESCRIBING
Promethazine is less suitable for prescribing for sedation.

EXCEPTIONS TO LEGAL CATEGORY
Prescription only medicine restriction does not apply to promethazine hydrochloride injection where administration is for saving life in emergency.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

Tablet
CAUTIONARY AND ADVISORY LABELS 2
PROMETHAZINE HYDROCHLORIDE (Non-proprietary)
Promethazine hydrochloride 10 mg Promethazine hydrochloride 10 mg tablets | 56 tablet [POD] £2.96 DT price + £2.96

Oral solution
CAUTIONARY AND ADVISORY LABELS 2
EXCIPIENTS: May contain Sulphites ELECTROLYTES: May contain Sodium
PHENERGAN (Sanofi)
Promethazine hydrochloride 1 mg per 1 ml Phenegran 5mg/5ml elixir (sugar-free) | 100 ml [POD] £2.85 DT price + £2.85
Solution for injection
EXCIPIENTS: May contain Sulfites
▶ Phenergan (Sanofi)
Promethazine hydrochloride 25 mg per 1 ml
Phenergan 25mg/1ml solution for injection ampoules | 10 ampoule PIP £6.74

Promethazine teoclolate

INDICATIONS AND DOSE
Nausea | Vertigo | Labyrinthine disorders
BY MOUTH
Child 5–9 years: 12.5–37.5 mg daily
Child 10–17 years: 25–75 mg daily; maximum 100 mg per day
Adult: 25–75 mg daily; maximum 100 mg per day
Motion sickness prevention (acts longer than promethazine hydrochloride)
BY MOUTH
Child 5–9 years: 12.5 mg once daily, dose to be taken at bedtime on night before travel, alternatively 12.5 mg once daily, dose to be taken 1–2 hours before travel
Child 10–17 years: 25 mg once daily, dose to be taken at bedtime on night before travel, alternatively 25 mg once daily, dose to be taken 1–2 hours before travel
Adult: 25 mg once daily, dose to be taken at bedtime on night before travel, alternatively 25 mg once daily, dose to be taken 1–2 hours before travel
Motion sickness treatment (acts longer than the hydrochloride)
BY MOUTH
Child 5–9 years: 12.5 mg, dose to be taken at onset of motion sickness, then 12.5 mg daily for 2 days, dose to be taken at bedtime
Child 10–17 years: 25 mg, dose to be taken at onset of motion sickness, then 25 mg once daily for 2 days, dose to be taken at bedtime
Adult: 25 mg, dose to be taken at onset of motion sickness, then 25 mg once daily for 2 days, dose to be taken at bedtime

SIDE-EFFECTS, FURTHER INFORMATION
Children and the elderly patients are more susceptible to side-effects. Drowsiness is a significant side-effect with most of the older antihistamines although paradoxical stimulation may occur rarely, especially with high doses or in children and the elderly. Drowsiness may diminish after a few days of treatment and is considerably less of a problem with the newer antihistamines.

▶ PREGNANCY Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity. Use in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor.

▶ BREAST FEEDING Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

▶ HEPATIC IMPAIRMENT Avoid in severe liver disease—increased risk of coma.

▶ RENAL IMPAIRMENT Use with caution.

▶ PATIENT AND CARER ADVICE Drowsiness may affect performance of skilled tasks (e.g. cycling or driving); sedating effects enhanced by alcohol.

▶ MEDICINAL FORMS

Tablet
CAUTIONARY AND ADVISORY LABELS 2
▶ Avomine (Manx Healthcare Ltd)
Promethazine teoclolate 25 mg
Avomine 25mg tablets | 10 tablet £1.13 | 28 tablet £3.13 DT price = £3.13

VACCINES (ALLERGEN-TYPE)

Bee venom extract

INDICATIONS AND DOSE
Hypersensitivity to bee venom
BY SUBCUTANEOUS INJECTION
▶ Adult: (consult product literature)

Important safety information
MHRA/CHM ADVICE (MARCH 2008 AND FEBRUARY 2009)
OVER-THE-COUNTER COUGH AND COLD MEDICINES FOR CHILDREN
Children under 6 years should not be given over-the-counter cough and cold medicines containing promethazine.

▶ CAUTIONS Acute porphyrias p. 864 · asthma · bronchiectasis · bronchitis · epilepsy · prostatic hypertrophy · pyloroduodenal obstruction · Reye’s syndrome · severe coronary artery disease · susceptibility to angle-closure glaucoma · urinary retention

▶ INTERACTIONS ▶ Appendix 1 (antihistamines).

▶ SIDE-EFFECTS

GENERAL SIDE-EFFECTS
▶ Rare Anaphylaxis · angioedema · angle-closure glaucoma · arrhythmias · blood disorders · bronchospasm · confusion · convulsions · depression · dizziness · extrapyramidal effects · hypersensitivity reactions · hypotension · liver dysfunction · palpitation · photosensitivity reactions · rashes · sleep disturbances · tremor

▶ Frequency not known Antimuscarinic effects · blurred vision · drowsiness · dry mouth · gastro-intestinal disturbances · headache · psychomotor impairment · restlessness · urinary retention

SPECIFIC SIDE-EFFECTS
▶ With intramuscular use injection pain
symptoms or signs of hypersensitivity develop (e.g. rash, urticaria, bronchospasm, faintness), even when mild, the patient should be observed until these have resolved completely.

- **PREGNANCY** Avoid.
- **PRESCRIBING AND DISPENSING INFORMATION** Each set of allergen extracts usually contains vials for the administration of graded amounts of allergen to patients undergoing hyposensitisation. Maintenance sets containing vials at the highest strength are also available. Product literature must be consulted for details of allergens, vial strengths, and administration.
- **NATIONAL FUNDING/ACCESS DECISIONS**

  **NICE technology appraisals (TAs)**
  - Pharmalgen for bee and wasp venom allergy (February 2012)
  - NICE TA246

  Pharmalgen® is an option for the treatment of IgE-mediated bee and wasp venom allergy in those who have had:
  - a severe systemic reaction to bee or wasp venom;
  - a moderate systemic reaction to bee or wasp venom and who have a raised baseline serum-tryptase concentration, a high risk of future stings, or anxiety about future stings.

  Treatment with Pharmalgen® should be initiated and monitored in a specialist centre experienced in venom immunotherapy. www.nice.org.uk/TA246

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **BEE VENOM EXTRACT (Non-proprietary)**
  - Bee venom 1.2 microgram powder and solvent for solution for injection vials | 1 vial £80 no price available
  - Bee venom 12 microgram powder and solvent for solution for injection vials | 1 vial £80 no price available
  - Bee venom 120 microgram powder and solvent for solution for injection vials | 1 vial £150.00
  - Bee venom 120 nano gram powder and solvent for solution for injection vials | 1 vial no price available

Grass pollen extract

**INDICATIONS AND DOSE**

Treatment of seasonal allergic hay fever due to grass pollen in patients who have failed to respond to anti-allergy drugs

**BY SUBCUTANEOUS INJECTION**

- Adult: (consult product literature)

Treatment of seasonal allergic hay fever due to grass pollen in patients who have failed to respond to anti-allergy drugs (initiated under specialist supervision)

**BY MOUTH**

- Adult: 1 tablet daily, treatment to be started at least 4 months before start of pollen season and continue for up to 3 years

- **DESENSITISING VACCINES**

  In view of concerns about the safety of desensitising vaccines, it is recommended that they are used by specialists and only for the following indications:
  - Seasonal allergic hay fever (caused by pollen) that has not responded to anti-allergic drugs;
  - Hypersensitivity to wasp and bee venoms.

Desensitising vaccines should generally be avoided or used with particular care in patients with asthma.

- **CONTRA-INDICATIONS** Consult product literature
- **CAUTIONS** Consult product literature
- **INTERACTIONS** Desensitising vaccines should be avoided in patients taking beta-blockers (adrenaline may be ineffective in case of a hypersensitivity reaction), or ACE inhibitors (risk of severe anaphylactoid reactions).
- **SIDE-EFFECTS**

  **SIDE-EFFECTS, FURTHER INFORMATION**

  Consult product literature.

  **Hypersensitivity reactions** Hypersensitivity reactions to immunotherapy can be life-threatening; bronchospasm usually develops within 1 hour and anaphylaxis within 30 minutes of injection. Therefore, cardiopulmonary resuscitation must be immediately available and patients need to be monitored for at least 1 hour after injection. If symptoms or signs of hypersensitivity develop (e.g. rash, urticaria, bronchospasm, faintness), even when mild, the patient should be observed until these have resolved completely.

  - **PREGNANCY** Should be avoided in pregnant women—consult product literature.

- **MONITORING REQUIREMENTS** The first dose of grass pollen extract should be (Grazax®) should be taken under medical supervision and the patient should be monitored for 20–30 minutes.

- **DIRECTIONS FOR ADMINISTRATION** Oral lyophilisates should be placed under the tongue and allowed to disperse. Advise patient not to swallow for 1 minute, or eat or drink for 5 minutes after taking the tablet. The first should be taken under medical supervision and the patient should be monitored for 20–30 minutes.

- **PRESCRIBING AND DISPENSING INFORMATION** Each set of allergen extracts usually contains vials for the administration of graded amounts of allergen to patients undergoing hyposensitisation. Maintenance sets containing vials at the highest strength are also available. Product literature must be consulted for details of allergens, vial strengths, and administration.

- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer oral lyophilisates.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Oral Lyophilisate**

- Grazax (ALK-Abello Ltd)
  - Pollinex Grasses + Rye (Allergy Therapeutics (UK) Ltd)

**Injection**

- Pollinex Grasses + Rye suspension for injection treatment and extension course vials | 4 vial £450.00

Tree pollen extract

**INDICATIONS AND DOSE**

Treatment of seasonal allergic hay fever due to tree pollen in patients who have failed to respond to anti-allergy drugs

**BY SUBCUTANEOUS INJECTION**

- Adult: (consult product literature)

**MEDICINAL FORMS**

- **Oral Lyophilisate**
  - Grazax (ALK-Abello Ltd)
  - Pollinex Grasses + Rye suspension for injection treatment and extension course vials | 4 vial £450.00

**Important safety information**

**DESENSITISING VACCINES**

In view of concerns about the safety of desensitising vaccines, it is recommended that they are used by specialists and only for the following indications:
Respiratory system

CONTRA-INDICATIONS
Consult product literature

CAUTIONS
Consult product literature

INTERACTIONS
Desensitising vaccines should be avoided in patients taking beta-blockers (adrenaline may be ineffective in case of a hypersensitivity reaction), or ACE inhibitors (risk of severe anaphylactoid reactions).

SIDE-EFFECTS

SIDE-EFFECTS, FURTHER INFORMATION
Consult product literature.

Hypersensitivity reactions
Hypersensitivity reactions to immunotherapy (especially to wasp and bee venom extracts) can be life-threatening; bronchospasm usually develops within 1 hour and anaphylaxis within 30 minutes of injection. Therefore, cardiopulmonary resuscitation must be immediately available and patients need to be monitored for at least 1 hour after injection. If symptoms or signs of hypersensitivity develop (e.g. rash, urticaria, bronchospasm, faintness), even when mild, the patient should be observed until these have resolved completely.

PREGNANCY
Avoid.

PRESCRIBING AND DISPENSING INFORMATION
Each set of allergen extracts usually contains vials for the administration of graded amounts of allergen to patients undergoing hypo sensitisation. Maintenance sets containing vials at the highest strength are also available. Product literature must be consulted for details of allergens, vial strengths, and administration.

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

Pharmalgen for bee and wasp venom allergy (February 2012) NICE TA246 Pharmalgen® is an option for the treatment of IgE-mediated bee and wasp venom allergy in those who have had:

- a severe systemic reaction to bee or wasp venom;
- a moderate systemic reaction to bee or wasp venom and who have a raised baseline serum-tryptase concentration, a high risk of future stings, or anxiety about future stings.

Treatment with Pharmalgen® should be initiated and monitored in a specialist centre experienced in venom immunotherapy. www.nice.org.uk/TA246

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Suspension for injection
- Pollinex Trees (Allergy Therapeutics (UK) Ltd)
  - Pollinex Trees No 3 suspension for injection 1ml vials | 1 vial (£75) no price available
  - Pollinex Trees No 2 suspension for injection 1ml vials | 1 vial (£75) no price available
  - Pollinex Trees No 1 suspension for injection 1ml vials | 1 vial (£75) no price available

Injection
- Pollinex Trees (Allergy Therapeutics (UK) Ltd)
  - Pollinex Trees suspension for injection treatment and extension course vials | 4 vial (£150) £450.00

Wasp venom extract

INDICATIONS AND DOSE
Hypersensitivity to wasp venom
BY SUBCUTANEOUS INJECTION
Adult: (consult product literature)

Important safety information
DESENSITISING VACCINES
In view of concerns about the safety of desensitising vaccines, it is recommended that they are used by specialists and only for the following indications:

- seasonal allergic hay fever (caused by pollen) that has not responded to anti-allergic drugs;
- hypersensitivity to wasp and bee venoms.

Desensitising vaccines should generally be avoided or used with particular care in patients with asthma.

CONTRA-INDICATIONS
Consult product literature

INTERACTIONS
Appendix 1 (wasp venom extracts). Contra-indicated in patients taking beta-blockers (adrenaline may be ineffective in case of a hypersensitivity reaction).

SIDE-EFFECTS
SIDE-EFFECTS, FURTHER INFORMATION
Consult product literature.

Hypersensitivity reactions
Hypersensitivity reactions to immunotherapy (especially to wasp and bee venom extracts) can be life-threatening; bronchospasm usually develops within 1 hour and anaphylaxis within 30 minutes of injection. Therefore, cardiopulmonary resuscitation must be immediately available and patients need to be monitored for at least 1 hour after injection. If symptoms or signs of hypersensitivity develop (e.g. rash, urticaria, bronchospasm, faintness), even when mild, the patient should be observed until these have resolved completely.

PREGNANCY
Avoid.

PRESCRIBING AND DISPENSING INFORMATION
Each set of allergen extracts usually contains vials for the administration of graded amounts of allergen to patients undergoing hypo sensitisation. Maintenance sets containing vials at the highest strength are also available. Product literature must be consulted for details of allergens, vial strengths, and administration.

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

Pharmalgen for bee and wasp venom allergy (February 2012) NICE TA246 Pharmalgen® is an option for the treatment of IgE-mediated bee and wasp venom allergy in those who have had:

- a severe systemic reaction to bee or wasp venom;
- a moderate systemic reaction to bee or wasp venom and who have a raised baseline serum-tryptase concentration, a high risk of future stings, or anxiety about future stings.

Treatment with Pharmalgen® should be initiated and monitored in a specialist centre experienced in venom immunotherapy. www.nice.org.uk/TA246

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Powder and solvent for solution for injection

WASP VENOM EXTRACT (Non-proprietary)
- Wasp venom 1.2 microgram Pharmalgen Wasp Venom 1.2microgram powder and solvent for solution for injection vials | 1 vial (£35) no price available
- Wasp venom 12 microgram Pharmalgen Wasp Venom 12microgram powder and solvent for solution for injection vials | 1 vial (£85) no price available
- Wasp venom 120 nanogram Pharmalgen Wasp Venom 120nanogram powder and solvent for solution for injection vials | 1 vial (£85) no price available
- Wasp venom 120 microgram Pharmalgen Wasp Venom maintenance set 120microgram vaccine powder and solvent for solution for injection vials | 1 vial (£35) no price available | 4 vial (£125) £150.00

2.1 Angioedema

Drugs used for Angioedema not listed below;
Adrenaline/epinephrine, p. 196
COMPLEMENT BLOCKERS

C1-esterase inhibitor

INDICATIONS AND DOSE

CINRYZE®
Acute attacks of hereditary angioedema (under expert supervision)
BY SLOW INTRAVENOUS INJECTION
Adult: 1000 units for 1 dose, repeated if necessary
Short-term prophylaxis of hereditary angioedema before dental, medical, or surgical procedures (under expert supervision)
BY SLOW INTRAVENOUS INJECTION
Adult: 1000 units for 1 dose, to be administered up to 24 hours before procedure
Long-term prophylaxis of severe, recurrent attacks of hereditary angioedema where acute treatment is inadequate, or when oral prophylaxis is inadequate or not tolerated (under expert supervision)
BY SLOW INTRAVENOUS INJECTION
Adult: 1000 units every 3–4 days, interval between doses to be adjusted according to response

BERINERT®
Acute attacks of hereditary angioedema (under expert supervision)
BY SLOW INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION
Adult: 20 units/kg
Short-term prophylaxis of hereditary angioedema before dental, medical, or surgical procedures (under expert supervision)
BY SLOW INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION
Adult: 1000 units for 1 dose, to be administered less than 6 hours before procedure

CAUTIONS
Vaccination against hepatitis A and hepatitis B may be required

SIDE-EFFECTS
Fever, headache, thrombosis (with high doses)

PREGNANCY
Manufacturer advises avoid unless essential.

PRESCRIBING AND DISPENSING INFORMATION
C1-esterase inhibitor is prepared from human plasma.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Powder for solution for injection
Berinert P (CSL Behring UK Ltd)
Conestat alfa 2100 unit Ruconest 2.100 unit powder for solution for injection vials | 1 vial £750.00

SELECTIVE BRADYKININ B2 ANTAGONISTS

Icatibant

INDICATIONS AND DOSE
Acute attacks of hereditary angioedema in patients with C1-esterase inhibitor deficiency
BY SUBCUTANEOUS INJECTION
Adult: 30 mg for 1 dose, then 30 mg after 6 hours if required, then 30 mg after 6 hours if required; maximum 3 doses per day

CAUTIONS
Ischaemic heart disease • stroke

SIDE-EFFECTS
Dizziness, erythema, headache, injection-site reactions, nausea, pruritus, pyrexia, rash

PREGNANCY
Manufacturer advises use only if potential benefit outweighs risk—toxicity in animal studies.

BREAST FEEDING
Manufacturer advises avoid for 12 hours after administration.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
Firazyr (Shire Pharmaceuticals Ltd)
Icatibant (as Icatibant acetate) 10 mg per 1 ml Firazyr 30 mg/3 ml solution for injection pre-filled syringes | 1 pre-filled disposable injection £1,395.00

Conestat alfa

INDICATIONS AND DOSE
Acute attacks of hereditary angioedema in patients with C1-esterase inhibitor deficiency
BY SLOW INTRAVENOUS INJECTION
Adult (body-weight up to 84 kg): 50 units/kg for 1 dose, to be administered over 5 minutes, dose may be repeated if necessary; maximum 2 doses per day
Adult (body-weight ≥ 84 kg and above): 4200 units for 1 dose, to be administered over 5 minutes, dose may be repeated if necessary; maximum 2 doses per day

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Powder and solvent for solution for injection
ELECTROLYTES: May contain Sodium
Berinert P (CSL Behring UK Ltd)
C1-esterase inhibitor 500 unit Berinert 500 unit powder and solvent for solution for injection vials | 1 vial £467.50
Cinryze (ViroPharma Ltd)
C1-esterase inhibitor 500 unit Cinryze 500 unit powder and solvent for solution for injection vials | 2 vial £1,336.00

MUCOLYTICS

Carbocisteine

INDICATIONS AND DOSE
Reduction of sputum viscosity
BY MOUTH
Adult: Initially 2.25 g daily in divided doses, then reduced to 1.5 g daily in divided doses, as condition improves

CONTRA-INDICATIONS
Active peptic ulceration
3.1 Cystic fibrosis

Mucolytics for cystic fibrosis

Mucolytics are prescribed to facilitate expectoration by reducing sputum viscosity. In some patients with chronic obstructive pulmonary disease and a chronic productive cough, mucolytics can reduce exacerbations; mucolytic therapy should be stopped if there is no benefit after a 4-week trial. Steam inhalation with postural drainage is effective in bronchiectasis and in some cases of chronic bronchitis.

Dornase alfa below is used to reduce sputum viscosity in patients with cystic fibrosis.

Nebulised hypertonic sodium chloride (3–7%) is used to mobilise lower respiratory tract secretions in mucus consolidation (e.g. cystic fibrosis). Nebulised hypertonic sodium chloride solution (3%) is used for mild to moderate acute viral bronchiolitis in infants.

Manitol, administered by inhalation, improves mucus clearance and is licensed for the treatment of cystic fibrosis as an add-on therapy to standard care.

Erdosteine

**INDICATIONS AND DOSE**

Symptomatic treatment of acute exacerbations of chronic bronchitis

**BY MOUTH**

- Adult: 300 mg twice daily for up to 10 days

- **CAUTIONS** History of peptic ulceration (may disrupt the gastric mucosal barrier)

- **SIDE-EFFECTS**
  - Rare Abdominal pain, diarrhoea, headache, nausea, rash, taste disturbance, urticaria, vomiting

- **PREGNANCY** Manufacturer advises avoid—no information available.

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT** Manufacturer advises max. 300 mg daily in mild to moderate impairment. Avoid in severe impairment.

- **RENAL IMPAIRMENT** Avoid if eGFR less than 25 mL/minute/1.73 m²—no information available.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  **Scottish Medicines Consortium (SMC) Decisions**

  The Scottish Medicines Consortium (October 2007) has advised that erdosteine (Erdotin®) is not recommended for the symptomatic treatment of acute exacerbations of chronic bronchitis.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Capsule**
  - Erdotin (Galen Ltd)
  - Erdosteine 300 mg Erdotin 300mg capsules | 20 capsule [PEN] £4.25 DT price = £4.25

- **RENAH IMPAIRMENT** No information available.

- **BREAST FEEDING** No information available.

- **PREGNANCY** Manufacturer advises avoid in first trimester.

- **SIDE-EFFECTS**
  - Very rare Abdominal pain, diarrhoea, headache, nausea, rash, taste disturbance, urticaria, vomiting

- **DRUG ACTION** Dornase alfa is a genetically engineered version of a naturally occurring human enzyme which cleaves extracellular deoxyribonucleic acid (DNA).

**INDICATIONS AND DOSE**

Management of cystic fibrosis patients with a forced vital capacity (FVC) of greater than 40% of predicted to improve pulmonary function

**BY INHALATION OF NEBULISED SOLUTION**

- Adult: 2500 units once daily, administered by jet nebuliser, patients over 21 years may benefit from twice daily dosage

**Dose equivalence and conversion**

Dornase alfa 1000 units is equivalent to 1 mg

- **SIDE-EFFECTS**
  - Rare Chest pain, conjunctivitis, dyspepsia, dysphonia, dysphonia, laryngitis, pharyngitis, pyrexia, rash, rhinitis, urticaria

- **PREGNANCY** No evidence of teratogenicity; manufacturer advises use only if potential benefit outweighs risk.

- **BREAST FEEDING** Amount probably too small to be harmful—manufacturer advises caution.

- **DIRECTIONS FOR ADMINISTRATION** Dornase alfa is administered by inhalation using a jet nebuliser, usually once daily at least 1 hour before physiotherapy; however, alternate-day therapy may be as effective as daily treatment. For use undiluted with jet nebulisers only; ultrasonic nebulisers are unsuitable.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Nebuliser liquid**
  - Pulmozyme (Roche Products Ltd)
  - Dornase alfa 1 mg per 1 ml Pulmozyme 2.5mg nebuliser liquid 2.5ml ampoules | 30 ampoule [PEN] £496.43 DT price = £496.43
**Ivacaftor**

**INDICATIONS AND DOSE**

Treatment of cystic fibrosis in patients who have a G551D mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (under expert supervision)

**BY MOUTH**
- Adult: 150 mg every 12 hours

**Dose adjustments due to interactions**
Reduce dose to 150 mg twice a week with concomitant use of itraconazole, ketoconazole, posaconazole, voriconazole, telithromycin, and clarithromycin. Reduce dose to 150 mg once daily with concomitant use of fluconazole and erythromycin.

- **CONTRA-INDICATIONS** Organ transplantation (no information available)
- **INTERACTIONS** → Appendix 1 (ivacaftor). Avoid grapefruit and Seville oranges.
- **SIDE-EFFECTS**
  - **Common or very common** Abdominal pain · diarrhoea · dizziness · ear discomfort · headache · nasal congestion · nasopharyngitis · oropharyngeal pain · pharyngolaryngeal pain · rash · rhinitis · tinnitus · upper respiratory tract infection
  - **Uncommon** Gynaecomastia · vestibular disorder
- **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk—no information available.
- **BREAST FEEDING** Manufacturer advises use only if potential benefit outweighs risk—no information available.
- **HEPATIC IMPAIRMENT** Max. 150 mg once daily in moderate impairment; in severe impairment, manufacturer recommends use only if potential benefit outweighs risk—starting dose 150 mg on alternate days, dosing interval adjusted according to clinical response and tolerability.
- **RENAL IMPAIRMENT** Caution in severe impairment.
- **PRE-TREATMENT SCREENING** If the patient’s genotype is unknown, a validated genotyping method should be performed to confirm the presence of the G551D mutation in at least one allele of the CFTR gene before starting treatment.
- **MONITORING REQUIREMENTS** Test liver function before treatment, every 3 months during the first year of treatment, then annually thereafter.
- **DIRECTIONS FOR ADMINISTRATION** Tablets should be taken with fat-containing food.
- **PRESCRIBING AND DISPENSING INFORMATION** Ivacaftor should be prescribed by a physician experienced in the treatment of cystic fibrosis.
- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer ivacaftor tablets.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**

**CAUTIONARY AND ADVISORY LABELS 5.25**
- Ivacaftor 150 mg Kalydeco 150mg tablets | 56 tablet | [PSM]
  - £14,000.00

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**Mannitol**

**INDICATIONS AND DOSE**

Treatment of cystic fibrosis as an add-on therapy to standard care

**BY INHALATION OF POWDER**
- Adult: Maintenance 400 mg twice daily, an initiation dose assessment must be carried out under medical supervision, for details of the initiation dose regimen, consult product literature

- **CONTRA-INDICATIONS** Bronchial hyperresponsiveness to inhaled mannitol · impaired lung function (forced expiratory volume in 1 second < 30% of predicted) · non-CF bronchiectasis
- **CAUTIONS** Asthma · haemoptysis
- **INTERACTIONS** → Appendix 1 (mannitol).
- **SIDE-EFFECTS**
  - **Common or very common** Cough · haemoptysis · headache · pharyngolaryngeal pain · throat irritation · vomiting · wheezing
  - **Uncommon** Acne · arthralgia · bronchospasm · dizziness · dysphonia · dysphagia · ear pain · eructation · flatulence · gastro-oesophageal reflux disease · glossodynia · hyperventilation · influenza-like illness · malaise · nausea · oral candidiasis · pharyngitis · pruritis · pyrexia · rash · rhinorrhea · stomatitis · transient insomnia
- **PREGNANCY** Manufacturer advises avoid.
- **BREAST FEEDING** Manufacturer advises avoid.
- **PRE-TREATMENT SCREENING** Patients must be assessed for bronchial hyperresponsiveness to inhaled mannitol before starting the therapeutic dose regimen; an initiation dose assessment must be carried out under medical supervision—for details of the initiation dose regimen, consult product literature.
- **DIRECTIONS FOR ADMINISTRATION** The dose should be administered 5–15 minutes after a bronchodilator and before physiotherapy; the second daily dose should be taken 2–3 hours before bedtime.
- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer mannitol inhalation powder.
- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE technology appraisals (TAs)** Mannitol dry powder for inhalation for treating cystic fibrosis (November 2012) NICE TA266

Mannitol dry powder for inhalation is recommended as an option for treating cystic fibrosis in adults:
- who cannot use dornase alfa (rhDNase) because of ineffectiveness, intolerance or inadequate response to dornase alfa (rhDNase), and
- whose lung function is rapidly declining (forced expiratory volume in 1 second decline greater than 2% annually), and
- for whom other osmotic agents are not considered appropriate. www.nice.org.uk/TA266

**Scottish Medicines Consortium (SMC) Decisions**
The Scottish Medicines Consortium, has advised (November 2013) that mannitol (Bronchitol®) is accepted for restricted use within NHS Scotland for the treatment of cystic fibrosis in adults aged 18 years and over as an add-on therapy to best standard of care. Mannitol is restricted to patients who are not currently using dornase alfa due to lack of response, intolerance, or ineffectiveness and have rapidly declining lung function and in whom other osmotic agents are considered unsuitable.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order
4 Cough and congestion

Aromatic inhalations, cough preparations and systemic nasal decongestants

Aromatic inhalations in adults

Inhalations containing volatile substances such as eucalyptus oil are traditionally used and although the vapour may contain little of the additive it encourages deliberate inspiration of warm moist air which is often comforting in bronchitis; boiling water should not be used owing to the risk of scalding. Inhalations are also used for the relief of nasal obstruction in acute rhinitis or sinusitis. Eucalyptus with menthol p. 259 inhalation is used to relieve sinussitis affecting the maxillary antrum.

Cough preparations in adults

Cough suppressants

Cough may be a symptom of an underlying disorder, such as asthma, gastro-oesophageal reflux disease, or rhinitis, which should be addressed before prescribing cough suppressants. Cough may be a side-effect of another drug, such as an ACE inhibitor, or it can be associated with smoking or environmental pollutants. Cough can also have a significant habit component. When there is no identifiable cause, cough suppressants may be useful, for example if sleep is disturbed. They may cause sputum retention and this may be harmful in patients with chronic bronchitis and bronchiectasis.

Cough suppressants are claimed to promote expulsion of bronchial secretions, but there is no evidence that any drug can specifically facilitate expectoration.

Compound preparations are on sale to the public for the treatment of cough and colds but should not be used in children under 6 years; the rationale for some is dubious. Care should be taken to give the correct dose and to not use more than one preparation at a time.

Systemic nasal decongestants

Nasal decongestants for administration by mouth may not be as effective as preparations for local application but they do not give rise to rebound nasal congestion on withdrawal. Pseudoephedrine hydrochloride p. 982 is available over the counter; it has few sympathomimetic effects.

Aromatic inhalations in children

The use of strong aromatic decongestants (applied as rubs or to pillows) is not advised for infants under the age of 3 months. Carers of young infants in whom nasal obstruction with mucus is a problem can readily be taught appropriate techniques of suction aspiration but sodium chloride 0.9% given as nasal drops is preferred; administration before feeds may ease feeding difficulties caused by nasal congestion.

Cough preparations in children

The use of over-the-counter cough suppressants containing codeine phosphate p. 360 should be avoided in children under 12 years and in children of any age known to be CYP2D6 ultra-rapid metabolisers. Cough suppressants containing similar opioid analgesics such as dextromethorphan and pholcodine p. 259 are not generally recommended in children and should be avoided in children under 6 years.

MHRA/CHM advice (March 2008 and February 2009)

Over-the-counter cough and cold medicines for children

Children under 6 years should not be given over-the-counter cough and cold medicines containing the following ingredients:

- Brompheniramine, chlorphenamine maleate, diphenhydramine, doxylamine, promethazine, or tripolidine (antihistamines);
- Dextromethorphan or pholcodine (cough suppressants);
- Guaifenesin or ipecacuanha (expectorants);
- Phenylephrine hydrochloride, pseudoephedrine hydrochloride, ephedrine hydrochloride, oxymetazoline, or xylometazoline hydrochloride (decongestants).

Over-the-counter cough and cold medicines can be considered for children aged 6–12 years after basic principles of best care have been tried, but treatment should be restricted to five days or less. Children should not be given more than 1 cough or cold preparation at a time because different brands may contain the same active ingredient; care should be taken to give the correct dose.

Drugs used for cough and congestion not listed below; Codeine phosphate, p. 360 · Methadone hydrochloride, p. 436 · Morphine hydrochloride, p. 367

Citric acid

(Formulated as Simple Linctus)

INDICATIONS AND DOSE

Cough

BY MOUTH

- Adult: 5 mL 3–4 times a day, this dose is for Simple Linctus, BP (2.5%)
Cough and congestion

Pholcodine

INDICATIONS AND DOSE
Dry cough

BY MOUTH USING LINCTUS

> Child 6-11 years: 2–5 mg 3–4 times a day
> Child 12-17 years: 5–10 mg 3–4 times a day
> Adult: 5–10 mg 3–4 times a day

MOUTH USING LINCTUS

Important safety information

MHRA/CHM ADVICE (MARCH 2008 AND FEBRUARY 2009)

OVER-THE-COUNTER COUGH AND COLD MEDICINES FOR CHILDREN

Children under 6 years should not be given over-the-counter cough and cold medicines containing pholcodine (cough suppressant). Over-the-counter cough and cold medicines should be considered for children aged 6–12 years after basic principles of best care have been tried, but treatment should be restricted to 5 days or less. Children should not be given more than 1 cough or cold preparation at a time because different brands may contain the same active ingredient; care should be taken to give the correct dose.

CONTRA-INDICATIONS Bronchiectasis - bronchiolitis (in children) - chronic bronchitis - chronic obstructive pulmonary disease (in adults) - patients at risk of respiratory failure

CAUTIONS Asthma - chronic cough - persistent cough - productive cough

INTERACTIONS Appendix 1 (pholcodine).

SIDE-EFFECTS Confusion - constipation - dizziness - drowsiness - excitation - nausea - rash - sputum retention - vomiting

PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk.

BREAST FEEDING Manufacturer advises avoid unless potential benefit outweighs risk – no information available.

HEPATIC IMPAIRMENT Avoid in hepatic impairment.

RENAI IMPAIRMENT Use with caution in renal impairment. Avoid in severe renal impairment.

PRESCRIBING AND DISPENSING INFORMATION Pholcodine is not generally recommended for children. Flavours of oral liquid formulations may include anise. When prepared extemporaneously, the BP states Pholcodine Linctus, BP consists of pholcodine 5 mg/5 ml in a suitable flavoured vehicle, containing citric acid monohydrate 1% and Pholcodine Linctus, Strong, BP consists of pholcodine 10 mg/5 ml in a suitable flavoured vehicle, containing citric acid monohydrate 2%

MENDELC FORMS

MENDELC FORMS

There can be variation in the licensing of different medicines containing the same drug.

INHALATION VAPOUR

EUCALYPTUS WITH MENTHOL (Non-proprietary)

Eucalyptus oil 100 microlitre per 1 ml, Magnesium carbonate light 70 mg per 1 ml, Menthicol 20 mg per 1 ml Menthicol and Eucalyptus inhalation | 100 ml G59 £1.19 DT price = £1.19

OPSIODS

Pholcodine

OPSIODS

INDICATIONS AND DOSE

Dry cough

BY MOUTH USING LINCTUS

> Child 6-11 years: 2–5 mg 3–4 times a day
> Child 12-17 years: 5–10 mg 3–4 times a day
> Adult: 5–10 mg 3–4 times a day

MOUTH USING LINCTUS

RESINS

Benzoin tincture

(Friars’ Balsam)

INDICATIONS AND DOSE

Aromatic inhalation for relief of nasal congestion

BY INHALATION

> Child: Add 5 mL to a pint of hot, not boiling, water and inhale the vapour; repeat after 4 hours if necessary
> Adult: Add 5 mL to a pint of hot, not boiling, water and inhale the vapour; repeat after 4 hours if necessary

SIDE-EFFECTS Allergic contact dermatitis

PRESCRIBING AND DISPENSING INFORMATION Tincture, balsamic acids approx. 4.5%. When prepared extemporaneously, the BP states Benzoin Tincture, Compound, BP consists of balsamic acids approx. 4.5%. Not recommended (applied as a rub or to pillows) for infants under 3 months.
5 Idiopathic pulmonary fibrosis

ANTIFIBROTICS

Pirfenidone

- **DRUG ACTION** The exact mechanism of action of pirfenidone is not yet understood, but it is believed to slow down the progression of idiopathic pulmonary fibrosis by exerting both antifibrotic and anti-inflammatory properties.

**INDICATIONS AND DOSE**

- Treatment of mild to moderate idiopathic pulmonary fibrosis (initiated under specialist supervision)
  - **BY MOUTH**
    - Adult: Initially 267 mg three times a day for 7 days, then increased to 534 mg three times a day for 7 days, then increased to 801 mg 3 times a day
  - **Dose adjustments due to interactions**
    - Caution with concomitant use with ciprofloxacin—reduce dose of pirfenidone to 534 mg three times daily with high-dose ciprofloxacin (750 mg twice daily)
    - Caution with concomitant use of drugs known to cause photosensitivity—phototoxic or photoinflammatory reactions, dosage adjustments may be required (consult product literature).

- **CONTRA-INDICATIONS** Cigarette smoking

- **CAUTIONS**
  - **CAUTION, FURTHER INFORMATION** Photosensitivity
    - Avoid exposure to direct sunlight—phototoxic or photoinflammatory reactions, dosage adjustment or treatment interruption may be required (consult product literature).
  - **Treatment interruption**
    - If treatment is interrupted for 14 consecutive days or more, the initial 2 week titration regimen should be repeated; if treatment is interrupted for less than 14 consecutive days, the dose can be resumed at the previous daily dose without titration.

- **INTERACTIONS** Appendix 1 (pirfenidone).

- **SIDE-EFFECTS**
  - Rare: Raised bilirubin in combination with raised hepatic transaminases

**SIDE-EFFECTS, FURTHER INFORMATION**

- Gastrointestinal side-effects may require dose reduction or treatment interruption—consult product literature.

- **PREGNANCY** Manufacturer advises avoid—no information available.

- **PREGNANCY** Common or very common
- **SIDE-EFFECTS** Interactions
- **PREGNANCY** Common or very common
- **SIDE-EFFECTS** Interactions

6 Respiratory depression, respiratory distress syndrome and apnoea

**Respiratory stimulants**

Respiratory stimulants (analeptic drugs) have a limited place in the treatment of ventilatory failure in patients with chronic obstructive pulmonary disease. They are effective only when given by intravenous injection or infusion and have a short duration of action. Their use has largely been replaced by ventilatory support including nasal intermittent positive pressure ventilation. However, occasionally when
ventilatory support is contra-indicated and in patients with hypercapnic respiratory failure who are becoming drowsy or comatose, respiratory stimulants in the short term may arouse patients sufficiently to co-operate and clear their secretions.

Respiratory stimulants can also be harmful in respiratory failure since they stimulate non-respiratory as well as respiratory muscles. They should only be given under expert supervision in hospital and must be combined with active physiotherapy. There is at present no oral respiratory stimulant available for long-term use in chronic respiratory failure.

**RESPIRATORY STIMULANTS**

**Doxapram hydrochloride**

**INDICATIONS AND DOSE**

**Postoperative respiratory depression**

**INITIALLY BY INTRAVENOUS INJECTION**

- Adult: Initially 1–1.5 mg/kg, to be administered over at least 30 seconds, repeated if necessary after intervals of one hour, alternatively (by intravenous infusion) 2–3 mg/minute, adjusted according to response

**Acute respiratory failure**

**BY INTRAVENOUS INFUSION**

- Adult: 1.5–4 mg/minute, adjusted according to response, to be given concurrently with oxygen and whenever possible monitor with frequent measurement of blood gas tensions

**CONTRA-INDICATIONS**

- Cerebral oedema
- cerebrovascular accident
- coronary artery disease
- epilepsy and other convulsive disorders
- hyperthyroidism
- physical obstruction of respiratory tract
- severe hypertension
- status asthmaticus

**CAUTIONS**

- Give with beta₂ agonist in bronchoconstriction
- give with oxygen in severe irreversible airways obstruction or severely decreased lung compliance (because of increased work load of breathing)
- hypertension
- impaired cardiac reserve
- phaeochromocytoma

**INTERACTIONS**

- See Appendix 1 (doxapram).

**SIDE-EFFECTS**

- Arrhythmias
- bradycardia
- bronchospasm
- chest pain
- confusion
- convulsions
- cough
- dizziness
- dyspnoea
- extrasystoles
- flushing
- hallucination
- headache
- hyperactivity
- hypertension
- incontinence
- laryngospasm
- muscle spasms
- nausea
- perineal warmth
- pyrexia
- tachycardia
- urinary retention
- vomiting

**PREGNANCY**

- No evidence of harm, but manufacturer advises avoid unless benefit outweighs risk.

**HEPATIC IMPAIRMENT**

- Use with caution.

**MONITORING REQUIREMENTS**

- Frequent arterial blood gas and pH measurements are necessary during treatment to ensure correct dosage.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Doxapram hydrochloride 20 mg per 1 ml**
- **Doxapram hydrochloride 100 mg/5 ml**
  - solution for injection ampoules | 5 ampoule (PO) £30.00–£110.00

**Infusion**

- **Doxapram hydrochloride 2 mg per 1 ml**
- **Doxapram hydrochloride 1 g/500 ml**
  - infusion bags | 1 bag (PO) no price available
Chapter 4
Nervous system

1 Dementia

Dementia
Acetylcholinesterase inhibiting drugs are used in the treatment of Alzheimer’s disease, specifically for mild to moderate disease. Rivastigmine p. 264 is also licensed for mild to moderate dementia associated with Parkinson’s disease. The evidence to support the use of these drugs relates to their cognitive enhancement.

Treatment with drugs for dementia should be initiated and supervised only by a specialist experienced in the management of dementia.

Benefit is assessed by repeating the cognitive assessment at around 3 months. Such assessment cannot demonstrate how the disease may have progressed in the absence of treatment but it can give a good guide to response. Up to half the patients given these drugs will show a slower rate of cognitive decline. Drugs for dementia should be discontinued in those thought not to be responding. Many specialists repeat the cognitive assessment 4 to 6 weeks after discontinuation to assess deterioration; if significant deterioration occurs during this short period, consideration should be given to restarting therapy.

ANTICHLINORESTASES

Donepezil hydrochloride

- **DRUG ACTION** Donepezil is a reversible inhibitor of acetylcholinesterase.

**INDICATIONS AND DOSE**
Mild to moderate dementia in Alzheimer’s disease

BY MOUTH
- Adult: Initially 5 mg once daily for one month, then increased if necessary up to 10 mg daily, doses to be given at bedtime

- **CAUTIONS** Asthma · chronic obstructive pulmonary disease · sick sinus syndrome · supraventricular conduction abnormalities · susceptibility to peptic ulcers

- **INTERACTIONS** → Appendix 1 (parasympathomimetics). Caution with concomitant antipsychotic treatment—increased risk of neuroleptic malignant syndrome.

- **SIDE-EFFECTS**
  - **Common or very common** Abnormal dreams · aggression · agitation · anorexia · diarrhoea · dizziness · fatigue · hallucinations · headache · insomnia · muscle cramps · nausea · pruritus · rash · syncope · urinary incontinence · vomiting
  - **Uncommon** Bradycardia · duodenal ulcers · gastric ulcers · gastro-intestinal haemorrhage · seizures
  - **Rare** AV block · extrapyramidal symptoms · hepatitis · potential for bladder outflow obstruction · sino-atrial block
  - **Very rare** Neuroleptic malignant syndrome

**SIDE-EFFECTS, FURTHER INFORMATION**
Acetylcholinesterase inhibitors can cause unwanted dose-related cholinergic effects and should be started at a low dose and the dose increased according to response and tolerability.

- **HEPATIC IMPAIRMENT** Caution in mild to moderate impairment. No information available for severe impairment.

- **DIRECTIONS FOR ADMINISTRATION** Donepezil orodispersible tablet should be placed on the tongue, allowed to disperse, and swallowed.

- **PATIENT AND CARER ADVICE** Patient or carers should be given advice on how to administer donepezil hydrochloride orodispersible tablets.

**NATIONAL FUNDING/ACCESS DECISIONS**
NICE technology appraisals (TAs)
- Donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer’s disease (March 2011) NICE TA217

These drugs can be used for the treatment of mild to moderate Alzheimer’s disease. Treatment should only be prescribed under the following conditions:

- Alzheimer’s disease must be diagnosed and treatment initiated by a specialist; treatment can be continued by general practitioners under a shared-care protocol;
- the carer’s view of the condition should be sought before and during treatment;
Dementia 263

Galantamine

**DRUG ACTION** Galantamine is a reversible inhibitor of acetylcholinesterase and it also has nicotinic receptor agonist properties.

**INDICATIONS AND DOSE**

**Mild to moderate dementia in Alzheimer’s disease**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

- Adult: Initially 4 mg twice daily for 4 weeks, increased to 8 mg twice daily for 4 weeks; maintenance 8–12 mg twice daily

**Mild to moderate dementia in Alzheimer’s disease**

**BY MOUTH USING MODIFIED-RELEASE CAPSULES**

- Adult: Initially 8 mg once daily for 4 weeks, increased to 16 mg once daily for 4 weeks; maintenance 16–24 mg daily

**CAUTIONS** Asthma - avoid in gastro-intestinal obstruction • avoid in urinary retention - avoid whilst recovering from bladder surgery - avoid whilst recovering from gastro-intestinal surgery - cardiac disease - chronic obstructive pulmonary disease - congestive heart failure - electrolyte disturbances - history of seizures - pulmonary infection - sick sinus syndrome - supraventricular conduction abnormalities - susceptibility to peptic ulcers - unstable angina

**INTERACTIONS** → Appendix 1 (parasympathomimetics).

**SIDE-EFFECTS**

- Common or very common Abdominal pain • anorexia • bradycardia • depression • diarrhoea • dizziness • drowsiness • dyspepsia • hallucination • headache • hypertension • malaise • muscle spasm • nausea • sweating • syncpe • tremor • vomiting • weight loss

- Uncommon Arrhythmias • blunted vision • dehydration • first-degree AV block • flushing • hypotension • muscular weakness • palpitation • paraesthesia • seizures • taste disturbance • tinnitus

- Rare Exacerbation of Parkinson’s disease • hepatitis

**SIDE-EFFECTS, FURTHER INFORMATION** Acetylcholinesterase inhibitors can cause unwanted dose-related cholinergic effects and should be started at a low dose and the dose increased according to response and tolerability.

**PREGNANCY** Use with caution.

**BREAST FEEDING** Avoid—no information available.

**HEPATIC IMPAIRMENT** For immediate-release preparations in moderate impairment, initially 4 mg once daily (preferably in the morning) for at least 7 days, then 4 mg twice daily for at least 4 weeks; max. 8 mg twice daily; avoid in severe impairment. For modified-release preparations in moderate impairment, initially 8 mg on alternate days (preferably in the morning) for 7 days, then 8 mg once daily for 4 weeks; max. 16 mg daily; avoid in severe impairment.

**RENAL IMPAIRMENT** Avoid if eGFR less than 9 ml/minute/1.73 m².

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer’s disease (March 2011) NICE TA217

See Donepezil, p. 262. www.nice.org.uk/TA217

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

- **Tablet**
  - Donepezil hydrochloride 5 mg Donepezil 5mg tablets | 28 tablet [Pod] £59.85 DT price = £1.31
  - Donepezil hydrochloride 10 mg Donepezil 10mg tablets | 28 tablet [Pod] £83.89 DT price = £1.65
  - Aricept (Eisai Ltd)
    - Donepezil hydrochloride 5 mg Aricept 5mg tablets | 28 tablet [Pod] £59.85 DT price = £1.31
    - Donepezil hydrochloride 10 mg Aricept 10mg tablets | 28 tablet [Pod] £83.89 DT price = £1.65
- **Orodispensible tablet**
  - Donepezil hydrochloride 5 mg Donepezil 5mg orodispersible tablets | 28 tablet [Pod] £59.85
  - Donepezil hydrochloride 5 mg Donepezil 5mg orodispersible tablets sugar free (sugar-free) | 28 tablet [Pod] £5.35–£7.99 DT price = £6.75
  - Donepezil hydrochloride 10 mg Donepezil 10mg orodispersible tablets sugar free (sugar-free) | 28 tablet [Pod] £8.16–£8.99 DT price = £8.50
  - Donepezil 10mg orodispersible tablets | 28 tablet [Pod] £83.89
  - Aricept Evess (Eisai Ltd)
    - Donepezil hydrochloride 5 mg Aricept Evess 5mg orodispersible tablets (sugar-free) | 28 tablet [Pod] £59.85 DT price = £6.75
    - Donepezil hydrochloride 10 mg Aricept Evess 10mg orodispersible tablets (sugar-free) | 28 tablet [Pod] £83.89 DT price = £8.50
- **Oral solution**
  - Donepezil hydrochloride 1 mg per 1 ml Donepezil 1mg/ml oral solution sugar free (sugar-free) | 150 ml [Pod] £37.50 DT price = £37.50

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet

- **Tablet**
  - **CAUTIONARY AND ADVISORY LABELS**
    - **GALANTAMINE (Non-proprietary)**
      - Galantamine (as Galantamine hydrobromide) 8 mg Galantamine 8mg tablets | 56 tablet [Pod] £95.25–£94.90 DT price = £61.09
      - Galantamine (as Galantamine hydrobromide) 12 mg Galantamine 12mg tablets | 56 tablet [Pod] £71.25–£79.80 DT price = £74.10
      - Reminyl (Shire Pharmaceuticals Ltd)
        - Galantamine (as Galantamine hydrobromide) 8 mg Reminyl 8mg tablets | 56 tablet [Pod] £68.32 DT price = £61.09
        - Galantamine (as Galantamine hydrobromide) 12 mg Reminyl 12mg tablets | 56 tablet [Pod] £80.40 DT price = £74.10
  - **Modified-release capsule**
  - **CAUTIONARY AND ADVISORY LABELS**
    - **GALANTAMINE (Non-proprietary)**
      - Galantamine (as Galantamine hydrobromide) 8 mg Galantamine 8mg capsule | 28 capsule [Pod] £51.88 DT price = £51.88
      - Galantamine (as Galantamine hydrobromide) 16 mg Galantamine 16mg capsules | 28 capsule [Pod] £35.49 DT price = £35.49
      - Galantamine (as Galantamine hydrobromide) 24 mg Galantamine 24mg capsules | 28 capsule [Pod] £79.80 DT price = £79.80
      - Brands may include: Acicarm XL; Constil XL; Elminco; Galantex XL; Galia XL; Gatalin XL; Gazylan XL; Lotprosin XL; Luventa XL
  - **Oral solution**
  - **CAUTIONARY AND ADVISORY LABELS**
    - **GALANTAMINE (Non-proprietary)**
      - Galantamine (as Galantamine hydrobromide) 4 mg per 1 ml Galantamine 20mg/5ml oral solution sugar free (sugar-free) | 100 ml [Pod] £43.70
      - Reminyl (Shire Pharmaceuticals Ltd)
        - Galantamine (as Galantamine hydrobromide) 4 mg per 1 ml Reminyl 4mg/ml oral solution (sugar-free) | 100 ml [Pod] £120.00
Rivastigmine

**DRUG ACTION** Rivastigmine is a reversible non-competitive inhibitor of acetylcholinesterase.

**INDICATIONS AND DOSE**

**Mild to moderate dementia in Alzheimer’s disease**

**BY MOUTH**
- Adult: Initially 1.5 mg twice daily, increased in steps of 1.5 mg twice daily, to a maximum of 4.5 mg twice daily (max. per dose 6 mg twice daily), if treatment interrupted for more than several days, titrate from 1.5 mg twice daily.

**BY TRANSDERMAL APPLICATION USING PATCHES**
- Adult: Apply 4.6 mg/24 hours daily for at least 4 weeks, increased if tolerated, up to 9.5 mg/24 hours daily for a further 6 months, then increased if necessary to 13.3 mg/24 hours daily, increased to 13.3 mg/24 hours patch if well tolerated and cognitive deterioration or functional decline demonstrated; use caution in patients with body-weight less than 50 kg, if treatment interrupted for more than 3 days, titrate from 4.6 mg/24 hours patch.

**Mild to moderate dementia in Parkinson’s disease**

**BY MOUTH**
- Adult: Initially 1.5 mg twice daily, increased in steps of 1.5 mg twice daily, to a maximum of 4.5 mg twice daily (max. per dose 6 mg twice daily), if treatment interrupted for more than several days, titrate from 1.5 mg twice daily.

**Dose equivalence and conversion**

When switching from oral to transdermal therapy, patients taking 3–6 mg by mouth daily should initially switch to 4.6 mg/24 hours patch, then titrate as above. Patients taking 9 mg by mouth daily should switch to 9.5 mg/24 hours patch if oral dose stable and well tolerated; if oral dose not stable or well tolerated, patients should switch to 4.6 mg/24 hours patch, then titrate as above. Patients taking 12 mg by mouth daily should switch to 9.5 mg/24 hours patch. The first patch should be applied on the day following the last oral dose.

**CAUTIONS**


**INTERACTIONS** → Appendix 1 (parasympathomimetics).

**SIDE-EFFECTS**


- **Uncommon** Atrial fibrillation - AV block - depression - syncope.

- **Rare** Angina - duodenal ulceration - gastric ulceration - rash - seizures.

- **Very rare** Gastro-intestinal haemorrhage - hallucinations - hypertension - pancreatitis - tachycardia.

- **Frequency not known** Aggression - dehydration - hepatitis - restlessness - sick sinus syndrome - skin hypersensitivity reactions.

**SIDE-EFFECTS, FURTHER INFORMATION**

Transdermal administration less likely to cause gastro-intestinal disturbance.

Treatment should be interrupted if gastro-intestinal side-effects occur and withheld until their resolution—retitrate dose if necessary. Acetylcholinesterase inhibitors can cause unwanted dose-related cholinergic effects and should be started at a low dose and the dose increased according to response and tolerability.

- **HEPATIC IMPAIRMENT** Titrate according to individual tolerability in mild to moderate impairment. Use with caution in severe impairment—no information available.

- **RENAL IMPAIRMENT** Titrate according to individual tolerability.

**MONITORING REQUIREMENTS** Monitor body-weight.

**DIRECTIONS FOR ADMINISTRATION**

- With transdermal use, apply patches to clean, dry, non-hairy, non-irritated skin on back, upper arm, or chest, removing after 24 hours and siting a replacement patch on a different area (avoid using the same area for 14 days).

**PATIENT AND CARER ADVICE**

**EXELON® TRANSDERMAL PATCHES.** Advise patients and carers of patch administration instructions, particularly to remove the previous day’s patch before applying the new patch—consult product literature.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**


**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (October 2007) that Exelon® patches should be restricted for use in patients with moderately severe Alzheimer’s disease under the conditions of the NICE guidance (September 2007) and when a transdermal patch is an appropriate choice of formulation.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

**CAUTIONARY AND ADVISORY LABELS 21, 25**

- **RIVASTIGMINE (Non-proprietary)**

  - Rivastigmine (as Rivastigmine hydrogen tartrate) 1.5 mg Rivastigmine 1.5 mg capsules 28 capsule £33.25 DT price = £3.25 | 56 capsule £66.51

  - Rivastigmine (as Rivastigmine hydrogen tartrate) 3 mg Rivastigmine 3 mg capsules 28 capsule £33.25 DT price = £3.27 | 56 capsule £66.51

  - Rivastigmine (as Rivastigmine hydrogen tartrate) 4.5 mg Rivastigmine 4.5 mg capsules 28 capsule £33.25 DT price = £3.27 | 56 capsule £66.51

  - Rivastigmine (as Rivastigmine hydrogen tartrate) 6 mg Rivastigmine 6 mg capsules 28 capsule £33.25 DT price = £3.27 | 56 capsule £66.51

  - Exelon (Novartis Pharmaceuticals UK Ltd)

  - Rivastigmine (as Rivastigmine hydrogen tartrate) 1.5 mg Exelon 1.5 mg capsules 28 capsule £33.25 DT price = £3.25 | 56 capsule £66.51

  - Rivastigmine (as Rivastigmine hydrogen tartrate) 3 mg Exelon 3 mg capsules 28 capsule £33.25 DT price = £3.25 | 56 capsule £66.51

  - Rivastigmine (as Rivastigmine hydrogen tartrate) 4.5 mg Exelon 4.5 mg capsules 28 capsule £33.25 DT price = £15.82 | 56 capsule £66.51

  - Rivastigmine (as Rivastigmine hydrogen tartrate) 6 mg Exelon 6 mg capsules 28 capsule £33.25 DT price = £15.74 | 56 capsule £66.51

  - Brands may include Kerstinol; Ninmavist
Oral solution

CAUTIONARY AND ADVISORY LABELS 21

▶ RIVASTIGMINE (Non-proprietary)

Rivastigmine (as Rivastigmine hydrochloride) 2 mg per 1 ml Rivastigmine 2mg/ml oral solution | 120 ml (Pharm) £96.75–£94.18

Rivastigmine 2mg/ml oral solution sugar free (sugar-free) | 120 ml (Pharm) £96.81–£96.82 DT price = £96.81

▶ Exelon (Novartis Pharmaceuticals UK Ltd)

Rivastigmine (as Rivastigmine hydrochloride tartrate) 2 mg per 1 ml Exelon 2mg/ml oral solution (sugar-free) | 120 ml (Pharm) £99.14 DT price = £96.81

Transdermal patch

▶ RIVASTIGMINE (Non-proprietary)

Rivastigmine 4.6 mg per 24 hour Rivastigmine 4.6mg/24hours transdermal patches | 30 patch (Pharm) £77.97 DT price = £77.97

Rivastigmine 9.5 mg per 24 hour Rivastigmine 9.5mg/24hours transdermal patches | 30 patch (Pharm) £31.69 DT price = £31.69

▶ Exelon (Novartis Pharmaceuticals UK Ltd)

Rivastigmine 4.6 mg per 24 hour Exelon 4.6mg/24hours transdermal patches | 30 patch (Pharm) £77.97 DT price = £77.97

Rivastigmine 9.5 mg per 24 hour Exelon 9.5mg/24hours transdermal patches | 30 patch (Pharm) £31.69 DT price = £31.69

Rivastigmine 13.3 mg per 24 hour Exelon 13.3mg/24hours transdermal patches | 30 patch (Pharm) £77.97 DT price = £77.97

▶ Brands may include Alzest, Eluden, Prometax, Rivatev, Somnition, Vokeze

NMDA RECEPTOR ANTAGONISTS

Memantine hydrochloride

▶ DRUG ACTION Memantine is a glutamate receptor antagonist.

INDICATIONS AND DOSE

Moderate to severe dementia in Alzheimer’s disease

BY MOUTH

▶ Adult: Initially 5 mg once daily, increased in steps of 5 mg at weekly intervals; maximum 20 mg per day

▶ CAUTIONS History of convulsions

▶ INTERACTIONS → Appendix 1 (memantine).

SIDE-EFFECTS

▶ Common or very common Constipation, dizziness, drowsiness, dyspnoea, headache, hypertension

▶ Uncommon Abnormal gait, confusion, fatigue, hallucinations, heart failure, thrombosis, vomiting

▶ Very rare Seizures

▶ Frequency not known Depression, pancreatitis, psychosis, suicidal ideation

▶ HEPATIC IMPAIRMENT Avoid in severe impairment—no information available.

▶ RENAL IMPAIRMENT Reduce dose to 10 mg daily if eGFR 30–49 mL/minute/1.73 m², if well tolerated after at least 7 days can be increased in steps to 20 mg daily; reduce dose to 10 mg daily if eGFR 5–29 mL/minute/1.73 m². Avoid if eGFR less than 5 mL/minute/1.73 m².

▶ DIRECTIONS FOR ADMINISTRATION Oral solution should be dosed onto a spoon or into a glass of water.

▶ NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

▶ Donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer’s disease (March 2011) NICE TA217

See Donepezil, p. 262. www.nice.org.uk/TA217

▶ MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

▶ MEMANTINE HYDROCHLORIDE (Non-proprietary)

Memantine hydrochloride 10 mg Memantine 10mg tablets | 28 tablet (Pharm) £34.50 DT price = £1.86 | 56 tablet (Pharm) £65.56 | 112 tablet (Pharm) £100.10

Memantine hydrochloride 20 mg Memantine 20mg tablets | 28 tablet (Pharm) £99.01 DT price = £2.63

▶ Ebixa (Lundbeck Ltd)

Memantine hydrochloride 5 mg Ebixa 5mg tablets | 7 tablet (Pharm) no price available

Memantine hydrochloride 10 mg Ebixa 10mg tablets | 7 tablet (Pharm) no price available | 28 tablet (Pharm) £34.50 DT price = £1.86 | 56 tablet (Pharm) £69.01 | 112 tablet (Pharm) £138.01

Memantine hydrochloride 15 mg Ebixa 15mg tablets | 7 tablet (Pharm) no price available

Memantine hydrochloride 20 mg Ebixa 20mg tablets | 7 tablet (Pharm) no price available | 28 tablet (Pharm) £69.01 DT price = £2.63

▶ Ebixa (Lundbeck Ltd)

Ebixa tablets treatment initiation pack | 28 tablet (Pharm) £43.13

▶ Brands may include Marixa, Nendamite

Oral solution

▶ MEMANTINE HYDROCHLORIDE (Non-proprietary)

Memantine hydrochloride 10 mg per 1 ml Memantine 10mg/ml oral solution sugar free (sugar-free) | 50 ml (Pharm) £55.00–£62.36 DT price = £62.24 (sugar-free) | 100 ml (Pharm) £110.00–£124.72

▶ Ebixa (Lundbeck Ltd)

Memantine hydrochloride 10 mg per 1 ml Ebixa 5mg/0.5ml pump actuation oral solution (sugar-free) | 50 ml (Pharm) £61.61 DT price = £62.24 (sugar-free) | 100 ml (Pharm) £123.23

2 Mental health disorders

2.1 Anxiety

Drugs used for Anxiety not listed below; Duloxetine, p. 288; Escitalopram, p. 285; Moclobemide, p. 283; Oxprenolol hydrochloride, p. 145; Paroxetine, p. 287; Pericyazine, p. 308; Perphenazine, p. 308; Pregabalin, p. 400; Trazodone hydrochloride, p. 291; Trifluoperazine, p. 310; Venlafaxine, p. 289

CARBAMATES

Meprobamate

INDICATIONS AND DOSE

Short-term use in anxiety—not recommended

BY MOUTH

▶ Adult: 400 mg 3–4 times a day

▶ Elderly: Up to 200 mg 3–4 times a day

Important safety information

The European Medicines Agency has recommended (January 2012) the suspension of all marketing authorisations for meprobamate because the risks, particularly of serious CNS side-effects, outweigh the benefits.

▶ CONTRA-INDICATIONS Acute porphyrias p. 864 - acute pulmonary insufficiency - respiratory depression

▶ CAUTIONS Abrupt withdrawal (may precipitate convulsions) - avoid prolonged use - debilitated elderly - epilepsy (may induce seizures) - history of alcohol abuse - history of drug abuse - marked personality disorder - muscle weakness - respiratory disease

▶ INTERACTIONS → Appendix 1 (anxiolytics and hypnotics).

SIDE-EFFECTS

▶ Common or very common Amnesia - ataxia (especially in the elderly) - confusion (especially in the elderly) - dependence - drowsiness the next day - lightheadedness the next day - muscle weakness - paradoxical increase in aggression

▶ Uncommon Changes in libido - dizziness - dysarthria - gastro-intestinal disturbances - gynaecomastia - headache - hypotension - incontinence - salivation changes -
slurred speech • tremor • urinary retention • vertigo • visual disturbances

▶ Rare Agranulocytosis • apnoea • blood disorders • jaundice • rashes • respiratory depression • skin reactions

▶ Frequency not known CNS effects • paradoxical excitement • paraesthesia • weakness

ʼ PREGNANCY  Avoid if possible.

ʼ BREAST FEEDING  Avoid. Concentration in milk may exceed maternal plasma concentrations fourfold and may cause drowsiness in infant.

ʼ HEPATIC IMPAIRMENT  Can precipitate coma.

ʼ RENAL IMPAIRMENT  Increased cerebral sensitivity. Start with small doses in severe impairment.

ʼ PATIENT AND CARER ADVICE  Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

ʼ LESS SUITABLE FOR PRESCRIBING  Meprobamate is less suitable for prescribing.

ʼ MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

Tablet

CAUTIONARY AND ADVISORY LABELS 2

ʼ MEPROBAMATE (Non-proprietary)
Meprobamate 400 mg Meprobamate 400 mg tablets | 84 tablet (£197.63–£200.54 DT price + £200.54 Schedule 3 (CD No Register)

HYPNOTICS AND SEDATIVES (BENZODIAZEPINE)

Benzodiazepines

ʼ CONTRA-INDICATIONS  Acute pulmonary insufficiency • marked neuromuscular respiratory weakness • sleep apnoea syndrome • unstable myocardial gravis

ʼ CAUTIONS  Avoid prolonged use (and abrupt withdrawal thereafter) • debilitated patients (reduce dose) • elderly (reduce dose) • history of alcohol dependence or abuse • history of drug dependence or abuse • myasthenia gravis • respiratory disease

ʼ CAUTIONS, FURTHER INFORMATION  Paradoxical effects  A paradoxical increase in hostility and aggression may be reported by patients taking benzodiazepines. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects.

ʼ INTERACTIONS  → Appendix 1 (anxiolytics and hypnotics).

ʼ SIDE-EFFECTS

Overdose  Benzodiazepines taken alone cause drowsiness, ataxia, dysarthritis, nystagmus, and occasionally respiratory depression, and coma. For details on the management of poisoning, see Benzodiazepines, under Emergency treatment of poisoning p. 1123.

ʼ PREGNANCY  Risk of neonatal withdrawal symptoms when used during pregnancy. Avoid regular use and use only if there is a clear indication such as seizure control. High doses administered during late pregnancy or labour may cause neonatal hypothermia, hypotonia, and respiratory depression.

ʼ RENAL IMPAIRMENT  Increased cerebral sensitivity to benzodiazepines.

ʼ PATIENT AND CARER ADVICE  Drowsiness may persist the next day and affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

For information on 2015 legislation regarding driving whilst taking certain controlled drugs, including benzodiazepines, see Drugs and driving under Guidance on prescribing p. 1.

Alprazolam

INDICATIONS AND DOSE

Short-term use in anxiety

BY MOUTH

ʼ Adult: 250–500 micrograms 3 times a day, increased if necessary up to 3 mg daily, for debilitated patients, use elderly dose

ʼ Elderly: 250 micrograms 2–3 times a day, increased if necessary up to 3 mg daily

ʼ CONTRA-INDICATIONS  Chronic psychosis • hyperkinesis • not for use alone to treat depression (or anxiety associated with depression) • obsessional states • phobic states • respiratory depression

ʼ CAUTIONS  Muscle weakness • organic brain changes • personality disorder (within the fearful group—dependent, avoidant, obsessive-compulsive) may increase risk of dependence

ʼ SIDE-EFFECTS

▶ Common or very common  Amnesia • ataxia (especially in the elderly) • confusion (especially in the elderly) • dependence • drowsiness the next day • lightheadedness the next day • muscle weakness • paradoxical increase in aggression

▶ Uncommon  Changes in libido • dizziness • dystarthritis • gastro-intestinal disturbances • gynaecomastia • headache • hypotension • incontinence • salivation changes • slurred speech • tremor • urinary retention • vertigo • visual disturbances

ʼ Rare  Agranulocytosis • apnoea • blood disorders • jaundice • respiratory depression • skin reactions

ʼ BREAST FEEDING  Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding.

ʼ HEPATIC IMPAIRMENT  Can precipitate coma. If treatment is necessary, benzodiazepines with shorter half-lives (such as temazepam or oxazepam) are safer. Start with smaller initial doses or reduce dose. Avoid in severe impairment.

ʼ RENAL IMPAIRMENT  Start with small doses in severe impairment.

ʼ PATIENT AND CARER ADVICE  May impair judgement and increase reaction time, and so affect ability to drive or operate machinery; they increase the effects of alcohol. Moreover the hangover effects of a night dose may impair driving on the following day.

ʼ NATIONAL FUNDING/ACCESS DECISIONS  NHS restrictions  Alprazolam tablets are not prescribable under the NHS.

ʼ MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 2

ʼ XANAX (Pfizer Ltd)
Xanax 250 microgram Xanax 250 microgram tablets | 60 tablet (£3.18 Schedule 4 (CD Benz))

Xanax 500 microgram Xanax 500 microgram tablets | 60 tablet (£6.09 Schedule 4 (CD Benz))
Chlordiazepoxide hydrochloride

INDICATIONS AND DOSE
Short-term use in anxiety
BY MOUTH
- Adult: 10 mg 3 times a day, increased if necessary to 60–100 mg daily in divided doses, for debilitated patients, use elderly dose
- Elderly: 5 mg 3 times a day, increased if necessary to 30–50 mg daily in divided doses

Treatment of alcohol withdrawal in moderate dependence
BY MOUTH
- Adult: 10–30 mg 4 times a day, dose to be gradually reduced over 5–7 days, consult local protocols for titration regimens

Treatment of alcohol withdrawal in severe dependence
BY MOUTH
- Adult: 10–50 mg 4 times a day and 10–40 mg as required for the first 2 days, dose to be gradually reduced over 7–10 days, consult local protocols for titration regimens; maximum 250 mg per day

CONTRA-INDICATIONS
- Chronic psychosis, hyperkinesia
- Not for use alone to treat depression (or anxiety associated with depression), obsessional states, phobic states, respiratory depression

CAUTIONS
- Muscle weakness, organic brain changes
- Personality disorder (within the fearful group—dependent, avoidant, obsessive–compulsive) may increase risk of dependence

SIDE-EFFECTS
- Common or very common
  - Amnesia; ataxia (especially in the elderly) - confusion (especially in the elderly)
  - Drowsiness next day
  - Lightheadedness next day
  - Muscle weakness, paradoxic increase in aggression
- Uncommon
  - Changes in libido - dizziness - dysarthria
  - Gastro-intestinal disturbances - gynaecomastia - headache
  - Hypotension - incontinence - salivation changes - slurred speech - tremor - urinary retention - vertigo - visual disturbances
- Rare
  - Apnoea - blood disorders - jaundice - respiratory depression - skin reactions

BREAST FEEDING
- Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding.

HEPATIC IMPAIRMENT
- Can precipitate coma. If treatment is necessary, benzodiazepines with shorter half-lives (such as temazepam or oxazepam) are safer. Start with smaller initial doses or reduce dose. Avoid in severe impairment.

RENAL IMPAIRMENT
- Start with small doses in severe impairment.

PATIENT AND CAREGIVER ADVICE
- May impair judgement and increase reaction time, and so affect ability to drive or operate machinery; chlordiazepoxide increases the effects of alcohol. Moreover the hangover effects of a night dose may impair driving on the following day.

NATIONAL FUNDING/ACCESS DECISIONS
- NHS restrictions. Librium® is not prescribable under the NHS.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

Tablet
- CAUTIONARY AND ADVISORY LABELS 2
- Chlordiazepoxide hydrochloride (Non-proprietary)
  - Chlordiazepoxide (as Chlordiazepoxide hydrochloride)
  - 10 mg Chlordiazepoxide 10mg tablets | 100 tablet | £49.50 DT

Capsule
- CAUTIONARY AND ADVISORY LABELS 2
- Chlordiazepoxide hydrochloride (Non-proprietary)
  - Chlordiazepoxide hydrochloride 5 mg
    - Chlordiazepoxide 5mg capsules | 28 capsule | £4.60 Schedule 4 (CD Benz)
    - 100 capsule | £10.96 DT price + £9.53 Schedule 4 (CD Benz)
  - Chlordiazepoxide hydrochloride 10 mg
    - Chlordiazepoxide 10mg capsules | 28 capsule | £5.15 Schedule 4 (CD Benz)
    - 100 capsule | £18.00 DT price + £16.08 Schedule 4 (CD Benz)
- Librium (Meda Pharmaceuticals Ltd)
  - Chlordiazepoxide hydrochloride 5 mg
    - Librium 5mg capsules | 100 capsule | £5.38 DT price + £9.53 Schedule 4 (CD Benz)
  - Chlordiazepoxide hydrochloride 10 mg
    - Librium 10mg capsules | 100 capsule | £7.46 DT price + £16.08 Schedule 4 (CD Benz)

Diazepam

INDICATIONS AND DOSE
Muscle spasm of varied aetiology
BY MOUTH
- Adult: 2–15 mg daily in divided doses, then increased if necessary to 60 mg daily, adjusted according to response, dose only increased in spastic conditions

Acute muscle spasm
BY INTRAMUSCULAR INJECTION OR BY SLOW INTRAVENOUS INJECTION
- Adult: 10 mg, then 10 mg after 4 hours if required, intravenous injection to be administered into a large vein at a rate of no more than 5 mg/minute

Tetanus
BY INTRAVENOUS INJECTION
- Child: 100–300 micrograms/kg every 1–4 hours
- Adult: 100–300 micrograms/kg every 1–4 hours

BY INTRAVENOUS INFUSION OR BY NASODUODENAL TUBE
- Child: 3–10 mg/kg, adjusted according to response, to be given over 24 hours
- Adult: 3–10 mg/kg, adjusted according to response, to be given over 24 hours

Muscle spasm in cerebral spasticity or in postoperative skeletal muscle spasm
BY MOUTH
- Child 1-11 months: Initially 250 micrograms/kg twice daily
- Child 1-4 years: Initially 2.5 mg twice daily
- Child 5-11 years: Initially 5 mg twice daily
- Child 12-17 years: Initially 10 mg twice daily; maximum 40 mg per day

Anxiety
BY MOUTH
- Adult: 2 mg 3 times a day, then increased if necessary to 15–30 mg daily in divided doses, for debilitated patients, use elderly dose
- Elderly: 1 mg 3 times a day, then increased if necessary to 7.5–15 mg daily in divided doses

Insomnia associated with anxiety
BY MOUTH
- Adult: 5–15 mg daily, to be taken at bedtime

Severe acute anxiety / Control of acute panic attacks / Acute alcohol withdrawal
INITIALLY BY INTRAMUSCULAR INJECTION OR BY SLOW INTRAVENOUS INJECTION
- Adult: 10 mg, then (by intramuscular injection or by intravenous injection) 10 mg after at least 4 hours if required, intravenous injection to be administered into a large vein, at a rate of not more than 5 mg/minute

continued →
Acute anxiety and agitation

BY RECTUM
- Adult: 500 micrograms/kg, then 500 micrograms/kg after 12 hours as required
- Elderly: 250 micrograms/kg, then 250 micrograms/kg after 12 hours as required

Acute drug-induced dystonic reactions

BY INTRAVENOUS INJECTION
- Adult: 5–10 mg, then 5–10 mg after at least 10 minutes as required, to be administered into a large vein, at a rate of not more than 5 mg/minute

Premedication

BY MOUTH
- Adult: 5–10 mg, to be given 1–2 hours before procedure, for depleted patients, use elderly dose
- Elderly: 2.5–5 mg, to be given 1–2 hours before procedure

BY INTRAVENOUS INJECTION
- Adult: 100–200 micrograms/kg, to be administered into a large vein at a rate of not more than 5 mg/minute, immediately before procedure

Sedation in dental procedures carried out in hospital

BY MOUTH
- Adult: Up to 20 mg, to be given 1–2 hours before procedure

Conscious sedation for procedures, and in conjunction with local anaesthesia

BY MOUTH
- Adult: 5–10 mg, to be given 1–2 hours before procedure, for depleted patients, use elderly dose
- Elderly: 2.5–5 mg, to be given 1–2 hours before procedure

Sedative cover for minor surgical and medical procedures

BY INTRAVENOUS INJECTION
- Adult: 10–20 mg, to be administered into a large vein over 2–4 minutes, immediately before procedure

Status epilepticus | Febrile convulsions | Convulsions due to poisoning

BY INTRAVENOUS INJECTION
- Neonate: 1.25–2.5 mg, then 1.25–2.5 mg after 10 minutes if required.
- Child 1 month-1 year: 5 mg, then 5 mg after 10 minutes if required
- Child 2-11 years: 5–10 mg, then 5–10 mg after 10 minutes if required
- Child 12-17 years: 10–20 mg, then 10–20 mg after 10 minutes if required
- Adult: 10–20 mg, then 10–20 mg after 10 minutes if required
- Elderly: 10 mg, then 10 mg after 10–15 minutes if required

BY RECTUM
- Neonate: 1.25–2.5 mg, then 1.25–2.5 mg after 10 minutes if required.
- Child 1 month-1 year: 5 mg, then 5 mg after 10 minutes if required
- Child 2-11 years: 5–10 mg, then 5–10 mg after 10 minutes if required
- Child 12-17 years: 10 micrograms/kg, repeated if necessary, to be given over 3–5 minutes
- Child 12-17 years: 5–10 mg, repeated if necessary, to be given over 3–5 minutes

Dyspnoea associated with anxiety in palliative care

BY MOUTH
- Adult: 5–10 mg daily

Pain of muscle spasm in palliative care

BY MOUTH
- Adult: 5–10 mg daily

**UNLICENSED USE**

**CONTRA-INDICATIONS**
- Avoid injections containing benzyl alcohol in neonates.
- Chronic psychosis (in adults).
- CNS depression.
- Compromised airway.
- Hypokinesia.
- Not for use alone to treat depression (or anxiety associated with depression).
- (in adults).
- Obsessive–compulsive.

**CAUTIONS**
- General caution.
- Muscle weakness.
- Organic brain changes.
- Parenteral administration (close observation required until full recovery from sedation).
- Personality disorder.
- (within the fearful group—dependent, avoidant, obsessive–compulsive).

**SPECIFIC CAUTIONS**
- With intravenous use.
- High risk of venous thrombophlebitis.
- With intravenous use (reduced by using an emulsion formulation).

**CAUTIONS, FURTHER INFORMATION**
- Special precautions for intravenous injection.
- When given intravenously for reversing respiratory depression with mechanical ventilation must be immediately available.

**SIDE-EFFECTS**
- General side-effects.
- Common or very common.
- Amnesia.
- Ataxia (in children).
- Ataxia (especially in the elderly).
- Confusion (in children).
- Confusion (especially in the elderly).
- Dependence.
- Drowsiness the next day.
- Lightheadedness.
- Muscle weakness.
- Paradoxical increase in aggression.
- Uncommon.
- Changes in libido.
- Dizziness.
- Dysarthria.
- Gastro-intestinal disturbances.
- Gynaecomastia.
- Headache.
- Hypotension.
- Incontinence.
- Salivation changes.
- Slurred speech.
- Tremor.
- Urinary retention.
- Vertigo.
- Visual disturbances.
- Rare.
- Apnoea.
- Blood disorders.
- Changes in libido.
- Headache.
- Hypotension.
- Jaundice.
- Respiratory depression.
- Skin reactions.
- Urinary retention.
- Vertigo.

**FREQUENCY NOT KNOWN**
- Delusions.
- Excitement.
- Hallucinations.
- Hypotonia.
- Irritability.
- Marked respiratory depression.
- Particularly high dose.
- Facilities for its treatment are essential.
- Psychosis.
- Restlessness.

**SPECIFIC SIDE-EFFECTS**
- With intravenous use.
- Pain.
- Thrombophlebitis.
- Venous thrombosis.

**PREGNANCY**
- Women who have seizures in the second half of pregnancy should be assessed for eclampsia before any...
change is made to antiepileptic treatment. Status epilepticus should be treated according to the standard protocol.

**Epilepsy and Pregnancy Register** All pregnant women with epilepsy, whether taking medication or not, should be encouraged to notify the UK Epilepsy and Pregnancy Register (Tel: 0800 389 1246).

- **BREAST FEEDING** Present in milk, and should be avoided if possible during breast-feeding.
- **HEPATIC IMPAIRMENT** Can precipitate coma. If treatment is necessary, benzodiazepines with shorter half lives are safer, such as temazepam or oxazepam. Start with smaller initial doses or reduce dose. Avoid in severe impairment.
- **RENAL IMPAIRMENT** Start with small doses in severe impairment.

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use **Diazepam** is adsorbed by plastics of infusion bags and giving sets.
- With intravenous use **Emulsion formulation preferred for intravenous injection.**
- With intravenous use in children For continuous intravenous infusion of diazepam emulsion, dilute to a concentration of max. 400 micrograms/mL with Glucose 5% or 10%; max. 6 hours between addition and completion of infusion. For continuous intravenous infusion of diazepam solution, dilute to a concentration of max. 50 micrograms/mL with Glucose 5% or Sodium Chloride 0.9%.
- With intravenous use in adults For intravenous infusion (solution) **Diazepam, Wockhardt,** give continuously in Glucose 5% or Sodium chloride 0.9%. Dilute to a concentration of not more than 10 mg in 200 mL.
- With intravenous use in adults For intravenous infusion (emulsion) **Diazemuls**, give continuously in Glucose 5% or 10%. May be diluted to a max. concentration of 200 mg in 500 mL; max. 6 hours between addition and completion of administration. May be given via drip tubing in Glucose 5% or 10% or Sodium chloride 0.9%.
- With intramuscular use or intravenous use in adults Solution for injection should not be diluted, except for intravenous infusion.
- With intramuscular use in adults Only use intramuscular route when oral and intravenous routes not possible.

- **PATIENT AND CARER ADVICE** May impair judgement and increase reaction time, and so affect ability to drive or perform skilled tasks; they increase the effects of alcohol. Moreover the hangover effects of a night dose may impair performance on the following day.

**Serotonergic Medications**

**INDICATIONS AND DOSE**

**Anxiety (short-term use)**

**By mouth**

- Adult: 5 mg 2–3 times a day, increased if necessary up to 45 mg daily, dose to be increased at intervals of 2–3 days; usual dose 15–30 mg daily in divided doses

- **CONTRA-INDICATIONS** Acute porphyrias p. 864 - epilepsy
- **CAUTIONS** Does not alleviate symptoms of benzodiazepine withdrawal

**CAUTIONS, FURTHER INFORMATION**

A patient taking a benzodiazepine still needs to have the benzodiazepine withdrawn gradually; it is advisable to do this before starting buspirone.

**INTERACTIONS** → Appendix 1 (anxiolytics and hypnotics).

**SIDE-EFFECTS**

- Common or very common Dizziness - excitement - headache - nausea - nervousness
- Rare Chest pain - confusion - drowsiness - dry mouth - fatigue - palpitation - seizures - sweating - tachycardia
- **PREGNANCY** Avoid.

**Breastfeeding** Avoid.
Nervous system

(Dexamphetamine sulfate)

CNS STIMULANTS (AMFETAMINE ISOMERS)

lisdexamfetamine mesilate p. (dexamfetamine sulfate below and amfetamines

Central nervous system stimulants include the

Attention deficit hyperactivity disorder

Attention deficit hyperactivity disorder

Central nervous system stimulants include the amfetamines (dexamfetamine sulfate below and lisdexamfetamine mesilate p. 271) and related drugs (e.g. methylphenidate hydrochloride p. 273). They have very few indications and in particular, should not be used to treat depression, obesity, senility, debility, or for relief of fatigue. CNS stimulants should be prescribed for children with severe and persistent symptoms of attention deficit hyperactivity disorder (ADHD), when the diagnosis has been confirmed by a specialist; children with moderate symptoms of ADHD can be treated with CNS stimulants when psychological interventions have been unsuccessful or are unavailable. Prescribing of CNS stimulants may be continued by general practitioners, under a shared-care arrangement. Treatment of ADHD often needs to be continued into adolescence, and may need to be continued into adulthood.

Drug treatment of ADHD should be part of a comprehensive treatment programme. The choice of medication should take into consideration co-morbid conditions (such as tic disorders, Tourette syndrome, and epilepsy), the adverse effect profile, potential for drug misuse, tolerance and dependance; and preferences of the patient and carers. Methylphenidate hydrochloride and atomoxetine are used for the management of ADHD; dexamfetamine sulfate and lisdexamfetamine mesilate are alternative in children who do not respond to these drugs.

The need to continue drug treatment for ADHD should be reviewed at least annually. This may involve suspending treatment.

CNS STIMULANTS (AMFETAMINE ISOMERS)

Dexamfetamine sulfate
(Desmethylamphetamine sulfate)

INDICATIONS AND DOSE

Narcolepsy
BY MOUTH
Adult: Initially 10 mg daily in divided doses, increased in steps of 10 mg every 1 week, maintenance dose to be given in 2–4 divided doses; maximum 60 mg per day

Elderly: Initially 5 mg daily in divided doses, increased in steps of 5 mg every 1 week, maintenance dose to be given in 2–4 divided doses; maximum 60 mg per day

Refactory attention deficit hyperactivity disorder (initiated under specialist supervision)

BY MOUTH
Child 6–17 years: Initially 2.5 mg 2–3 times a day, increased in steps of 5 mg daily if required, dose to be increased at weekly intervals, increased if necessary up to 1 mg/kg daily, maintenance dose to be given in 2–4 divided doses, up to 20 mg daily (40 mg daily has been required in some children)

Adult: Initially 5 mg twice daily, dose is increased at weekly intervals according to response, maintenance dose to be given in 2–4 divided doses; maximum 60 mg per day

UNLICENSED USE Not licensed for use in adults for refractory attention deficit hyperactivity disorder.

CONTRA-INDICATIONS Advanced arteriosclerosis (in adults) - agitated states - cardiovascular disease - history of alcohol abuse - history of drug abuse - hyperexcitability - hyperthyroidism - moderate hypertension - severe hypertension - structural cardiac abnormalities

CAUTIONS Anorexia - bipolar disorder - history of epilepsy (discontinue if seizures occur) - mild hypertension - psychosis - susceptibility to angle-closure glaucoma - tics - Tourette syndrome

CAUTIONS, FURTHER INFORMATION

Tics and Tourette syndrome Discontinue use if tics occur.

Growth restriction in children Monitor height and weight as growth restriction may occur during prolonged therapy (drug-free periods may allow catch-up in growth but withdraw slowly to avoid inducing depression or renewed hyperactivity).

INTERACTIONS Appendix 1 (sympathomimetics).

SIDE-EFFECTS


Very rare Angle-closure glaucoma

Frequency not known Choreoathetoid movements (in predisposed individuals) - dyskinesia (in predisposed individuals) - increased appetite - tics (in predisposed individuals)

Overdose Amphetamines cause wakefulness, excessive activity, paranoia, hallucinations, and hypertension followed by exhaustion, convulsions, hyperthermia, and coma. See Stimulants under Emergency treatment of poisoning, p. 1123.

PREGNANCY Avoid (retrospective evidence of uncertain significance suggesting possible embryotoxicity).

BREAST FEEDING Significant amount in milk—avoid.

RENAI IMPAIRMENT Use with caution.
Lisdexamfetamine mesilate

**DRUG ACTION** Lisdexamfetamine is a prodrug of dexamfetamine.

**INDICATIONS AND DOSE**

Attention deficit hyperactivity disorder refractory to methylphenidate (initiated by a specialist) by mouth

- **Child 6-17 years:** Initially 30 mg once daily, increased in steps of 20 mg every week if required, dose to be taken in the morning, discontinue if response insufficient after 1 month; maximum 70 mg per day
- **Adult:** Initially 30 mg once daily, increased in steps of 20 mg every week if required, dose to be taken in the morning, discontinue if response insufficient after 1 month; maximum 70 mg per day

**UNLICENSED USE**

Not licensed for use in adults for attention deficit hyperactivity disorder.

**CONTRA-INDICATIONS** Advanced arteriosclerosis - agitated states - hypereexcitability - hyperthyroidism - moderate hypertension - severe hypertension - symptomatic cardiovascular disease

**CAUTIONS** Anorexia - bipolar disorder - history of alcohol abuse - history of cardiac abnormalities - history of cardiovascular disease - history of drug abuse - may lower seizure threshold (discontinue if seizures occur) - psychosis - susceptibility to angle-closure glaucoma - tics - Tourette syndrome

**TREATMENT CESSATION** Avoid abrupt withdrawal.

**DIRECTIONS FOR ADMINISTRATION**

- With oral use in children Tablets can be halved.

**PRESCRIBING AND DISPENSING INFORMATION**

Data on safety and efficacy of long-term use not complete.

**PATIENT AND CARER ADVICE**

**DRUGS AND DRIVING** Prescribers and other healthcare professionals should advise patients if treatment is likely to affect their ability to perform skilled tasks (e.g. driving). This applies especially to drugs with sedative effects; patients should be warned that these effects are increased by alcohol. General information about a patient’s fitness to drive is available from the Driver and Vehicle Licensing Agency at [www.dvla.gov.uk](http://www.dvla.gov.uk).

For information on 2012 legislation regarding driving whilst taking certain controlled drugs, including amfetamines, see *Drugs and driving* under Guidance on prescribing p. 1.

**NATIONAL FUNDING/ACCESS DECISIONS**

NICE technology appraisals (TAs)

- Methylenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) (March 2006) NICE TA98

Dexamfetamine is recommended, within its licensed indications, as an option for the management of ADHD in children and adolescents. [www.nice.org.uk/TA98](http://www.nice.org.uk/TA98)

**MEDICINAL FORMS**

There can be variations in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension, modified-release capsule

- **Tablet**
  - DEXAMFETAMINE SULFATE (Non-proprietary)
  - Dexamfetamine sulfate 5 mg Dexamfetamine 5mg tablets | 28 tablet [P] £24.75 DT price £24.75 Schedule 2 (CD)

- **Oral solution**
  - DEXAMFETAMINE SULFATE (Non-proprietary)
  - Dexamfetamine sulfate 1 mg per 1 ml Dexamfetamine 5mg/5ml oral solution sugar free (sugar-free) | 500 ml [P] £109.04 DT price £109.04 Schedule 2 (CD)

**SIDE-EFFECTS**

- Common or very common Abdominal cramps - aggression - decreased appetite - diarrhoea - dizziness - dry mouth - dysphoria - growth restriction in children - headache - lable mood - malaise - mydriasis - nausea - pyrexia - sleep disturbances - tics - vomiting - weight loss


- Very rare Angle-closure glaucoma

- Frequency not known Cardiomyopathy - choreoathetoid movements (in predisposed individuals) - dyskinesia (in predisposed individuals) - euphoria - seizures - Tourette syndrome (in predisposed individuals)

**OVERDOSE**


**PREGNANCY**

Manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING**

Manufacturer advises avoid—present in human milk.

**RENAL IMPAIRMENT**

Max. dose 50 mg daily in severe impairment.

**MONITORING REQUIREMENTS**

- Monitor for aggressive behaviour or hostility during initial treatment.
- Monitor growth in children.
- Pulse, blood pressure, psychiatric symptoms, appetite, weight and height should be recorded at initiation of therapy, following each dose adjustment, and at least every 6 months thereafter.

**TREATMENT CESSATION**

Avoid abrupt withdrawal.

**DIRECTIONS FOR ADMINISTRATION**

Swallow whole or mix contents of capsule in yoghurt or a glass of water or orange juice; contents should be dispersed completely and consumed immediately.

**PATIENT AND CARER ADVICE**

Patients and carers should be counselled on the administration of capsules.

**DRUGS AND DRIVING**

Prescribers and other healthcare professionals should advise patients if treatment is likely to affect their ability to perform skilled tasks (e.g. driving). This applies especially to drugs with sedative effects; patients should be warned that these effects are increased by alcohol. General information about a patient’s fitness to drive is available from the Driver and Vehicle Licensing Agency at [www.dvla.gov.uk](http://www.dvla.gov.uk).
For information on 2015 legislation regarding driving whilst taking certain controlled drugs, including amphetamines, see Drugs and driving under Guidance on prescribing p. 1.

● MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS 3, 25

Lisdexamfetamine dimesylate (Non-proprietary)

=! Lisdexamfetamine dimesylate 30 mg

Elvanse Adult 30 mg capsules | 28 capsule (£158.24 DT price = £58.24)

Schedule 2 (CD)

=! Lisdexamfetamine dimesylate 50 mg

Elvanse Adult 50 mg capsules | 28 capsule (£283.16 DT price = £83.16)

Schedule 2 (CD)

=! Elvanse (Shire Pharmaceuticals Ltd)

CNS STIMULANTS (NORADRENALINE REUPTAKE INHIBITORS)

Atomoxetine

INDICATIONS AND DOSE

Attention deficit hyperactivity disorder (initiated by a specialist)

BY MOUTH

● Child 6-17 years (body-weight 70 kg and above): Initially 40 mg daily for 7 days, dose is increased according to response; maintenance 80 mg daily, total daily dose may be given either as a single dose in the morning or in 2 divided doses with last dose no later than early evening, high daily doses to be given under the direction of a specialist; maximum 120 mg per day

● Child 6-17 years (body-weight up to 70 kg): Initially 500 micrograms/kg daily for 7 days, dose is increased according to response; maintenance 1.2 mg/kg daily, total daily dose may be given either as a single dose in the morning or in 2 divided doses with last dose no later than early evening, high daily doses to be given under the direction of a specialist; maximum 1.8 mg/kg per day; maximum 120 mg per day

● Adult (body-weight up to 70 kg): Initially 500 micrograms/kg daily for 7 days, dose is increased according to response; maintenance 1.2 mg/kg daily, total daily dose may be given either as a single dose in the morning or in 2 divided doses with last dose no later than early evening, high daily doses to be given under the direction of a specialist; maximum 1.8 mg/kg per day; maximum 120 mg per day

● Adult (body-weight 70 kg and above): Initially 40 mg daily for 7 days, dose is increased according to response; maintenance 80–100 mg daily, total daily dose may be given either as a single dose in the morning or in 2 divided doses with last dose no later than early evening, high daily doses to be given under the direction of a specialist; maximum 120 mg per day

● UNLICENSED USE

○ In children Doses above 100 mg daily not licensed.

○ In adults Dose maximum of 120 mg not licensed.

Atomoxetine doses in BNF may differ from those in product literature.

● CONTRA-INDICATIONS Phaeochromocytoma - severe cardiovascular disease - severe cerebrovascular disease

● CAUTIONS QT-interval prolongation - aggressive behaviour - cardiovascular disease - cerebrovascular disease - emotional lability - history of seizures - hostility - hypertension - mania - psychosis - structural cardiac abnormalities - susceptibility to angle-closure glaucoma - tachycardia

● INTERACTIONS → Appendix 1 (atomoxetine). Avoid concomitant use of drugs that prolong QT interval.

● SIDE-EFFECTS

○ Common or very common Abdominal pain - anorexia - anxiety - constipation - depression - dermatitis - dizziness - drowsiness - dry mouth - dyspepsia - flatulence - flushing - headache - chills - increased blood pressure - irritability - lethargy - malaise - mydriasis - nausea - palpitation - paraesthesia - prostatitis - rash - sexual dysfunction - sleep disturbances - sweating - tachycardia - taste disturbances - tremor - urinary dysfunction - vomiting

○ Uncommon Aggression - cold extremities - emotional lability - hostility - hypoaesthesia - menstrual disturbances - muscle spasms - pruritus - psychosis - QT-interval prolongation - suicidal ideation - syncope - tics

○ Rare Raynaud’s phenomenon - seizures

○ Very rare Angle-closure glaucoma - hepatic disorders

● PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk.

● BREAST FEEDING Avoid-present in milk in animal studies.

● HEPATIC IMPAIRMENT Halve dose in moderate impairment. Quarter dose in severe impairment.

● MONITORING REQUIREMENTS

○ Monitor for appearance or worsening of anxiety, depression or tics.

○ Pulse, blood pressure, psychiatric symptoms, appetite, weight and height should be recorded at initiation of therapy, following each dose adjustment, and at least every 6 months thereafter.

● PATIENT AND CARER ADVICE

Medicines for Children leaflet: Atomoxetine for attention deficit hyperactivity disorder (ADHD) www.medicinesforchildren.org.uk/atomoxetine-attention-deficit-hyperactivity-disorder-adhd

Suicidal ideation Following reports of suicidal thoughts and behaviour, patients and their carers should be informed about the risk and told to report clinical worsening, suicidal thoughts or behaviour, irritability, agitation, or depression. Hepatic impairment Following rare reports of hepatic disorders, patients and carers should be advised of the risk and be told how to recognise symptoms; prompt medical attention should be sought in case of abdominal pain, unexplained nausea, malaise, darkening of the urine, or jaundice.

● NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

○ Methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) (March 2006) NICE TA98

Atomoxetine is recommended, within its licensed indications, as an option for the management of ADHD in children and adolescents. www.nice.org.uk/TA98

● MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

Capsule

CAUTIONARY AND ADVISORY LABELS 3

○ Strattera (Eli Lilly and Company Ltd)

Atomoxetine (as Atomoxetine hydrochloride) 10 mg Strattera 10mg capsules | 7 capsule (£15.62) 28 capsule (£62.46 DT price = £62.46

Atomoxetine (as Atomoxetine hydrochloride) 18 mg Strattera 18mg capsules | 7 capsule (£15.62) 28 capsule (£62.46 DT price = £62.46
Attention deficit hyperactivity disorder

### Methylphenidate hydrochloride

#### CNS STIMULANTS (SYMPATHOMIMETICS, CENTRALLY ACTING)

**INDICATIONS AND DOSE**

**Attention deficit hyperactivity disorder (initiated under specialist supervision)**

**BY MOUTH**
- **Child 6-17 years:** Initially 5 mg 1–2 times a day, increased in steps of 5–10 mg daily if required, at weekly intervals, increased if necessary up to 60 mg daily in 2–3 divided doses, increased if necessary up to 2.1 mg/kg daily in 2–3 divided doses, the licensed maximum dose is 60 mg daily in 2–3 doses, higher dose under the direction of a specialist, discontinue if no response after 1 month, if effect wears off in evening (with rebound hyperactivity) a dose at bedtime may be appropriate (establish need with trial bedtime dose). Treatment may be started using a modified-release preparation; maximum 90 mg per day.
- **Adult:** Initially 5 mg 2–3 times a day, dose is increased if necessary at weekly intervals according to response, increased if necessary up to 100 mg daily in 2–3 divided doses, if effect wears off in evening (with rebound hyperactivity) a dose at bedtime may be appropriate (establish need with trial bedtime dose). Treatment may be started using a modified-release preparation.

**Narcolepsy**

**BY MOUTH**
- **Adult:** 10–60 mg daily in divided doses; usual dose 20–30 mg daily in divided doses, dose to be taken before meals.

**CONCERTA**

**Attention deficit hyperactivity disorder**

**BY MOUTH**
- **Child 6-17 years:** Initially 18 mg once daily, dose to be taken in the morning; adjusted at weekly intervals according to response; maximum 108 mg per day.

**Dose equivalence and conversion**

Total daily dose of 15 mg of standard-release formulation is considered equivalent to **Concerta** XL 18 mg once daily.

**MEDIKINET**

**Attention deficit hyperactivity disorder**

**BY MOUTH**
- **Child 6-17 years:** Initially 10 mg once daily, dose to be taken in the morning with breakfast; adjusted at weekly intervals according to response; increased if necessary up to 2.1 mg/kg daily, licensed max. dose is 60 mg daily, to be increased to higher dose only under direction of specialist; discontinue if no response after 1 month; maximum 90 mg per day.
- **Adult:** Initially 10 mg once daily, dose to be taken in the morning with breakfast; adjusted at weekly intervals according to response; maximum 100 mg per day.

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<th>Strength</th>
<th>BNF Price</th>
<th>Model Price</th>
<th>DT Price</th>
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<td>80mg capsules</td>
<td>28 capsule (P) £62.46 DT price = £62.46</td>
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</tr>
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</table>

**EQUASYM**

**Attention deficit hyperactivity disorder**

**BY MOUTH**
- **Child 6-17 years:** Initially 10 mg once daily, dose to be taken in the morning before breakfast; increased gradually at weekly intervals if necessary; increased if necessary up to 2.1 mg/kg daily, licensed max. dose is 60 mg daily, to be increased to higher dose only under direction of specialist; discontinue if no response after 1 month; maximum 90 mg per day.
- **Adult:** Initially 10 mg once daily, dose to be taken in the morning before breakfast; increased gradually at weekly intervals if necessary; maximum 100 mg per day.

**UNLICENSED USE**

Not licensed for use in children under 6 years; doses over 60 mg daily not licensed; doses of **Concerta** XL over 54 mg daily not licensed. Not licensed for use in narcolepsy. Not licensed for use in adults for attention deficit hyperactivity disorder.

**CONTRA-INDICATIONS**

- Anorexia nervosa · arrhythmias · cardiomyopathy · cardiovascular disease · cerebrovascular disorders · heart failure · hyperthyroidism · phaeochromocytoma · psychosis · severe depression · severe hypertension · structural cardiac abnormalities · suicidal ideation · uncontrolled bipolar disorder · vasculitis

**CAUTIONS**

- Agitation · alcohol dependence · anxiety · drug dependence · epilepsy (discontinue if increased seizure frequency) · family history of Tourette syndrome · susceptibility to angle-closure glaucoma · tics

**CONCERTA**

**Dysphagia (dose form not appropriate) · restricted gastro-intestinal lumen (dose form not appropriate)**

**INTERACTIONS**

Appendix 1 (sympathomimetics).

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain · aggression · alopecia · anorexia · arrhythmias · arthralgia · asthenia · changes in blood pressure · cough · depression · diarrhoea · dizziness · drowsiness · dry mouth · dyspepsia · fever · growth restriction · headache · insomnia · irritability · movement disorders · nasopharyngitis · nausea · nervousness · palpitation · pruritus · rash · reduced weight gain · tachycardia · tics · vomiting

- **Uncommon** Abnormal dreams · confusion · constipation · dysphagia · epistaxis · haematuria · muscle cramps · suicidal ideation · urinary frequency

- **Rare** Angina · sweating · visual disturbances

- **Very rare** Angle-closure glaucoma · blood disorders · cerebral arteritis · dependence · erythema multiforme · exfoliative dermatitis · hepatic dysfunction · leucopenia · myocardial infarction · neurologic malignant syndrome · psychosis · seizures · thrombocytopenia · tolerance · Tourette syndrome

- **Frequency not known** Bradycardia · convulsions · supraventricular tachycardia

**PREGNANCY**

Limited experience—avoid unless potential benefit outweighs risk.

**BREAST FEEDING**

Limited information available—avoid.

**MONITORING REQUIREMENTS**

- Monitor for psychiatric disorders.
- Pulse, blood pressure, psychiatric symptoms, appetite, weight and height should be recorded at initiation of therapy, following each dose adjustment, and at least every 6 months thereafter.

**TREATMENT CESSATION**

Avoid abrupt withdrawal.

**DIRECTIONS FOR ADMINISTRATION**

Contents of capsule can be sprinkled on a tablespoon of apple sauce or yoghurt (then swallowed immediately without chewing).
2.3 Bipolar disorder and mania

**Drugs used for mania and hypomania**

Antimanic drugs are used to control acute attacks and to prevent recurrence of episodes of mania or hypomania. Long-term treatment of bipolar disorder should continue for at least two years from the last manic episode and up to five years if the patient has risk factors for relapse. An antidepressant drug may also be required for the treatment of co-existing depression, but should be avoided in patients with rapid-cycling bipolar disorder, a recent history of hypomania, or with rapid mood fluctuations.

**Benzodiazepines**

Use of benzodiazepines (such as lorazepam p. 412) may be helpful in the initial stages of treatment for behavioural disturbance or agitation; they should not be used for long periods because of the risk of dependence.

**Antipsychotic drugs**

Antipsychotic drugs (normally olanzapine p. 315, quetiapine p. 318, or risperidone p. 319) are useful in acute episodes of mania and hypomania; if the response to antipsychotic drugs is inadequate, lithium or valproate may be added. An antipsychotic drug may be used concomitantly with lithium or valproate in the initial treatment of severe acute mania.

Olanzapine p. 315 can be used for the long-term management of bipolar disorder in patients whose manic episode responded to olanzapine p. 315 therapy. It can be given either as monotherapy, or in combination with lithium or valproate if the patient has frequent relapses or continuing functional impairment.

Asenapine p. 276, a second-generation antipsychotic, is licensed for the treatment of moderate to severe manic episodes associated with bipolar disorder.

When discontinuing antipsychotics, the dose should be reduced gradually over at least 4 weeks if the patient is continuing with other antimanic drugs; if the patient is not continuing with other antimanic drugs or if there is a history of manic relapse, a withdrawal period of up to 3 months should be considered.
Carbamazepine

Carbamazepine p. 387 may be used under specialist supervision for the prophylaxis of bipolar disorder (manic-depressive disorder) in patients unresponsive to a combination of other prophylactic drugs; it is used in patients with rapid-cycling manic-depressive illness (4 or more affective episodes per year). The dose of carbamazepine p. 387 should not normally be increased if an acute episode of mania occurs.

Valproate

Valproate p. 387 may be used under specialist supervision for the prophylaxis of bipolar disorder (manic-depressive disorder) in patients with rapid-cycling manic-depressive illness (4 or more affective episodes per year). The dose of carbamazepine p. 387 should not normally be increased if an acute episode of mania occurs.

Lithium

Lithium salts are used in the prophylaxis and treatment of mania, hypomania and depression in bipolar disorder (manic-depressive disorder), and in the prophylaxis and treatment of recurrent unipolar depression. Lithium is also used as concomitant therapy with antidepressant medication in patients who have had an incomplete response to treatment for acute bipolar depression and to augment other antidepressants in patients with treatment-resistant depression [unlicensed indication]. It is also licensed for the treatment of aggressive or self-harming behaviour.

The decision to give prophylactic lithium requires specialist advice, and must be based on careful consideration of the likelihood of recurrence in the individual patient, and the benefit of treatment weighed against the risks. The full prophylactic effect of lithium may not occur for six to twelve months after the initiation of therapy. Olanzapine p. 315 or valproate (given alone or as an adjunctive therapy with lithium) are alternative prophylactic treatments in patients who experience frequent relapses or continued functional impairment.


Valproate

Valproic acid (as the semisodium salt) and sodium valproate p. 403 are used for the treatment of manic episodes associated with bipolar disorder. Valproate (valproic acid below and sodium valproate) is also used for the prophylaxis of bipolar disorder; however, it should not normally be prescribed for women of childbearing potential. In patients of bipolar disorder; however, it should not normally be prescribed for women of childbearing potential. In patients of bipolar disorder; however, it should not normally be prescribed for women of childbearing potential. In patients of bipolar disorder; however, it should not normally be prescribed for women of childbearing potential. In patients of bipolar disorder; however, it should not normally be prescribed for women of childbearing potential. In patients of bipolar disorder; however, it should not normally be prescribed for women of childbearing potential. In patients of bipolar disorder; however, it should not normally be prescribed for women of childbearing potential. In patients of bipolar disorder; however, it should not normally be prescribed for women of childbearing potential. In patients of bipolar disorder; however, it should not normally be prescribed for women of childbearing potential. In patients of bipolar disorder; however, it should not normally be prescribed for women of childbearing potential.

Migraine prophylaxis

BY MOUTH

Adult: Initially 250 mg twice daily, then increased if necessary to 1 g daily in divided doses

CONVULEX®

Epilepsy

BY MOUTH

Child: Total daily dose to be given in 2–4 divided doses (consult product literature)

Adult: Total daily dose to be given in 2–4 divided doses (consult product literature)

Dose equivalence and conversion

Sodium valproate also contains sodium valproate, but nevertheless care is needed if switching or making changes.

Unlicensed use

Not licensed for migraine prophylaxis.

Contra-indications

Acute porphyrias p. 864 • family history of severe hepatic dysfunction

Caution

Systemic lupus erythematosus

Caution, further information

Liver toxicity Liver dysfunction (including fatal hepatic failure) has occurred in association with valproate (especially in children under 3 years and in those with metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation) usually in first 6 months and usually involving multiple antiepileptic therapy. Raised liver enzymes during valproate treatment are usually transient but patients should be reassessed clinically and liver function (including prothrombin time) monitored until return to normal—discontinue if abnormally prolonged prothrombin time (particularly in association with other relevant abnormalities).

Consider vitamin D supplementation in patients that are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium.

Interactions

Appendix 1 (valproic acid).

Side-effects

Common or very common Diarrhoea • gastric irritation • hyperammonaemia • nausea • thrombocytopenia • transient hair loss (growth may be curly) • weight gain

Uncommon Aggression • ataxia • behavioural disturbances • hyperactivity • increased alertness • tremor • vasculitis

Rare Anaemia • blood disorders • confusion • drowsiness • hallucinations • hearing loss • hepatic dysfunction • lethargy • leucopenia • pancytopenia • rash • stupor

Very rare Acne • coma • dementia • encephalopathy • enuresis • extrapyramidal symptoms • Fanconi’s syndrome • gynaecomastia • hirsutism • hyponatraemia • increase in bleeding time • pancreatitis • peripheral oedema • reduced bone mineral density • Stevens-Johnson syndrome • suicidal ideation • toxic epidermal necrolysis

Frequency not known Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome • hypersensitivity reactions • male infertility • menstrual disturbances • syndrome of inappropriate secretion of antidiuretic hormone

Side-effects, further information

Hepatic dysfunction Withdraw treatment immediately if persistent vomiting and abdominal pain, anorexia, jaundice, oedema, malaise, drowsiness, or loss of seizure control.

Conception and contraception

Valproate is associated with teratogenic risks and should not be used in women of child-bearing potential unless there is no safer alternative—this should be fully considered and discussed before prescribing for women of child-bearing age.
Effective contraception advised in women of child-bearing potential.

- **Pregnancy** Valproate is associated with the highest risk of major and minor congenital malformations (in particular neural tube defects), and long-term neurodevelopmental effects. Valproate should not be used during pregnancy or in women of child-bearing potential unless there is no safer alternative and only after a careful discussion of the risks. If valproate is to be used during pregnancy, the lowest effective dose should be prescribed in divided doses to avoid peaks in plasma-valproate concentrations; doses greater than 1 g daily are associated with an increased risk of teratogenicity. Specialist prenatal monitoring should be instigated when valproate has been taken in pregnancy. Neonatal bleeding (related to hypofibrinohaemia) and neonatal hepatotoxicity also reported. The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

- **Breastfeeding** Amount too small to be harmful.

- **Hepatic Impairment** Avoid if possible—hepatotoxicity and hepatic failure may occasionally occur (usually in first 6 months). Avoid in active liver disease.

- **Renal Impairment** Reduce dose.

### Monitoring Requirements

- **Monitor closely if dose greater than 10 mg/kg daily.**
- **Monitor liver function before therapy and during first 6 months especially in patients most at risk.**
- **Measure full blood count and ensure no undue potential for bleeding before starting and before surgery.**

### Effect on Laboratory Tests

- **False-positive urine tests for ketones.**

### Treatment Cessation

If treatment with valproate is stopped, reduce the dose gradually over at least 4 weeks.

### Prescribing and Dispensing Information

Patients being treated for epilepsy may need to be maintained on a specific manufacturer’s branded or generic oral valproic acid product.

### Patient and Carer Advice

Blood or hepatic disorders Patients or their carers should be told how to recognise signs and symptoms of blood or liver disorders and advised to seek immediate medical attention if symptoms develop. Pancreatitis Patients or their carers should be told how to recognise signs and symptoms of pancreatitis and advised to seek immediate medical attention if symptoms such as abdominal pain, nausea, or vomiting develop. Counselling advised on pregnancy.

### Medicinal Forms

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension gastro-resistant tablet

- **Depakote (Sanofi)**
  - Valproic acid (as Valproate semisodium) 250 mg Depakote 250mg gastro-resistant tablets | 90 tablet [P] £14.60 DT price = £14.40
  - Valproic acid (as Valproate semisodium) 500 mg Depakote 500mg gastro-resistant tablets | 90 tablet [P] £29.15 DT price = £29.15

Gastro-resistant capsule

- **Convulex** (Pfizer Ltd)
  - Valproic acid 150 mg Convulex 150mg gastro-resistant capsules | 100 capsule [P] £0.60
  - Valproic acid 300 mg Convulex 300mg gastro-resistant capsules | 100 capsule [P] £1.20
  - Valproic acid 500 mg Convulex 500mg gastro-resistant capsules | 100 capsule [P] £1.20

### LITHIUM SALTS

#### Lithium salts

- **Contra-Indications** Addison’s disease - cardiac insufficiency - dehydration - family history of Brugada syndrome - low sodium diets - personal history of Brugada syndrome - rhythm disorder - untreated hypothyroidism

- **Caution** Avoid abrupt withdrawal - cardiac disease - concurrent ECT (may lower seizure threshold) - diuretic treatment (risk of toxicity) - elderly (reduce dose) - epilepsy (may lower seizure threshold) - myasthenia gravis - psoriasis (risk of exacerbation) - QT interval prolongation - review dose as necessary in diarrhoea - review dose as necessary in intercurrent infection (especially if sweating profusely) - review dose as necessary in vomiting - surgery

- **Caution, Further Information**

**Long-term use** Long-term use of lithium has been associated with thyroid disorders and mild cognitive and memory impairment. Long-term treatment should therefore be undertaken only with careful assessment of risk and benefit, and with monitoring of thyroid function every 6 months (more often if there is evidence of deterioration).
The need for continued therapy should be assessed regularly and patients should be maintained on lithium after 3–5 years only if benefit persists.

- **INTERACTIONS** → Appendix 1 (lithium).
  - Caution with concomitant use of drugs and any therapy that may lower seizure threshold.
  - Caution with concomitant use of drugs that prolong the QT interval.
  - Lithium toxicity is made worse by sodium depletion, therefore concurrent use of diuretics (particularly thiazides) is hazardous and should be avoided.

- **SIDE-EFFECTS**
  - Very rare: Nystagmus
  - Frequency not known: Acneiform eruptions, alopecia, anorexia, arthralgia, AV block, benign intracranial hypertension, bradycardia, cardiomyopathy, cognitive impairment, dry mouth, dysgeusia, ECG changes, electrolyte imbalance, encephalopathy, euthyroid goitre, extrapyramidal side-effects, fine tremor, gastritis, gastro-intestinal disturbances, hallucinations, hyperparathyroidism, hypersalivation, hypothyroidism, hypothyroidism, kidney changes, leucocytosis, malaise, memory loss, myalgia, myasthenia gravis, nephrogenic diabetes insipidus, nephrotic syndrome, oedema, other skin disorders, parathyroid adenoma, peripheral neuropathy, polydipsia, polyuria, psychosis, vertigo.
  - QT interval prolongation, Raynaud’s phenomena, renal impairment, sexual dysfunction, sinus node dysfunction, speech disorder, thyroid changes, vertigo, weight changes.

**Overdose**

- Signs of intoxication require withdrawal of treatment and include increasing gastro-intestinal disturbances (vomiting, diarrhoea), visual disturbances, polyuria, muscle weakness, fine tremor increasing to coarse tremor, CNS disturbances (confusion and drowsiness increasing to lack of coordination, restlessess, stupor); abnormal reflexes, myoclonus, incontinence, hypernatraemia. With severe overdose (serum-lithium concentration above 2 mmol/litre) seizures, cardiac arrhythmias (including sino-atrial block, bradycardia and first-degree heart block), blood pressure changes, circulatory failure, renal failure, coma and sudden death reported.

For details on the management of poisoning, see Lithium, under Emergency treatment of poisoning p. 1123.

- **CONCEPTION AND CONTRACTION**
  - Manufacturer advises effective contraception during treatment for women of child-bearing potential.

- **PREGNANCY**
  - Avoid if possible, particularly in the first trimester (risk of teratogenicity, including cardiac abnormalities).
  - Dose requirements increased during the second and third trimesters (but on delivery return abruptly to normal).
  - Close monitoring of serum-lithium concentration advised in pregnancy (risk of toxicity in neonate).

- **BREAST FEEDING**
  - Present in milk and risk of toxicity in infant—avoid.

- **RENAL IMPAIRMENT**
  - Caution in mild to moderate impairment. Avoid in severe impairment.
  - In renal impairment monitor serum-lithium concentration closely and adjust dose accordingly.

- **MONITORING REQUIREMENTS**
  - Serum concentrations: Lithium salts have a narrow therapeutic/toxic ratio and should therefore not be prescribed unless facilities for monitoring serum-lithium concentrations are available.
  - Samples should be taken 12 hours after the dose to achieve a serum-lithium concentration of 0.4–1 mmol/litre (lower end of the range for maintenance therapy and elderly patients).

- A target serum-lithium concentration of 0.8–1 mmol/litre is recommended for acute episodes of mania, and for patients who have previously relapsed or have sub-syndromal symptoms. It is important to determine the optimum range for each individual patient.
  - Routine serum-lithium monitoring should be performed weekly after initiation and after each dose change until concentrations are stable, then every 3 months thereafter. Additional serum-lithium measurements should be made if a patient develops significant intercurrent disease or if there is a significant change in a patient’s sodium or fluid intake.

- **Renal function should be monitored at baseline and every 6 months thereafter** (more often if there is evidence of deterioration or if the patient has other risk factors, such as starting ACE inhibitors, NSAIDs, or diuretics).

- Assess cardiac and thyroid function before initiating, and thereafter every 6 months on stabilised regimens.

- **TREATMENT CESSATION**
  - While there is no clear evidence of withdrawal or rebound psychosis, abrupt discontinuation of lithium increases the risk of relapse. If lithium is to be discontinued, the dose should be reduced gradually over a period of at least 4 weeks (preferably over a period of up to 3 months). Patients and their carers should be warned of the risk of relapse if lithium is discontinued abruptly. If lithium is stopped or is to be discontinued abruptly, consider changing therapy to an atypical antipsychotic or valproate.

- **PATIENT AND CARER ADVICE**

  - **Driving and skilled tasks** May impair performance of skilled tasks (e.g. driving, operating machinery).

  - Lithium treatment packs
    - A lithium treatment pack should be given to patients on initiation of treatment with lithium.
    - The pack consists of a patient information booklet, lithium alert card, and a record book for tracking serum-lithium concentration. Packs may be purchased from 3M: 0845 610 1112 nhsforms@mm.m.org.uk

  - Patients should be advised to report signs and symptoms of lithium toxicity, hypothyroidism, renal dysfunction (including polyuria and polydipsia), and benign intracranial hypertension (persistent headache and visual disturbance).
  - Maintain adequate fluid intake and avoid dietary changes which reduce or increase sodium intake.

### Lithium carbonate

#### INDICATIONS AND DOSE

- **Treatment and prophylaxis of mania** | **Treatment and prophylaxis of bipolar disorder** | **Treatment and prophylaxis of recurrent depression** | **Treatment and prophylaxis of aggressive or self-harming behaviour**

**B Y M O U T H**

- Adult: Dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

**CAMCOLIT™ TABLET**

- **Treatment of mania** | **Treatment of bipolar disorder** | **Treatment of recurrent depression** | **Treatment of aggressive or self-harming behaviour**

**BY MOUTH**

- Adult: Initially 1–1.5 g daily, dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then
every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

- Elderly: Reduce initial dose, dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

**LISKONUM®**

**Treatment of mania | Treatment of bipolar disorder | Treatment of recurrent depression | Treatment of aggressive or self-harming behaviour**

**BY MOUTH**

- Adult: Initially 300–400 mg daily, dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

- Elderly: Initially 225 mg twice daily, dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

**Prophylaxis of mania | Prophylaxis of bipolar disorder | Prophylaxis of recurrent depression | Prophylaxis of aggressive or self-harming behaviour**

**CAMCOLIT® MODIFIED-RELEASE TABLET**

**Treatment of mania | Treatment of bipolar disorder | Treatment of recurrent depression | Treatment of aggressive or self-harming behaviour**

**BY MOUTH**

- Adult: Initially 1–1.5 g daily, dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

- Elderly: Reduce initial dose, dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

**Prophylaxis of mania | Prophylaxis of bipolar disorder | Prophylaxis of recurrent depression | Prophylaxis of aggressive or self-harming behaviour**

**BY MOUTH**

- Adult: Initially 300–400 mg daily, dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

**PRIADEL® TABLETS**

**Treatment and prophylaxis of mania | Treatment and prophylaxis of bipolar disorder | Treatment and prophylaxis of recurrent depression | Treatment and prophylaxis of aggressive or self-harming behaviour**

**BY MOUTH**

- Adult (body-weight up to 49 kg): Initially 200–400 mg daily, dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

- Adult (body-weight 50 kg and above): Initially 0.4–1.2 g once daily, alternatively initially 0.4–1.2 g daily in 2 divided doses, dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

**Preparations vary widely in bioavailability:** changing the preparation requires the same precautions as initiation of treatment.
Lithium citrate

INDICATIONS AND DOSE
Treatment and prophylaxis of mania | Treatment and prophylaxis of bipolar disorder | Treatment and prophylaxis of recurrent depression | Treatment and prophylaxis of aggressive or self-harming behaviour

BY MOUTH
- Adult: Dosed adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter; doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised
- Adult (body-weight up to 49 kg): Initially 509 mg twice daily, dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter; doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised
- Elderly (body-weight above 50 kg): Initially 1018–3054 g daily in 2 divided doses, dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

LI-LIQUID™

Treatment and prophylaxis of mania | Treatment and prophylaxis of bipolar disorder | Treatment and prophylaxis of recurrent depression | Treatment and prophylaxis of aggressive or self-harming behaviour

BY MOUTH
- Adult (body-weight up to 49 kg): Initially 520 mg twice daily, dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised
- Adult (body-weight 50 kg and above): Initially 1040–3120 g daily in 2 divided doses, dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised
- Elderly (body-weight above 50 kg): Initially 1040 g daily in 2 divided doses, dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised
- Elderly (body-weight above 50 kg): Initially 520 mg twice daily, dose adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter, doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

Antidepressant drugs

Antidepressant drugs are effective for treating moderate to severe depression associated with psychomotor and physiological changes such as loss of appetite and sleep...
disturbance; improvement in sleep is usually the first benefit of therapy. Ideally, patients with moderate to severe depression should be treated with psychological therapy in addition to drug therapy. Antidepressant drugs are also effective for dysthymia (lower grade chronic depression (typically of at least 2 years duration)). Antidepressant drugs should not be used routinely in mild depression, and psychological therapy should be considered initially; however, a trial of antidepressant therapy may be considered in cases refractory to psychological treatments or in those associated with psychosocial or medical problems. Drug treatment of mild depression may also be considered in patients with a history of moderate or severe depression.

Choice
The major classes of antidepressant drugs include the tricyclic and related antidepressants, the selective serotonin re-uptake inhibitors (SSRIs), and the monoamine oxidase inhibitors (MAOIs). A number of antidepressant drugs cannot be accommodated easily into this classification. There is little to choose between the different classes of antidepressant drugs in terms of efficacy, so choice should be based on the individual patient’s requirements, including the presence of concomitant disease, existing therapy, suicide risk, and previous response to antidepressant therapy. Since there may be an interval of 2 weeks before the antidepressant action takes place, elective conversion treatment may be required in severe depression when delay is hazardous or intolerable. During the first few weeks of treatment, there is an increased potential for agitation, anxiety, and suicidal ideation.

SSRIs are better tolerated and are safer in overdose than other classes of antidepressants and should be considered first-line for treating depression. In patients with unstable angina or who have had a recent myocardial infarction, sertraline p. 288 has shown to be safe. Tricyclic antidepressants have similar efficacy to SSRIs but are more likely to be discontinued because of side-effects; toxicity in overdose is also a problem. SSRIs are less sedating and have fewer antimuscarinic and cardiovascular effects than tricyclic antidepressants.

MAOIs have dangerous interactions with some foods and drugs, and should be reserved for use by specialists. Although anxiety is often present in depressive illness (and may be the presenting symptom), the use of an antipsychotic or an anxiolytic may mask the true diagnosis. Anxiolytics or antipsychotic drugs should therefore be used with caution in depression but they are useful adjuncts in agitated patients. Augmenting antidepressants with antipsychotics under specialist supervision may also be necessary in patients who have depression with psychotic symptoms.

St John’s wort (Hypericum perforatum) is a popular herbal remedy on sale to the public for treating mild depression. It should not be prescribed or recommended for depression because St John’s wort can induce drug metabolising enzymes and a number of important interactions with conventional drugs, including conventional antidepressants, have been identified. Furthermore, the amount of active ingredient varies between different preparations of St John’s wort and switching from one to another can change the degree of enzyme induction. If a patient stops taking St John’s wort, the concentration of interacting drugs may increase, leading to toxicity.

Management
Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment. Treatment should be continued for at least 4 weeks (6 weeks in the elderly) before considering whether to switch antidepressant due to lack of efficacy. In cases of partial response, continue for a further 2–4 weeks (elderly patients may take longer to respond). Following remission, antidepressant treatment should be continued at the same dose for at least 6 months (about 12 months in the elderly), or for at least 12 months in patients receiving treatment for generalised anxiety disorder (as the likelihood of relapse is high). Patients with a history of recurrent depression should receive maintenance treatment for at least 2 years.

Hyponatraemia and Antidepressant Therapy Hyponatraemia (usually in the elderly and possibly due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants; however, it has been reported more frequently with SSRIs than with other antidepressants. Hyponatraemia should be considered in all patients who develop drowsiness, confusion, or convulsions while taking an antidepressant.

Suicidal Behaviour and Antidepressant Therapy The use of antidepressants has been linked with suicidal thoughts and behaviour; children, young adults, and patients with a history of suicidal behaviour are particularly at risk. Where necessary patients should be monitored for suicidal behaviour, self-harm, or hostility, particularly at the beginning of treatment or if the dose is changed.

Serotonin syndrome Serotonin syndrome or serotonin toxicity is a relatively uncommon adverse drug reaction caused by excessive central and peripheral serotonergic activity. Onset of symptoms, which range from mild to life-threatening, can occur within hours or days following the initiation, dose escalation, or overdose of a serotonergic drug, the addition of a new serotonergic drug, or the replacement of one serotonergic drug by another without allowing a long enough washout period in-between, particularly when the first drug is an irreversible MAOI or a drug with a long half-life. Severe toxicity, which is a medical emergency, usually occurs with a combination of serotonergic drugs, one of which is generally an MAOI.

The characteristic symptoms of serotonin syndrome fall into 3 main areas, although features from each group may not be seen in all patients—neuromuscular hyperactivity (such as tremor, hyperreflexia, clonus, myoclonus, rigidity), autonomic dysfunction (tachycardia, blood pressure changes, hyperthermia, diaphoresis, shivering, diarrhoea), and altered mental state (agitation, confusion, mania).

Treatment consists of withdrawal of the serotonergic medication and supportive care; specialist advice should be sought.

Failure to respond Failure to respond to initial treatment with an SSRI may require an increase in the dose, or switching to a different SSRI or mirtazapine p. 291. Other second-line choices include lofepramine p. 297, moclobemide p. 283, and reboxetine p. 284. Other tricyclic antidepressants and venlafaxine p. 289 should be considered for more severe forms of depression; irreversible MAOIs should only be prescribed by specialists. Failure to respond to a second antidepressant may require the addition of another antidepressant of a different class, or use of an augmenting agent (such as lithium, aripiprazole p. 312 [unlicensed], olanzapine p. 315 [unlicensed], quetiapine p. 318, or risperidone p. 319 [unlicensed]), but such adjunctive treatment should be initiated only by doctors with special experience of these combinations. Electroconvulsive therapy may be initiated in severe refractory depression.

Anxiety disorders and obsessive-compulsive disorder Management of acute anxiety generally involves the use of a benzodiazepine or buspirone hydrochloride p. 269. For chronic anxiety (of longer than 4 weeks’ duration) it may be appropriate to use an antidepressant. Combined therapy with a benzodiazepine may be required until the antidepressant takes effect. Patients with generalised anxiety disorder, a form of chronic anxiety, should be offered...
psychological treatment before initiating an antidepressant. If drug treatment is needed, an SSRI such as escitalopram p. 285, paroxetine p. 287, or sertraline p. 288 [unlicensed], can be used. Duloxetine p. 288 and venlafaxine p. 289 (serotonin and noradrenaline reuptake inhibitors) are also recommended for the treatment of generalised anxiety disorder, if the patient cannot tolerate SSRIs or serotonin and noradrenaline reuptake inhibitors (or if treatment has failed to control symptoms), pregabalin p. 400 can be considered.


Panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and phobic states such as social anxiety disorder are treated with SSRIs. Clomipramine hydrochloride p. 294 or imipramine hydrochloride p. 296 can be used second-line in panic disorder [unlicensed]; clomipramine hydrochloride p. 294 can also be used second-line for obsessive-compulsive disorder. Moclobemide p. 283 is licensed for the treatment of social anxiety disorder.

**Tricyclic and related antidepressant drugs**

**Choice**

Tricyclic and related antidepressants block the re-uptake of both serotonin and noradrenaline, although to different extents. For example, clomipramine hydrochloride p. 294 is more selective for serotoninergic transmission, and imipramine hydrochloride p. 296 is more selective for noradrenergic transmission. Tricyclic and related antidepressant drugs can be roughly divided into those with additional sedative properties and those that are less sedating. Agitated and anxious patients tend to respond best to the sedative compounds, whereas withdrawn and apathetic patients will often obtain most benefit from the less sedating ones. Those with **sedative** properties include amitriptyline hydrochloride p. 292, clomipramine hydrochloride p. 294, doxepin hydrochloride p. 295, doxepin p. 296, mianserin hydrochloride p. 290, trazodone hydrochloride p. 291, and trimipramine p. 299. Those with **less sedative** properties include imipramine hydrochloride p. 296, lofepramine p. 297, and nortriptyline p. 298.

Tricyclic and related antidepressants also have varying degrees of antimuscarinic side-effects and cardiotoxicity in overdosage, which may be important in individual patients. Lofepramine has a lower incidence of side-effects and is less dangerous in overdosage but is infrequently associated with hepatic toxicity. Imipramine hydrochloride is also well established, but has more marked antimuscarinic side-effects than other tricyclic and related antidepressants. Amitriptyline hydrochloride and doxepin hydrochloride are effective but they are particularly dangerous in overdosage and are not recommended for the treatment of depression; doxepin hydrochloride should be initiated by a specialist.

**Dosage**

About 10 to 20% of patients fail to respond to tricyclic and related antidepressant drugs and inadequate dosage may account for some of these failures. It is important to use doses that are sufficiently high for effective treatment but not so high as to cause toxic effects. Low doses should be used for initial treatment in the elderly. In most patients the long half-life of tricyclic antidepressant drugs allows once-daily administration, usually at night; the use of modified-release preparations is therefore unnecessary.

Some tricyclic antidepressants are used in the management of panic and other anxiety disorders. Some tricyclic antidepressants may also have a role in some forms of neuralgia and in nocturnal enuresis in children.

**Children and adolescents**

Studies have shown that tricyclic antidepressants are not effective for treating depression in children.

**Monoamine-oxidase inhibitors**

Monoamine-oxidase inhibitors are used much less frequently than tricyclic and related antidepressants, or SSRIs and related antidepressants because of the dangers of dietary and drug interactions and the fact that it is easier to prescribe MAOIs when tricyclic antidepressants have been unsuccessful than vice versa.

Tranylcypromine p. 283 has a greater stimulant action than phenelzine p. 283 or isocarboxazid p. 282 and is more likely to cause a hypertensive crisis. Isocarboxazid and phenelzine are more likely to cause hepatotoxicity than tranylcypromine.

Moclobemide p. 283 should be reserved as a second line treatment.

Phobic patients and depressed patients with atypical, hypochondriacal, or hysterical features are said to respond best to MAOIs. However, MAOIs should be tried in any patients who are refractory to treatment with other antidepressants as there is occasionally a dramatic response. Response to treatment may be delayed for 3 weeks or more and may take an additional 1 or 2 weeks to become maximal.

**Other antidepressant drugs**

The thioxanthene flupentixol p. 305 (Fluanxol®) has antidepressant properties when given by mouth in low doses. Flupentixol is also used for the treatment of psychoses.

**Drugs used for Depression not listed below; Flupentixol, p. 305 · Lithium carbonate, p. 277 · Lithium citrate, p. 279 · Quetiapine, p. 318

**MELATONIN RECEPTOR AGONISTS**

**Agomelatine**

**DRUG ACTION** A melatonin receptor agonist and a selective serotonin-receptor antagonist; it does not affect the uptake of serotonin, noradrenaline, or dopamine.

**INDICATIONS AND DOSE**

**Major depression**

**BY MOUTH**

Adult: 25 mg daily, dose to be taken at bedtime, dose to be increased if necessary after 2 weeks, increased if necessary to 50 mg daily, dose to be taken at bedtime

**Dose adjustments due to interactions**

Caution—dose adjustment may be necessary if smoking started or stopped during treatment.

**CONTRA-INDICATIONS** Dementia · patients over 75 years of age

**CAUTIONS** Bipolar disorder · diabetes · excessive alcohol consumption · hypomania · mania · non-alcoholic fatty liver disease · obesity

**INTERACTIONS** → Appendix 1 (agomelatine).

Caution with concomitant use of drugs associated with hepatic injury.

**SIDE-EFFECTS**

- Common or very common Abdominal pain · agitation · anxiety · back pain · constipation · diarrhoea · dizziness · drowsiness · fatigue · headache · increased serum transaminases · nausea · sleep disturbances · sweating · vomiting

- Uncommon Blurred vision · eczema · paraesthesia · restless legs syndrome · tinnitus

- Rare Hepatic failure · hepatic injury · hepatitis · rash · weight changes

- Frequency not known Pruritus · suicidal behaviour
SIDE-EFFECTS, FURTHER INFORMATION

Suicidal behaviour The use of antidepressants has been linked with suicidal thoughts and behaviour; children, young adults, and patients with a history of suicidal behaviour are particularly at risk. Where necessary patients should be monitored for suicidal behaviour, self-harm, or hostility, particularly at the beginning of treatment or if the dose is changed.

PREGNANCY Manufacturer advises avoid.

BREAST FEEDING Avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT Avoid. Do not start if serum transaminases exceed 3 times the upper limit of reference range.

RENAL IMPAIRMENT Caution in moderate to severe impairment.

MONITORING REQUIREMENTS Test liver function before treatment and after 3, 6, 12 and 24 weeks of treatment, and then regularly thereafter when clinically indicated (restart monitoring schedule if dose increased); discontinue if serum transaminases exceed 3 times the upper limit of reference range or symptoms of liver disorder.

PATIENT AND CARER ADVICE Hepatotoxicity Patients should be told how to recognise signs of liver disorder, and advised to seek immediate medical attention if symptoms such as dark urine, light coloured stools, jaundice, bruising, fatigue, abdominal pain, or purpura develop. Patients should be given a booklet with more information on the risk of hepatic side-effects.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

» Valdoxan (Servier Laboratories Ltd)

Agomelatine 25 mg Valdoxan 25mg tablets | 28 tablet (POS) £30.00
DT price = £30.00

MONOAMINE-OXIDASE A AND B INHIBITORS (IRREVERSIBLE)

Monoamine-oxidase inhibitors

DRUG ACTION MAOIs inhibit monoamine oxidase, thereby causing an accumulation of amine neurotransmitters.

CONTRA-INDICATIONS Cerebrovascular disease, not indicated in manic phase, phaeochromocytoma

CAUTIONS Acute porphyria, avoid in agitated patients, blood disorders, cardiovascular disease, concurrent electroconvulsive therapy, diabetes mellitus, elderly (great caution), epilepsy, severe hypertensive reactions to certain drugs and foods, surgery

INTERACTIONS » Appendix 1 (MAOIs).

The metabolism of some amine drugs such as indirect-acting sympathomimetics (present in many cough and decongestant preparations) is inhibited and their pressor action may be potentiated; the pressor effect of tyramine (in some foods, such as mature cheese, pickled herring, broad bean pods, and Bovril®, Oxo®, Marmite® or any similar meat or yeast extract or fermented soya bean extract) may also be dangerously potentiated. These interactions may cause a dangerous rise in blood pressure. An early warning symptom may be a throbbing headache. The danger of interaction persists for up to 2 weeks after treatment with MAOIs is discontinued. Some psychiatrists use selected tricyclics in conjunction with MAOIs but this is hazardous, indeed potentially lethal, except in experienced hands and there is no evidence that the combination is more effective than when either constituent is used alone.

SIDE-EFFECTS

» Common or very common Dizziness, postural hypotension (especially in elderly)

» Uncommon Agitation, arrhythmias, blurred vision, confusion, constipation, convulsions, difficulty in micturition, drowsiness, dry mouth, elevated liver enzymes, euphoria, fatigue, gastrointestinal disturbances, hallucinations, headache, hyperreflexia, insomnia, leucopenia, myoclonic movement, nervousness, nyctagmus, oedema, psychotic episodes with hypomanic behaviour, purpura, rashes, sexual disturbances, suicidal behaviour, sweating, tremors, weakness, weight gain with inappropriate appetite

» Rare Fatal progressive hepatocellular necrosis

» Frequency not known Jaundice, hypoglycaemia, paraesthesia, peripheral neuritis, peripheral neuropathy (may be due to pyridoxine deficiency)

SIDE-EFFECTS, FURTHER INFORMATION

Risk of postural hypotension and hypertensive responses Discontinue use if palpitations or frequent headaches occur.

PREGNANCY Increased risk of neonatal malformations—manufacturer advises avoid unless there are compelling reasons.

HEPATIC IMPAIRMENT MAOIs may cause idiosyncratic hepatotoxicity if used in patients with hepatic impairment.

MONITORING REQUIREMENTS Monitor blood pressure (risk of postural hypotension and hypertensive responses).

TREATMENT CESSATION If possible avoid abrupt withdrawal. MAOIs are associated with withdrawal symptoms on cessation of therapy. Symptoms include agitation, irritability, ataxia, movement disorders, insomnia, drowsiness, vivid dreams, cognitive impairment, and slowed speech. Withdrawal symptoms occasionally experienced when discontinuing MAOIs include hallucinations and paranoid delusions. If possible MAOIs should be withdrawn slowly. Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment).

PATIENT AND CARER ADVICE Drowsiness may affect performance of skilled tasks (e.g. driving). Patients should be advised to eat only fresh foods and avoid food that is suspected of being stale or off; game should be avoided. The danger of interaction persists for up to 2 weeks after treatment with MAOIs is discontinued. Patients should also be advised to avoid alcoholic drinks or de-alcoholised (low alcohol) drinks.

Isocarboxazid

INDICATIONS AND DOSE

Depressive illness

BY MOUTH

» Adult: Initially 30 mg daily until improvement occurs, initial dose may be given in single or divided doses, dose may be increased if necessary after 4 weeks up to 60 mg daily for 4–6 weeks, dose to be increased under
close supervision only, then reduced to 10–20 mg daily, usual maintenance dose, but up to 40 mg may be required
  ▶ Elderly: 5–10 mg daily

● **BREAST FEEDING** Avoid.
● **HEPATIC IMPAIRMENT** Avoid in hepatic impairment.
● **RENAL IMPAIRMENT** Use with caution.
● **LESS SUITABLE FOR PRESCRIBING** Less suitable for prescribing.

● **MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

  Tablet
  CAUTIONARY AND ADVISORY LABELS 3, 10
  ▶ ISO CARBOXAZID (Non-proprietary)
  Iso carboxazid 10 mg Iso carboxazid 10mg tablets | 56 tablet [P] £13.95

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### Phenelzine

**INDICATIONS AND DOSE**

**Depressive illness**

**BY MOUTH**

- Adult: Initially 15 mg 3 times a day, response is usually seen within first week; dose may be increased if necessary after 2 weeks if response is not evident, increased if necessary to 15 mg 4 times a day, doses up to 30 mg three times a day may be used in hospital patients, then reduced to 15 mg once daily on alternate days, response may not become apparent for up to 4 weeks, once satisfactory response has been achieved, reduce dose gradually to lowest suitable maintenance dose (15 mg on alternate days may be adequate)

- Elderly: 10 mg 3 times a day

- Very rare: Seizures

- Common or very common: Confusion, extreme restlessness (with the traditional (irreversible) MAOIs, but patients still need to avoid sympathomimetics such as ephedrine and pseudoephedrine. In addition, moclobemide should not be given with another antidepressant. Owing to its short duration of action no treatment-free period is required after it has been stopped but it should not be started until at least a week after a tricyclic or related antidepressant or an SSRI or related antidepressant has been stopped (at least 5 weeks in the case of fluoxetine), or for at least a week after an MAOI has been stopped.

- SIDE-EFFECTS
  - Rare: Galactorrhoea - hyponatraemia - raised liver enzymes
  - Frequency not known: Agitation - confusional states - dizziness - dry mouth - gastrointestinal disorders - headache - oedema - paraesthesia - restlessness - skin reactions - sleep disturbances - visual disturbances

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### Tranzylcypromine

**INDICATIONS AND DOSE**

**Depressive illness**

**BY MOUTH**

- Adult: Initially 10 mg twice daily, dose to be taken at a time no later than 3 p.m., dose may be increased if necessary after 1 week, increased if necessary to 10 mg daily, dose to be taken in the morning and 20 mg daily, dose to be taken in the afternoon, doses above 30 mg daily, under close supervision only; maintenance 10 mg daily

- Elderly: 5–10 mg daily

- Very rare: Seizures

- Common or very common: Confusion, extreme restlessness (with the traditional (irreversible) MAOIs, but patients still need to avoid sympathomimetics such as ephedrine and pseudoephedrine. In addition, moclobemide should not be given with another antidepressant. Owing to its short duration of action no treatment-free period is required after it has been stopped but it should not be started until at least a week after a tricyclic or related antidepressant or an SSRI or related antidepressant has been stopped (at least 5 weeks in the case of fluoxetine), or for at least a week after an MAOI has been stopped.

- SIDE-EFFECTS
  - Rare: Galactorrhoea - hyponatraemia - raised liver enzymes
  - Frequency not known: Agitation - confusional states - dizziness - dry mouth - gastrointestinal disorders - headache - oedema - paraesthesia - restlessness - skin reactions - sleep disturbances - visual disturbances

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### Moclobemide

**DRUG ACTION** Moclobemide is reported to act by reversible inhibition of monoamine oxidase type A (it is therefore termed a RIMA).

**INDICATIONS AND DOSE**

**Depressive illness**

**BY MOUTH**

- Adult: Initially 300 mg daily in divided doses, adjusted according to response; usual dose 150–600 mg daily, dose to be taken after food

- Social anxiety disorder

**BY MOUTH**

- Adult: Initially 300 mg daily for 3 days, then increased to 600 mg daily in 2 divided doses continued for 8–12 weeks to assess efficacy

- **CONTRA-INDICATIONS** Acute confusional states • phaeochromocytoma

- **CAUTIONS** Avoid in agitated or excited patients (or give with sedative for up to 2–3 weeks) • may provoke manic episodes in bipolar disorders • thyrotoxicosis

- **INTERACTIONS** → Appendix 1 (moclobemide).

- The risk of drug interactions is claimed to be less than with the traditional (irreversible) MAOIs, but patients still need to avoid sympathomimetics such as ephedrine and pseudoephedrine. In addition, moclobemide should not be given with another antidepressant. Owing to its short duration of action no treatment-free period is required after it has been stopped but it should not be started until at least a week after a tricyclic or related antidepressant or an SSRI or related antidepressant has been stopped (at least 5 weeks in the case of fluoxetine), or for at least a week after an MAOI has been stopped.

- SIDE-EFFECTS
  - Rare: Galactorrhoea - hyponatraemia - raised liver enzymes
  - Frequency not known: Agitation - confusional states - dizziness - dry mouth - gastrointestinal disorders - headache - oedema - paraesthesia - restlessness - skin reactions - sleep disturbances - visual disturbances
SELECTIVE SEROTONIN RE- UPTAKE INHIBITORS

Reboxetine

**DRUG ACTION** Reboxetine is a selective inhibitor of noradrenaline re-uptake.

**INDICATIONS AND DOSE**

**BY MOUTH**

- **Adult**:
  - 4 mg twice daily, then increased if necessary to 10 mg/24 hours after 3–4 weeks in divided doses; maximum 12 mg per day

**CAUTIONS**
- Bipolar disorder
- History of cardiovascular disease
- History of epilepsy
- Postural hypotension
- Susceptibility to angle-closure glaucoma
- Urinary retention

**INTERACTIONS** → Appendix 1 (reboxetine).

**SIDE-EFFECTS**

- **Common or very common**
  - Anorexia, chills, constipation, dizziness, dry mouth, headache, impaired visual accommodation, impotence, insomnia, lowering of plasma-potassium concentration on prolonged administration in the elderly, nausea, palpitation, postural hypotension, sweating, tachycardia, urinary retention, vasodilatation
- **Very rare**
  - Angle-closure glaucoma

Raynaud’s syndrome, suicidal behaviour, testicular pain, vomiting

**PREGNANCY** Use only if potential benefit outweighs risk—limited information available.

**BREAST FEEDING** Small amount present in milk—use only if potential benefit outweighs risk.

**HEPATIC IMPAIRMENT** Initial dose 2 mg twice daily, increased according to tolerance.

**RENAI IMPAIRMENT** Initial dose 2 mg twice daily, increased according to tolerance.

**TREATMENT CESSATION** Caution—avoid abrupt withdrawal.

**PATIENT AND CARER ADVICE** Counselling advised.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

| Reboxetine (as Reboxetine mesilate) 4 mg | Edronax 4mg tablets |
| 60 tablet PT | £18.91 DT price = £18.91 |

**NORADRENALINE RE- UPTAKE INHIBITORS**

- **Drug action** Selectively inhibit the re-uptake of serotonin (5-hydroxytryptamine, 5-HT).
- **Contra-indications** Poorly controlled epilepsy—SSRIs should not be used if the patient enters a manic phase.
- **Caution** Cardiac disease—concurrent electroconvulsive therapy—diabetes mellitus—epilepsy (discontinue if convulsions develop)—history of bleeding disorders (especially gastro-intestinal bleeding)—history of mania—susceptibility to angle-closure glaucoma
- **Interactions** → Appendix 1 (antidepressants, SSRI).
  - Caution with other drugs that increase the risk of bleeding.
  - **Side-effects**
    - **Common or very common**
      - Abdominal pain (dose-related)—constipation (dose-related)—diarrhoea (dose-related)—dyspepsia (dose-related)—gastro-intestinal effects (dose-related)—nausea (dose-related)—vomiting (dose-related)
    - **Uncommon**
      - Serotonin syndrome
    - **Very rare**
      - Angle-closure glaucoma
    - **Frequency not known**

**SIDE-EFFECTS, FURTHER INFORMATION**

**Hypersensitivity reactions** If hypersensitivity reactions (including rash) occur, consider discontinuation—may be sign of impending serious systemic reaction, possibly associated with vasculitis.

**Overdose** Symptoms of poisoning by selective serotonin re-uptake inhibitors include nausea, vomiting, agitation, tremor, nystagmus, drowsiness, and sinus tachycardia; convulsions may occur. Rarely, severe poisoning results in the serotonin syndrome, with marked neuropsychiatric effects, neuromuscular hyperactivity, and autonomic instability; hyperthermia, rhabdomyolysis, renal failure, and coagulopathies may develop.
For details on the management of poisoning, see Selective serotonin re-uptake inhibitors, under Emergency treatment of poisoning p. 1123.

- **PREGNANCY** Manufacturers advise avoid during pregnancy unless the potential benefit outweighs the risk. There is a small increased risk of congenital heart defects when taken during early pregnancy. If used during the third trimester there is a risk of neonatal withdrawal symptoms, and persistent pulmonary hypertension in the newborn has been reported.

- **TREATMENT CESSATION** Gastro-intestinal disturbances, headache, anxiety, dizziness, paraesthesia, electric shock sensation in the head, neck, and spine, tinnitus, sleep disturbances, fatigue, influenza-like symptoms, and sweating are the most common features of abrupt withdrawal of an SSRI or marked reduction of the dose; palpitation and visual disturbances can occur less commonly. The dose should be tapered over at least a few weeks to avoid these effects. For some patients, it may be necessary to withdraw treatment over a longer period; consider obtaining specialist advice if symptoms persist. Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment).

- **PATIENT AND CARER ADVICE** May also impair performance of skilled tasks (e.g. driving, operating machinery).

### Citalopram

**INDICATIONS AND DOSE**

**Depressive illness**

BY MOUTH USING TABLETS
- Adult: 20 mg once daily, increased in steps of 20 mg daily if required, dose to be increased at intervals of 3–4 weeks; maximum 40 mg per day
- Elderly: 10–20 mg once daily; maximum 20 mg per day

BY MOUTH USING ORAL DROPS
- Adult: 16 mg once daily, increased in steps of 16 mg daily if required, dose to be increased at intervals of 3–4 weeks; maximum 32 mg per day
- Elderly: 8–16 mg daily; maximum 16 mg per day

**Panic disorder**

BY MOUTH USING TABLETS
- Adult: Initially 10 mg daily, increased in steps of 10 mg daily if required, dose to be increased gradually; usual dose 20–30 mg daily; maximum 40 mg per day
- Elderly: Initially 10 mg daily, increased in steps of 10 mg daily if required, dose to be increased gradually; maximum 20 mg per day

BY MOUTH USING ORAL DROPS
- Adult: Initially 8 mg once daily, increased in steps of 8 mg if required, dose to be increased gradually; usual dose 16–24 mg daily; maximum 32 mg per day
- Elderly: Initially 8 mg once daily, increased in steps of 8 mg if required, dose to be increased gradually; maximum 16 mg per day

**Dose equivalence and conversion**

4 oral drops (8 mg) is equivalent in therapeutic effect to 10 mg tablet.

- **CONTRA-INDICATIONS** QT-interval prolongation
- **CAUTIONS** Susceptibility to QT-interval prolongation
- **INTERACTIONS** Avoid concomitant administration of drugs that prolong QT interval.
- **SIDE-EFFECTS** abnormal dreams, aggressiveness, amnesia, bradycardia, confusion, coughing, euphoria, haemorrhage, hepatitis, hypokalaemia, impaired concentration, increased salivation, malaise, micturition disorders, migraine, mydriasis, oedema, palpitation, paradoxical increased anxiety during initial treatment of panic disorder (reduce dose); paraesthesia; polyuria; postural hypotension; pruritus; QT-interval prolongation; rhinitis; tachycardia; tinnitus; taste disturbance; yawning
- **BREAST FEEDING** Present in milk—use with caution.
- **HEPATIC IMPAIRMENT** Use doses at lower end of range; for tablets up to maximum 20 mg; for oral solution up to maximum 16 mg.
- **RENAL IMPAIRMENT** No information available for eGFR less than 20 mL/minute/1.73 m².

**DIRECTIONS FOR ADMINISTRATION** Cipramil® oral drops should be mixed with water, orange juice, or apple juice before taking.

**PATIENT AND CARER ADVICE** Patients should be advised of the effects of citalopram on driving. Counselling on administration of oral drops is advised.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**

- **CITALOPRAM (Non-proprietary)**
  - Citalopram (as Citalopram hydrobromide) 10 mg Citalopram 10mg tablets | 28 tablet (P99) £8.90 DT price = £1.05
  - Citalopram (as Citalopram hydrobromide) 20 mg Citalopram 20mg tablets | 28 tablet (P99) £15.99 DT price = £1.09
  - Citalopram (as Citalopram hydrobromide) 40 mg Citalopram 40mg tablets | 28 tablet (P99) £27.00 DT price = £1.18
  - Cipramil® (Lundbeck Ltd)
    - Citalopram (as Citalopram hydrobromide) 20 mg Cipramil 20mg tablets | 28 tablet (P99) £8.95 DT price = £1.09

**Oral drops**

EXCIPIENTS: May contain Alcohol

- **CITALOPRAM (Non-proprietary)**
  - Citalopram (as Citalopram hydrochloride) 40 mg per 1 ml Citalopram 40mg/ml oral drops sugar free (sugar-free) | 15ml (P99) £20.16 DT price = £1.56
  - Cipramil® (Lundbeck Ltd)
    - Citalopram (as Citalopram hydrochloride) 40 mg per 1 ml Cipramil 40mg/ml drops (sugar-free) | 15ml (P99) £10.08 DT price = £0.86

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**Escitalopram**

**DRUG ACTION** Escitalopram is the active enantiomer of citalopram.

**INDICATIONS AND DOSE**

Depressive illness | Generalised anxiety disorder | Obsessive-compulsive disorder

BY MOUTH
- Adult: 10 mg once daily; increased if necessary up to 20 mg daily
- Elderly: Initially 5 mg once daily; maximum 10 mg per day

**Panic disorder**

BY MOUTH
- Adult: Initially 5 mg once daily for 7 days, then increased to 10 mg daily; maximum 20 mg per day
- Elderly: Initially 2.5 mg once daily; maximum 10 mg per day
Fluoxetine

INDICATIONS AND DOSE

Major depression

BY MOUTH

- Adult: Initially 20 mg daily, dose is increased after 3–4 weeks if necessary, and at appropriate intervals thereafter, daily dose may be administered as a single or divided dose; maximum 60 mg per day
- Elderly: Initially 20 mg daily, dose is increased after 3–4 weeks if necessary, and at appropriate intervals thereafter, daily dose may be administered as a single or divided dose; usual maximum dose is 40 mg but doses up to 60 mg can be used

Bulimia nervosa

BY MOUTH

- Adult: 60 mg daily, daily dose may be administered as a single or divided dose
- Elderly: Up to 40 mg daily, daily dose may be administered as a single or divided dose; usual maximum dose is 40 mg but doses up to 60 mg can be used

Obsessive compulsive disorder

BY MOUTH

- Adult: 20 mg daily, increased if necessary up to 60 mg daily, daily dose may be administered as a single or divided dose, dose to be increased gradually, review treatment if inadequate response after 10 weeks; maximum 60 mg per day
- Elderly: 20 mg daily, increased if necessary up to 40 mg daily, daily dose may be administered as a single or divided dose, dose to be increased gradually, review treatment if inadequate response after 10 weeks, usual maximum dose is 40 mg but doses up to 60 mg can be used

PHARMACOKINETICS

Consider the long half-life of fluoxetine when adjusting dosage (or in overdosage).

- SIDE-EFFECTS
  - Abnormal dreams, fatigue, paraesthesia, pyrexia, restlessness, sinusitis, yawning
  - Alopoeia, bruxism, confusion, epistaxis, menstrual disturbances, mydriasis, oedema, pruritus, syncope, tachycardia, taste disturbance, tinnitus
  - Aggression, bradycardia, depersonalisation
  - Paradoxical increased anxiety during initial treatment of panic disorder (reduce dose), postural hypotension, QT interval prolongation, thrombocytopenia

- MEDICINAL FORMS

  There can be variation in the licensing of different medicines containing the same drug.

  Tablet
  - ESCITALOPRAM (Non-proprietary)
  - Escitalopram (as Escitalopram oxalate) 5 mg: Escitalopram 5mg tablets | 28 tablet [PCE] £1.26–£8.97 DT price = £1.26
  - Escitalopram (as Escitalopram oxalate) 10 mg: Escitalopram 10mg tablets | 28 tablet [PCE] £1.53–£14.16 DT price = £1.53
  - Escitalopram (as Escitalopram oxalate) 20 mg: Escitalopram 20mg tablets | 28 tablet [PCE] £2.07–£23.94 DT price = £2.07
  - Cipralex (Lundbeck Ltd)
  - Escitalopram (as Escitalopram oxalate) 5 mg: Cipralex 5mg tablets | 28 tablet [PCE] £0.97 DT price = £1.26
  - Escitalopram (as Escitalopram oxalate) 10 mg: Cipralex 10mg tablets | 28 tablet [PCE] £14.91 DT price = £1.53
  - Escitalopram (as Escitalopram oxalate) 20 mg: Cipralex 20mg tablets | 28 tablet [PCE] £25.20 DT price = £2.07
  - Oral drops
  - Cipralex (Lundbeck Ltd)
  - Escitalopram (as Escitalopram oxalate) 20 mg per 1 ml: Cipralex 20mg/ml oral drops (sugar-free) | 15 ml [PCE] £20.16

  Dispersible tablet
  - CAUTIONARY AND ADVISORY LABELS 10
  - Olena (AMCo)
  - Fluoxetine (as Fluoxetine hydrochloride) 20 mg: Olena 20mg dispersible tablets (sugar-free) | 28 tablet [PCE] £3.44 DT price = £3.44

  Capsule
  - FLUOXETINE (Non-proprietary)
  - Fluoxetine (as Fluoxetine hydrochloride) 20 mg: Fluoxetine 20mg capsules | 30 capsule [PCE] £23.75 DT price = £1.16
  - Fluoxetine (as Fluoxetine hydrochloride) 60 mg: Fluoxetine 60mg capsules | 30 capsule [PCE] £144.00 DT price = £26.17
  - Prozac (Eli Lilly and Company Ltd)
  - Fluoxetine (as Fluoxetine hydrochloride) 20 mg: Prozac 20mg capsules | 30 capsule [PCE] £1.50 DT price = £1.16
  - Brands may include Oxaclin

  Oral solution
  - FLUOXETINE (Non-proprietary)
  - Fluoxetine (as Fluoxetine hydrochloride) 4 mg per 1 ml: Fluoxetine 20mg/5ml oral solution | 70 ml [PCE] £12.75 DT price = £3.69
  - Fluoxetine 20mg/5ml oral solution sugar free (sugar-free) | 70 ml [PCE] £5.70
**Fluvoxamine maleate**

**INDICATIONS AND DOSE**

**Depressive illness**

**BY MOUTH**

- Adult: Initially 50–100 mg daily, dose to be increased gradually, then increased if necessary up to 300 mg daily, doses over 150 mg daily are given in divided doses; maintenance 100 mg daily

**Obsessive-compulsive disorder**

**BY MOUTH**

- Adult: Initially 50 mg daily, dose to be taken in the evening, dose is increased gradually if necessary after several weeks, doses over 150 mg daily are given in divided doses, then increased if necessary up to 300 mg daily; maintenance 100–300 mg daily, if no improvement in obsessive-compulsive disorder within 10 weeks, treatment should be reconsidered

**SIDE-EFFECTS**

- Common or very common: Malaise, palpitation, tachycardia
- Uncommon: Ataxia, confusion, postural hypotension
- Rare: Abnormal liver function, usually asymptomatic (discontinue treatment)
- Frequency not known: Neuroleptic malignant syndrome–like event, paraesthesia, taste disturbance

**BREAST FEEDING**

Present in milk—avoid.

**HEPATIC IMPAIRMENT**

Start with low dose.

**RENAL IMPAIRMENT**

Start with low dose.

**PATIENT AND CARER ADVICE**

Patients should be counselled about the effects on driving.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**

**FLUVOXAMINE MALEATE (Non-proprietary)**

Fluvoxamine maleate 50 mg, Fluvoxamine 50 mg tablets | 60 tablet | £18.95 DT price = £17.03

Fluvoxamine maleate 100 mg, Fluvoxamine 100 mg tablets | 30 tablet | £18.90 DT price = £17.03

Faverin (BGP Products Ltd)

Fluvoxamine maleate 50 mg, Faverin 50 mg tablets | 60 tablet | £17.10 DT price = £17.03

Fluvoxamine maleate 100 mg, Faverin 100 mg tablets | 30 tablet | £17.10 DT price = £17.03

**Obsessive-compulsive disorder**

**BY MOUTH**

- Adult: Initially 20 mg daily, dose to be taken in the morning, increased in steps of 10 mg, dose to be increased gradually, to 40 mg daily, no evidence of greater efficacy at higher doses; maximum 60 mg per day
- Elderly: Initially 20 mg daily, dose to be taken in the morning, increased in steps of 10 mg, dose to be increased gradually; maximum 40 mg per day

**Panic disorder**

**BY MOUTH**

- Adult: Initially 10 mg daily, dose to be taken in the morning, increased in steps of 10 mg, dose to be increased gradually, to 40 mg daily, no evidence of greater efficacy at higher doses; maximum 60 mg per day
- Elderly: Initially 10 mg daily, dose to be taken in the morning, increased in steps of 10 mg, dose to be increased gradually; maximum 40 mg per day

**CAUTIONS**

Achromydria - high gastric pH

**CAUTIONS, FURTHER INFORMATION**

Achromydria or high gastric pH Causes reduced absorption of the oral suspension.

**SIDE-EFFECTS**

- Common or very common: Abnormal dreams, raised cholesterol, yawning
- Uncommon: Arrhythmias, confusion, urinary incontinence
- Rare: Depersonalisation, neuroleptic malignant syndrome–like event, panic attacks, paradoxical increased anxiety during initial treatment of panic disorder (reduce dose); restless legs syndrome
- Very rare: Acute glaucoma, hepatic disorders, hepatitis, peripheral oedema, priapism
- Frequency not known: Extrapyramidal reactions, orofacial dystonias, tinnitus, withdrawal reactions

**PREGNANCY**

Increased risk of congenital malformations, especially if used in the first trimester.

**BREAST FEEDING**

Present in milk but amount too small to be harmful.

**HEPATIC IMPAIRMENT**

Reduce dose.

**RENAL IMPAIRMENT**

Reduce dose if eGFR less than 30 mL/minute/1.73 m².

**TREATMENT CESSATION**

Associated with a higher risk of withdrawal reactions.

**PATIENT AND CARER ADVICE**

Patients should be counselled about the effect on driving.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

**Tablet**

**CAUTIONARY AND ADVISORY LABELS**

**PAROXETINE (Non-proprietary)**

Paroxetine (as Paroxetine hydrochloride) 10 mg, Paroxetine 10 mg tablets | 28 tablet | £14.21–£18.12 DT price = £17.47

Paroxetine (as Paroxetine hydrochloride) 20 mg, Paroxetine 20 mg tablets | 30 tablet | £3.29 DT price = £2.29

Paroxetine (as Paroxetine hydrochloride) 30 mg, Paroxetine 30 mg tablets | 30 tablet | £3.36 DT price = £1.95

Seroxat (GlaxoSmitheKline UK Ltd)

Paroxetine (as Paroxetine hydrochloride) 10 mg, Seroxat 10 mg tablets | 28 tablet | £14.21 DT price = £17.47

Paroxetine (as Paroxetine hydrochloride) 20 mg, Seroxat 20 mg tablets | 30 tablet | £15.23 DT price = £2.29

Paroxetine (as Paroxetine hydrochloride) 30 mg, Seroxat 30 mg tablets | 30 tablet | £26.74 DT price = £1.95
Sertraline

**INDICATIONS AND DOSE**

**Depressive illness**
- **Adult:** Initially 50 mg daily, then increased in steps of 50 mg at least every 1 week if required; maintenance 50 mg daily; maximum 200 mg per day

**Obsessive-compulsive disorder**
- **Adult:** Initially 50 mg daily, then increased in steps of 50 mg at least every 1 week if required; maximum 200 mg per day

**Panic disorder | Post-traumatic stress disorder | Social anxiety disorder**
- **Adult:** Initially 25 mg daily for 1 week, then increased to 50 mg daily, then increased in steps of 50 mg at least every 1 week if required, increase only if response is partial and if drug is tolerated; maximum 200 mg per day

**SIDE-EFFECTS**
- Aggression • amnesia • bronchospasm • hepatitis • hypercholesterolaemia • hyperprolactinaemia • hypertension • hypoglycaemia • hypothyroidism • jaundice • leucopenia • liver failure • menstrual irregularities • palpitation • pancreatitis • paraesthesia • postural hypotension • stomatitis • tachycardia • tinnitus • urinary incontinence

**BREAST FEEDING**
- Not known to be harmful but consider discontinuing breast-feeding.

**HEPATIC IMPAIRMENT**
- Reduce dose or increase dose interval in mild or moderate impairment. Avoid in severe impairment.

**RENAL IMPAIRMENT**
- Use with caution.

**PATIENT AND CARER ADVICE**
- Patients should be counselled on the effects on driving.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**
- **SERTRALINE (Non-proprietary)**
  - Sertraline (as Sertraline hydrochloride) 50 mg | 28 tablet [†] £19.25 DT price = £1.46
  - Sertraline (as Sertraline hydrochloride) 100 mg | 28 tablet [†] £25.09 DT price = £1.66
- **Lustral** (Pfizer Ltd)
  - Sertraline (as Sertraline hydrochloride) 50 mg | 28 tablet [‡] £17.82 DT price = £1.46
  - Sertraline (as Sertraline hydrochloride) 100 mg | 28 tablet [‡] £29.16 DT price = £1.66

**SEROTONIN AND NORADRENALINE RE-UPTAKE INHIBITORS**

**Duloxetine**
- **DRUG ACTION**
  - Inhibits the re-uptake of serotonin and noradrenaline.

**INDICATIONS AND DOSE**

**Major depressive disorder**
- **BY MOUTH**
  - **Adult:** 60 mg once daily

**Generalised anxiety disorder**
- **BY MOUTH**
  - **Adult:** Initially 30 mg once daily, increased if necessary to 60 mg once daily; maximum 120 mg per day

**Diabetic neuropathy**
- **BY MOUTH**
  - **Adult:** 60 mg once daily, discontinue if inadequate response after 2 months; review treatment at least every 3 months, maximum dose to be given in divided doses; maximum 120 mg per day

**Moderate to severe stress urinary incontinence**
- **BY MOUTH**
  - **Adult (female):** 40 mg twice daily, patient should be assessed for benefit and tolerability after 2–4 weeks, alternatively initially 20 mg twice daily for 2 weeks, this can minimise side effects, then increased to 40 mg twice daily, the patient should be assessed for benefit and tolerability after 2–4 weeks.

**CAUTIONS**
- Bleeding disorders • cardiac disease • elderly • history of mania • history of seizures • hypertension (avoid if uncontrolled) • raised intra-ocular pressure • susceptibility to angle-closure glaucoma

**INTERACTIONS**
- Appendix 1 (duloxetine). Caution with concomitant use of drugs that increase risk of bleeding.

**SIDE-EFFECTS**
- Common or very common Abdominal pain • abnormal dreams • anorexia • anxiety • constipation • decreased appetite • diarrhoea • dizziness • drowsiness • dry mouth • dyspepsia • fatigue • flatulence • headache • hot flush • insomnia • nausea • nervousness • palpitation • paraesthesia • pruritis • sexual dysfunction • sweating • tremor • visual disturbances • vomiting • weakness • weight changes

- Uncommon Bruisism • cold extremities • dysphagia • gastritis • halitosis • hepatitis • hypertension • hypothyroidism • impaired attention • impaired temperature regulation • movement disorders • muscle twitching • musculoskeletal pain • photosensitivity • postural hypotension • raised cholesterol • stomatitis • syncope • tachycardia • taste disturbance • thirst • urinary disturbances • vertigo

- Rare Mania

- Very rare Angle-closure glaucoma

- Frequency not known Anaphylaxis • angioedema • chest pain • hallucinations • hypersensitivity reactions • hyponatraemia • rash • seizures • Stevens-Johnson syndrome • suicidal behaviour • supraventricular arrhythmia • urticaria

**PREGNANCY**
- Toxicity in animal studies—avoid in patients with stress urinary incontinence; in other conditions use only if potential benefit outweighs risk. Risk of neonatal withdrawal symptoms if used near term.

**BREAST FEEDING**
- Present in milk—manufacturer advises avoid.

**HEPATIC IMPAIRMENT**
- Manufacturer advises avoid.

**RENAL IMPAIRMENT**
- Avoid if eGFR less than 30 mL/minute/1.73 m².

**TREATMENT CESSATION**
- Nausea, vomiting, headache, anxiety, dizziness, paraesthesia, sleep disturbances, and tremor are the most common features of abrupt withdrawal or marked reduction of the dose; dose should be reduced over at least 1–2 weeks.

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**Oral suspension**

**CAUTIONARY AND ADVISORY LABELS 5, 21**

- **Seroxat** (GlaxoSmithKline UK Ltd) Paroxetine (as Paroxetine hydrochloride) 2 mg per 1 ml Seroxat 20mg/10ml liquid (sugar-free) | 150 ml [†] £9.12 DT price = £9.12
Venlafaxine

**INDICATIONS AND DOSE**

**Major depression**

- **By mouth using immediate-release medicines**
  - Adult: Initially 75 mg daily in 2 divided doses, then increased if necessary up to 375 mg daily, dose to be increased if necessary at intervals of at least 2 weeks, faster dose titration may be necessary in some patients; maximum 375 mg per day
- **By mouth using modified-release medicines**
  - Adult: Initially 75 mg once daily, increased if necessary up to 375 mg once daily, dose to be increased if necessary at intervals of at least 2 weeks, faster dose titration may be necessary in some patients; maximum 375 mg per day

**Generalised anxiety disorder**

- **By mouth using modified-release medicines**
  - Adult: 75 mg once daily, increased if necessary up to 225 mg once daily, dose to be increased at intervals of at least 2 weeks; maximum 225 mg per day

**Social anxiety disorder**

- **By mouth using modified-release medicines**
  - Adult: 75 mg once daily, there is no evidence of greater efficacy at higher doses, increased if necessary up to 225 mg once daily, dose to be increased if necessary at intervals of at least 2 weeks; maximum 225 mg per day

**CONTRA-INDICATIONS**

Conditions associated with high risk of cardiac arrhythmia - uncontrolled hypertension

**CAUTIONS**

Diabetes - heart disease (monitor blood pressure) - history of bleeding disorders - history of epilepsy - history or family history of mania - susceptibility to angle-closure glaucoma

**INTERACTIONS**

Appendix 1 (venlafaxine). Comitant use of drugs that increase risk of bleeding.

**SIDE-EFFECTS**

- **Common or very common**
  - Abnormal dreams - anorexia - anxiety - anxiety (on withdrawal) - asthenia - changes in serum cholesterol - chills - confusion - constipation - difficulty with micturition - dizziness - dizziness (on withdrawal) - drowsiness - dry mouth - gastro-intestinal disturbances (on withdrawal) - headache - headache (on withdrawal) - hypertension - hypotension - insomniam - menstrual disturbances - mydriasis - nausea - nervousness - palpitation - paraesthesia (on withdrawal) - sensory disturbances - sexual dysfunction - sleep disturbances (on withdrawal) - sweating - sweating (on withdrawal) - tremor - tremor (on withdrawal) - vasodilatation - visual disturbances - vomiting - weight changes - yawning
- **Uncommon**
- **Rare**
  - Akathisia - extrapyramidal symptoms - hypomania - mania - seizures - urinary incontinence
- **Very rare**
  - Angle-closure glaucoma
- **Frequency not known**

**PREGNANCY**

Avoid unless potential benefit outweighs risk—toxicity in animal studies. Risk of withdrawal effects in neonate.

**BREAST FEEDING**

Present in milk—avoid.

**HEPATIC IMPAIRMENT**

Consider reducing dose by 50% in mild or moderate impairment; use with caution and reduce dose by at least 50% in severe impairment.

**RENAL IMPAIRMENT**

Use with caution. Use half normal dose (immediate-release tablets may be given once daily) if eGFR less than 30 mL/minute/1.73 m².

**TREATMENT CESSATION**

Associated with a higher risk of withdrawal effects compared with other antidepressants. Gastro-intestinal disturbances, headache, anxiety, dizziness, paraesthesia, tremor, sleep disturbances, and sweating are most common features of withdrawal if treatment stopped abruptly or if dose reduced markedly; dose should be reduced over several weeks.

**PATIENT AND CARER ADVICE**

May affect performance of skilled tasks (e.g. driving).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, powder

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 3**

- **VENLAFAXINE (Non-proprietary)**
  - Venlafaxine (as Venlafaxine hydrochloride) 37.5 mg
  - Venlafaxine 37.5 mg tablets | 56 tablet (POD) £20.00 DT price = £2.37
  - Venlafaxine (as Venlafaxine hydrochloride) 75 mg
  - Venlafaxine 75 mg tablets | 56 tablet (POD) £30.00 DT price = £2.66
  - Brands may include ViePax

**Modified-release tablet**

**CAUTIONARY AND ADVISORY LABELS 3, 21, 25**

- Sunvenix XL (Sun Pharmaceuticals UK Ltd)
  - Venlafaxine (as Venlafaxine hydrochloride) 75 mg
  - Sunvenix XL 75 mg tablets | 30 tablet (POD) £11.14 DT price = £1.12
  - Venlafaxine (as Venlafaxine hydrochloride) 150 mg
  - Sunvenix XL 150 mg tablets | 30 tablet (POD) £18.64 DT price = £1.87

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (September 2006) that duloxetine (Cymbalta®) should be restricted for use by specialists when other treatments for diabetic peripheral neuropathic pain are unsuitable or inadequate.

**CONTRA-INDICATIONS**

Conditions associated with high risk of cardiac arrhythmia - uncontrolled hypertension

**CAUTIONS**

Diabetes - heart disease (monitor blood pressure) - history of bleeding disorders - history of epilepsy - history or family history of mania - susceptibility to angle-closure glaucoma

**INTERACTIONS**

Appendix 1 (venlafaxine). Comitant use of drugs that increase risk of bleeding.
Mianserin hydrochloride

INDICATIONS AND DOSE
Depressive illness (particularly where sedation is required)

- Adult: Initially 30–40 mg daily in divided doses, alternately initially 30–40 mg once daily, dose to be taken at bedtime, increase dose gradually as necessary; usual dose 30–90 mg
- Elderly: Initially 30 mg daily in divided doses, alternately initially 30 mg once daily, dose to be taken at bedtime, increase dose gradually as necessary; usual dose 30–90 mg

CONTRA-INDICATIONS
Acute porphyrias p. 864.
arrhythmias - during the manic phase of bipolar disorder.
heart block - immediate recovery period after myocardial infarction
CAUTIONS
Cardiovascular disease - chronic constipation - diabetes - epilepsy - history of bipolar disorder - history of psychosis - hyperthyroidism (risk of arrhythmias) - increased intra-ocular pressure - patients with a significant risk of suicide - phaeochromocytoma (risk of arrhythmias) - prostatic hypertrophy - susceptibility to angle-closure glaucoma - urinary retention

CAUTIONS, FURTHER INFORMATION
Treatment should be stopped if the patient enters a manic phase.
Elderly patients are particularly susceptible to many of the side-effects of tricyclic antidepressants; low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side-effects.

INTERACTIONS
Antidepressants, tricyclic (related).

SIDE-EFFECTS
Common or very common: Agitation - anxiety - arrhythmia - blurred vision - confusion - dizziness - dry mouth - ECG changes, heart block - irritability - paraesthesia - postural hypotension - sleep disturbances - sudden death of patients with cardiac disease - tachycardia
Rare: Dysarthria - extrapyramidal symptoms - paralytic ileus - tremor - urinary retention
Very rare: Constipation - neuroleptic malignant syndrome - precipitation of angle-closure glaucoma
Frequency not known: Alopecia - anorexia - arthralgia - arthritis - blood dyscrasias - breast enlargement - changes in blood sugar - chills (on withdrawal) - convulsions - delusions - galactorrhoea - gynaecomastia - haematological reactions - hallucinations - headache (on withdrawal) - hepatic reactions - hypomania - hypotension - increased appetite - influenza-like symptoms (on withdrawal) - Insomnia (on withdrawal) - jaundice - mania - movement disorders (on withdrawal) - myalgia (on withdrawal) - nausea - nausea (on withdrawal) - oedema - photosensitivity - pruritus - rash - sexual dysfunction - suicidal behaviour - sweating - sweating (on withdrawal) - taste disturbance - tinnitus - urticaria - vivid dreams (on withdrawal) - vomiting - weight gain - weight loss

SIDE-EFFECTS, FURTHER INFORMATION
The patient should be encouraged to persist with treatment as some tolerance to these side-effects seems to develop. They are reduced if low doses are given initially and then gradually increased, but this must be balanced against the need to obtain a full therapeutic effect as soon as possible.

OVERDOSE
Emergency treatment of poisoning
The tricyclic-related antidepressant drugs may be associated with a lower risk of cardio toxicity in overdosage.
Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. For details on the management of poisoning see Tricyclic and related antidepressants under Emergency treatment of poisoning, p. 1123.
Pregnancy
Avoid.
Breast Feeding
The amount secreted into breast milk is too small to be harmful.

Hepatic impairment
Sedative effects are increased in hepatic impairment. Avoid in severe liver disease.

Renal impairment
Caution in renal impairment.

Monitoring requirements
A full blood count is recommended every 4 weeks during the first 3 months of treatment; clinical monitoring should continue subsequently and treatment should be stopped and a full blood count obtained if fever, sore throat, stomatitis, or other signs of infection develop.

Treatment cessation
Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.

Prescribing and dispensing information
Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdosage.

Patient and carer advice
Drowsiness may affect the performance of skilled tasks (e.g. driving). Effects of alcohol enhanced.
Mirtazapine

**DRUG ACTION** Mirtazapine is a presynaptic alpha₂-adrenoceptor antagonist which increases central noradrenergic and serotonergic neurotransmission.

**INDICATIONS AND DOSE**

**Major depression**

**BY MOUTH**

- **Adult:** Initially 15–30 mg daily for 2–4 weeks, dose to be taken at bedtime, then adjusted according to response to up to 45 mg once daily; increased if necessary up to 45 mg daily in 2 divided doses.

**CAUTIONS** Cardiac disorders - diabetes mellitus - elderly - history of bipolar depression - history of seizures - history of urinary retention - hypotension - psychoses (may aggravate psychotic symptoms) - susceptibility to angle-closure glaucoma

**INTERACTIONS** Appendix 1 (mirtazapine).

**SIDE-EFFECTS**

- **Common or very common** Abnormal dreams - agitation (on withdrawal) - anxiety - anxiety (on withdrawal) - arthralgia - confusion - dizziness - dizziness (on withdrawal) - drowsiness - dry mouth - fatigue - headache (on withdrawal) - increased appetite - insomnia - myalgia - nausea (on withdrawal) - oedema - postural hypotension - tremor - vomiting (on withdrawal) - weight gain

- **Uncommon** Hallucinations - mania - movement disorders - syncope

- **Rare** Aggression - myoclonus - pancreatitis

- **Frequency not known** Angle-closure glaucoma - blood disorders - convulsions - dysarthria - hypersalivation - hyponatraemia - inappropriate secretion of antidiuretic hormone - sedation during initial treatment - Stevens-Johnson syndrome - suicidal behaviour - toxic epidermal necrolysis

**PREGNANCY** Use with caution—limited experience; monitor neonate for withdrawal effects.

**BREAST FEEDING** Present in milk; use only if potential benefit outweighs risk.

**HEPATIC IMPAIRMENT** Use with caution. Discontinue if jaundice occurs.

**RENAL IMPAIRMENT** Clearance reduced by 30% if eGFR less than 40 mL/minute/1.73 m²; clearance reduced by 50% if eGFR less than 10 mL/minute/1.73 m².

**TREATMENT CESSATION** Nausea, vomiting, dizziness, agitation, anxiety, and headache are most common features of withdrawal if treatment stopped abruptly or if dose reduced markedly; dose should be reduced over several weeks.

**DIRECTIONS FOR ADMINISTRATION** Orosuspensory tablet (Zispin SolTab) should be placed on the tongue, allowed to disperse and swallowed.

**PATIENT AND CARER ADVICE** Counselling on administration of orosuspensory tablet advised.

Blood Disorders Patients should be advised to report any fever, sore throat, stomatitis or other signs of infection during treatment. Blood count should be performed and the drug stopped immediately if blood dyscrasia suspected.
CAUTIONS, FURTHER INFORMATION
Treatment should be stopped if the patient enters a manic phase. Elderly patients are particularly susceptible to many of the side-effects of tricyclic antidepressants; low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side-effects.

INTERACTIONS
Antidepressants, tricyclic (related).

SIDE-EFFECTS
- Rare
  - Extrapyramidal symptoms - paralytic ileus
- Very rare
  - precipitation of angle-closure glaucoma
- Frequency not known
  - agitation - alopecia - anorexia - anxiety - arrhythmia - arthralgia - blurred vision - breast enlargement - changes in blood sugar - chills (on withdrawal) - confusion - constipation - convulsions - delusions - dizziness - drowsiness - dry mouth - dysarthria - dyspepsia - dyspnoea - ECG changes - galactorrhoea - gynaecomastia - haematological reactions - hallucinations - headache (on withdrawal) - heart block - hepatic reactions - hypersalivation - hypertension - hypomania - hypopatraemia - increased appetite - influenza-like symptoms (on withdrawal) - insomnia (on withdrawal) - irritability - mania - movement disorders (on withdrawal) - myalgia - myalgia (on withdrawal) - nausea - nausea (on withdrawal) - palpitation - paranaesthesia - photosensitivity - postural hypotension - priapism (discontinue immediately) - pruritus - rash - sexual dysfunction - sleep disturbances - sudden death of patients with cardiac disease - sweating - sweating (on withdrawal) - tachycardia - taste disturbance - tinnitus - tremor - urinary retention - urticaria - vivid dreams (on withdrawal) - vomiting - weight gain - weight loss

SIDE-EFFECTS, FURTHER INFORMATION
The patient should be encouraged to persist with treatment as some tolerance to these side-effects seems to develop. They are reduced if low doses are given initially and then gradually increased, but this must be balanced against the need to obtain a full therapeutic effect as soon as possible.

OVERDOSE
Emergency treatment of poisoning. The tricyclic-related antidepressant drugs may be associated with a lower risk of cardio toxicity in overdosage. Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. For details on the management of poisoning see Tricyclic and related antidepressants under Emergency treatment of poisoning, p. 1123.

PREGNANCY
Avoid during first trimester—limited information available. Monitor infant for signs of withdrawal if used until delivery.

BREAST FEEDING
The amount secreted into breast milk is too small to be harmful.

HEPATIC IMPAIRMENT
Sedative effects are increased in hepatic impairment. Avoid in severe liver disease.

RENAL IMPAIRMENT
Use with caution in severe impairment.

TREATMENT CESSATION
Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.

PRESCRIBING AND DISPENSING INFORMATION
Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdosage.

PATIENT AND CARER ADVICE
Drowsiness may affect the performance of skilled tasks (e.g. driving). Effects of alcohol enhanced.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension.

TRICYCLIC ANTIDEPRESSANTS
Amitriptyline hydrochloride

INDICATIONS AND DOSE
Abdominal pain or discomfort (in patients who have not responded to laxatives, loperamide, or antispasmodics)

BY MOUTH
- Adult: Initially 5–10 mg daily, to be taken at night; increased in steps of 10 mg at least every 2 weeks as required; maximum 50 mg per day.

Depressive illness (but not recommended)

BY MOUTH
- Adult: Initially 75 mg daily in divided doses, alternatively initially 75 mg once daily, dose to be taken at bedtime, increased if necessary to 150–200 mg daily, dose to be increased gradually
- Elderly: Initially 30–75 mg daily in divided doses, alternatively initially 30–75 mg once daily, dose to be taken at bedtime, increased if necessary to 150–200 mg daily, dose to be increased gradually

Neuropathic pain

BY MOUTH
- Adult: Initially 10 mg once daily, increased if necessary to 75 mg once daily, dose to be taken at night, dose to be increased gradually, higher doses to be given on specialist advice

Migraine prophylaxis

BY MOUTH
- Adult: Initially 10 mg once daily, then increased if necessary to 50–75 mg once daily (max. per dose 150 mg), dose to be taken at night

UNLICENSED USE
licensed for use in abdominal pain or discomfort in patients who have not responded to laxatives, loperamide, or antispasmodics.

- **CONTRA-INDICATIONS** Acute porphyrias p. 864 - arrhythmias - during manic phase of bipolar disorder - heart block - immediate recovery period after myocardial infarction

- **CAUTIONS** Cardiovascular disease - chronic constipation - diabetes - epilepsy - history of bipolar disorder - history of psychosis - hyperthyroidism (risk of arrhythmias) - increased intra-ocular pressure - patients with a significant risk of suicide - phaeochromocytoma (risk of arrhythmias) - prostatic hypertrophy - susceptibility to angle-closure glaucoma - urinary retention

**CAUTIONS, FURTHER INFORMATION**

Treatment should be stopped if the patient enters a manic phase. Elderly patients are particularly susceptible to many of the side-effects of tricyclic antidepressants; low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side-effects.

- **INTERACTIONS** Appendix 1 (Antidepressants, tricyclic).

- **SIDE-EFFECTS**

  - **Common or very common** Abdominal pain - fatigue - hypertension - mydriasis - oedema - palpitation - restlessness - stomatitis

  - **Rare** Dysthria - extrapyramidal symptoms - paralytic ileus - tremor

  - **Very rare** Neuroleptic malignant syndrome - precipitation of angle-closure glaucoma

  - **Frequency not known** Agitation - alopecia - anorexia - anxiety - arthrythmia - blurred vision - breast enlargement - changes in blood sugar - chills (on withdrawal) - confusion - constipation - convulsions - delusions - dizziness - drowsiness - dry mouth - ECG changes - galactorrhoea - gynaecomastia - haematological reactions - hallucinations - headache (on withdrawal) - heart block - hepatic reactions - hypomania - hypotenraemia - increased appetite - increased intra-ocular pressure - influenza-like symptoms (on withdrawal) - Insomnia (on withdrawal) - irritability - mania - movement disorders (on withdrawal) - myalgia (on withdrawal) - nausea - nausea (on withdrawal) - paraesthesia - photosensitivity - postural hypotension - pruritus - rash - sexual dysfunction - sleep disturbances - sudden death of patients with cardiac disease - suicidal behaviour - sweating - sweating (on withdrawal) - tachycardia - taste disturbance - tinnitus - urinary retention - urticaria - vivid dreams (on withdrawal) - vomiting - weight gain - weight loss

**SIDE-EFFECTS, FURTHER INFORMATION**

The patient should be encouraged to persist with treatment as some tolerance to these side-effects seems to develop. They are reduced if low doses are given initially and then gradually increased, but this must be balanced against the need to obtain a full therapeutic effect as soon as possible.

- **Overdose** Overdosage with amitriptyline is associated with a relatively high rate of fatality. Symptoms of overdose may include dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. For details on the management of poisoning, see Tricyclic and related antidepressants, under Emergency treatment of poisoning p. 1123.

- **PREGNANCY** Use only if potential benefit outweighs risk.

- **BREAST FEEDING** The amount secreted into breast milk is too small to be harmful.

- **HEPATIC IMPAIRMENT** Sedative effects are increased in hepatic impairment. Avoid in severe liver disease.

- **TREATMENT CESSATION** Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. Risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.

- **PRESCRIBING AND DISPENSING INFORMATION** Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdosage.

- **PATIENT AND CARER ADVICE** Drowsiness may affect the performance of skilled tasks (e.g. driving). Effects of alcohol enhanced.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 2**

- **AMITRIPTYLINE HYDROCHLORIDE (Non-proprietary)**
  - Amitriptyline hydrochloride 10 mg Amitriptyline 10mg tablets | 28 tablet (£0.12 DT price = £1.05
  - Amitriptyline hydrochloride 25 mg Amitriptyline 25mg tablets | 28 tablet (£0.10 DT price = £1.10
  - Amitriptyline hydrochloride 50 mg Amitriptyline 50mg tablets | 28 tablet (£0.19 DT price = £1.19

**Oral solution**

**CAUTIONARY AND ADVISORY LABELS 2**

- **AMITRIPTYLINE HYDROCHLORIDE (Non-proprietary)**
  - Amitriptyline hydrochloride 10mg/5ml oral solution sugar free (sugar-free) | 150 ml (£30 £22.60-£26.00
  - Amitriptyline hydrochloride 5mg/1ml oral solution sugar free (sugar-free) | 150 ml (£30 £18.00 DT price = £18.00
  - Amitriptyline hydrochloride 10mg/5ml oral solution sugar free (sugar-free) | 150 ml (£30 £19.20 DT price = £19.20

**Amitriptyline with perphenazine**

The properties listed below are those particular to the combination only. For the properties of the components please consider, amitriptyline hydrochloride p. 292, perphenazine p. 308.

**INDICATIONS AND DOSE**

**Depression with anxiety**

**BY MOUTH**

- Adult: 1 tablet 3 times a day, an additional tablet may be taken at bedtime when required

**LESS SUITABLE FOR PRESCRIBING** Less suitable for prescribing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 2**

- **Triptafen (AMCo)**
  - Amitriptyline hydrochloride 25 mg, Perphenazine 2 mg Triptafen tablets | 100 tablet (£33.13
Clomipramine hydrochloride

INDICATIONS AND DOSE

Depressive illness
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
**Adult:** Initially 10 mg daily, then increased if necessary to 30–150 mg daily in divided doses, dose to be increased gradually, alternatively increased if necessary to 30–150 mg once daily, dose to be taken at bedtime; maximum 250 mg per day
**Elderly:** Initially 10 mg daily, then increased to 30–75 mg daily, dose to be increased carefully over approximately 10 days

Phobic and obsessional states
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
**Adult:** Initially 25 mg daily, then increased to 100–150 mg daily, dose to be increased gradually over 2 weeks; maximum 250 mg per day
**Elderly:** Initially 10 mg daily, then increased to 100–150 mg daily, dose to be increased gradually over 2 weeks; maximum 250 mg per day

Adjunctive treatment of cataplexy associated with narcolepsy
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
**Adult:** Initially 10 mg daily, dose to be gradually increased until satisfactory response; increased if necessary to 10–75 mg daily

ANAFRANIL SR®
Depressive illness
BY MOUTH
**Adult:** Initially 10 mg once daily, then increased if necessary to 30–150 mg once daily, to be taken at bedtime, doses to be titrated using clomipramine capsules, dose to be increased gradually; maximum 250 mg per day
**Elderly:** Initially 10 mg once daily, then increased to 30–75 mg once daily, dose to be increased carefully over approximately 10 days, doses to be titrated using clomipramine capsules

Phobic and obsessional states
BY MOUTH
**Adult:** Initially 25 mg once daily, then increased to 100–150 mg once daily, dose to be increased gradually over 2 weeks, doses to be titrated using clomipramine capsules; maximum 250 mg per day
**Elderly:** Initially 10 mg once daily, then increased to 100–150 mg once daily, dose to be increased gradually over 2 weeks, doses to be titrated using clomipramine capsules; maximum 250 mg per day

Adjunctive treatment of cataplexy associated with narcolepsy
BY MOUTH
**Adult:** Initially 10 mg once daily, dose to be gradually increased until satisfactory response; usual dose 10–75 mg once daily, doses to be titrated using clomipramine capsules

- **CONTRA-INDICATIONS** Acute porphyrias p. 864; arrhythmias during the manic phase of bipolar disorder; heart block; immediate recovery period after myocardial infarction
- **CAUTIONS** Cardiovascular disease, chronic constipation, diabetes, epilepsy, history of bipolar disorder, history of psychosis, hyperthyroidism (risk of arrhythmias), increased intra-ocular pressure, patients with a significant risk of suicide, phaeochromocytoma (risk of arrhythmias), prostatic hypertrophy, susceptibility to angle-closure glaucoma, urinary retention

- **INTERACTIONS** Appendix 1 (antidepressants, tricyclic.

- **SIDE-EFFECTS**
  - Common or very common Abdominal pain, agitation, alopecia, anxiety, arthralgia, blurred vision, breast enlargement, changes in blood sugar, chills (on withdrawal), confusion, constipation, convulsions, delusions, dizziness, dry mouth, ECG changes, galactorrhoea, gynaecomastia, haematological reactions, hallucinations, headache (on withdrawal), heart block, hepatic reactions, hypomana, hypotension, increased appetite, influenza-like symptoms (on withdrawal), insomnia (on withdrawal), irritability, mania, movement disorders (on withdrawal), myalgia (on withdrawal), nausea, nausea (on withdrawal), paraesthesia, photosensitivity, postural hypotension, pruritus, rash, sexual dysfunction, sleep disturbances, sudden death of patients with cardiac disease, suicidal behaviour, sweating, sweating (on withdrawal), tachycardia, taste disturbance, tinnitus, urinary retention, urticaria, vivid dreams (on withdrawal), vomiting, weight gain, weight loss

SIDE-EFFECTS, FURTHER INFORMATION
The patient should be encouraged to persist with treatment as some tolerance to these side-effects seems to develop. They are reduced if low doses are given initially and then gradually increased, but this must be balanced against the need to obtain a full therapeutic effect as soon as possible.

Overdose Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hyperthermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. For details on the management of poisoning see Tricyclic and related antidepressants under Emergency treatment of poisoning, p. 1123.

- **PREGNANCY** Neonatal withdrawal symptoms reported if used during third trimester.

- **BREAST FEEDING** The amount secreted into breast milk is too small to be harmful.

- **HEPATIC IMPAIRMENT** Sedative effects are increased in hepatic impairment. Avoid in severe liver disease.

- **TREATMENT CESSATION** Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.

- **PRESCRIBING AND DISPENSING INFORMATION** Limited quantities of tricyclic antidepressants should be
Dosulepin hydrochloride (Dothiepin hydrochloride)

**INDICATIONS AND DOSE**

Depressive illness (particularly where sedation is required) (initiated by a specialist)

*BY MOUTH*

- **Adult:** Initially 75 mg daily in divided doses, alternatively initially 75 mg once daily, dose to be taken at bedtime, increased if necessary to 150 mg daily, doses to be increased gradually; up to 225 mg daily in some circumstances (e.g. hospital use).
- **Elderly:** Initially 50–75 mg daily in divided doses, alternatively initially 50–75 mg once daily, dose to be taken at bedtime, increased if necessary to 75–150 mg daily, doses to be increased gradually; up to 225 mg daily in some circumstances (e.g. hospital use).

**CONTRA-INDICATIONS**

Acute porphyrias p. 864 - arrhythmias - during the manic phase of bipolar disorder - heart block - immediate recovery period after myocardial infarction

**CAUTIONS**

Cardiovascular disease - chronic constipation - diabetes - epilepsy - history of bipolar disorder - history of psychosis - hyperthyroidism (risk of arrhythmias) - increased intra-ocular pressure - patients with a significant risk of suicide - phaeochromocytoma (risk of arrhythmias) - prostatic hypertrophy - susceptibility to angle-closure glaucoma - urinary retention

**CAUTIONS, FURTHER INFORMATION**

Treatment should be stopped if the patient enters a manic phase. Elderly patients are particularly susceptible to many of the side-effects of tricyclic antidepressants; low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side-effects.

**INTERACTIONS**

Appendix 1 (antidepressants, tricyclic).

**SIDE-EFFECTS**

- Rare: Dysarthria - extrapyramidal symptoms - paralytic ileus - tremor.
- Very rare: Neuroleptic malignant syndrome - precipitation of angle-closure glaucoma.

**FREQUENCY NOT KNOWN**

Agitation - alopecia - anorexia - anxiety - arrhythmias - changes in blood sugar - chills (on withdrawal) - confusion - constipation - convulsions - delusions - dizziness - dry mouth - ECG changes - galactorrhoea - gynaecomastia - haematological reactions - hallucinations - headache (on withdrawal) - heart block - hepatic reactions - hypomana - hypotension - increased appetite - increased intraocular pressure - influenza-like symptoms (on withdrawal) - insomnia (on withdrawal) - irritability - mania - movement disorders (on withdrawal) - myalgia (on withdrawal) - nausea - nausea (on withdrawal) - paraesthesia - photosensitivity - postural hypotension - pruritus - rash - sexual dysfunction - sleep disturbances - sudden death of patients with cardiac disease - suicidal behaviour - sweating - sweating (on withdrawal) - tachycardia - taste disturbance - tinnitus - urinary retention - urticaria - vivid dreams (on withdrawal) - vomiting - weight gain - weight loss.

**SIDE-EFFECTS, FURTHER INFORMATION**

The patient should be encouraged to persist with treatment as some tolerance to these side-effects seems to develop. They are reduced if low doses are given initially and then gradually increased, but this must be balanced against the need to obtain a full therapeutic effect as soon as possible.

**OVERDOSE**

Overdosage with dosulepin is associated with a relatively high rate of fatality. Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. For details on the management of poisoning see Tricyclic and related antidepressants under Emergency treatment of poisoning, p. 1123.

- **PREGNANCY**

Use only if potential benefit outweighs risk.

- **BREAST FEEDING**

The amount secreted into breast milk is too small to be harmful.

- **HEPATIC IMPAIRMENT**

Sedative effects are increased in hepatic impairment. Avoid in severe liver disease.

- **TREATMENT CESSATION**

Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge. (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.

**PRESCRIBING AND DISPENSING INFORMATION**

Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdose. A maximum prescription equivalent to 2 weeks’ supply of 75 mg daily should be considered in patients with increased risk factors for suicide at initiation of treatment, during any dose adjustment, and until improvement occurs.

- **PATIENT AND CARER ADVICE**

Drowsiness may affect the performance of skilled tasks (e.g. driving). Effects of alcohol enhanced.

- **LESS SUITABLE FOR PRESCRIBING**

Dosulepin hydrochloride is less suitable for prescribing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension.
Tablet

**CAUTIONARY AND ADVISORY LABELS 2**
- **DOSULEPIN HYDROCHLORIDE** (Non-proprietary)
  - Dosulepin hydrochloride 75 mg: Dosulepin 75mg tablets | 28 tablet (BNF) £2.15 DT price + £1.80
- Prothiaden (Teofarma)
  - Dosulepin hydrochloride 75 mg: Prothiaden 75mg tablets | 28 tablet (BNF) £2.97 DT price + £1.80

Capsule

**CAUTIONARY AND ADVISORY LABELS 2**
- **DOSULEPIN HYDROCHLORIDE** (Non-proprietary)
  - Dosulepin hydrochloride 25 mg: Dosulepin 25mg capsules | 28 capsule (BNF) £1.86 DT price + £1.86
- Prothiaden (Teofarma)
  - Dosulepin hydrochloride 25 mg: Prothiaden 25mg capsules | 28 capsule (BNF) £1.70 DT price + £1.86

**Doxepin**

**INDICATIONS AND DOSE**

**Depressive illness (particularly where sedation is required)**

**BY MOUTH**
- **Adult:** Initially 75 mg daily in divided doses, alternatively 75 mg once daily, adjusted according to response, dose to be taken at bedtime; maintenance 25–300 mg daily, doses above 100 mg given in 3 divided doses
- **Elderly:** Start with lower doses and adjust according to response

**CONTRA-INDICATIONS**
- Acute porphyrias p. 864.
- arrhythmias - during manic phase of bipolar disorder - heart block - immediate recovery period after myocardial infarction (in adults)
- **CAUTIONS**
  - Cardiovascular disease - chronic constipation - diabetes - epilepsy - history of bipolar disorder - history of psychosis - hyperthyroidism (risk of arrhythmias) - increased intra-ocular pressure - patients with significant risk of suicide - phaeochromocytoma (risk of arrhythmias) - prostatic hypertrophy - susceptibility to angle-closure glaucoma - urinary retention

**CAUTIONS, FURTHER INFORMATION**

Treatment should be stopped if the patient enters a manic phase.

**Elderly** Elderly patients are particularly susceptible to many of the side-effects of tricyclic antidepressants; low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side-effects.

**INTERACTIONS** → Appendix 1 (antidepressants, tricyclic).

**SIDE-EFFECTS**
- Common or very common: Agitation - anxiety - confusion - dizziness - drowsiness - irritability - paraesthesia - sleep disturbances
- Rare: Dysarthria - extrapyramidal symptoms - paralytic ileus - tremor
- Very rare: Neuroleptic malignant syndrome - precipitation of angle-closure glaucoma
- Frequency not known: Abdominal pain - alopecia - anorexia - arthralgia - blurred vision - breast enlargement - changes in blood sugar - chills (on withdrawal) (in adults) - constipation - convulsions - delusions - diarrhoea - dry mouth - ECG changes (in adults) - flushing - galactorrhoea - gynaecomastia - haematological reactions - hallucinations - headache (on withdrawal) - heart block - hepatic reactions - hypomania - hypotension - increased appetite - influenza-like symptoms (on withdrawal) - insomnia (on withdrawal) - mania - movement disorders (on withdrawal) - myalgia (on withdrawal) - nausea - nausea (on withdrawal) - oedema - photosensitivity - postural hypotension - pruritus - rash - sexual dysfunction - stomatitis - sudden death of patients with cardiac disease
- suicidal behaviour - sweating - sweating (on withdrawal) - tachycardia - taste disturbance - tinnitus - urinary retention - urticaria - vivid dreams (on withdrawal) - vomiting - weight gain - weight loss

**SIDE-EFFECTS, FURTHER INFORMATION**

The patient should be encouraged to persist with treatment as some tolerance to these side-effects seems to develop. They are reduced if low doses are given initially and then gradually increased, but this must be balanced against the need to obtain a full therapeutic effect as soon as possible.

**Overdose**

Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. For details on the management of poisoning see Tricyclic and related antidepressants under Emergency treatment of poisoning, p. 1123.

**PREGNANCY**

Use with caution—limited information available.

**BREAST FEEDING**

The amount secreted into breast milk is too small to be harmful. Accumulation of metabolite may cause sedation and respiratory depression in neonate.

**HEPATIC IMPAIRMENT**

Sedative effects are increased in hepatic impairment. Avoid in severe liver disease.

**RENAL IMPAIRMENT**

Use with caution.

**TREATMENT CESSATION**

Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.

**PRESCRIBING AND DISPENSING INFORMATION**

Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdosage.

**PATIENT AND CARER ADVICE**

Drowsiness may affect performance of skilled tasks (e.g. driving). Effects of alcohol enhanced.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension, capsule

Capsule

**CAUTIONARY AND ADVISORY LABELS 2**
- **DOXEPIN** (Non-proprietary)
  - Doxepin (as Doxepin hydrochloride) 25 mg: Doxepin 25mg capsules | 28 capsule (BNF) £48.00 DT price + £48.00
  - Doxepin (as Doxepin hydrochloride) 50 mg: Doxepin 50mg capsules | 28 capsule (BNF) £84.00 DT price + £84.00

**Imipramine hydrochloride**

**INDICATIONS AND DOSE**

**Depressive illness**

**BY MOUTH**
- **Adult:** Initially up to 75 mg daily in divided doses, then increased to 150–200 mg daily, up to 150 mg may be given as a single dose at bedtime, dose to be increased gradually
- **Elderly:** Initially 10 mg daily, increased to 30–50 mg daily, dose to be increased gradually
Depressive illness in hospital patients

**BY MOUTH**
- Adult: Initially up to 75 mg daily in divided doses, dose to be increased gradually, increased to up to 300 mg daily in divided doses

**Nocturnal enuresis**
- Child 6-7 years: 25 mg once daily, to be taken at bedtime, initial period of treatment (including gradual withdrawal) 3 months—full physical examination before further course
- Child 8-10 years: 25–50 mg once daily, to be taken at bedtime, initial period of treatment (including gradual withdrawal) 3 months—full physical examination before further course
- Child 11-17 years: 50–75 mg once daily, to be taken at bedtime, initial period of treatment (including gradual withdrawal) 3 months—full physical examination before further course

**SIDE-EFFECTS**
- Common or very common: Fatigue, flushing, headache, palpitation, restlessness
- Rare: Extrapyramidal symptoms, paralytic ileus
- Very rare: Abdominal pain, aggression, allergic alveolitis, cardiac decompensation, diarrhoea, dry mouth, dysarthria, ECG changes, galactorrhoea, gynaecomastia, haematological reactions, hallucinations, headache (on withdrawal), heart block, hepatic reactions, hypomania, hyponatraemia, increased appetite, influenza-like symptoms (on withdrawal), insomnia (on withdrawal), irritability, mania, movement disorders (on withdrawal), myalgia (on withdrawal), nausea, nausea (on withdrawal), paraesthesia, photosensitivity, postural hypotension, pruritus, rash, sexual dysfunction, sleep disturbances, sudden death of patients with cardiac disease, suicidal behaviour, sweating, sweating (on withdrawal), tachycardia, taste disturbance, tinnitus, tremor, urinary retention, urticaria, vivid dreams (on withdrawal), vomiting, weight gain, weight loss

**SIDE-EFFECTS, FURTHER INFORMATION**
- In adults The patient should be encouraged to persist with treatment as some tolerance to these side-effects seems to develop. They are reduced if low doses are given initially and then gradually increased, but this must be balanced against the need to obtain a full therapeutic effect as soon as possible.
- **Overdose** Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. For details on the management of poisoning see Tricyclic and related antidepressants under Emergency treatment of poisoning, p. 1123.
- **PREGNANCY** Colic, tachycardia, dyspnoea, irritability, muscle spasms, respiratory depression and withdrawal symptoms reported in neonates when used in the third trimester.
- **BREAST FEEDING** The amount secreted into breast milk is too small to be harmful.
- **HEPATIC IMPAIRMENT** Sedative effects are increased in hepatic impairment. Avoid in severe liver disease.
- **RENAL IMPAIRMENT** Use with caution in severe impairment.
- **TREATMENT CESSATION** Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 4 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic antidepressants should be withdrawn slowly.
- **PRESCRIBING AND DISPENSING INFORMATION** Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdosage.
- **PATIENT AND CARER ADVICE** Drowsiness may affect the performance of skilled tasks (e.g. driving). Effects of alcohol enhanced. Medicines for Children leaflet: Imipramine www.medicinesforchildren.org.uk/imipramine

**MEDICINAL FORMS**

<table>
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<th>Strength</th>
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</tbody>
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**Lofepramine**

**INDICATIONS AND DOSE**

**Depressive illness**
- **BY MOUTH**
  - Adult: 140–210 mg daily in divided doses
  - Elderly: May respond to lower doses
- **CONTRA-INDICATIONS** Acute porphyrias p. 864 – arrhythmias – during the manic phase of bipolar disorder –...
heart block - immediate recovery period after myocardial infarction

- **CAUTIONS** Cardiovascular disease - chronic constipation - diabetes - epilepsy - history of bipolar disorder - history of psychosis - hyperthyroidism (risk of arrhythmias) - increased intra-ocular pressure - patients with a significant risk of suicide - phaeochromocytoma (risk of arrhythmias) - prostatic hypertrophy - susceptibility to angle-closure glaucoma - urinary retention

**TREATMENT CESSATION** Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.

- **PRESCRIBING AND DISPENSING INFORMATION** Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdosage.

**PATIENT AND CARER ADVICE** Drowsiness may affect the performance of skilled tasks (e.g. driving). Effects of alcohol enhanced.

- **MEDITICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

**SIDE-EFFECTS**

- **Common or very common** Agitation - anxiety - confusion - dizziness - irritability - paraesthesia - postural hypotension - sleep disturbances
- **Rare** Extrapyramidal symptoms - paralytic ileus
- **Very rare** Neuroleptic malignant syndrome - precipitation of angle-closure glaucoma

**SIDE-EFFECTS, FURTHER INFORMATION**

- **Frequency not known** Alopecia - anorexia - arrhythmias - blurred vision - breast enlargement - changes in blood sugar - chills (on withdrawal) - constipation - convulsions - delusions - dizziness - dryness - dry mouth - drowsiness - dryness of mouth - ECG changes - galactorrhoea - gynaecomastia - haematological reactions - hallucinations - headache - head block - hepatic reactions - hypomania - hypotension - increased appetite - influenza-like symptoms (on withdrawal) - insomnia (on withdrawal) - mania - movement disorders (on withdrawal) - myalgia (on withdrawal) - nausea - nausea (on withdrawal) - oedema - photosensitivity - pruritus - rash - sexual dysfunction - sudden death of patients with cardiac disease - suicidal behaviour - sweating - sweating (on withdrawal) - tachycardia - taste disturbance - tinnitus - tremor - urinary retention - urticaria - vivid dreams (on withdrawal) - vomiting - weight gain - weight loss

**SIDE-EFFECTS, FURTHER INFORMATION**

The patient should be encouraged to persist with treatment as some tolerance to these side-effects seems to develop. They are reduced if low doses are taken initially and then gradually increased, but this must be balanced against the need to obtain a full therapeutic effect as soon as possible.

**OVERDOSE** Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. For details on the management of poisoning see Tricyclic and related antidepressants under Emergency treatment of poisoning, p. 1123.

**PREGNANCY** Neonatal withdrawal symptoms and respiratory depression reported if used during third trimester.

**BREAST FEEDING** The amount secreted into breast milk is too small to be harmful.

**HEPATIC IMPAIRMENT** Sedative effects are increased in hepatic impairment. Avoid in severe liver disease.

**RENAL IMPAIRMENT** Avoid in severe impairment.

**REFERENCES**

- **INDICATIONS AND DOSE**

**INDICATIONS AND DOSE**

**Depression**

**BY MOUTH**

- **Adult**: To be initiated at a low dose, then increased if necessary to 75–100 mg daily in divided doses, alternatively increased if necessary to 75–100 mg once daily; maximum 150 mg per day
- **Elderly**: To be initiated at a low dose, then increased if necessary to 30–50 mg daily in divided doses

**Neuropathic pain**

**BY MOUTH**

- **Adult**: Initially 10 mg once daily, to be taken at night, increased if necessary to 75 mg daily, dose to be increased gradually; higher doses to be given under specialist supervision

**UNLICENSED USE** Not licensed for use in neuropathic pain.

**CONTRA-INDICATIONS**

- **Acute porphyrias p. 864** - arrhythmias - during the manic phase of bipolar disorder - heart block - immediate recovery period after myocardial infarction

**CAUTIONS**

- **Cardiovascular disease** - chronic constipation - diabetes - epilepsy - history of bipolar disorder - history of psychosis - hyperthyroidism (risk of arrhythmias) - increased intra-ocular pressure - patients with a significant risk of suicide - phaeochromocytoma (risk of arrhythmias) - prostatic hypertrophy - susceptibility to angle-closure glaucoma - urinary retention

**CAUTIONS, FURTHER INFORMATION**

Treatment should be stopped if the patient enters a manic phase. Elderly patients are particularly susceptible to many of the side-effects of tricyclic antidepressants; low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side-effects.
Tramipramine

**INDICATIONS AND DOSE**

Depressive illness (particularly where sedation required)

**BY MOUTH**
- Adult: Initially 50–75 mg daily in divided doses, alternatively initially 50–75 mg once daily, dose to be taken at bedtime, increased if necessary to 150–300 mg daily
- Elderly: Initially 10–25 mg 3 times a day, maintenance 75–150 mg daily

**CONTRA-INDICATIONS**
Acute porphyrias p. 864 · arrhythmias · during the manic phase of bipolar disorder · heart block · immediate recovery period after myocardial infarction

**CAUTIONS**
Cardiovascular disease · chronic constipation · diabetes · epilepsy · history of bipolar disorder · history of psychosis · hyperthyroidism (risk of arrhythmias) · increased intra-ocular pressure · patients with a significant risk of suicide · phaeochromocytoma (risk of arrhythmias) · prostatic hypertrophy · susceptibility to angle-closure glaucoma · urinary retention

**CAUTIONS, FURTHER INFORMATION**
Treatment should be stopped if the patient enters a manic phase.
Elderly patients are particularly susceptible to many of the side-effects of tricyclic antidepressants; low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side-effects.

**INTERACTIONS**
Appendix 1 (antidepressants, tricyclic).

**SIDE-EFFECTS**
- Rare Paralytic ileus
- Very rare Neuroleptic malignant syndrome · precipitation of angle-closure glaucoma
- Frequency not known Abdominal pain · agitation · alopcaia · anorexia · anxiety · arrhythmia · blurred vision · breast enlargement · changes in blood sugar · chills (on withdrawal) · confusion · constipation · convulsions · delusions · diarrhoea · dizziness · dry mouth · dysarthria · ECG changes · flushing · galactorrhoea · gynaecomastia · haematological reactions · hallucinations · headache (on withdrawal) · heart block · hepatic reactions · hypomania · hypotenraemia · increased appetite · influenza-like symptoms (on withdrawal) · insomnia (on withdrawal) · irritability · mania · movement disorders (on withdrawal) · myalgia (on withdrawal) · nausea · nausea (on withdrawal) · oedema · parasthesia · photosensitivity · postural hypotension · pruritis · rash · sexual dysfunction · sleep disturbances · stomatitis · sudden death of patients with cardiac disease · suicidal behaviour · sweating · sweating (on withdrawal) · tachycardia · taste disturbance · tinnitus · tremor · urinary retention · urticaria · vivid dreams (on withdrawal) · vomiting · weight gain · weight loss

**SIDE-EFFECTS, FURTHER INFORMATION**
The patient should be encouraged to persist with treatment as some tolerance to these side-effects seems to develop. They are reduced if low doses are given initially and then gradually increased, but this must be balanced against the need to obtain a full therapeutic effect as soon as possible.

**OVERDOSE**
Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. For details on the management of poisoning see Tricyclic and related antidepressants under Emergency treatment of poisoning, p. 1123.

**PREGNANCY**
Use only if potential benefit outweighs risk.

**BREAST FEEDING**
The amount secreted into breast milk is too small to be harmful.

**HEPATIC IMPAIRMENT**
Sedative effects are increased in hepatic impairment. Avoid in severe liver disease.

**MONITORING REQUIREMENTS**
Manufacturer advises plasma-nortriptyline concentration monitoring if dose above 100 mg daily, but evidence of practical value uncertain.

**TREATMENT CESSION**
Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.

**PRESCRIBING AND DISPENSING INFORMATION**
Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdosage.

**PATIENT AND CARER ADVICE**
Drowsiness may affect the performance of skilled tasks (e.g. driving). Effects of alcohol enhanced.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORTRIPTYLINE (Non-proprietary)</td>
</tr>
<tr>
<td>Nortriptyline (as Nortriptyline hydrochloride)</td>
</tr>
<tr>
<td>10 mg Nortriptyline 10mg tablets</td>
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<tr>
<td>25 mg Nortriptyline 25mg tablets</td>
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to develop. They are reduced if low doses are given initially and then gradually increased, but this must be balanced against the need to obtain a full therapeutic effect as soon as possible.

**Overdose** Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Diluted pupils and urinary retention also occur. For details on the management of poisoning see Tricyclic and related antidepressants under Emergency treatment of poisoning, p. 1123.

- **PREGNANCY** Use only if potential benefit outweighs risk.
- **BREAST FEEDING** The amount secreted into breast milk is too small to be harmful.
- **HEPATIC IMPAIRMENT** Sedative effects are increased in hepatic impairment. Avoid in severe liver disease.
- **TREATMENT CESSATION** Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). If possible tricyclic and related antidepressants should be withdrawn slowly.
- **PRESCRIBING AND DISPENSING INFORMATION** Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdosage.
- **PATIENT AND CARER ADVICE** Drowsiness may affect the performance of skilled tasks (e.g. driving). Effects of alcohol enhanced.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

### Tablet

- **CAUTIONARY AND ADVISORY LABELS 2**
- **TRIMIPRAMINE (Non-proprietary)**
  - Trimipramine (as Trimipramine maleate) 10 mg Trimipramine 10mg tablets | 28 tablet £1.50 DT price = £3.30 | 84 tablet £5.00 no price available
  - Trimipramine (as Trimipramine maleate) 25 mg Trimipramine 25mg tablets | 28 tablet £5.30 DT price = £13.50 | 84 tablet £10.00 no price available

### Capsule

- **CAUTIONARY AND ADVISORY LABELS 2**
- **TRIMIPRAMINE (Non-proprietary)**
  - Trimipramine (as Trimipramine maleate) 50 mg Trimipramine 50mg capsules | 28 capsule £5.00 DT price = £13.00

**2.6 Psychoses and schizophrenia**

### Psychoses and related disorders

**Advice of Royal College of Psychiatrists on doses of antipsychotic drugs above BNF upper limit**

Unless otherwise stated, doses in the BNF are licensed doses—any higher dose is therefore unlicensed

- Consider alternative approaches including adjuvant therapy and newer or second-generation antipsychotic drugs such as clozapine.
- Bear in mind risk factors, including obesity; particular caution is indicated in older patients, especially those over 70.
- Consider potential for drug interactions—see interactions: Appendix 1 (antipsychotics).
- Carry out ECG to exclude untoward abnormalities such as prolonged QT interval; repeat ECG periodically and
reduce dose if prolonged QT interval or other adverse cardiac abnormality develops.

- Increase dose slowly and not more often than once weekly.
- Carry out regular pulse, blood pressure, and temperature checks; ensure that patient maintains adequate fluid intake.
- Consider high-dose therapy to be for limited period and review regularly; abandon if no improvement after 3 months (return to standard dosage).

Important: When prescribing an antipsychotic for administration on an emergency basis, the intramuscular dose should be lower than the corresponding oral dose (owing to absence of first-pass effect), particularly if the patient is very active (increased blood flow to muscle considerably increases the rate of absorption). The prescription should specify the dose for each route and should not imply that the same dose can be given by mouth or by intramuscular injection. The dose of antipsychotic for emergency use should be reviewed at least daily.

Antipsychotic drugs

Antipsychotic drugs are also known as ‘neuroleptics’ and (misleadingly) as ‘major tranquillisers’. In the short term they are used to calm disturbed patients whatever the underlying psychopathology, which may be schizophrenia, brain damage, mania, toxic delirium, or agitated depression. Antipsychotic drugs are used to alleviate severe anxiety but this too should be a short-term measure.

Schizophrenia

The aim of treatment is to alleviate the suffering of the patient (and carer) and to improve social and cognitive functioning. Many patients require life-long treatment with antipsychotic medication. Antipsychotic drugs relieve positive psychotic symptoms such as thought disorder, hallucinations, and delusions, and prevent relapse; they are usually less effective on negative symptoms such as apathy and social withdrawal. In many patients, negative symptoms persist between episodes of treated positive symptoms, but earlier treatment of psychotic illness may protect against the development of negative symptoms over time. Patients with acute schizophrenia generally respond better than those with chronic symptoms.

Long-term treatment of a patient with a definitive diagnosis of schizophrenia is usually required after the first episode of illness in order to prevent relapses. Doses that are effective in acute episodes should generally be continued as prophylaxis.

First-generation antipsychotic drugs

The first-generation antipsychotic drugs act predominantly by blocking dopamine D2 receptors in the brain. First-generation antipsychotic drugs are not selective for any of the four dopamine pathways in the brain and so can cause a range of side-effects, particularly extrapyramidal symptoms and elevated prolactin. The phenothiazine derivatives can be divided into 3 main groups:

- **Group 1**: chlorpromazine hydrochloride p. 304, levomepromazine p. 345, and promazine hydrochloride p. 320, generally characterised by pronounced sedative effects and moderate antimuscarinic and extrapyramidal side-effects.
- **Group 2**: pericyazine p. 308 and pipotiazine palmitate, generally characterised by moderate sedative effects, but fewer extrapyramidal side-effects than groups 1 or 3.
- **Group 3**: fluphenazine decanoate p. 306, perphenazine p. 308, prochlorperazine p. 309, and trifluoperazine p. 310, generally characterised by fewer sedative and antimuscarinic effects, but more pronounced extrapyramidal side-effects than groups 1 and 2.

Butyrophenones (benperidol p. 300 and haloperidol p. 306) resemble the group 3 phenothiazines in their clinical properties. Thioxanthenes (flupentixol p. 305 and zuclopenthixol p. 311) have moderate sedative, antimuscarinic effects, and extrapyramidal effects. Diphenylbutylpiperidines (pimozide p. 306) and the substituted benzamides (sulpiride p. 310) have reduced sedative, antimuscarinic, and extrapyramidal effects.

Second-generation antipsychotic drugs

The second-generation antipsychotic drugs (sometimes referred to as atypical antipsychotic drugs) act on a range of receptors in comparison to first-generation antipsychotic drugs and have more distinct clinical profiles, particularly with regard to side-effects.

Prescribing for the elderly

The balance of risks and benefit should be considered before prescribing antipsychotic drugs for elderly patients. In elderly patients with dementia, antipsychotic drugs are associated with a small increased risk of mortality and an increased risk of stroke or transient ischaemic attack. Furthermore, elderly patients are particularly susceptible to postural hypotension and to hyper- and hypothermia in hot or cold weather.

It is recommended that:

- Antipsychotic drugs should not be used in elderly patients to treat mild to moderate psychotic symptoms.
- Initial doses of antipsychotic drugs in elderly patients should be reduced (to half the adult dose or less), taking into account factors such as the patient’s weight, comorbidity, and concomitant medication.
- Treatment should be reviewed regularly.

Side effects of antipsychotic drugs

Side-effects caused by antipsychotic drugs are common and contribute significantly to non-adherence to therapy.

Extrapyramidal symptoms occur most frequently with the piperazine phenothiazines (fluphenazine, perphenazine, prochlorperazine, and trifluoperazine), the butyrophenones (benperidol and haloperidol), and the first-generation depot preparations. They are easy to recognise but cannot be predicted accurately because they depend on the dose, the type of drug, and on individual susceptibility.

Extrapyramidal symptoms consist of:

- **parkinsonian symptoms** (including tremor), which may occur more commonly in adults or the elderly and may appear gradually;
- **dystonia** (abnormal face and body movements) and **dyskinesia**, which occur more commonly in children or young adults after large initial doses and may resemble an exacerbation of the condition being treated;
- **akathisia** (restlessness), which characteristically occurs after large initial doses and may resemble an exacerbation of the condition being treated;
- **tardive dyskinesia** (rhythmic, involuntary movements of tongue, face, and jaw), which usually develops on long-term therapy or with high dosage, but it may develop on short-term treatment with low doses—short-lived tardive dyskinesia may occur after withdrawal of the drug.

**Parkinsonian symptoms** remit if the drug is withdrawn and may be suppressed by the administration of antimuscarinic drugs. However, routine administration of such drugs is not justified because not all patients are affected and they may unmask or worsen tardive dyskinesia.

**Tardive dyskinesia** is the most serious manifestation of extrapyramidal symptoms; it is of particular concern because it may be irreversible on withdrawing therapy and treatment is usually ineffective. In children, tardive dyskinesia is more likely to occur when the antipsychotic drug is withdrawn. However, some manufacturers suggest that drug withdrawal at the earliest signs of tardive dyskinesia (fine vermiform movements of the tongue) may halt its full development. Tardive dyskinesia occurs fairly
frequently, especially in the elderly, and treatment must be carefully and regularly reviewed. Most antipsychotic drugs, both first- and second-generation, increase prolactin concentration to some extent because dopamine inhibits prolactin release. Aripiprazole reduces prolactin because it is a dopamine-receptor partial agonist. Risperidone, amisulpride, and first-generation antipsychotic drugs are most likely to cause symptomatic hyperprolactinaemia. The clinical symptoms of hyperprolactinaemia include sexual dysfunction, reduced bone mineral density, menstrual disturbances, breast enlargement, and galactorrhoea. Sexual dysfunction is one of the main causes of non-adherence to antipsychotic medication; physical illness, psychiatric illness, and substance misuse are contributing factors. Antipsychotic-induced sexual dysfunction is caused by more than one mechanism. Reduced dopamine transmission and hyperprolactinaemia decrease libido; antimuscarinic effects can cause disorders of arousal; and alpha-1-adrenoceptor antagonists are associated with erection and ejaculation problems in men. Risperidone and haloperidol commonly cause sexual dysfunction. If sexual dysfunction is thought to be antipsychotic-induced, dose reduction or switching medication should be considered. Antipsychotic drugs have been associated with cardiovascular side-effects such as tachycardia, arrhythmias, and hypotension. QT-interval prolongation is a particular concern with pimozide and haloperidol. There is also a higher probability of QT-interval prolongation in patients using any intravenous antipsychotic drug, or any antipsychotic drug or combination of antipsychotic drugs with doses exceeding the recommended maximum. Cases of sudden death have occurred. Hyperglycaemia and sometimes diabetes can occur with antipsychotic drugs, particularly clozapine, olanzapine, quetiapine, and risperidone. All antipsychotic drugs may cause weight gain, but the risk and extent varies. Clozapine and olanzapine commonly cause weight gain. Hypotension and interference with temperature regulation Hypotension and interference with temperature regulation are dose-related side-effects that are liable to cause dangerous falls and hypothermia or hyperthermia in the elderly. Clozapine, chlorpromazine, lurasidone, and quetiapine can cause postural hypotension (especially during initial dose titration) which may be associated with syncope or reflex tachycardia in some patients. Neuroleptic malignant syndrome (hyperthermia, fluctuating level of consciousness, muscle rigidity, and autonomic dysfunction with pallor, tachycardia, labile blood pressure, sweating, and urinary incontinence) is a rare but potentially fatal side-effect of all antipsychotic drugs. Discontinuation of the antipsychotic drug is essential because there is no proven effective treatment, but bromocriptine and dantrolene have been used. The syndrome, which usually lasts for 5–7 days after drug discontinuation, may be unduly prolonged if depot preparations have been used. Blood dyscrasias Perform blood counts if unexplained infection or fever develops.

Choice There is little meaningful difference in efficacy between each of the antipsychotic drugs (other than clozapine p. 313), and response and tolerability to each antipsychotic drug varies. There is no first-line antipsychotic drug which is suitable for all patients. Choice of antipsychotic medication is influenced by the patient’s medication history, the degree of sedation required (although tolerance to this usually develops), and consideration of individual patient factors such as risk of extrapyramidal side-effects, weight gain, impaired glucose tolerance, QT-interval prolongation, or the presence of negative symptoms. Second generation antipsychotic drugs may be better at treating the negative symptoms of schizophrenia. Second-generation antipsychotic drugs should be prescribed if extrapyramidal side-effects are a particular concern. Of these, aripiprazole p. 312, clozapine p. 313, olanzapine p. 315, and quetiapine p. 318 are least likely to cause extrapyramidal side-effects. Although amisulpride p. 312 is a dopamine-receptor antagonist, extrapyramidal side-effects are less common than with the first-generation antipsychotic drugs because amisulpride selectively blocks mesolimbic dopamine receptors, and extrapyramidal symptoms are caused by blockade of the striatal dopamine pathway. Aripiprazole p. 312 has negligible effect on the QT interval. Other antipsychotic drugs with a reduced tendency to prolong QT interval include amisulpride p. 312, clozapine p. 313, fluphenazine p. 305, fluphenazine decanoate p. 306, olanzapine p. 315, perphenazine p. 308, prochlorperazine p. 309, risperidone p. 319, and sulpiride p. 310. Schizophrenia is associated with insulin resistance and diabetes; the risk of diabetes is increased in patients with schizophrenia who take antipsychotic drugs. First-generation antipsychotic drugs are less likely to cause diabetes than second-generation antipsychotic drugs, and of the first-generation antipsychotic drugs, fluphenazine decanoate p. 306 and haloperidol p. 306 are lowest risk. Olanzapine p. 312 and aripiprazole p. 312 have the lowest risk of diabetes of the second-generation antipsychotic drugs. Amisulpride, aripiprazole, haloperidol, sulpiride p. 310, and trifluoperazine p. 310 are least likely to cause weight gain. The antipsychotic drugs with the lowest risk of sexual dysfunction are aripiprazole p. 312 and quetiapine p. 318. Olanzapine p. 315 may be considered if sexual dysfunction is judged to be secondary to hyperprolactinaemia. Hyperprolactinaemia is usually not clinically significant with aripiprazole, clozapine p. 313, olanzapine, and quetiapine treatment. When changing from other antipsychotic drugs, a reduction in prolactin concentration may increase fertility. Patients should receive an antipsychotic drug for 4–6 weeks before it is deemed ineffective. Prescribing more than one antipsychotic drug at a time should be avoided except in exceptional circumstances (e.g. clozapine augmentation or when changing medication during titration) because of the increased risk of adverse effects such as extrapyramidal symptoms, QT-interval prolongation, and sudden cardiac death. Clozapine is licensed for the treatment of schizophrenia in patients unresponsive to, or intolerant of, other antipsychotic drugs. Clozapine should be introduced if schizophrenia is not controlled despite the sequential use of two or more antipsychotic drugs (one of which should be a second-generation antipsychotic drug), each for at least 6–8 weeks. If symptoms do not respond adequately to an optimised dose of clozapine, plasma-clozapine concentration should be checked before adding a second antipsychotic drug to augment clozapine; allow 8–10 weeks’ treatment to assess response. Patients must be registered with a clozapine patient monitoring service.

Monitoring Full blood count, urea and electrolytes, and liver function test monitoring is required at the start of therapy with antipsychotic drugs, and then annually thereafter. Blood lipids and weight should be measured at baseline, at 3 months (weight should be measured at frequent intervals during the first 3 months), and then yearly. Fasting blood glucose should be measured at baseline, at 4–6 months, and then yearly.
Before initiating antipsychotic drugs, an ECG may be required, particularly if physical examination identifies cardiovascular risk factors, if there is a personal history of cardiovascular disease, or if the patient is being admitted as an inpatient.

Blood pressure monitoring is advised before starting therapy and frequently during dose titration of antipsychotic drugs.

Other uses
Some antipsychotic drugs can be used for the treatment of nausea and vomiting, chorea, and motor tics. Chlorpromazine hydrochloride p. 304 and haloperidol p. 306 can be used for intractable hiccups. Benperidol p. 300 is used in deviant antisocial sexual behaviour but its value is not established.

Psychomotor agitation should be investigated for an underlying cause; it can be managed with low doses of chlorpromazine hydrochloride or haloperidol used for short periods. Antipsychotic drugs can be used with caution for the short-term treatment of severe agitation and restlessness in the elderly.

Equivalent doses of oral antipsychotics
These equivalences are intended only as an approximate guide; individual dosage instructions should also be checked; patients should be carefully monitored after any change in medication. Equivalent daily dose of antipsychotic drug:

- Chlorpromazine 100 mg
- Clozapine 50 mg
- Haloperidol 2–3 mg
- Pimozide 2 mg
- Risperidone 0.5–1 mg
- Sulpiride 200 mg
- Trifluoperazine 5 mg

Important: These equivalences must not be extrapolated beyond the maximum dose for the drug. Higher doses require careful titration in specialist units and the equivalences shown here may not be appropriate.

Dosage
After an initial period of stabilisation, in most patients, the total daily oral dose can be given as a single dose. The Royal College of Psychiatrists has published advice on doses of antipsychotic drugs above BNF upper limit.

Antipsychotic depot injections
Long-acting depot injections are used for maintenance therapy especially when compliance with oral treatment is unreliable. However, depot injections of conventional antipsychotics may give rise to a higher incidence of extrapyramidal reactions than oral preparations; extrapyramidal reactions occur less frequently with second-generation antipsychotic depot preparations, such as risperidone p. 319 and olanzapine enbomate p. 316.

Choice
There is no clear-cut division in the use of the conventional antipsychotics, but zuclopenthixol p. 311 may be suitable for the treatment of agitated or aggressive patients whereas flupentixol decanoate p. 305 can cause over-excitement in such patients. Zuclopenthixol decanoate may be more effective in preventing relapses than other conventional antipsychotic depot preparations. The incidence of extrapyramidal reactions is similar for the conventional antipsychotics.

Equivalent doses of depot antipsychotics

<table>
<thead>
<tr>
<th>Antipsychotic drug/interval</th>
<th>Dosage (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flupentixol decanoate / 2 weeks</td>
<td>40</td>
</tr>
<tr>
<td>Fluphenazine decanoate / 2 weeks</td>
<td>25</td>
</tr>
<tr>
<td>Haloperidol (as decanoate) / 4 weeks</td>
<td>100</td>
</tr>
<tr>
<td>Pipotiazine palmitate / 4 weeks</td>
<td>50</td>
</tr>
<tr>
<td>Zuclopenthixol decanoate / 2 weeks</td>
<td>200</td>
</tr>
</tbody>
</table>

Important: These equivalences must not be extrapolated beyond the maximum dose for the drug

These equivalences are intended only as an approximate guide; individual dosage instructions should also be checked; patients should be carefully monitored after any change in medication.

Dosage
Individual responses to neuroleptic drugs are variable and to achieve optimum effect, dosage and dosage interval must be titrated according to the patient’s response.

ANTIPSYCHOTICS (FIRST-GENERATION)

Antipsychotic drugs

- **CAUTIONS** Blood dyscrasias - cardiovascular disease - conditions predisposing to seizures - depression - epilepsy - history of jaundice - myasthenia gravis - Parkinson’s disease (may be exacerbated) - photosensitisation (may occur with higher dosages) - prostatic hypertrophy - severe respiratory disease - susceptibility to angle-closure glaucoma

- **CAUTIONS, FURTHER INFORMATION**
  - **Cardiovascular disease** An ECG may be required, particularly if physical examination identifies cardiovascular risk factors, personal history of cardiovascular disease, or if the patient is being admitted as an inpatient.

- **INTERACTIONS** ▶ Appendix 1 (antipsychotics).
  - Increased risk of toxicity with myelosuppressive drugs.

- **SIDE-EFFECTS** ▶ Rare Neuroleptic malignant syndrome—discontinue (potentially fatal)
  - Very rare Precipitation of angle-closure glaucoma

- **Overdose** Phenothiazines cause less depression of consciousness and respiration than other sedatives. Hypotension, hypothermia, sinus tachycardia, and arrhythmias may complicate poisoning. For details on the management of poisoning see Antipsychotics under Emergency treatment of poisoning, p. 1123.
Nervous system
Chlorpromazine hydrochloride

Pregnancy
Extrapyramidal effects and withdrawal syndrome have been reported occasionally in the neonate when antipsychotic drugs are taken during the third trimester of pregnancy. Following maternal use of antipsychotic drugs in the third trimester, neonates should be monitored for symptoms including agitation, hypertonia, hypotonia, tremor, drowsiness, feeding problems, and respiratory distress.

Breastfeeding
There is limited information available on the short- and long-term effects of antipsychotic drugs on the breast-fed infant. Animal studies indicate possible adverse effects of antipsychotic medicines on the developing nervous system. Chronic treatment with antipsychotic drugs whilst breast-feeding should be avoided unless absolutely necessary. Phenothiazine derivatives are sometimes used in breast-feeding women for short-term treatment of nausea and vomiting.

Monitoring requirements
- It is advisable to monitor prolactin concentration at the start of therapy, at 6 months, and then yearly. Patients taking antipsychotic drugs not normally associated with symptomatic hyperprolactinaemia should be considered for prolactin monitoring if they show symptoms of hyperprolactinaemia (such as breast enlargement and galactorrhoea).
- Patients with schizophrenia should have physical health monitoring (including cardiovascular disease risk assessment) at least once per year.

Patient and carer advice
Drowsiness may affect performance of skilled tasks (e.g. driving or operating machinery), especially at start of treatment; effects of alcohol are enhanced. As photosensitisation may occur with higher dosages, patients should avoid direct sunlight.

Chlorpromazine hydrochloride

Indications and dose
Schizophrenia and other psychoses | Mania | Short-term adjunctive management of severe anxiety | Psychomotor agitation, excitement, and violent or dangerously impulsive behaviour

By mouth
- Adult: Initially 25 mg 3 times a day, adjusted according to response, alternatively initially 75 mg once daily, adjusted according to response, dose to be taken at night; maintenance 75–300 mg daily, increased if necessary up to 1 g daily, this dose may be required in psychoses, take a third to half adult dose in the elderly and debilitated patients

By rectum
- Adult: 100 mg every 6–8 hours, dose expressed as chlorpromazine base

Intractable hiccup

By mouth
- Adult: 25–50 mg 3–4 times a day

Relief of acute symptoms of psychoses (under expert supervision)

By deep intramuscular injection
- Adult: 25–50 mg every 6–8 hours

Nausea and vomiting of terminal illness (where other drugs have failed or are not available)

By mouth
- Child 1-5 years: 500 micrograms/kg every 4–6 hours; maximum 40 mg per day
- Child 6–11 years: 500 micrograms/kg every 4–6 hours; maximum 75 mg per day
- Child 12–17 years: 10–25 mg every 4–6 hours
- Adult: 30–25 mg every 4–6 hours

By rectum
- Adult: 100 mg every 6–8 hours

Dose adjustments due to interactions
Dose adjustment may be necessary if smoking started or stopped during treatment.

Dose equivalence and conversion
For each therapeutic effect 100 mg chlorpromazine base given rectally as a suppository = 20–25 mg chlorpromazine hydrochloride by intramuscular injection = 40–50 mg of chlorpromazine base or hydrochloride given by mouth.

Unlicensed use
Rectal route is not licensed.

Contra-indications
CNS depression · comatose states · hypothyroidism · phaeochromocytoma

Caution
Diabetes

Side-effects
Side-effects, further information
Acute dystonic reactions Phenothiazines can induce acute dystonic reactions such as facial and skeletal muscle spasms and oculogyric crises; children (especially girls, young women, and those under 10 kg) are particularly susceptible.

Hepatic impairment Can precipitate coma; phenothiazines are hepatotoxic.

Renal impairment Start with small doses in severe renal impairment because of increased cerebral sensitivity.

Monitoring requirements
- With intramuscular use Patients should remain supine, with blood pressure monitoring for 30 minutes after intramuscular injection.
- Handling and storage Owing to the risk of contact sensitisation, pharmacists, nurses, and other health workers should avoid direct contact with chlorpromazine; tablets should not be crushed and solutions should be handled with care.

Medicinal forms
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: suppository, oral suspension, oral solution, capsule

Tablet
Cautionary and advisory labels 2, 11

Chlorpromazine hydrochloride (Non-proprietary)
Chlorpromazine hydrochloride 25 mg Chlorpromazine 25 mg tablets | 28 tablet | £6.45 DT price = £2.31
Chlorpromazine hydrochloride 50 mg Chlorpromazine 50 mg tablets | 28 tablet | £6.00 DT price = £2.24
Chlorpromazine hydrochloride 100 mg Chlorpromazine 100 mg tablets | 28 tablet | £6.25 DT price = £2.39

Oral solution
Cautionary and advisory labels 2, 11

Chlorpromazine hydrochloride (Non-proprietary)
Chlorpromazine hydrochloride 5 mg per 1 ml Chlorpromazine 25 mg/5 ml syrup | 150 ml | £2.35 DT price = £2.35
Chlorpromazine 25 mg/5 ml oral solution sugar free (sugar-free) | 150 ml | £2.35
Chlorpromazine 25 mg/5 ml oral solution | 150 ml | £2.35 DT price = £2.35
Chlorpromazine hydrochloride 20 mg per 1 ml Chlorpromazine 100 mg/5 ml oral solution | 150 ml | £5.50 DT price = £5.50
Flupentixol (Flupenthixol)

INDICATIONS AND DOSE
Schizophrenia and other psychoses, particularly with apathy and withdrawal but not mania or psychotic motor hyperactivity

BY MOUTH
- Adult: Initially 3–9 mg twice daily, adjusted according to response, for debilitated patients, use elderly dose; maximum 18 mg per day
- Elderly: Initially 0.75–4.5 mg twice daily, adjusted according to response

Depressive Illness
- Adult: Initially 1 mg once daily, dose to be taken in the morning, increased if necessary to 2 mg after 1 week, doses above 2 mg to be given in divided doses, last dose to be taken before 4 pm; discontinue if no response after 1 week at maximum dosage; maximum 3 mg per day
- Elderly: Initially 500 micrograms daily, dose to be taken in the morning, then increased if necessary to 1 mg after 1 week, doses above 1 mg to be given in divided doses, last dose to be taken before 4 pm; discontinue if no response after 1 week at maximum dosage; maximum 1.5 mg per day

CONTRA-INDICATIONS
- Circulatory collapse
- CNS depression
- Comatose states
- Excitable patients
- Overactive patients
- Phaeochromocytoma

CAUTIONS
- Acute porphyrias
- Cardiovascular disease
- Nephrotic syndrome
- Diabetes mellitus
- Severe renal impairment because of increased cerebral sensitivity
- Prolongation of QT interval

INTERACTIONS
- Avoid concomitant administration of drugs that prolong QT interval.

SIDE-EFFECTS
- Asthenia
- Dysphoria
- Hypersalivation
- Myalgia
- Sudden death
- Torsade de Pointes

SIDE-EFFECTS, FURTHER INFORMATION
- Less sedating but extrapyramidal symptoms frequent.
- Avoid concomitant administration of drugs that prolong QT interval.

PREGNANCY
- Avoid unless potential benefit outweighs risk.

BREAST FEEDING
- Present in breast milk—avoid.

HEPATIC IMPAIRMENT
- Can precipitate coma.

RENAL IMPAIRMENT
- Start with small doses of antipsychotic drugs in severe renal impairment because of increased cerebral sensitivity.
- Manufacturer advises caution in renal failure.

PATIENT AND CARER ADVICE
- Although drowsiness may occur, can also have an alerting effect so should not be taken in the evening.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.
- Solution for injection
  - Largactil
    - Chlorpromazine hydrochloride 25 mg per 1 ml
    - 50 mg/ml solution for injection ampoules | 10 ampoule £7.51

Flupentixol decanoate (Flupenthixol Decanoate)

INDICATIONS AND DOSE
Maintenance in schizophrenia and other psychoses

BY DEEP INTRAMUSCULAR INJECTION
- Adult: Test dose 20 mg, dose to be injected into the upper outer buttock or lateral thigh, then 20–40 mg after at least 7 days, then 20–40 mg every 2–4 weeks, adjusted according to response, usual maintenance dose 50 mg every 4 weeks to 300 mg every 2 weeks; maximum 400 mg per week
- Elderly: Dose is initially quarter to half adult dose

CONTRA-INDICATIONS
- Children
- CNS depression
- Comatose states
- Excitable patients
- Overactive patients
- Phaeochromocytoma

CAUTIONS
- An alternative antipsychotic may be necessary if symptoms such as aggression or agitation appear—avoid in Acute porphyrias
- Diabetes mellitus
- Increased cerebral sensitivity
- Torsade de Pointes

SIDE-EFFECTS
- Erythema
- Hyperglycaemia
- Mood elevating effect
- Nodules
- Pain at injection site

SIDE-EFFECTS, FURTHER INFORMATION
- Less sedating but extrapyramidal symptoms frequent.

HEPATIC IMPAIRMENT
- Can precipitate coma.

RENAL IMPAIRMENT
- Start with small doses in severe renal impairment because of increased cerebral sensitivity.

MONITORING REQUIREMENTS
- Treatment requires careful monitoring for optimum effect.

DIRECTIONS FOR ADMINISTRATION
- In general not more than 2–3 mL of oily injection should be administered at any one site. Correct injection technique (including use of z-track technique) and rotation of injection sites are essential. When initiating therapy with sustained-release preparations of conventional antipsychotics, patients should first be given a small test-dose as undesirable side-effects are prolonged.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
- Depixol (Flupentixol decanoate) (Lundbeck Ltd)
  - Flupentixol decanoate 20 mg per 1 ml
    - Depixol 40 mg/2 ml solution for injection ampoules | 10 ampoule £25.39
    - Depixol 80 mg/1 ml solution for injection ampoules | 10 ampoule £15.17
  - Flupentixol decanoate 100 mg per 1 ml
    - Depixol Conc 100 mg/1 ml solution for injection ampoules | 10 ampoule £62.51

- Psytixol
  - Flupentixol decanoate 20 mg per 1 ml
    - Psytixol 40 mg/2 ml solution for injection ampoules | 10 ampoule £25.38
  - Flupentixol decanoate 100 mg per 1 ml
    - Psytixol 50 mg/0.5 ml solution for injection ampoules | 10 ampoule £53.12
Fluphenazine decanoate

**INDICATIONS AND DOSE**

Maintenance in schizophrenia and other psychoses

*BY DEEP INTRAMUSCULAR INJECTION*

- Adult: Test dose 12.5 mg, dose to be administered into the gluteal muscle, then 12.5–100 mg after 4–7 days, then 12.5–100 mg every 14–35 days, adjusted according to response
- Elderly: Test dose 6.25 mg, dose to be administered into the gluteal muscle, then 12.5–100 mg after 4–7 days, then 12.5–100 mg every 14–35 days, adjusted according to response

**Dose adjustments due to interactions**

Dose adjustment may be necessary if smoking started or stopped during treatment.

- CONTRA-INDICATIONS: Children - CNS depression - comatose states - marked cerebral atherosclerosis - phaeochromocytoma
- CAUTIONS: QT-interval prolongation - when transferring from oral to depot therapy, the dose by mouth should be reduced gradually
- INTERACTIONS: Avoid concomitant drugs that prolong QT interval.
- SIDE-EFFECTS: Erythema - inappropriate antidiuretic hormone secretion - nodules - oedema - pain at injection site - swelling - systemic lupus erythematosus
- SIDE-EFFECTS, FURTHER INFORMATION

Less sedating and fewer antimuscarinic or hypotensive symptoms, but extrapyramidal symptoms, particularly dystonic reactions and akathisia, more frequent. Extrapyramidal symptoms usually appear a few hours after injection and continue for about 2 days but may be delayed.

If the dose needs to be reduced to alleviate side-effects, it is important to recognise that the plasma-drug concentration may not fall for some time after reducing the dose, therefore it may be a month or longer before side-effects subside.

- HEPATIC IMPAIRMENT: Avoid in hepatic failure. Can precipitate coma; phenothiazines are hepatotoxic.
- RENAL IMPAIRMENT: Manufacturer advises caution. Start with small doses of antipsychotic drugs in severe renal impairment because of increased cerebral sensitivity. Avoid in renal failure.
- MONITORING REQUIREMENTS: Treatment requires careful monitoring for optimum effect.
- DIRECTIONS FOR ADMINISTRATION: In general not more than 2–3 mL of oily injection should be administered at any one site. Correct injection technique (including use of z-track technique) and rotation of injection sites are essential. When initiating therapy with sustained-release preparations of conventional antipsychotics, patients should first be given a small test-dose as undesirable side-effects are prolonged.

- MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Excipients: May contain Sesame oil
- **Fluphenazine decanoate 25 mg per 1 ml** Modecate (Sanofi) 5 ampoule (£) £22.22
- **Fluphenazine decanoate 100 mg per 1 ml** Modecate Concentrate 100mg/1ml solution for injection ampoules 1 5 ampoule (£) £43.73
- **Fluphenazine decanoate 50mg/0.5ml solution for injection ampoules** 5 ampoule (£) £8.51

Flupentixol decanoate

**INDICATIONS AND DOSE**

Schizophrenia | Psychoses | Mania and hypomania | Organic brain damage (depending on symptoms)

*BY MOUTH*

- Adult: Initially 2–20 mg once daily, alternatively initially 2–20 mg daily in divided doses; maintenance 1–3 mg 3 times a day, adjusted according to response, daily maximum to be given in divided doses; for debilitated patients, use elderly dose; maximum 20 mg per day
- Elderly: Initially 1–10 mg once daily, alternatively initially 1–10 mg daily in divided doses; maintenance 1–3 mg 3 times a day, adjusted according to response, daily maximum to be given in divided doses; maximum 20 mg per day

*BY INTRAMUSCULAR INJECTION*

- Adult: Initially 2–5 mg, repeated if necessary, repeated dose given according to response and tolerability, for debilitated patients, use elderly dose; maximum 12 mg per day
- Elderly: Initially 1–2.5 mg, repeated if necessary, repeated dose given according to response and tolerability; maximum 12 mg per day

Agitation and restlessness in the elderly

*BY MOUTH*

- Elderly: Initially 0.75–1.5 mg 2–3 times a day, adjusted according to response

Management of mental or behavioural problems such as aggression, hyperactivity and self-mutilation in the mentally retarded and in patients with organic brain damage (depending on symptoms) | Gilles de la Tourette syndrome | Severe tics | Intractable hiccup | Adjunct to short-term management of moderate to severe psychomotor agitation, excitement and, violent or dangerously impulsive behaviour

*BY MOUTH*

- Adult: Initially 1.5–3 mg 2–3 times a day, alternatively initially 3–5 mg 2–3 times a day, higher dose in severely affected or resistant patients; maintenance 0.5–1 mg 3 times a day, increased if necessary to 2–3 mg 3 times a day, once symptoms are controlled, gradually reduce dose to the lowest effective maintenance dose, for debilitated patients, use elderly dose
- Elderly: Initially 0.75–1.5 mg 2–3 times a day, alternatively initially 1.5–2.5 mg 2–3 times a day, higher dose in severely affected or resistant patients; maintenance 0.5–1 mg 3 times a day, increased if necessary to 2–3 mg 3 times a day, once symptoms are controlled, gradually reduce dose to the lowest effective maintenance dose

Nausea and vomiting

*BY INTRAMUSCULAR INJECTION*

- Adult: 1–2 mg

Nausea and vomiting in palliative care

*BY MOUTH*

- Adult: Initially 1.5 mg 1–2 times a day, increased if necessary to 5–10 mg daily in divided doses
Haloperidol decanoate

INDICATIONS AND DOSE

Maintenance in schizophrenia and other psychoses

BY DEEP INTRAMUSCULAR INJECTION

- Adult: Initially 50 mg every 4 weeks, increased in steps of 50 mg if required, increased if necessary to 300 mg every 4 weeks. Higher doses may be needed in some patients, dose to be administered into gluteal muscle, if 2-weekly administration preferred, doses should be halved.
- Elderly: Initially 12.5–25 mg every 4 weeks, if 2-weekly administration preferred, doses should be halved.

Dose adjustments due to interactions

Dose adjustment may be necessary if smoking started or stopped during treatment.

Important safety information

When prescribing, dispensing or administering, check that this is the correct preparation—this preparation is used for maintenance treatment and should not be confused with depot preparations which are usually used in the community or clinics for maintenance treatment.

CONTRA-INDICATIONS

Bradycardia - CNS depression - comatose states - lesions of the basal ganglia - Parkinson’s disease - phaeochromocytoma - QT-interval prolongation

CAUTIONS

Arteriosclerosis - hypocalcaemia - hypokalaemia - hypomagnesaemia - metabolic disturbances - subarachnoid haemorrhage - thyrotoxicosis

INTERACTIONS

Avoid concomitant administration of drugs that prolong QT interval.

SIDE-EFFECTS

Common or very common - Depression - weight loss - Uncommon - Dysphoria - oedema - Rare - Bronchospasm - hypoglycaemia - inappropriate antidiuretic hormone secretion - photosensitivity reactions - pigmentation

Frequency not known - Hypertension - Stevens-Johnson syndrome - sweating - toxic epidermal necrolysis

SIDE-EFFECTS, FURTHER INFORMATION

Less sedating and fewer antimuscarinic or hypotensive symptoms.

PREGNANCY

Avoid unless benefits outweigh risks.

HEPATIC IMPAIRMENT

Can precipitate coma.

RENAIS IMPAIRMENT

Start with small doses in severe renal impairment because of increased cerebral sensitivity.

MONITORING REQUIREMENTS

Baseline ECG required before treatment—assess need for further ECGs during treatment on an individual basis.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

Tablet

CAUTIONARY AND ADVISORY LABELS

HALOPERIDOL (Non-proprietary)

Haloperidol 500 microgram Haloperidol 500microgram tablets 28 tablet $1.01–$1.10

Haloperidol 1.5 mg Haloperidol 1.5mg tablets 28 tablet $3.00 DT price = $2.50

Haloperidol 5 mg Haloperidol 5mg tablets 28 tablet $7.25 DT price = $3.30

Haloperidol 10 mg Haloperidol 10mg tablets 28 tablet $12.99 DT price = $12.26

Haloperidol 20 mg Haloperidol 20mg tablets 28 tablet $21.63–$22.00 DT price = $21.75

Capsule

CAUTIONARY AND ADVISORY LABELS

HALOPERIDOL (Non-proprietary)

Haloperidol 1 mg per 1 ml Haloperidol 5mg/5ml oral solution sugar-free (sugar-free) 100 ml $35.99 DT price = $26.81 (sugar-free) 500 ml $32.05

Haloperidol 2 mg per 1 ml Haloperidol 10mg/5ml oral solution sugar-free (sugar-free) 100 ml $46.75 DT price = $7.10 (sugar-free) 500 ml $35.50

Haloperidol 2 mg per 1 ml Haloperidol 2mg/ml oral solution (sugar-free) 100 ml $46.75 DT price = $7.10

Solution for injection

HALOPERIDOL (Non-proprietary)

Haloperidol 5 mg per 1 ml Haloperidol 5mg/1ml solution for injection ampoules 10 ampoule $8.65 DT price = $8.65

Important safety information

When prescribing, dispensing or administering, check that this is the correct preparation—this preparation is used for maintenance treatment and should not be used for the rapid control of an acute episode.

CONTRA-INDICATIONS

Bradycardia - children - CNS depression - comatose states - lesions of the basal ganglia - Parkinson’s disease - phaeochromocytoma - QT-interval prolongation

CAUTIONS

Arteriosclerosis - hypocalcaemia - hypokalaemia - hypomagnesaemia - metabolic disturbances - subarachnoid haemorrhage - thyrotoxicosis - when transferring from oral to depot therapy, the dose by mouth should be reduced gradually.

INTERACTIONS

Avoid concomitant administration of drugs that prolong QT interval.

SIDE-EFFECTS

Common or very common - Depression - weight loss - Uncommon - Dysphoria - oedema - Rare - Bronchospasm - hypoglycaemia - inappropriate antidiuretic hormone secretion - photosensitivity reactions - pigmentation

Frequency not known - Erythema - hypertension - nodules - pain may occur at injection site - Stevens-Johnson syndrome - sweating - swelling - toxic epidermal necrolysis

SIDE-EFFECTS, FURTHER INFORMATION

Less sedating and fewer antimuscarinic or hypotensive symptoms.

HEPATIC IMPAIRMENT

Can precipitate coma.

RENAIS IMPAIRMENT

Start with small doses in severe renal impairment because of increased cerebral sensitivity.
Pericyazine
(Periciazine)

**INDICATIONS AND DOSE**

Schizophrenia | Psychoses
---|---
**BY MOUTH**
- Adult: Initially 75 mg daily in divided doses, then increased in steps of 25 mg every 1 week, adjusted according to response; maximum 300 mg per day
- Elderly: Initially 15–30 mg daily in divided doses, then increased in steps of 25 mg every 1 week, adjusted according to response; maximum 300 mg per day

Short-term adjunctive management of severe anxiety, psychomotor agitation, and violent or dangerously impulsive behaviour

**CONTRA-INDICATIONS**
- CNS depression
- Comatose states
- Phaeochromocytoma

**SIDE-EFFECTS**
- Common or very common: Hypotension (when treatment initiated)
- Frequency not known: Respiratory depression

**SIDE-EFFECTS, FURTHER INFORMATION**
- More sedating.
- Hepatic impairment: Can precipitate coma; phenothiazines are hepatotoxic.
- Renal impairment: Avoid in renal impairment.

**PERICYAZINE (Non-proprietary)**
- **Pericyazine 2.5 mg** Pericyazine 2.5mg tablets | 84 tablet [PDr]
  - £16.93 | 100 tablet [PDr] no price available

Perphenazine

**INDICATIONS AND DOSE**

Schizophrenia and other psychoses | Mania | Short-term adjunctive management of anxiety | Severe psychomotor agitation, excitement, and violent or dangerously impulsive behaviour | Severe nausea and vomiting unresponsive to other anti-emetics

**BY MOUTH**
- Adult: Initially 4 mg 3 times a day, adjusted according to response; maximum 24 mg per day
- Elderly: Initially 1–2 mg 3 times a day; maximum 12 mg per day

**PERICYAZINE (Non-proprietary)**
- **Pericyazine 10mg** Pericyazine 10mg tablets | 84 tablet [PDr]
  - £43.75 | 100 tablet [PDr] no price available

**Oral solution**
- **Pericyazine 2 mg per 1 ml** Pericyazine 10mg/5ml oral solution | 100 ml [PDr]
  - £46.00–£46.01 DT price = £46.01

**CONTRA-INDICATIONS**
- Agitation in the elderly
- CNS depression
- Comatose states
- Phaeochromocytoma
- Restlessness in the elderly

**CAUTIONS**
- With oral use: hypothyroidism

**SIDE-EFFECTS**
- Rare: Systemic lupus erythematosus
- Frequency not known: Dystonic reactions

**SIDE-EFFECTS, FURTHER INFORMATION**
- Less sedating.
- Acute dystonic reactions: Phenothiazines can all induce acute dystonic reactions such as facial and skeletal muscle spasms and oculogyric crises; children (especially girls, young women, and those under 10 kg) are particularly susceptible.
- Hepatic impairment: Can precipitate coma; phenothiazines are hepatotoxic.
- Renal impairment: Start with small doses in severe renal impairment because of increased cerebral sensitivity.

**PERICYAZINE (Non-proprietary)**
- **Pericyazine 10 mg** Pericyazine 10mg tablets | 84 tablet [PDr]
  - £43.75 | 100 tablet [PDr] no price available

**Oral solution**
- **Pericyazine 2 mg per 1 ml** Pericyazine 10mg/5ml oral solution | 100 ml [PDr]
  - £46.00–£46.01 DT price = £46.01

Perphenazine

**INDICATIONS AND DOSE**

Schizophrenia and other psychoses | Mania | Short-term adjunctive management of anxiety | Severe psychomotor agitation, excitement, and violent or dangerously impulsive behaviour | Severe nausea and vomiting unresponsive to other anti-emetics

**BY MOUTH**
- Adult: Initially 4 mg 3 times a day, adjusted according to response; maximum 24 mg per day
- Elderly: Initially 1–2 mg 3 times a day; maximum 12 mg per day

**CONTRA-INDICATIONS**
- Agitation in the elderly
- CNS depression
- Comatose states
- Phaeochromocytoma
- Restlessness in the elderly

**CAUTIONS**
- With oral use: hypothyroidism

**SIDE-EFFECTS**
- Rare: Systemic lupus erythematosus
- Frequency not known: Dystonic reactions

**SIDE-EFFECTS, FURTHER INFORMATION**
- Less sedating.
- Acute dystonic reactions: Phenothiazines can all induce acute dystonic reactions such as facial and skeletal muscle spasms and oculogyric crises; children (especially girls, young women, and those under 10 kg) are particularly susceptible.
- Hepatic impairment: Can precipitate coma; phenothiazines are hepatotoxic.
- Renal impairment: Start with small doses in severe renal impairment because of increased cerebral sensitivity.

**PERICYAZINE (Non-proprietary)**
- **Pericyazine 10 mg** Pericyazine 10mg tablets | 84 tablet [PDr]
  - £43.75 | 100 tablet [PDr] no price available

**Oral solution**
- **Pericyazine 2 mg per 1 ml** Pericyazine 10mg/5ml oral solution | 100 ml [PDr]
  - £46.00–£46.01 DT price = £46.01

**CONTRA-INDICATIONS**
- Agitation in the elderly
- CNS depression
- Comatose states
- Phaeochromocytoma
- Restlessness in the elderly

**CAUTIONS**
- With oral use: hypothyroidism

**SIDE-EFFECTS**
- Rare: Systemic lupus erythematosus
- Frequency not known: Dystonic reactions

**SIDE-EFFECTS, FURTHER INFORMATION**
- Less sedating.
- Acute dystonic reactions: Phenothiazines can all induce acute dystonic reactions such as facial and skeletal muscle spasms and oculogyric crises; children (especially girls, young women, and those under 10 kg) are particularly susceptible.
- Hepatic impairment: Can precipitate coma; phenothiazines are hepatotoxic.
- Renal impairment: Start with small doses in severe renal impairment because of increased cerebral sensitivity.

**PERICYAZINE (Non-proprietary)**
- **Pericyazine 10 mg** Pericyazine 10mg tablets | 84 tablet [PDr]
  - £43.75 | 100 tablet [PDr] no price available

**Oral solution**
- **Pericyazine 2 mg per 1 ml** Pericyazine 10mg/5ml oral solution | 100 ml [PDr]
  - £46.00–£46.01 DT price = £46.01

**CONTRA-INDICATIONS**
- Agitation in the elderly
- CNS depression
- Comatose states
- Phaeochromocytoma
- Restlessness in the elderly

**CAUTIONS**
- With oral use: hypothyroidism

**SIDE-EFFECTS**
- Rare: Systemic lupus erythematosus
- Frequency not known: Dystonic reactions

**SIDE-EFFECTS, FURTHER INFORMATION**
- Less sedating.
- Acute dystonic reactions: Phenothiazines can all induce acute dystonic reactions such as facial and skeletal muscle spasms and oculogyric crises; children (especially girls, young women, and those under 10 kg) are particularly susceptible.
- Hepatic impairment: Can precipitate coma; phenothiazines are hepatotoxic.
- Renal impairment: Start with small doses in severe renal impairment because of increased cerebral sensitivity.

**PERICYAZINE (Non-proprietary)**
- **Pericyazine 10 mg** Pericyazine 10mg tablets | 84 tablet [PDr]
  - £43.75 | 100 tablet [PDr] no price available

**Oral solution**
- **Pericyazine 2 mg per 1 ml** Pericyazine 10mg/5ml oral solution | 100 ml [PDr]
  - £46.00–£46.01 DT price = £46.01
Psychoses and schizophrenia 309

Prochlorperazine

INDICATIONS AND DOSE

Schizophrenia and other psychoses | Mania

BY MOUTH

- Adult: 12.5 mg twice daily for 7 days, dose to be adjusted at intervals of 4–7 days according to response; usual dose 75–100 mg daily
- Adult: 12.5–25 mg 2–3 times a day

Short-term adjunctive management of severe anxiety

BY MOUTH

- Adult: 15–20 mg daily in divided doses; maximum 40 mg per day

Nausea and vomiting, acute attack

BY MOUTH

- Adult: Initially 20 mg, then 10 mg after 2 hours
- BY DEEP INTRAMUSCULAR INJECTION
- Adult: 12.5 mg as required, to be followed if necessary after 6 hours by an oral dose

Nausea and vomiting, prevention

BY MOUTH

- Adult: 5–10 mg 2–3 times a day
- BY DEEP INTRAMUSCULAR INJECTION
- Adult: 12.5 mg as required, to be followed if necessary after 6 hours by an oral dose

Prevention and treatment of nausea

BY MOUTH

- Child 1-11 years (body-weight 10 kg and above): 250 micrograms/kg 2–3 times a day
- Child 12-17 years: 5–10 mg up to 3 times a day if required
- BY DEEP INTRAMUSCULAR INJECTION
- Child 2–4 years: 1.25–2.5 mg up to 3 times a day if required
- Child 5–11 years: 5–6.25 mg up to 3 times a day if required
- Child 12-17 years: 12.5 mg up to 3 times a day if required

Labyrinthine disorders

INITIALLY BY MOUTH

- Adult: 5 mg 3 times a day, (by mouth) increased if necessary to 30 mg daily in divided doses, dose to be increased gradually, then reduced to 5–10 mg daily, dose is reduced after several weeks

Nausea and vomiting in previously diagnosed migraine

BY MOUTH USING BUCCAL TABLET

- Child 12–17 years: 3–6 mg twice daily, tablets to be placed high between upper lip and gum and left to dissolve
- Adult: 3–6 mg twice daily, tablets to be placed high between upper lip and gum and left to dissolve

SIDE-EFFECTS

- Rare Hypotension
- Frequency not known Glycosuria; serious arrhythmias

SIDE-EFFECTS, FURTHER INFORMATION

- Less sedating.
- Acute dystonic reactions such as facial and skeletal muscle spasms and oculogyric crises; children (especially girls, young women, and those under 10 kg) are particularly susceptible.
- Can precipitate coma.
- Phenothiazines can all induce acute dystonic reactions such as facial and skeletal muscle spasms and oculogyric crises; children (especially girls, young women, and those under 10 kg) are particularly susceptible.

CAUTIONS

- Elderly (in adults). Hypotension (more likely after intramuscular injection).

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

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<tbody>
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<td>CAUTIONARY AND ADVISORY LABELS 2</td>
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<td>Prochlorperazine maleate 5 mg Prochlorperazine 5 mg tablets</td>
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<td>Stemetil (Sanofi)</td>
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<td>Buccastem (Alliance Pharmaceuticals Ltd)</td>
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<td>CAUTIONARY AND ADVISORY LABELS 2</td>
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<tr>
<td>Stemetil 5 mg/5 ml syrup</td>
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**INDICATIONS AND DOSE**

Schizophrenia and other psychoses | Short-term adjunctive management of psychomotor agitation, excitement, and violent or dangerously impulsive behaviour

**INDICATIONS AND DOSE**

Schizophrenia with predominantly negative symptoms

- **BY MOUTH**
  - Adult: 200–400 mg twice daily; maximum 800 mg per day
  - Elderly: Lower initial dose to be given, increased gradually according to response

Schizophrenia with mainly positive symptoms

- **BY MOUTH**
  - Adult: 200–400 mg twice daily; maximum 2.4 g per day
  - Elderly: Lower initial dose to be given, increased gradually according to response

- **CONTRA-INDICATIONS** CNS depression · comatose states · phaeochromocytoma
- **CAUTIONS** Aggressive patients (even low doses may aggravate symptoms) · agitated patients (even low doses may aggravate symptoms) · excited patients (even low doses may aggravate symptoms)
- **SIDE-EFFECTS** Hepatitis
- **HEPATIC IMPAIRMENT** Can precipitate coma.
- **RENAL IMPAIRMENT** Start with small doses in severe renal impairment because of increased cerebral sensitivity.
- **MONITORING REQUIREMENTS** Sulpiride does not affect blood pressure to the same extent as other antipsychotic drugs and so blood pressure monitoring is not mandatory for this drug.
- **PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid formulations may include lemon and aniseed.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

**Tablet**

- CAUTIONARY AND ADVISORY LABELS 2
- **SULPIRIDE (Non-proprietary)**
  - Sulpiride 200 mg Sulpiride 200mg tablets | 30 tablet £ 20.00 DT price = £ 18.63
  - Sulpiride 400 mg Sulpiride 400mg tablets | 30 tablet £ 40.00 DT price = £ 38.89
  - Dolmatil (Sanofi)
  - Sulpiride 200 mg Dolmatil 200mg tablets | 100 tablet £ 6.00
  - Sulpiride 400 mg Dolmatil 400mg tablets | 100 tablet £ 19.00

**Oral solution**

- CAUTIONARY AND ADVISORY LABELS 2
- **SULPIRIDE (Non-proprietary)**
  - Sulpiride 40 mg per 1 ml Sulpiride 200mg/5ml oral solution sugar free (sugar-free) | 150 ml £ 25.38 DT price = £ 25.38
  - Sulpor (Rosemont Pharmaceuticals Ltd)
  - Sulpiride 40 mg per 1 ml Sulpor 200mg/5ml oral solution sugar free (sugar-free) | 150 ml £ 25.38 DT price = £ 25.38

**Trifluoperazine**

**INDICATIONS AND DOSE**

Schizophrenia and other psychoses | Short-term adjunctive management of psychomotor agitation, excitement, and violent or dangerously impulsive behaviour

**INDICATIONS AND DOSE**

**BY MOUTH**

- Adult: Initially 5 mg twice daily for 1 week, then increased in steps of 5 mg daily, dose then to be increased at intervals of 3 days, according to response
- Elderly: Initially up to 2.5 mg twice daily for 1 week, then increased in steps of 5 mg daily, dose then to be increased at intervals of 3 days, according to response

**Short-term adjunctive management of severe anxiety**

**BY MOUTH**

- Adult: 2–4 mg daily in divided doses, increased if necessary to 6 mg daily
- Elderly: Up to 2 mg daily in divided doses, increased if necessary to 6 mg daily

**Severe nausea and vomiting**

**BY MOUTH**

- Adult: 2–4 mg daily in divided doses; maximum 6 mg per day

- **CONTRA-INDICATIONS** CNS depression · comatose states · phaeochromocytoma
- **SIDE-EFFECTS** Anorexia · dystonic reactions · muscle weakness
- **SIDE-EFFECTS, FURTHER INFORMATION** Extrapyramidal symptoms are more frequent, especially at doses exceeding 6 mg daily. Phenothiazines can all induce acute dystonic reactions such as facial and skeletal muscle spasms and oculogyric crises; children (especially girls, young women, and those under 10 kg) are particularly susceptible.
- **HEPATIC IMPAIRMENT** Can precipitate coma; phenothiazines are hepatotoxic.
- **RENAL IMPAIRMENT** Start with small doses in severe renal impairment because of increased cerebral sensitivity.
- **MONITORING REQUIREMENTS** Trifluoperazine does not affect blood pressure to the same extent as other antipsychotic drugs and so blood pressure monitoring is not mandatory for this drug.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- CAUTIONARY AND ADVISORY LABELS 2
- **TRIFLUOPERAZINE (Non-proprietary)**
  - Trifluoperazine (as Trifluoperazine hydrochloride) 1 mg Trifluoperazine 1mg tablets | 112 tablet £ 54.00 DT price = £ 54.00
  - Trifluoperazine (as Trifluoperazine hydrochloride) 5 mg Trifluoperazine 5mg tablets | 112 tablet £ 123.20 DT price = £ 177.00

**Oral solution**

- CAUTIONARY AND ADVISORY LABELS 2
- **TRIFLUOPERAZINE (Non-proprietary)**
  - Trifluoperazine (as Trifluoperazine hydrochloride) 200 microgram per 1 ml Trifluoperazine 1mg/5ml oral solution sugar free (sugar-free) | 200 ml £ 65.73 DT price = £ 65.73
  - Trifluoperazine (as Trifluoperazine hydrochloride) 1 mg per 1 ml Trifluoperazine 5mg/5ml oral solution sugar free (sugar-free) | 150 ml £ 25.50 DT price = £ 25.50
**Zuclopenthixol**

**INDICATIONS AND DOSE**

**Schizophrenia and other psychoses**

**BY MOUTH**

- Adult: Initially 20–30 mg daily in divided doses, increased if necessary up to 150 mg daily; usual maintenance 20–50 mg daily (max. per dose 40 mg), for debilitated patients, use elderly dose.

- Elderly: Initially 5–15 mg daily in divided doses, increased if necessary up to 150 mg daily; usual maintenance 20–50 mg daily (max. per dose 40 mg).

**RENA L IMPAIRMENT**

- Consider serum-level monitoring in patients with hepatic impairment.

**HEPATIC IMPAIRMENT**

- Halve dose. Can precipitate coma.

**SIDE-EFFECTS**

- Urinary frequency
- Urinary incontinence
- Weight loss (less common than weight gain)
- Apathetic states
- Increased cerebral sensitivity.

**CONTRA-INDICATIONS**

- Apathetic states • CNS depression • comatose states • phaeochromocytoma • withdrawn states

**CAUTIONS**

- Avoid in Acute porphyrias p. 864

**MEDICAL FORMS**

- There can be a variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Clopixol Acuphase (Lundbeck Ltd) Zuclopenthixol acetate 50 mg per 1 ml Clopixol Acuphase 50mg/1ml solution for injection ampoules 5 ampoule DT price = £24.21

**Zuclopenthixol decanoate**

**INDICATIONS AND DOSE**

**Maintenance in schizophrenia and paranoid psychoses**

**BY DEEP INTRAMUSCULAR INJECTION**

- Adult: Test dose 100 mg, dose to be administered into the upper outer buttock or lateral thigh, followed by 200–500 mg after at least 7 days, then 200–500 mg every 1–4 weeks, adjusted according to response, higher doses of more than 500mg can be used; do not exceed 600 mg weekly.

- Elderly: A quarter to half usual starting dose to be used when transferring from oral to depot therapy. the dose by mouth should be reduced gradually.

**SIDE-EFFECTS**

- Erythema • nodules • pain at injection site • swelling

**CONTRA-INDICATIONS**

- Children • CNS depression • comatose states • phaeochromocytoma

**CAUTIONS**

- Avoid in Acute porphyrias p. 864

**MEDICAL FORMS**

- There can be a variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Clopixol Acuphase (Lundbeck Ltd) Zuclopenthixol decanoate 400 mg/4 ml solution for injection vials 10 vials DT price = £16.13

**Zuclopenthixol acetate**

**INDICATIONS AND DOSE**

**Short-term management of acute psychosis | Short-term management of exacerbation of chronic psychosis**

**BY DEEP INTRAMUSCULAR INJECTION**

- Adult: 50–150 mg, then 50–150 mg after 2–3 days, repeated if necessary maximum duration of treatment 2 weeks, to be administered into the gluteal muscle or lateral thigh, 1 additional dose may be needed 1–2 days after the first injection, maximum cumulative dose 400 mg in 2 weeks and maximum 4 injections, if maintenance treatment necessary change to an oral antipsychotic 2–3 days after last injection, or to a longer acting antipsychotic depot injection given concomitantly with last injection of zuclopenthixol acetate.

- Elderly: 50–100 mg, then 50–100 mg after 2–3 days, repeated if necessary maximum duration of treatment 2 weeks, to be administered into the gluteal muscle or lateral thigh, 1 additional dose may be needed 1–2 days after the first injection, maximum cumulative dose 400 mg in 2 weeks and maximum 4 injections, if maintenance treatment necessary change to an oral antipsychotic 2–3 days after last injection, or to a longer acting antipsychotic depot injection given concomitantly with last injection of zuclopenthixol acetate.

**CONTRA-INDICATIONS**

- Children • CNS depression • comatose states • phaeochromocytoma

**CAUTIONS**

- Avoid in Acute porphyrias p. 864 • QT interval prolongation • when transferring from oral to depot therapy, the dose by mouth should be reduced gradually

**INTERACTIONS**

- Avoid concomitant use of drugs that prolong QT interval.

**SIDE-EFFECTS**

- Erythema • nodules • pain at injection site • swelling

**SIDE-EFFECTS, FURTHER INFORMATION**

- If the dose needs to be reduced to alleviate side-effects, it is important to recognise that the plasma-drug concentration may not fall for some time after reducing the dose, therefore it may be a month or longer before side-effects subside.

**HEPATIC IMPAIRMENT**

- Can precipitate coma.

**RENA L IMPAIRMENT**

- Start with small doses in severe renal impairment because of increased cerebral sensitivity.

**MONITORING REQUIREMENTS**

- Treatment requires careful monitoring for optimum effect.

**DIRECTIONS FOR ADMINISTRATION**

- In general not more than 2–3 mL of oily injection should be administered at
any one site. Correct injection technique (including use of z-track technique) and rotation of injection sites are essential. When initiating therapy with sustained-release preparations of conventional antipsychotics, patients should first be given a small test-dose as undesirable side-effects are prolonged.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Solution for injection**
  - **Clozapine (Zuclopenthixol decanoate)** (Lundbeck Ltd)
    - Zuclopenthixol decanoate 200 mg per 1 ml (Clozapine 200mg/1ml solution for injection ampoules | 10 ampoule $\text{P} \text{Pami } €31.51$ DT price = €31.51
    - Zuclopenthixol decanoate 500 mg per 1 ml (Clozapin Conc 500mg/1ml solution for injection ampoules | 5 ampoule $\text{P} \text{Pami } €37.18$ DT price = €37.18

- **ANTIPSYCHOTICS (SECOND-GENERATION)**

  - **Amisulpride**
    - **DRUG ACTION** Amisulpride is a selective dopamine receptor antagonist with high affinity for mesolimbic D₂ and D₃ receptors.
    - **INDICATIONS AND DOSE**
      - **Acute psychotic episode in schizophrenia**
        - **BY MOUTH**
          - Adult: 400–800 mg daily in 2 divided doses, adjusted according to response; maximum 1.2 g per day
      - **Schizophrenia with predominantly negative symptoms**
        - **BY MOUTH**
          - Adult: 50–300 mg daily
    - **CONTRA-INDICATIONS** CNS depression • comatose states • phaeochromocytoma • pre-pubertal children • prolactin-dependent tumours
    - **SIDE-EFFECTS**
      - Common or very common Anxiety
      - Uncommon Bradycardia
    - **PREGNANCY** Avoid.
    - **BREAST FEEDING** Avoid—no information available.
    - **RENAL IMPAIRMENT** Halve dose if eGFR 30–60 mL/minute/1.73 m². Use one-third dose if eGFR 10–30 mL/minute/1.73 m². No information available if eGFR less than 10 mL/minute/1.73 m².
    - **MONITORING REQUIREMENTS** Amisulpride does not affect blood pressure to the same extent as other antipsychotic drugs and so blood pressure monitoring is not mandatory for this drug.
    - **PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid formulations may include caramel.
    - **MEDICINAL FORMS**
      - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

  **Tablet**
  - $\text{CAYIONARY AND ADVISORY LABELS 2}$
    - **Amisulpride 50 mg** Amisulpride 50mg tablets | 60 tablet $\text{P} \text{Pami } €27.00$ DT price = €3.45
    - **Amisulpride 100 mg** Amisulpride 100mg tablets | 60 tablet $\text{P} \text{Pami } €51.27$ DT price = €5.79
    - **Amisulpride 200 mg** Amisulpride 200mg tablets | 60 tablet $\text{P} \text{Pami } €66.00$ DT price = €9.66
    - **Amisulpride 400 mg** Amisulpride 400mg tablets | 60 tablet $\text{P} \text{Pami } €113.20$ DT price = €15.83
    - **Solian** (Sanofi)
      - **Amisulpride 50 mg** Solian 50 tablets | 60 tablet $\text{P} \text{Pami } €22.76$ DT price = €3.45

- **Histamine H₁ receptor antagonist with weak D₂ receptor antagonism.**
  - **Aripiprazole**
    - **DRUG ACTION** Aripiprazole is a dopamine D₂ partial agonist with weak 5-HT₁A partial agonism and 5-HT₂A receptor antagonism.
    - **INDICATIONS AND DOSE**
      - **Maintenance in schizophrenia in patients stabilised with oral aripiprazole**
        - **INITIALLY BY INTRAMUSCULAR INJECTION**
          - **Adult:** 400 mg every 1 month, to be injected into the gluteal muscle, minimum of 26 days between injections, for dose adjustment due to side effects or concomitant use of interacting drugs, consult product literature and (by mouth) 10–20 mg daily continued for 14 consecutive days after the first injection, for missed depot doses consult product literature
      - **Schizophrenia**
        - **INITIALLY BY MOUTH**
          - **Adult:** 10–15 mg once daily; (by mouth) usual dose 15 mg once daily (max, per dose 30 mg once daily), for dose adjustments due to concomitant use of interacting drugs—consult product literature
      - **Treatment and recurrence prevention of mania**
        - **BY MOUTH**
          - **Adult:** 15 mg once daily, increased if necessary up to 30 mg once daily, for dose adjustments due to concomitant use of interacting drugs—consult product literature
      - **Control of agitation and disturbed behaviour in schizophrenia**
        - **BY INTRAMUSCULAR INJECTION**
          - **Adult:** Initially 5.25–15 mg for 1 dose, alternatively usual dose 9.75 mg for 1 dose, followed by 5.25–15 mg after 2 hours if required, maximum 3 injections daily; maximum daily combined oral and parenteral dose 30 mg, for dose adjustments due to concomitant use of interacting drugs—consult product literature

  **Important safety information**
  - When prescribing, dispensing, or administering, check that the correct preparation is used—the preparation usually used in hospital for the rapid control of an acute episode (solution for injection containing aripiprazole 7.5 mg/mL) should not be confused with depot preparations (aripiprazole 400 mg vial with solvent), which are usually used in the community or clinics for maintenance treatment.
    - **CONTRA-INDICATIONS**
      - **GENERAL CONTRA-INDICATIONS:**
        - CNS depression • comatose state • phaeochromocytoma
**SPECIFIC CONTRA-INDICATIONS:**
- With intramuscular use do not use in children

**CAUTIONS**

**GENERAL CAUTIONS:**
Cerebrovascular disease - elderly (reduce initial dose)

**SPECIFIC CAUTIONS:**
- With intramuscular use when transferring from oral to depot therapy, the dose by mouth should be reduced gradually

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**
- Common or very common Anxiety, hypersalivation, malaise
- Uncommon Depression, dry mouth
- Frequency not known Alopecia, anorexia, bradycardia, hepatitis, hyponatraemia, infection, laryngospasm, myalgia, oedema, oopharyngeal spasm, pancreatitis, pathological gambling, respiratory disorders, rhabdomyolysis, suicidal ideation, sweating, urinary disorders

**SPECIFIC SIDE-EFFECTS**
- With intramuscular use erythema, nodules, pain at injection site, swelling

**SIDE-EFFECTS, FURTHER INFORMATION**
- With intramuscular use If the dose needs to be reduced to alleviate side-effects, it is important to recognise that the plasma-drug concentration may not fall for some time after reducing the dose of the depot injection, therefore it may be a month or longer before side-effects subside.
- **PREGNANCY** Use only if potential benefit outweighs risk.
- **BREAST FEEDING** Manufacturer advises avoid—present in milk.

**HEPATIC IMPAIRMENT** Use with caution in severe impairment (oral treatment preferred to intramuscular administration).

**MONITORING REQUIREMENTS** Aripiprazole does not affect blood pressure to the same extent as other antipsychotic drugs and so blood pressure monitoring is not mandatory for this drug.

- With intramuscular use Treatment requires careful monitoring for optimum effect.

**DIRECTIONS FOR ADMINISTRATION**
- With oral use Orodispersible tablets should be placed on the tongue and allowed to dissolve, or be dispersed in water and swallowed.
- With intramuscular use Correct injection technique (including the use of z-track technique) and rotation of injection sites are essential.

**PATIENT AND CARER ADVICE**
- With oral use Patients or carers should be given advice on how to administer aripiprazole orodispersible tablets.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

| INDIQUEMENT AND ADVISORY LABELS 2 | ARIPIPRAZOLE 5 mg | Aripiprazole 5 mg tablets | 28 tablet | POM | £69.04 |
| - | Aripiprazole 10 mg | Aripiprazole tablets | 28 tablet | POM | £69.04 |
| - | Aripiprazole 15 mg | Aripiprazole tablets | 28 tablet | POM | £69.04 |
| - | Aripiprazole 30 mg | Aripiprazole tablets | 28 tablet | POM | £112.08 |

**Orodispersible tablet**

| INDIQUEMENT AND ADVISORY LABELS 2 | ARIPIPRAZOLE (Non-proprietary) | Aripiprazole 10 mg | Aripiprazole tablets | 28 tablet | POM | £69.04 |
| - | Aripiprazole 15 mg | Aripiprazole tablets | 28 tablet | POM | £88.93 |
| - | Aripiprazole 30 mg | Aripiprazole tablets | 28 tablet | POM | £88.93 |

**INDICATIONS AND DOSE**

**Schizophrenia in patients unresponsive to, or intolerant of, conventional antipsychotic drugs**

**BY MOUTH**
- Adult 18–59 years: 12.5 mg 1–2 times a day for day 1, then 25–50 mg for day 2, then increased, if tolerated, in steps of 25–50 mg daily, dose to be increased gradually over 14–21 days, increased to up to 300 mg daily in divided doses, larger dose to be taken at night, up to 200 mg daily may be taken as a single dose at bedtime; increased in steps of 50–100 mg 1–2 times a week if required, it is preferable to increase once a week; usual dose 200–450 mg daily, restarting after interval of more than 48 hours, 12.5 mg once or twice on first day (but may be feasible to increase more quickly than on initiation)—extreme caution if previous respiratory or cardiac arrest with initial dosing; maximum 900 mg per day
- Adult 60 years and over: 12.5 mg once daily for day 1, then increased to 25–37.5 mg for day 2, then increased, if tolerated, in steps of up to 25 mg daily, dose to be increased gradually over 14–21 days, increased to up to 300 mg daily in divided doses, larger dose at to be taken night, up to 200 mg daily may be taken as a single dose at bedtime; increased in steps of 50–100 mg 1–2 times a week if required, it is preferable to increase once a week; usual dose 200–450 mg daily, restarting after interval of more than 48 hours, 12.5 mg once or twice on first day (but may be feasible to increase more quickly than on initiation)—extreme caution if previous respiratory or cardiac arrest with initial dosing; maximum 900 mg per day

**Clozapine**

**DRUG ACTION** Clozapine is a dopamine D₂, dopamine D₃, D₄, 5-HT₁A, alpha₁-adrenoceptor, and muscarinic-receptor antagonist.

**INDICATIONS AND DOSE**

**Psychoses and schizophrenia**

- Aripiprazole 10 mg | Aripiprazole 10 mg orodispersible tablets sugar free (sugar-free) | 28 tablet | POM | £69.04 |
- Aripiprazole 15 mg | Aripiprazole 15 mg orodispersible tablets sugar free (sugar-free) | 28 tablet | POM | £69.04 |
- Aripiprazole 10 mg | Aripiprazole 10 mg orodispersible tablets sugar free (sugar-free) | 28 tablet | POM | £69.04 |
- Aripiprazole 15 mg | Aripiprazole 15 mg orodispersible tablets sugar free (sugar-free) | 28 tablet | POM | £69.04 |

**Oral solution**

| INDIQUEMENT AND ADVISORY LABELS 2 | ARIPIPRAZOLE (Non-proprietary) | Aripiprazole 1 mg per 1 ml | Aripiprazole 1ml/ml oral solution | 150 ml | no price available |
| - | Aripiprazole 1 mg per 1 ml | Aripiprazole tablets | 150 ml | POM | £102.00 |

**Solution for injection**

| INDIQUEMENT AND ADVISORY LABELS 2 | ARIPIPRAZOLE (Non-proprietary) | Aripiprazole 7.5 mg per 1 ml | Aripiprazole 7.5 mg per 1 ml | 1 vial | POM | £3.43 |
| - | Aripiprazole 400 mg | Aripiprazole 400 mg powder and solvent for suspension for injection | 1 vial | POM | £320.41 |
Psychosis in Parkinson’s disease

BY MOUTH

- Adult: 12.5 mg once daily, dose to be taken at bedtime, then increased in steps of 12.5 mg up to twice weekly, adjusted according to response; usual dose 25–37.5 mg once daily, dose to be taken at bedtime, increased in steps of 12.5 mg once weekly, this applies only in exceptional cases, increased if necessary up to 100 mg daily in 1–2 divided doses; Usual maximum 50 mg/24 hours

Dose adjustments due to interactions

Dose adjustment may be necessary if smoking started or stopped during treatment.

- CONTRA-INDICATIONS Alcoholic and toxic psychoses - bone-marrow disorders - coma - drug intoxication - history of agranulocytosis - history of circulatory collapse - history of neutropenia - paralytic ileus - severe cardiac disorders (e.g. myocarditis) - severe CNS depression - uncontrolled epilepsy

- CAUTIONS Age over 60 years - prostatic hypertrophy - susceptibility to angle-closure glaucoma - taper off other antipsychotics before starting

CAUTIONS, FURTHER INFORMATION

Agranulocytosis Neutropenia and potentially fatal agranulocytosis reported. Leucocyte and differential blood counts must be normal before starting; monitor counts every week for 18 weeks then at least every 2 weeks and if clozapine continued and blood count stable after 1 year at least every 4 weeks (and 4 weeks after discontinuation); if leucocyte count below 3000/mm³ or if absolute neutrophil count below 1500/mm³ discontinue permanently and refer to haematologist. Patients who have a low white blood cell count because of benign ethnic neutropenia may be started on clozapine with the agreement of a haematologist. Avoid drugs which depress leucopoiesis; patients should report immediately symptoms of infection, especially influenza-like illness.

Myocarditis and cardiomyopathy Fatal myocarditis (most commonly in first 2 months) and cardiomyopathy reported.

- Perform physical examination and take full medical history before starting

- Specialist examination required if cardiac abnormalities or history of heart disease found—clozapine initiated only in absence of severe heart disease and if benefit outweighs risk

- Persistent tachycardia especially in first 2 months should prompt observation for other indicators for myocarditis or cardiomyopathy

- If myocarditis or cardiomyopathy suspected clozapine should be stopped and patient evaluated urgently by cardiologist

- Discontinue permanently in clozapine-induced myocarditis or cardiomyopathy

Intestinal obstruction Impairment of intestinal peristalsis, including constipation, intestinal obstruction, faecal impaction, and paralytic ileus, (including fatal cases) reported. Clozapine should be used with caution in patients receiving drugs that may cause constipation (e.g. antimuscarinic drugs) or in those with a history of colonic disease or lower abdominal surgery. It is essential that constipation is recognised and actively treated.

- INTERACTIONS Avoid concomitant use of clozapine with drugs that have a substantial potential for causing agranulocytosis.

- SIDE-EFFECTS

  - Common or very common Anorexia - constipation - hypersalivation - malaise - speech disorders - urinary incontinence

  - Uncommon Agranulocytosis

  - Rare Circulatory collapse - dysphagia - hepatitis - myocarditis - pancreatitis - pericarditis - pneumonia - pulmonary aspiration

  - Very rare Cardiomyopathy - hypercholesterolaemia - hypertriglyceridaemia - interstitial nephritis - intestinal obstruction (including fatal cases) - myocardial infarction - obsessive compulsive disorder - paroxysmal gland enlargement - respiratory depression

  - Frequency not known Hepatic disorders - hepatic failure - muscle disorders - renal failure

SIDE-EFFECTS, FURTHER INFORMATION

Hypersalivation Hypersalivation associated with clozapine therapy can be treated with hyoscine hydrobromide [unlicensed indication], provided that the patient is not at particular risk from the additive antimuscarinic side-effects of hyoscine and clozapine.

- PREGNANCY Use with caution.

- BREAST FEEDING Avoid.


- RENAL IMPAIRMENT Avoid in severe impairment.

- MONITORING REQUIREMENTS

  - Monitor leucocyte and differential blood counts. Clozapine requires differential white blood cell monitoring weekly for 18 weeks, then fortnightly for up to one year, and then monthly as part of the clozapine patient monitoring service.

  - Close medical supervision during initiation (risk of collapse because of hypotension and convulsions).

  - Blood lipids and weight should be measured at baseline, at 3 months (weight should be measured at frequent intervals during the first 3 months), and then yearly with antipsychotics. Patients taking clozapine require more frequent monitoring of these parameters: every 3 months for the first year, then yearly.

  - Fasting blood glucose should be measured at baseline, at 4–6 months, and then yearly. Patients taking clozapine should have fasting blood glucose tested at baseline, after one months’ treatment, then every 4–6 months.

  - Patient, prescriber, and supplying pharmacist must be registered with the appropriate Patient Monitoring Service—it takes several days to do this.

- TREATMENT CESSION On planned withdrawal reduce dose over 1–2 weeks to avoid risk of rebound psychosis. If abrupt withdrawal necessary observe patient carefully.

- DIRECTIONS FOR ADMINISTRATION Shake oral suspension well for 90 seconds when dispensing or if visibly settled and stand for 24 hours before use; otherwise shake well for 10 seconds before use. May be diluted with water.

- PATIENT AND CARER ADVICE Patients or carers should be given advice on how to administer clozapine oral suspension.

- MEDICINAL FORMS

  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

Table

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<thead>
<tr>
<th>Tablet</th>
<th>CAUTIONARY AND ADVISORY LABELS 2, 10</th>
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<tr>
<td>Clozaril (Novartis Pharmaceuticals UK Ltd)</td>
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<tr>
<td>Clozapine 25 mg</td>
<td>Clozaril 25mg tablets</td>
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<td>84 tablet £3.02</td>
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<td>Clozaril 100 mg</td>
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- Denzapine (Britannia Pharmaceuticals Ltd) |
| Clozapine 25 mg | Denzapine 25mg tablets | 84 tablet £0.79 |
| £16.64 | 100 tablet £19.80 |
| Clozapine 100 mg | Denzapine 100mg tablets | 84 tablet £0.79 |
| £66.53 | 100 tablet £79.20 |
Lurasidone hydrochloride

**DRUG ACTION** Lurasidone is a dopamine D₂, 5-HT₆, alpha₂A- and alpha₁C-receptor antagonist, and is a partial agonist at 5-HT₁A receptors.

**INDICATIONS AND DOSE**

**Schizophrenia**

- **BY MOUTH**
  - Adult: Initially 37 mg once daily, increased if necessary up to 148 mg once daily
  - Schizophrenia when given with concomitant moderate CYP3A4 inhibitors (e.g. diltiazem, erythromycin, fluconazole, and verapamil)
  - **BY MOUTH**
  - Adult: Initially 18.5 mg once daily (max. per dose 74 mg once daily)

**CAUTIONS** High doses in elderly - susceptibility to QT-interval prolongation

**INTERACTIONS** Contra-indicated with concomitant use of potent CYP3A4 inhibitors. Contra-indicated with concomitant use of potent CYP3A4 inducers. Caution with concomitant use of drugs that prolong the QT interval.

**SIDE-EFFECTS**

- **Common or very common** Anxiety - musculoskeletal stiffness
- **Uncommon** Catatonia - decreased appetite - dysarthria - dysuria - hot flush - myalgia - nightmares
- **Frequency not known** Angina - AV block - bradycardia - dysphagia - panic attacks - pruritus - suicidal behaviour - vertigo
- **PREGNANCY** Use only if potential benefit outweighs risks—limited information available.
- **HEPATIC IMPAIRMENT** Initially 18.5 mg once daily, up to max. 74 mg once daily in moderate impairment. Use with caution in severe impairment—initially 18.5 mg once daily, up to max. 37 mg once daily.
- **RENAL IMPAIRMENT** Initially 18.5 mg once daily, up to max. 74 mg once daily if eGFR less than 50 mL/minute/1.73 m². Manufacturer advises use only if potential benefit outweighs risks if eGFR less than 15 mL/minute/1.73 m².

**DIRECTIONS FOR ADMINISTRATION** Patients on doses higher than 111 mg once daily whose treatment is interrupted for longer than 3 days should restart on 111 mg once daily and titrate to usual dose; for all other doses, restart on usual dose.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Tablet**
  - CAUTIONARY AND ADVISORY LABELS 2, 21, 25
  - **Luca®** (Sunovion Pharmaceuticals Europe Ltd)
  - **Lurasidone (as Lurasidone hydrochloride) 18.5 mg** Luca® 18.5mg tablets | 28 tablet [POD] £90.72
  - **Lurasidone (as Lurasidone hydrochloride) 37 mg** Luca® 37mg tablets | 28 tablet [POD] £90.72

**Contra-indications**

- With intramuscular use acute myocardial infarction - bradycardia - recent heart surgery - severe hypotension - sick sinus syndrome - unstable angina
- **CAUTIONS** Bone-marrow depression - diabetes mellitus (risk of exacerbation or ketoadiposis) - hypereosinophilic disorders - low leucocyte count - low neutrophil count - myeloproliferative disease - paralytic ileus

**Cautions, further information**

CNS and respiratory depression Blood pressure, pulse and respiratory rate should be monitored for at least 4 hours after intramuscular injection, particularly in those also

Lurasidone (as Lurasidone hydrochloride) 74 mg Latuda 74mg tablets | 28 tablet [POD] £90.72

Olanzapine

**DRUG ACTION** Olanzapine is a dopamine D₂, D₃, D₄, 5-HT₆, histamine-1-, and muscarinic-receptor antagonist.

**INDICATIONS AND DOSE**

**Schizophrenia | Combination therapy for mania**

- **BY MOUTH**
  - Adult: 10 mg daily, adjusted according to response, usual dose 5–20 mg daily, doses greater than 10 mg daily only after reassessment, when one or more factors present that might result in slower metabolism (e.g. female gender, elderly, non-smoker) consider lower initial dose and more gradual dose increase; maximum 20 mg per day
  - **Preventing recurrence in bipolar disorder**
  - Adult: 10 mg daily, adjusted according to response, usual dose 5–20 mg daily, doses greater than 15 mg daily only after reassessment, when one or more factors present that might result in slower metabolism (e.g. female gender, elderly, non-smoker) consider lower initial dose and more gradual dose increase; maximum 20 mg per day
  - **Monotherapy for mania**
  - Adult: 15 mg daily, adjusted according to response, usual dose 5–20 mg daily, doses greater than 15 mg daily only after reassessment, when one or more factors present that might result in slower metabolism (e.g. female gender, elderly, non-smoker) consider lower initial dose and more gradual dose increase;
  - **Control of agitation and disturbed behaviour in schizophrenia or mania**
  - **BY INTRAMUSCULAR INJECTION**
    - Adult: Initially 5–10 mg for 1 dose; usual dose 10 mg for 1 dose, followed by 5–10 mg after 2 hours if required, maximum 3 injections daily for 3 days; maximum daily combined oral and parenteral dose 20 mg, when one or more factors present that might result in slower metabolism (e.g. female gender, elderly, non-smoker) consider lower initial dose and more gradual dose increase
    - Elderly: Initially 2.5–5 mg, followed by 2.5–5 mg after 2 hours if required, maximum 3 injections daily for 3 days; maximum daily combined oral and parenteral dose 20 mg, when one or more factors present that might result in slower metabolism (e.g. female gender, elderly, non-smoker) consider lower initial dose and more gradual dose increase

**Dose adjustments due to interactions**

Dose adjustment may be necessary if smoking started or stopped during treatment.
receiving a benzodiazepine or another antipsychotic (leave at least one hour between administration of olanzapine intramuscular injection and parenteral benzodiazepines).

- **SIDE-EFFECTS**
  - **GENERAL SIDE-EFFECTS**
  - Common or very common Arthralgia - hypercholesterolaemia - hypertriglyceridaemia - increased appetite - malaise - oedema
  - Uncommon Alopecia - amnesia - bradycardia - epistaxis
  - Rare Hepatitis - pancreatitis - rhabdomyolysis

- **SPECIFIC SIDE-EFFECTS**
  - With intramuscular use hypoventilation - sinus pause

- **PREGNANCY** Use only if potential benefit outweighs risk.

- **BREAST FEEDING** Avoid—present in milk.

- **HEPATIC IMPAIRMENT** Consider initial dose of 5 mg daily.

- **RENAL IMPAIRMENT** Consider initial dose of 5 mg daily.

- **MONITORING REQUIREMENTS**
  - Blood lipids and weight should be measured at baseline, at 3 months (weight should be measured at frequent intervals during the first 3 months), and then yearly with antipsychotic drugs. Patients taking olanzapine require more frequent monitoring of these parameters: every 3 months for the first year, then yearly.
  - Fasting blood glucose should be measured at baseline, at 4–6 months, and then yearly. Patients taking olanzapine should have fasting blood glucose tested at baseline, after one month’s treatment, then every 4–6 months.

- **DIRECTIONS FOR ADMINISTRATION**
  - Olanzapine orodispersible tablet may be placed on the tongue and allowed to dissolve, or dispersed in water, orange juice, apple juice, milk, or coffee.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - With intramuscular use When prescribing, dispensing, or administering, check that this injection is the correct preparation—this preparation is usually used in hospital for the rapid control of an acute episode and should not be confused with depot preparations which are usually used in the community or clinics for maintenance treatment.

- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer orodispersible tablets.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

### Table

**CAUTIONARY AND ADVISORY LABELS 2**

- **Olanzapine (Non-proprietary)**
  - Olanzapine 2.5 mg Olanzapine 2.5mg tablets | 28 tablet £2.85 DT price = £1.02
  - Olanzapine 5 mg Olanzapine 5mg tablets | 28 tablet £43.70 DT price = £1.17
  - Olanzapine 7.5 mg Olanzapine 7.5mg tablets | 28 tablet £65.55 DT price = £1.19 | 56 tablet £131.10
  - Olanzapine 10 mg Olanzapine 10mg tablets | 28 tablet £87.40 DT price = £1.59
  - Olanzapine 15 mg Olanzapine 15mg tablets | 28 tablet £119.18 DT price = £1.67
  - Olanzapine 20 mg Olanzapine 20mg tablets | 28 tablet £158.90 DT price = £1.96
  - Zyprexa (Eli Lilly and Company Ltd)
    - Olanzapine 2.5 mg Zyprexa 2.5mg tablets | 28 tablet £21.85 DT price = £1.02
    - Olanzapine 5 mg Zyprexa 5mg tablets | 28 tablet £43.70 DT price = £1.17
    - Olanzapine 7.5 mg Zyprexa 7.5mg tablets | 56 tablet £131.10
    - Olanzapine 10 mg Zyprexa 10mg tablets | 28 tablet £87.40 DT price = £1.59
    - Olanzapine 15 mg Zyprexa 15mg tablets | 28 tablet £119.18 DT price = £1.67
    - Olanzapine 20 mg Zyprexa 20mg tablets | 28 tablet £158.90 DT price = £1.96

### Oral lyophilisate

- **Zyprexa Velotabs (Eli Lilly and Company Ltd)**
  - Olanzapine 2.5 mg Zyprexa 5mg Velotabs (sugar-free) | 28 tablet £48.07 DT price = £48.07
  - Olanzapine 5 mg Zyprexa 10mg Velotabs (sugar-free) | 28 tablet £87.40 DT price = £87.40
  - Olanzapine 15 mg Zyprexa 15mg Velotabs (sugar-free) | 28 tablet £131.10 DT price = £131.10
  - Olanzapine 20 mg Zyprexa 20mg Velotabs (sugar-free) | 28 tablet £174.79 DT price = £174.79

### Olanzapine embonate

(Olanzapine pamoate)

**INDICATIONS AND DOSE**

- Maintenance in schizophrenia in patients tolerant to olanzapine by mouth (patients taking 10 mg oral olanzapine daily)
  - **BY DEEP INTRAMUSCULAR INJECTION**
    - Adult 18-75 years: Initially 210 mg every 2 weeks, alternatively initially 405 mg every 4 weeks, then maintenance 150 mg every 2 weeks, alternatively maintenance 300 mg every 4 weeks, maintenance dose to be started after 2 months of initial treatment, dose to be administered into the gluteal muscle, consult product literature if supplementation with oral olanzapine required
- Maintenance in schizophrenia in patients tolerant to olanzapine by mouth (patients taking 15 mg oral olanzapine daily)
  - **BY DEEP INTRAMUSCULAR INJECTION**
    - Adult 18-75 years: Initially 300 mg every 2 weeks, then maintenance 210 mg every 2 weeks, alternatively maintenance 405 mg every 4 weeks, maintenance dose to be started after 2 months of initial treatment, dose to be administered into the gluteal muscle, consult product literature if supplementation with oral olanzapine required
- Maintenance in schizophrenia in patients tolerant to olanzapine by mouth (patients taking 20 mg oral olanzapine daily)
  - **BY DEEP INTRAMUSCULAR INJECTION**
    - Adult: Initially 300 mg every 2 weeks, then maintenance 300 mg every 2 weeks (max. per dose 300 mg every 2 weeks), adjusted according to response, dose to be administered into the gluteal muscle, consult product literature if supplementation with oral olanzapine required

### Brands may include Zalasta;

- **Orodispersible tablet**

- **CAUTIONARY AND ADVISORY LABELS 2**

- **EXCEPTIONS:** May contain Aspartame

- **OLANZAPINE (Non-proprietary)**
  - Olanzapine 5 mg Olanzapine 5mg orodispersible tablets sugar free (sugar-free) | 28 tablet p<sub>DT</sub> £40.86 DT price = £2.67
  - Olanzapine 5mg orodispersible tablets | 28 tablet p<sub>DT</sub> £1.19–£4.99 DT price = £2.46
  - Olanzapine 10 mg Olanzapine 10mg orodispersible tablets | 28 tablet p<sub>DT</sub> £1.65–£5.99 DT price = £3.10
  - Olanzapine 10mg orodispersible tablets sugar free (sugar-free) | 28 tablet p<sub>DT</sub> £74.29 DT price = £3.67
  - Olanzapine 15 mg Olanzapine 15mg orodispersible tablets sugar free (sugar-free) | 28 tablet p<sub>DT</sub> £111.44 DT price = £4.64
  - Olanzapine 15mg orodispersible tablets | 28 tablet p<sub>DT</sub> £2.25–£6.99 DT price = £3.83
  - Olanzapine 20 mg Olanzapine 20mg orodispersible tablets sugar free (sugar-free) | 28 tablet p<sub>DT</sub> £148.57 DT price = £6.43
  - Olanzapine 20mg orodispersible tablets | 28 tablet p<sub>DT</sub> £1.01–£7.99 DT price = £4.67

- **Brands may include Arkolamyl; Zalasta**
Dose adjustments due to interactions
Dose adjustment may be necessary if smoking started or stopped during treatment.

Important safety information
When prescribing, dispensing or administering, check that this is the correct preparation—this preparation is used for maintenance treatment and should not be used for the rapid control of an acute episode.

● CONTRA-INDICATIONS
  Children

● CAUTIONS
  Bone-marrow depression • diabetes mellitus (risk of exacerbation or ketoacidosis) • hypereosinophilic disorders • low leucocyte count • low neutrophil count • myeloproliferative disease • paralytic ileus • when transferring from oral to depot therapy, the dose by mouth should be reduced gradually

● SIDE-EFFECTS
  Common or very common
  Arthralgia • hypercholesterolaemia • hypertriglyceridaemia • increased appetite • malaise • oedema
  Uncommon
  Alopecia • anemia • bradycardia • epistaxis
  Rare
  Hepatitis • pancreatitis • rhabdomyolysis
  Frequency not known
  Erythema • nodules • pain at injection site • swelling

SIDE-EFFECTS, FURTHER INFORMATION
If the dose needs to be reduced to alleviate side-effects, it is important to recognise that the plasma-drug concentration may not fall for some time after reducing the dose, therefore it may be a month or longer before side-effects subside.

Overdose
Post-injection reactions have been reported leading to signs and symptoms of overdose.

Pregnancy
Use only if potential benefit outweighs risk.

Breast feeding
Avoid—present in milk.

Hepatic impairment
Initially 150 mg every 4 weeks; increase with caution in moderate impairment.

Renal impairment
Initially 150 mg every 4 weeks.

Monitoring requirements
Observe patient for at least 3 hours after injection.

Treatment requires careful monitoring for optimum effect.

Blood lipids and weight should be measured at baseline, at 3 months (weight should be measured at frequent intervals during the first 3 months), and then yearly with antipsychotic drugs. Patients taking olanzapine require more frequent monitoring of these parameters: every 3 months for the first year, then yearly.

Fasting blood glucose should be measured at baseline, at 4–6 months, and then yearly. Patients taking olanzapine should have fasting blood glucose tested at baseline, after one month’s treatment, then every 4–6 months.

DIRECTIONS FOR ADMINISTRATION
Correct injection technique (including use of z-track technique) and rotation of injection sites are essential.

Medicinal forms
There can be variation in the licensing of different medicines containing the same drug.

Powder and solvent for suspension for injection
- Zypadhera (El Lilly and Company Ltd)
  Olanzapine (as Olanzapine embonate monohydrate)
  210 mg Zypadhera 210mg powder and solvent for suspension for injection vials [1 vial (P30) £14.22 (Hospital only)]
  Olanzapine (as Olanzapine embonate monohydrate)
  300 mg Zypadhera 300mg powder and solvent for suspension for injection vials [1 vial (P30) £22.64 (Hospital only)]
  Olanzapine (as Olanzapine embonate monohydrate)
  405 mg Zypadhera 405mg powder and solvent for suspension for injection vials [1 vial (P30) £28.52 (Hospital only)]

Paliperidine

- Drug action
  Paliperidine is a metabolite of risperidone.

Indications and dose
Maintenance in schizophrenia in patients previously responsive to paliperidone or risperidone

By deep intramuscular injection
- Adult: 150 mg for 1 dose on day 1, then 100 mg for 1 dose on day 8, to be injected into the deltoid muscle, dose subsequently adjusted at monthly intervals according to response; maintenance 75 mg once a month, alternatively maintenance 25–150 mg once a month, following the second dose, monthly maintenance doses can be administered into either the deltoid or gluteal muscle, for missed doses see product literature

Schizophrenia | Psychotic or manic symptoms of schizoaffective disorder

By mouth
- Adult: 6 mg once daily, dose to be taken in the morning, then adjusted in steps of 3 mg if required, dose to be adjusted over at least 5 days; usual dose 3–12 mg daily

Contra-indications
- With intramuscular use
- Children

Cautions

General cautions
Cataract surgery (risk of intraoperative floppy iris syndrome) • elderly patients with dementia • elderly patients with risk factors for stroke • predisposition to gastro-intestinal obstruction • prolactin-dependent tumours

Specific cautions
- With intramuscular use
- When transferring from oral to depot therapy, the dose by mouth should be reduced gradually

Side-effects

General side-effects
Common or very common
  Anxiety • appetite changes • arthralgia • depression • epistaxis • hypertension • infection • malaise • myalgia • oedema • respiratory disorders • sleep disorders • toothache • urinary disorders

Uncommon
  Alopecia • elevated plasma-cholesterol concentrations • elevated plasma-triglyceride concentrations • hypoaesthesia • parasthesia • taste disturbances • tinnitus • visual disorders

Rare
  Inappropriate antidiuretic hormone secretion • intestinal obstruction • intra-operative floppy iris syndrome • pancreatitis • pulmonary embolism • rhabdomyolysis

Specific side-effects
- With intramuscular use
  Erythema • nodules • pain at injection site • swelling

Side-effects, further information
- With intramuscular use
  If the dose needs to be reduced to alleviate side-effects, it is important to recognise that the plasma-drug concentration may not fall for some time after reducing the dose, therefore it may be a month or longer before side-effects subside.

Pregnancy
Use only if potential benefit outweighs risk— toxicity in animal studies; if discontinuation during pregnancy is necessary, withdraw gradually.

Breast feeding
Avoid—present in milk.

Hepatic impairment
Caution in severe impairment—no information available.

Renal impairment
- With oral use
  Initially 3 mg once daily if eGFR 50–80 mL/minute/1.73 m² (max. 6 mg once daily).
Quetiapine

**DRUG ACTION** Quetiapine is a dopamine D<sub>2</sub>, dopamine D<sub>3</sub>, 5-HT<sub>2A</sub>, alpha<sub>1</sub>-adrenoceptor, and histamine<sub>1</sub> receptor antagonist.

**INDICATIONS AND DOSE**

**Schizophrenia**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

- Adult: 25 mg twice daily for days 1, then 50 mg twice daily for days 2, then 100 mg twice daily for days 3, then 150 mg twice daily for days 4, then, adjusted according to response, usual dose 300–450 mg daily in 2 divided doses, the rate of dose titration may need to be slower and the daily dose lower in elderly patients; maximum 750 mg per day

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

- Adult: 300 mg once daily for days 1, then 600 mg once daily for days 2, then, adjusted according to response, usual dose 600 mg once daily, maximum dose under specialist supervision; maximum 800 mg per day

- Elderly: Initially 50 mg once daily, adjusted according to response. Adjusted in steps of 50 mg daily

**Treatment of mania in bipolar disorder**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

- Adult: 50 mg twice daily for days 1, then 100 mg twice daily for days 2, then 150 mg twice daily for days 3, then 200 mg twice daily for days 4, then, adjusted in steps of up to 200 mg daily, adjusted according to response, usual dose 400–800 mg daily in 2 divided doses, the rate of dose titration may need to be slower and the daily dose lower in elderly patients; maximum 800 mg per day

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

- Adult: 300 mg once daily for days 1, then 600 mg once daily for days 2, then, adjusted according to response, usual dose 400–800 mg once daily

- Elderly: Initially 50 mg once daily, adjusted according to response. Adjusted in steps of 50 mg daily

**Treatment of depression in bipolar disorder**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

- Adult: 50 mg once daily for days 1, dose to be taken at bedtime, then 100 mg once daily for days 2, then 200 mg once daily for days 3, then 300 mg once daily for days 4, then, adjusted according to response; usual dose 300 mg once daily, the rate of dose titration may need to be slower and the daily dose lower in elderly patients; maximum 600 mg per day

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

- Adult: 50 mg once daily for days 1, dose to be taken at bedtime, then 100 mg once daily for days 2, then 200 mg once daily for days 3, then 300 mg once daily for days 4, then, adjusted according to response; usual dose 300 mg once daily; maximum 600 mg per day

**Prevention of mania and depression in bipolar disorder**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

- Adult: Continue at the dose effective for treatment of bipolar disorder and adjust to lowest effective dose; usual dose 300–800 mg daily in 2 divided doses

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

- Adult: Continue at the dose effective for treatment of bipolar disorder and adjust to lowest effective dose; usual dose 300–800 mg once daily

**Adjuvant treatment of major depression**

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

- Adult: 50 mg once daily for 2 days, dose to be taken at bedtime, then 150 mg once daily for 2 days, then, adjusted according to response, usual dose 150–300 mg once daily

- Elderly: Initially 50 mg once daily for 3 days, then increased if necessary to 100 mg once daily for 4 days, then, adjusted in steps of 50 mg, adjusted according to response, usual dose 50–300 mg once daily, dose of 300 mg should not be reached before day 22 of treatment

**Dose equivalence and conversion**

Patients can be switched from immediate-release to modified-release tablets at the equivalent daily dose; to maintain clinical response, dose titration may be required.

**CAUTIONS** Cerebrovascular disease - elderly - patients at risk of aspiration pneumonia - treatment of depression in patients under 25 years (increased risk of suicide)

**SIDE-EFFECTS**

- **Common or very common** Asthenia - dysarthria - dysphonia - elevated plasma-cholesterol concentrations - elevated plasma-triglyceride concentrations - increased appetite - irritability - peripheral oedema - sleep disorders

- **Uncommon** Hypoatraemia - hypothyroidism - restless legs syndrome - rhinitis

- **Rare** Hepatitis - pancreatitis
Psychoses and schizophrenia

Risperidone

**DRUG ACTION** Risperidone is a dopamine D₂, 5-HT₆, alpha₁,adrenoceptor, and histamine-1 receptor antagonist.

**INDICATIONS AND DOSE**

Schizophrenia and other psychoses in patients tolerant to risperidone by mouth and taking oral risperidone up to 4 mg daily.

**BY DEEP INTRAMUSCULAR INJECTION**

- Adult: Initially 25 mg every 2 weeks, to be administered into the deltoid or gluteal muscle, adjusted in steps of 12.5 mg at least every 4 weeks.

**(max. per dose 50 mg every 2 weeks), during initiation risperidone by mouth may need to be continued for 4–6 weeks; risperidone by mouth may also be used during dose adjustment of depot injection**

Schizophrenia and other psychoses in patients tolerant to risperidone by mouth and taking oral risperidone over 4 mg daily.

**BY DEEP INTRAMUSCULAR INJECTION**

- Adult: Initially 37.5 mg every 2 weeks, adjusted in steps of 12.5 mg at least every 4 weeks (max. per dose 50 mg every 2 weeks), during initiation risperidone by mouth may need to be continued for 4–6 weeks; risperidone by mouth may also be used during dose adjustment of depot injection.

Acute and chronic psychoses

**BY MOUTH**

- Adult: 2 mg daily in 1–2 divided doses for day 1, then 4 mg daily in 1–2 divided doses for day 2, slower titration is appropriate in some patients, usual dose 4–6 mg daily, doses above 10 mg daily only if benefit considered to outweigh risk; maximum 16 mg per day.

**BY MOUTH**

- Elderly: Initially 50 micrograms twice daily, then increased in steps of 500 micrograms twice daily, increased to 1–2 mg twice daily.

**Mania**

**BY MOUTH**

- Adult: Initially 2 mg once daily, then increased in steps of 1 mg daily if required; usual dose 1–6 mg daily.

**BY MOUTH**

- Elderly: Initially 500 micrograms twice daily, then increased in steps of 500 micrograms twice daily, increased to 1–2 mg twice daily.

Short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer’s dementia unresponsive to non-pharmacological interventions and when there is a risk of harm to self or others.

**BY MOUTH**

- Adult: Initially 250 micrograms twice daily, then increased in steps of 250 micrograms twice a day on alternate days, adjusted according to response; usual dose 500 micrograms twice daily (max. per dose 1 mg twice daily).

**CONTRA-INDICATIONS**

- With intramuscular use children.

**CAUTIONS**

**GENERAL CAUTION**

Avoid in Acute porphyrias p. 864 · cataract surgery (risk of intra-operative floppy iris syndrome) · dehydration · dementia with Lewy bodies · prolactin-dependent tumours.

**SPECIFIC CAUTIONS**

- With intramuscular use when transferring from oral to depot therapy, the dose by mouth should be reduced gradually.

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- **Common or very common** Anxiety · appetite changes · arthralgia · depression · epistaxis · hypertension · infection · malaise · myalgia · oedema · respiratory disorders · sleep disorders · toothache · urinary disorders.

- **Uncommon** Alopaeia · elevated plasma-cholesterol concentrations · elevated plasma-tryglucerylceride concentrations · hypoesthesia · parasthesia · taste disturbances · tinnitus · visual disorders.

- **Rare** Inappropriate antidiuretic hormone secretion · intestinal obstruction · intra-operative floppy iris syndrome · pancreatitis · pulmonary embolism · rhabdomyolysis.
SPECIFIC SIDE-EFFECTS
- With intramuscular use erythema · nodules · pain at injection site · swelling

SIDE-EFFECTS, FURTHER INFORMATION
- With intramuscular use If the dose needs to be reduced to alleviate side-effects, it is important to recognise that the plasma-drug concentration may not fall for some time after reducing the dose, therefore it may be a month or longer before side-effects subside.
- PREGNANCY Use only if potential benefit outweighs risk.
- BREAST FEEDING Use only if potential benefit outweighs risk—small amount present in milk.
- HEPATIC IMPAIRMENT
- With intramuscular use If an oral dose of at least 2 mg daily is tolerated, 25 mg as a depot injection can be given every 2 weeks.
- With oral use Initial and subsequent oral doses should be halved.
- RENAL IMPAIRMENT Initial and subsequent oral doses should be halved.
- MONITORING REQUIREMENTS
- With intramuscular use Treatment requires careful monitoring for optimum effect.
- DIRECTIONS FOR ADMINISTRATION
- With oral use Orodispersible tablets should be placed on the tongue, allowed to dissolve and swallowed. Oral liquid may be diluted with any non-alcoholic drink, except tea.
- With intramuscular use Correct injection technique (including the use of x-ray technique) and rotation of injection sites are essential.
- PATIENT AND CARER ADVICE
- With oral use Patients or carers should be given advice on how to administer risperidone orodispersible tablets. Patients or carers should be given advice on how to administer risperidone oral liquid; counselling on use of dose syringe advised.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

**Tablet**

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<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
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<tbody>
<tr>
<td><strong>RISPERIDONE (Non-proprietary)</strong></td>
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<tr>
<td>Risperidone 500 microgram</td>
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<td>Risperidone 8 mg</td>
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<td>Risperdal (Janssen-Cilag Ltd)</td>
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<td>Risperdal 1 mg</td>
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**Orodispersible tablet**

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<th>CAUTIONARY AND ADVISORY LABELS</th>
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<tr>
<td><strong>RISPERIDONE (Non-proprietary)</strong></td>
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<tr>
<td>Risperidone 500 microgram</td>
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<td>Risperdal Quiklet (Janssen-Cilag Ltd)</td>
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<td>Risperidone 1 mg</td>
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<td>Risperidone 2 mg</td>
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**Oral solution**

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<td><strong>RISPERIDONE (Non-proprietary)</strong></td>
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<tr>
<td>Risperidone 1 mg per 1 mL</td>
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<td>Risperdal (Janssen-Cilag Ltd)</td>
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**Powder and solvent for suspension for injection**

| **Risperdal Consta (Janssen-Cilag Ltd)** |
| Risperidone 25 mg | | Risperdal Consta 25mg powder and solvent for suspension for injection vials | 1 vial | £75.69 |
| Risperidone 37.5 mg | | Risperdal Consta 37.5mg powder and solvent for suspension for injection vials | 1 vial | £111.32 |
| Risperidone 50 mg | | Risperdal Consta 50mg powder and solvent for suspension for injection vials | 1 vial | £142.76 |

Drugs used for Dystonias and other involuntary movements not listed below: Chlorpromazine, Clozapine, Haloperidol

**ANTIPSYCHOTICS (FIRST-GENERATION)**

Promazine hydrochloride

The properties listed below are those particular to the drug only. For properties common to the class, see Antipsychotics, p. 303.

**INDICATIONS AND DOSE**

Short-term adjunctive management of psychomotor agitation

**BY MOUTH**

- Adult: 100–200 mg 4 times a day
Dystonias and other involuntary movements

Agitation and restlessness in elderly
BY MOUTH
» Elderly: 25–50 mg 4 times a day

- CONTRA-INDICATIONS  CNS depression · comatose states · phaeochromocytoma
- CAUTIONS Cerebral arteriosclerosis
- SIDE-EFFECTS Haemolytic anaemia
- HEPATIC IMPAIRMENT Can precipitate coma; phenothiazines are hepatotoxic.
- RENAL IMPAIRMENT Start with small doses in severe renal impairment because of increased cerebral sensitivity.
- LESS SUITABLE FOR PRESCRIBING Promazine hydrochloride is less suitable for prescribing.

- MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

Tablet
CAUTIONARY AND ADVISORY LABELS 2
» PROMAZINE HYDROCHLORIDE (non-proprietary)
  Promazine hydrochloride 25 mg Promazine 25mg tablets 100 tablet (P) £9.50
  Promazine hydrochloride 50 mg Promazine 50mg tablets 100 tablet (P) £17.49

Oral solution
CAUTIONARY AND ADVISORY LABELS 2
» PROMAZINE HYDROCHLORIDE (non-proprietary)
  Promazine hydrochloride 5 mg per 1 ml Promazine 25mg/5ml syrup 150 ml (P) £1.50 DT price = £1.87
  Promazine 25mg/5ml oral solution 150 ml (P) £1.87 DT price = £1.87
  Promazine hydrochloride 10 mg per 1 ml Promazine 50mg/5ml syrup 150 ml (P) £3.50 DT price = £3.93
  Promazine 50mg/5ml oral solution 150 ml (P) £3.93 DT price = £4.93

CNS STIMULANTS

Piracetam

INDICATIONS AND DOSE
Adjunctive treatment of cortical myoclonus
BY MOUTH
» Adult: Initially 7.2 g daily in 2–3 divided doses, then increased in steps of 4.8 g every 3–4 days, adjusted according to response, subsequently, attempts should be made to reduce dose of concurrent therapy; maximum 24 g per day

- CONTRA-INDICATIONS Cerebral haemorrhage · Huntington’s chorea
- CAUTIONS Gastric ulcer · history of haemorrhagic stroke · increased risk of bleeding · major surgery · underlying disorders of haemostasis
- INTERACTIONS Caution with concomitant drugs that increase bleeding.
- SIDE-EFFECTS
  » Common or very common Hyperkinesia · nervousness · weight gain
  » Uncommon Abdominal pain · anxiety · asthenia · ataxia · confusion · depression · dermatitis · diarrhea · drowsiness · haemorrhagic disorder · hallucination · headache · insomnia · nausea · pruritus · urticaria · vertigo · vomiting
- PREGNANCY Avoid.
- BREAST FEEDING Avoid.
- HEPATIC IMPAIRMENT Adjust dose if both hepatic and renal impairment.
- RENAL IMPAIRMENT Use two-thirds of normal dose if eGFR 50–80 mL/minute/1.73 m²; use one-third of normal dose in 2 divided doses if eGFR 30–50 mL/minute/1.73 m²; use one-sixth of normal dose as a single dose if eGFR 20–30 mL/minute/1.73 m². Avoid if eGFR less than 20 mL/minute/1.73 m².
- TREATMENT CESSATION Avoid abrupt withdrawal.
- PRESCRIBING AND DISPENSING INFORMATION Piracetam has been used in children 16 years and over as adjunctive treatment for cortical myoclonus.
- DIRECTIONS FOR ADMINISTRATION Follow the oral solution with a glass of water (or soft drink) to reduce bitter taste.

- MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet
CAUTIONARY AND ADVISORY LABELS 3
» Nootropil (UCB Pharma Ltd)
  Piracetam 250 mg Nootropil 250mg tablets 10 tablet (P) £11.75
  Piracetam 1.2 gram Nootropil 1.2g tablets 60 tablet (P) £10.97

Oral solution
CAUTIONARY AND ADVISORY LABELS 3
» Nootropil (UCB Pharma Ltd)
  Piracetam 33.3 mg per 1 ml Nootropil 33% oral solution (sugar-free) 300 ml (P) £16.31

MONOAMINE DEPLETING DRUGS

Tetrabenazine

INDICATIONS AND DOSE
Movement disorders due to Huntington’s chorea, hemiballismus, senile chorea, and related neurological conditions
BY MOUTH
» Adult: Initially 25 mg 3 times a day, then increased, if tolerated, in steps of 25 mg every 3–4 days; maximum 200 mg per day
» Elderly: Lower initial dose may be necessary

Moderate to severe tardive dyskinesia
BY MOUTH
» Adult: Initially 12.5 mg daily, dose to be gradually increased according to response

- CONTRA-INDICATIONS Depression · parkinsonism · phaeochromocytoma · prolactin-dependent tumours
- CAUTIONS Susceptibility to QT-interval prolongation
- INTERACTIONS Appendix 1 (tetrabenazine).
Caution with concomitant use of drugs that prolong QT interval.

- SIDE-EFFECTS
  » Common or very common Anxiety · confusion · constipation · depression · diarrhoea · drowsiness · dysphagia · hypotension · insomnia · nausea · parkinsonism · vomiting
  » Uncommon Altered consciousness level · extrapyramidal disorders · hyperthermia
  » Rare Neuroleptic malignant syndrome
  » Very rare Rhabdomyolysis
  » Frequency not known Agitation · amnesia · ataxia · bradycardia · disorientation · dizziness · dry mouth · dyspepsia
- PREGNANCY Avoid unless essential—toxicity in animal studies.
- BREAST FEEDING Avoid.
- HEPATIC IMPAIRMENT Use half initial dose and slower dose titration in mild to moderate impairment. Use with caution in severe impairment.
- RENAL IMPAIRMENT Use with caution.
- TREATMENT CESSATION Avoid abrupt withdrawal.

TREATMENT CESSATION
Avoid abrupt withdrawal.
PATIENT AND CARER ADVICE May affect performance of skilled tasks (e.g. driving).

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Tablet

CAUTIONARY AND ADVISORY LABELS

TETRABENAZINE (Non-proprietary)
- Tetrabenazine 25 mg Tetrabenazine 25mg tablets | 112 tablet POM no price available DT price = £100.00
- Revocon (Sun Pharmaceuticals UK Ltd) Tetrabenazine 25 mg Revocon 25mg tablets | 112 tablet POM £100.00 DT price = £100.00
- Xenazine (Alliance Pharmaceuticals Ltd) Tetrabenazine 25 mg Xenazine 25 tablets | 112 tablet POM £100.00 DT price = £100.00

NEUROPROTECTIVE AGENTS

Riluzole

INDICATIONS AND DOSE
To extend life in patients with amyotrophic lateral sclerosis, initiated by specialist experienced in the management of motor neurone disease

BY MOUTH
- Adult: 50 mg twice daily

CONTRA-INDICATIONS
- Acute porphyria

CAUTIONS
- History of abnormal hepatic function (consult product literature for details) - Interstitial lung disease

CAUTIONS, FURTHER INFORMATION
- Interstitial lung disease Perform chest radiography if symptoms such as dry cough or dyspnoea develop; discontinue if interstitial lung disease is diagnosed.

SIDE-EFFECTS
- Common or very common Abdominal pain · asthenia · diarrhoea · dizziness · drowsiness · headache · nausea · oral paraesthesia · tachycardia · vomiting
- Uncommon Anaemia · angioedema · interstitial lung disease · pancreatitis
- Rare Neutropenia
- Very rare Hepatitis

SIDE-EFFECTS, FURTHER INFORMATION
- Neutropenia White blood cell counts should be determined in febrile illness; neutropenia requires discontinuation of riluzole.

PREGNANCY
- Avoid—no information available.

BREAST FEEDING
- Avoid—no information available.

HEPATIC IMPAIRMENT
- Avoid.

RENAL IMPAIRMENT
- Avoid—no information available.

PATIENT AND CARER ADVICE
- Dizziness or vertigo may affect performance of skilled tasks (e.g. driving). Blood disorders Patients or their carers should be told how to recognise signs of neutropenia and advised to seek immediate medical attention if symptoms such as fever occur.

NATIONAL FUNDING/ACCESS DECISIONS
- NICE technology appraisals (TAs)
  - Riluzole for motor neurone disease (January 2001) NICE TA20 Riluzole is recommended for treating the amyotrophic lateral sclerosis (ALS) form of motor neurone disease (MND). Treatment should be initiated by a specialist in MND but it can then be supervised under a shared-care arrangement involving the general practitioner. www.nice.org.uk/TA20

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension, powder

Tablet
- RILUZOLE (Non-proprietary) Riluzole 50 mg Riluzole 50mg tablets | 56 tablet POM £320.00 DT price = £29.61
- Rilutek (Sanofi) Riluzole 50 mg Rilutek 50mg tablets | 56 tablet POM £320.33 DT price = £29.61

Tafamidis

INDICATIONS AND DOSE
Treatment of transthyretin familial amyloid polyneuropathy (TTR-FAP) in patients with stage 1 symptomatic polyneuropathy to delay peripheral neurological impairment (initiated under specialist supervision)

BY MOUTH
- Adult: 20 mg once daily

SIDE-EFFECTS
- Abdominal pain · diarrhoea · urinary tract infection · vaginal infection

CONCEPTION AND CONTRACEPTION
- Exclude pregnancy before treatment and ensure effective contraception during and for one month after stopping treatment.

PREGNANCY
- Avoid (toxicity in animal studies).

BREAST FEEDING
- Avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT
- Caution in severe impairment—no information available.

PRESCRIBING AND DISPENSING INFORMATION
- Tafamidis should be prescribed in addition to standard treatment, but before liver transplantation; it should be discontinued in patients who undergo liver transplantation.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS
- Vyndaqel (Pfizer Ltd)
  - Tafamidis 20 mg Vyndaqel 20mg capsules | 30 capsule POM £10.685.00

NEUROTOXINS (BOTULINUM TOXINS)

Botulinum toxin type A

INDICATIONS AND DOSE
- Treatment of focal spasticity (including hand and wrist disability associated with stroke) (specialist use only) | Blepharospasm (specialist use only) | Hemifacial spasm (specialist use only) | Spasmodytic torticolis (specialist use only) | Severe hyperhidrosis of the axillae (specialist use only) | Prophylaxis of headaches in adults with chronic migraine (specialist use only) | Temporary improvement of moderate to severe wrinkles between the eyebrows in adults under 65 years (specialist use only) | Ankle disability due to lower limb spasticity associated with stroke (specialist use only) | Management of bladder dysfunctions (specialist use only) | Temporary improvement of moderate to severe crow’s feet (specialist use only)

BY SUBCUTANEOUS INJECTION OR BY INTRADERMAL INJECTION OR BY INTRAMUSCULAR INJECTION
- Adult: (consult product literature)

Dose equivalence and conversion
Important: information is specific to each individual preparation.
When used for axillary hyperhidrosis

When used for blepharospasm

▶ When used for focal upper-limb specificity associated with stroke: nausea

When used for hemifacial spasm

When used for spasmodic torticollis

▶ When used for hemifacial spasm

When used for blepharospasm or hemifacial spasm

When used for axillary hyperhidrosis

When used for blepharospasm

▶ When used for focal upper-limb specificity associated with stroke.
Botulinum toxin type B

INDICATIONS AND DOSE
Spasmodic torticollis (cervical dystonia) (specialist use only)
by intramuscular injection
- Adult: Initially 5000–10 000 units, adjusted according to response, dose to be divided between 2–4 most affected muscles
Dose equivalence and conversion
Important: information specific to each individual preparation.

CONTRA-INDICATIONS
Neuromuscular disorders - neuromuscular junctional disorders

CAUTIONS
History of dysphagia or aspiration - off-label use (risk of toxin spread) - tolerance may occur

SIDE-EFFECTS
- Common or very common
  - Dry mouth - dyspepsia - dysphagia - dysphonia - headache - increased electromyographic jitter in some distant muscles - influenza-like symptoms - myasthenia - neck pain - taste disturbances - visual disturbances - worsening torticollis
- Frequency not known
  - Aspiration pneumonia - constipation - exaggerated muscle weakness - malaise - paresthesia - respiratory disorders - vomiting

PREGNANCY
Low risk of systemic absorption but avoid unless essential.

BREAST FEEDING
Low risk of systemic absorption but avoid unless essential.

DIRECTIONS FOR ADMINISTRATION
Injection may be diluted with sodium chloride 0.9%.

PRESCRIBING AND DISPENSING INFORMATION
Important: not interchangeable with other botulinum toxin preparations.

PATIENT AND CARER ADVICE
Patients should be warned of the signs and symptoms of toxin spread, such as muscle weakness and breathing difficulties; they should be advised to seek immediate medical attention if swallowing, speech or breathing difficulties occur.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
- NeuroBloc (Elisai Ltd)
  - Botulinum toxin type B 5000 unit per 1 ml NeuroBloc 5000 units/1ml solution for injection vials | 1 vial PDR £148.27 (Hospital only)
  - Botulinum toxin type B 1000 units/0.5ml solution for injection vials | 1 vial PDR £197.69 (Hospital only)
  - Botulinum toxin type B 2500 units/0.5ml solution for injection vials | 1 vial PDR £111.20 (Hospital only)

3.2 Parkinson’s disease

Parkinson’s disease

Parkinson’s disease
In idiopathic Parkinson’s disease, the progressive degeneration of pigmented neurons in the substantia nigra leads to a deficiency of the neurotransmitter dopamine. The resulting neurochemical imbalance in the basal ganglia causes the characteristic signs and symptoms of the illness. Drug therapy does not prevent disease progression, but it improves most patients’ quality of life.

Patients with suspected Parkinson’s disease should be referred to a specialist to confirm the diagnosis; the diagnosis should be reviewed every 6–12 months.

Features resembling those of Parkinson’s disease can occur in diseases such as progressive supranuclear palsy and multiple system atrophy, but they do not normally show a sustained response to the drugs used in the treatment of idiopathic Parkinson’s disease.

When initiating treatment, patients should be advised about its limitations and possible side-effects. About 5–10% of patients with Parkinson’s disease respond poorly to treatment.

Treatment is usually not started until symptoms cause significant disruption of daily activities. Levodopa, non-ergot-derived dopamine-receptor agonists, or monoamine-oxidase-B inhibitors can be prescribed for initial treatment in early Parkinson’s disease. Therapy with two or more antiparkinsonian drugs may be necessary as the disease progresses. Most patients eventually require levodopa and subsequently develop motor complications.

Elderly
Antiparkinsonian drugs can cause confusion in the elderly. It is particularly important to initiate treatment with low doses and to increase the dose gradually.

Dopaminergic drugs used in Parkinson’s disease
Dopamine-receptor agonists
The dopamine-receptor agonists have a direct action on dopamine receptors. Initial treatment of Parkinson’s disease is often with the dopamine-receptor agonist pramipexole p. 336, ropinirole p. 338, and rotigotine p. 339. The ergot-derived dopamine-receptor agonists bromocriptine p. 333, cabergoline p. 334, and pergolide p. 336 are rarely used because of the risk of fibrotic reactions.

When used alone, dopamine-receptor agonists cause fewer motor complications in long-term treatment compared with levodopa treatment but the overall motor performance improves slightly less. The dopamine-receptor agonists are associated with more psychiatric side-effects than levodopa.

Dopamine-receptor agonists are also used with levodopa in more advanced disease. If a dopamine-receptor agonist is added to levodopa therapy, the dose of levodopa needs to be reduced.

Apomorphine hydrochloride p. 332 is a potent dopamine-receptor agonist that is sometimes helpful in advanced
disease for patients experiencing unpredictable ‘off’ periods with levodopa treatment. Apomorphine hydrochloride should be initiated in a specialist clinic. After an overnight withdrawal of oral antiparkinsonian medication to induce an ‘off’ episode, the threshold dose of apomorphine hydrochloride is determined. Oral antiparkinsonian medication is then restarted. The patient must be taught to self-administer apomorphine hydrochloride by subcutaneous injection into the lower abdomen or outer thigh at the first sign of an ‘off’ episode. Once treatment has been established it may be possible to gradually reduce other antiparkinsonian medications.

**Levodopa**

Levodopa, the amino-acid precursor of dopamine, acts by replenishing depleted striatal dopamine. It is given with an extracerebral dopa-decarboxylase inhibitor, which reduces the peripheral conversion of levodopa to dopamine, thereby limiting side-effects such as nausea, vomiting, and cardiovascular effects; additionally, effective brain dopamine concentrations are achieved with lower doses of levodopa. The extracerebral dopa-decarboxylase inhibitors used with levodopa are benserazide (in co-beneldopa p. 328) and carbidopa (in co-careldopa p. 329).

Levodopa, in combination with a dopa-decarboxylase inhibitor, is useful in the elderly or frail, in patients with other significant illnesses, and in those with more severe symptoms. It is effective and well tolerated in the majority of patients.

Levodopa therapy should be initiated at a low dose and increased in small steps; the final dose should be as low as possible. Intervals between doses should be chosen to suit the needs of the individual patient.

Nausea and vomiting with co-beneldopa or co-careldopa are rarely dose-limiting and domperidone p. 346 can be useful in controlling these effects.

Levodopa treatment is associated with potentially troublesome motor complications including response fluctuations and dyskinesias. Response fluctuations are characterised by large variations in motor performance, with normal function during the ‘on’ period, and weakness and restricted mobility during the ‘off’ period. ‘End-of-dose’ deterioration with progressively shorter duration of benefit also occurs. Modified-release preparations may help with ‘end-of-dose’ deterioration or nocturnal immobility and rigidity. Motor complications are particularly problematic in young patients treated with levodopa.

**Monoamine-oxidase-B inhibitors**

Rasagiline p. 340 and selegeline hydrochloride p. 340 are monoamine-oxidase-B inhibitors used in Parkinson’s disease. Early treatment with selegeline hydrochloride alone can delay the need for levodopa therapy.

**Antimuscarinic drugs used in parkinsonism**

Antimuscarinic drugs can be useful in drug-induced parkinsonism, but they are generally not used in idiopathic Parkinson’s disease because they are less effective than dopaminergic drugs and they are associated with cognitive impairment.

The antimuscarinic drugs orphenadrine hydrochloride below, procyclidine hydrochloride p. 326, and trihexyphenidyl hydrochloride p. 326 reduce the symptoms of parkinsonism induced by antipsychotic drugs, but there is no justification for giving them routinely in the absence of parkinsonian side-effects. Tardive dyskinesia is not improved by antimuscarinic drugs and may be made worse.

In idiopathic Parkinson’s disease, antimuscarinic drugs reduce tremor and rigidity but they have little effect on bradykinesia. They may be useful in reducing sialorrhoea.

There are no important differences between the antimuscarinic drugs, but some patients tolerate one better than another.

Procyclidine hydrochloride can be given parenterally and is effective emergency treatment for acute drug-induced dystonic reactions.

If treatment with an antimuscarinic is ineffective, intravenous diazepam p. 267 can be given for life-threatening acute drug-induced dystonic reactions.

**Drugs used in essential tremor, chorea, tics, and related disorders**

Tetrabenazine p. 321 is mainly used to control movement disorders in Huntington’s chorea and related disorders. Tetrabenazine can also be prescribed for the treatment of tardive dyskinesia if switching or withdrawing the causative antipsychotic drug is not effective. It acts by depleting nerve endings of dopamine. It is effective in only a proportion of patients and its use may be limited by the development of depression.

Haloperidol p. 306 [unlicensed indication], olanzapine p. 315 [unlicensed indication], risperidone p. 319 [unlicensed indication], and quetiapine p. 318 [unlicensed indication] can also be used to suppress chorea in Huntington’s disease.

Haloperidol can also improve motor tics and symptoms of Tourette syndrome and related chorea. Other treatments for Tourette syndrome include pimozide p. 308 [unlicensed indication] (important: ECG monitoring required), clonidine hydrochloride p. 137 [unlicensed indication], and sulphpride p. 310 [unlicensed indication]. Trihexyphenidyl hydrochloride p. 326 in high dosage can also improve some movement disorders; it is sometimes necessary to build the dose up over many weeks. Chlorpromazine hydrochloride p. 304 and haloperidol p. 306 are used to relieve intractable hiccup.

Propranolol hydrochloride p. 146 or another beta-adrenoceptor blocking drug may be useful in treating essential tremor or tremors associated with anxiety or thyrotoxicosis.

Primidone p. 401 in some cases provides relief from benign essential tremor; the dose is increased slowly to reduce side-effects.

Piracetam p. 321 is used as an adjunctive treatment for myoclonus of cortical myoclonus of cortical origin. After an acute episode, attempts should be made every 6 months to decrease or discontinue treatment.

Riluzole p. 322 is used to extend life in patients with motor neurone disease who have amyotrophic lateral sclerosis.

**Torsion dystonia and other involuntary movements**

Treatment with botulinum toxin type A p. 322 can be considered after an acquired non-progressive brain injury if rapid-onset spasticity causes postural or functional difficulties.

**ANTIMUSCARINICS**

**Orphenadrine hydrochloride**

- **DRUG ACTION** Orphenadrine exerts its antiparkinsonian action by reducing the effects of the relative central cholinergic excess that occurs as a result of dopamine deficiency.

**INDICATIONS AND DOSE**

Parkinsonism | Drug-induced extrapyramidal symptoms (but not tardive dyskinesia)

- **BY MOUTH**
  - **Adult:** Initially 150 mg daily in divided doses, then increased in steps of 50 mg every 2–3 days, adjusted according to response; usual dose 150–300 mg daily in divided doses; maximum 400 mg per day
  - **Elderly:** Preferably dose at lower end of range
Nervous system

**MEDICINAL FORMS**

- Tablet
  - ORPHENADINE HYDROCHLORIDE (Non-proprietary)
    - Procyclidine hydrochloride 50 mg
  - Dispal (Astellas Pharma Ltd)
    - Orphenadrine hydrochloride 50 mg tablets
    - 28 tablet (£4.45 DT price = £1.87)
    - 100 tablet (£8.94)
    - 500 tablet (£44.63)

**ORPHENADINE HYDROCHLORIDE (Non-proprietary)**

- Orphenadrine hydrochloride 10 mg per 1 ml
  - 150 ml (£27.30)

**INDICATIONS AND DOSE**

**Parkinsonism | Extrapyramidal symptoms (but not tardive dyskinesia)**

- Adult: 2.5 mg 3 times a day, then increased in steps of 2.5–5 mg daily if required; increased if necessary up to 30 mg daily in 2–4 divided doses, to be increased at 2–3 day intervals. Maximum daily dose only to be used in exceptional circumstances; maximum 60 mg per day.
- Elderly: Lower end of range preferable

**SIDE-EFFECTS**

- Urinary retention
- Drowsiness
- Impaired coordination
- Insomnia
- Seizures
- Very rare: Angle-closure glaucoma
- Frequency not known: Anxiety, blurred vision, confusion, constipation, dizziness, dry mouth, euphoria, hallucinations, impaired memory, nausea, rash, restlessness, tachycardia, vomiting

**INTERACTIONS**

- Nervous system: Acute porphyrias p. 864 - gastrointestinal obstruction - myasthenia gravis
- Cardiovascular disease: elderly - hypertension - in patients susceptible to angle-closure glaucoma - liable to abuse - prostatic hypertrophy - psychotic disorders - pyrexia
- INTERACTIONS → Appendix 1 (antimuscarinics).
- Many drugs have antimuscarinic effects; concomitant use of two or more such drugs can increase side-effects such as dry mouth, urine retention, and constipation. Concomitant use of other drugs with antimuscarinic effects can also lead to confusion in the elderly.

**CONTRA-INDICATIONS**

- Acute dystonia
- BY INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INJECTION
  - Adult: 5–10 mg, occasionally, more than 10 mg, dose usually effective in 5–10 minutes but may need 30 minutes for relief
  - Elderly: Lower end of range preferable

**TREATMENT CESSATION**


**PREGNANCY**

- Use only if potential benefit outweighs risk.

**BREAST FEEDING**

- No information available.

**RENAI IMPAIRMENT**

- Use with caution.

**SIDE-EFFECTS**

- Angle-closure glaucoma - blurred vision - confusion - constipation - dizziness - dry mouth - euphoria - gingivitis - hallucinations - impaired memory - nausea - rash - tachycardia - vomiting

**TREATMENT CESSATION**


**PATIENT AND CARER ADVICE**

- May affect performance of skilled tasks (e.g. driving).

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

**Tablet**

- ORPHENADINE HYDROCHLORIDE (Non-proprietary)
  - Procyclidine hydrochloride 5 mg
  - Dispal (Astellas Pharma Ltd)
  - Orphenadrine hydrochloride 50 mg tablets
  - 28 tablet (£6.45 DT price = £1.87)
  - 100 tablet (£8.94)
  - 500 tablet (£44.63)

**Oral solution**

- ORPHENADINE HYDROCHLORIDE (Non-proprietary)
  - Orphenadrine hydrochloride 10 mg per 1 ml
  - 150 ml (£27.30)

**Trihexyphenidyl hydrochloride**

**DRUG ACTION**

- Trihexyphenidyl exerts its antiparkinsonian action by reducing the effects of the relative central cholinergic excess that occurs as a result of dopamine deficiency.

**INDICATIONS AND DOSE**

- Parkinson's disease (if used in combination with carbidopa or co-beneldopa)
  - Adult: Maintenance 2–6 mg daily in divided doses, use not recommended because of toxicity in the elderly and the risk of aggravating dementia
Parkinson's disease 327

**INDICATIONS AND DOSE**
Adjunct to co-beneldopa or co-careldopa in Parkinson's disease with 'end-of-dose' motor fluctuations (under expert supervision)

**BY MOUTH**
- Adult: 200 mg, dose to be given with each dose of levodopa with dopa-decarboxylase inhibitor; maximum 2 g per day

**CONTRA-INDICATIONS**
- History of neuroleptic malignant syndrome - history of non-traumatic rhabdomyolysis - phaeochromocytoma

**CAUTIONS**
- Concurrent levodopa dose may need to be reduced by about 10–30% - ischaemic heart disease

**SIDE-EFFECTS**
- Common or very common Abdominal pain - abnormal dreams - confusion - constipation - diarrhea - dizziness - dry mouth - dyskinesia - dystonia - fatigue - hallucinations - insomnia - ischaemic heart disease - nausea - sweating - urine may be coloured reddish-brown - vomiting
- Uncommon Myocardial infarction
- Rare Rash
- Very rare Agitation - anorexia - urticaria - weight loss
- Frequency not known Colitis - hepatitis - neuroleptic malignant syndrome - rhabdomyolysis - skin, hair, and nail discoloration

**PREGNANCY**
- Avoid—no information available.

**BREAST FEEDING**
- Avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**
- Avoid.

**TREATMENT CESSATION**
- Avoid abrupt withdrawal.

**PATIENT AND CARER ADVICE**
- Patient counselling is advised (may colour urine reddish-brown, concomitant iron containing products).

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

**Tablet**
- ENTCPHONEHALYDROCHLORIDE (Non-proprietary)
  - Trimepyridyld hydrochloride 2 mg: Trimepyridyld 2mg tablets | 84 tablet [POM] £11.80 DT price = £9.22
  - Trimepyridyld hydrochloride 5 mg: Trimepyridyld 5mg tablets | 84 tablet [POM] £17.91 DT price = £17.91

**Oral solution**
- EXCIPIENTS: May contain Propylene glycol
- Trimepyridyld hydrochloride 1 mg per 1 ml Trimepyridyld 5mg/5ml oral solution | 200 ml [POM] £20.00 DT price = £20.00

**Tolcapone**

**DRUG ACTION**
Tolcapone prevents the peripheral breakdown of levodopa, by inhibiting catechol-O-methyltransferase, allowing more levodopa to reach the brain.

**INDICATIONS AND DOSE**
Adjunct to co-beneldopa or co-careldopa in Parkinson's disease with 'end-of-dose' motor fluctuations if another inhibitor of peripheral catechol-O-methyltransferase inappropriate (under expert supervision)

**BY MOUTH**
- Adult: 100 mg 3 times a day (max. per dose 200 mg 3 times a day) continuing beyond 3 weeks only if substantial improvement, leave 6 hours between each dose; first daily dose should be taken at the same time as levodopa with dopa-decarboxylase inhibitor, dose maximum only in exceptional circumstances
Nervous system

Co-beneldopa

INDICATIONS
Phaeochromocytoma · previous history of hyperthermia · previous history of neuroleptic malignant syndrome · previous history of rhabdomyolysis · severe dyskinesia

CAUTIONS
Most patients receiving more than 600 mg levodopa daily require reduction of levodopa dose by about 30%

CAUTIONS, FURTHER INFORMATION
Hepatotoxicity Potentially life-threatening hepatotoxicity including fulminant hepatic failure reported rarely, usually in women and during the first 6 months, but late-onset liver injury also reported; discontinue if abnormal liver function tests or symptoms of liver disorder; do not re-introduce tolcapone once discontinued.

INTERACTIONS
▶ Appendix 1 (tolcapone).

SIDE-EFFECTS
▶ Common or very common Abdominal pain · anorexia · chest pain · confusion · constipation · diarrhoea · dizziness · drowsiness · dyskinesia · dyspepsia · dystonia · excessive dreaming · hallucinations · headache · hepatotoxicity · nausea · sleep disturbances · sweating · syncope · urinary discoloration · vomiting · xerostomia
▶ Frequency not known Neuroleptic malignant syndrome reported on dose reduction or withdrawal · rhabdomyolysis reported on dose reduction or withdrawal

PREGNANCY
Toxicity in animal studies—use only if potential benefit outweighs risk.

BREAST FEEDING
Avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT
Avoid.

RENAL IMPAIRMENT
Caution if eGFR less than 60 mL/minute. Avoid.

MONITORING REQUIREMENTS
Test liver function before treatment, and monitor every 2 weeks for first year, every 4 weeks for next 6 months and then every 8 weeks thereafter (restart monitoring schedule if dose increased).

TREATMENT CESSATION
Avoid abrupt withdrawal.

PATIENT AND CARER ADVICE
Patients should be told how to recognise signs of liver disorder and advised to seek immediate medical attention if symptoms such as anorexia, nausea, vomiting, fatigue, abdominal pain, dark urine, or pruritus develop.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
CAUTIONARY AND ADVISORY LABELS 14, 25
▶ Tasmar (Meda Pharmaceuticals Ltd).
Tolcapone 100 mg. Tasmar 100mg tablets | 100 tablet | £95.20

DOPAMINE PRECURSORS

Co-beneldopa

INDICATIONS AND DOSE
Parkinson’s disease
INITIALLY BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
▶ Adult: Initially 50 mg 3–4 times a day, then (by mouth) increased in steps of 100 mg daily, dose to be increased once or twice weekly according to response; (by mouth) maintenance 400–800 mg daily in divided doses
▶ Elderly: Initially 50 mg 1–2 times a day, then (by mouth) increased in steps of 50 mg daily, dose to be increased every 3–4 days according to response

Parkinson’s disease (in advanced disease)
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
▶ Adult: Initially 100 mg 3 times a day, then increased in steps of 100 mg daily, dose to be increased once or twice weekly according to response; maintenance 400–800 mg daily in divided doses

Parkinson’s disease (patients not taking levodopa/dopa-decarboxylase inhibitor therapy)
BY MOUTH USING MODIFIED-RELEASE MEDICINES
▶ Adult: Initially 1 capsule 3 times a day; maximum 6 capsules per day

Parkinson’s disease (patients transferring from immediate-release levodopa/dopa-decarboxylase inhibitor preparations)
BY MOUTH USING MODIFIED-RELEASE MEDICINES
▶ Adult: Initially 1 capsule substituted for every 100 mg of levodopa and given at same dosage frequency, increased every 2–3 days according to response; average increase of 50% needed over previous levodopa dose and titration may take up to 4 weeks, supplementary dose of immediate-release Madopar® may be needed with first morning dose; if response still poor to total daily dose of Madopar® CR plus Madopar® corresponding to 1.2 g levodopa—consider alternative therapy.

Dose equivalence and conversion
Dose is expressed as levodopa.

Important safety information

IMPEL CONTROL DISORDERS
Treatment with levodopa is associated with impulse control disorders, including pathologic gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders. If the patient develops an impulse control disorder, levodopa should be withdrawn or the dose reduced until the symptoms resolve.

CAUTIONS
Cushing’s syndrome · diabetes mellitus · endocrine disorders · history of convulsions · history of myocardial infarction with residual arrhythmia · history of peptic ulcer · hyperthyroidism · osteomalacia · phaeochromocytoma · psychiatric illness (avoid if severe and discontinue if deterioration) · severe cardiovascular disease · severe pulmonary disease · susceptibility to angle-closure glaucoma

INTERACTIONS
▶ Appendix 1 (co-beneldopa, levodopa).

SIDE-EFFECTS
▶ Common or very common Abnormal dreams · anorexia · anxiety · arrhythmias · chorea · confusion · dementia · depression · dizziness · drowsiness · dry mouth · dyskinesia · dystonia · euphoria · fatigue · insomnia · nausea · palpitations · postural hypotension · psychosis · syncope · taste disturbances · vomiting
▶ Uncommon Ataxia · chest pain · constipation · diarrhoea · dysphagia · flatulence · hand tremor · hoarseness · hypersalivation · hypertension · malaise · muscle cramps · oedema · reddish discoloration of the urine and other body fluids · weakness · weight changes
▶ Rare Abdominal pain · activation of Hornet’s syndrome · activation of malignant melanoma · agitation · agranulocytosis · alopecia · blepharospasm · blurred vision · bruxism · convulsions · diplopia · disorientation · duodenal ulcer · dyspepsia · dysphonia · exantherma · flushing · gastro-intestinal bleeding · haemolytic anaemia · headache · Henoch-Schönlein purpura · hiccups · leucopenia · neuroleptic malignant syndrome (associated with abrupt withdrawal) · non-haemolytic anaemia · oculogyric crisis · paraesthesia · phlebitis · priapism · pupil dilatation · reduced mental acuity · sweating · thrombocytopenia · trismus · urinary incontinence · urinary retention
▶ Very rare Angle-closure glaucoma · suicidal ideation
▶ Frequency not known Compulsive behaviour
PATIENT AND CARER ADVICE

PRESCRIBING AND DISPENSING INFORMATION

Co-beneldopa is a mixture of benserazide hydrochloride and levodopa in mass proportions corresponding to 1 part of benserazide and 4 parts of levodopa. When transferring patients from another levodopa/dopa-decarboxylase inhibitor preparation, the previous preparation should be discontinued 12 hours before (although interval can be shorter). When switching from modified-release levodopa to dispersible co-beneldopa, reduce dose by approximately 30%. When administered as an adjunct to other antiparkinsonian drugs, once therapeutic effect apparent, the other drugs may be reduced or withdrawn.

PATIENT AND CARER ADVICE

Sudden onset of sleep Excessive daytime sleepiness and sudden onset of sleep can occur with co-beneldopa. Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring. Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour. Patients or carers should be given advice on how to administer co-beneldopa dispersible tablets.

MEDI C INAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Dispersible tablet

CAUTIONARY AND ADVISORY LABELS 10, 14, 21

Madopar (Roche Products Ltd)
Benserazide (as Benserazide hydrochloride) 12.5 mg, Levodopa 50 mg Madopar 50mg/12.5mg dispersible tablets (sugar-free) | 100 tablet (PSt) £5.90 DT price = £5.90
Benserazide (as Benserazide hydrochloride) 25 mg, Levodopa 100 mg Madopar 100mg/25mg dispersible tablets (sugar-free) | 100 tablet (PSt) £10.45 DT price = £10.45

Capsule

CAUTIONARY AND ADVISORY LABELS 10, 14, 21

Benserazide (as Benserazide hydrochloride) 25 mg, Levodopa 100 mg/Benserazide hydrochloride 10 mg, Levodopa 200 mg by mouth using modified-release tablets

INDICATIONS AND DOSE

Parkinson’s disease

BY MOUTH

Adult: Initially 25/100 mg 3 times a day, then increased in steps of 12.5/50 mg once daily or on alternate days, adjusted according to response, alternatively increased in steps of 25/100 mg once daily or on alternate days, adjusted according to response; dose increased until 800 mg levodopa (with 200 mg carbidopa) daily in divided doses is reached, then maintenance up to 200/2000 mg daily in divided doses, adjusted according to response, when co-careldopa is used, the total daily dose of carbidopa should be at least 70 mg. A lower dose may not achieve full inhibition of extracerebral dopa-decarboxylase, with a resultant increase in side-effects

Parkinson’s disease—alternative regimen

BY MOUTH

Adult: Initially 12.5/50 mg 3–4 times a day, alternatively initially 10/100 mg 3–4 times a day, then increased in steps of 12.5/50 mg once daily or on alternate days, adjusted according to response, alternatively increased in steps of 10/100 mg once daily or on alternate days, adjusted according to response; dose increased until 800 mg levodopa (with up to 200 mg carbidopa) daily in divided doses is reached, then maintenance up to 200/2000 mg daily in divided doses, adjusted according to response, when co-careldopa is used, the total daily dose of carbidopa should be at least 70 mg. A lower dose may not achieve full inhibition of extracerebral dopa-decarboxylase, with a resultant increase in side-effects

Dose equivalence and conversion

The proportions are expressed in the form x/y where x and y are the strengths in milligrams of carbidopa and levodopa respectively.

CARAMENT® CR

Parkinson’s disease (patients not receiving levodopa/dopa-decarboxylase inhibitor preparations, expressed as levodopa)

BY MOUTH USING MODIFIED-RELEASE TABLETS

Adult: Initially 100–200 mg twice daily, dose to be given at least 6 hours apart; dose adjusted according to response at intervals of at least 2 days

Parkinson’s disease (patients transferring from immediate-release levodopa/dopa-decarboxylase inhibitor preparations)

BY MOUTH USING MODIFIED-RELEASE TABLETS

Adult: Discontinue previous preparation at least 12 hours before first dose of Carament®; substitute Carament® CR to provide a similar amount of levodopa daily and extend dosing interval by 30–50%; dose then adjusted according to response at intervals of at least 2 days.

continued
UNCOMMON

Common or very common

INTERACTIONS

myocardial infarction with residual arrhythmia
• Severe Parkinson's disease inadequately controlled by other preparations
  • Adult: Administered as intestinal gel, for use with enteral tube (consult product literature)

Important safety information

IMPULSE CONTROL DISORDERS

Treatment with levodopa is associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders. If the patient develops an impulse control disorder, levodopa should be withdrawn or the dose reduced until the symptoms resolve.

• CAUTIONS
  • Cushing’s syndrome • diabetes mellitus • endocrine disorders • history of convulsions • history of myocardial infarction with residual arrhythmia • history of peptic ulcer • hypothyroidism • osteomalacia • phaeochromocytoma • psychiatric illness (avoid if severe and discontinue if deterioration) • severe cardiovascular disease • severe pulmonary disease • susceptibility to angle-closure glaucoma

• INTERACTIONS → Appendix 1 (co-careldopa, levodopa).

• SIDE-EFFECTS
  • Common or very common
    • Abnormal dreams • anorexia • anxiety • arrhythmias • chorea • confusion • dementia • depression • dizziness • drowsiness • dry mouth • dyskinesia • dystonia • euphoria • fatigue • insomnia • nausea • palpitations • postural hypotension • psychosis • syncope • taste disturbances • vomiting
  • Uncommon
    • Ataxia • chest pain • constipation • diarrhoea • dysphagia • flatulence • hand tremor • hoarseness • hypersalivation • hypertension • malaise • muscle cramps • oedema • reddish discoloration of the urine and other body fluids • weakness • weight changes
  • Rare
    • Abdominal pain • activation of Horner’s syndrome • activation of malignant melanoma • agitation • agranulocytosis • alopecia • blepharospasm • blurred vision • bruxism • convulsions • diplopia • disorientation • duodenal ulcer • dyspepsia • dysphonia • exanthema • flushing • gastro-intestinal bleeding • haemolytic anaemia • headache • Henoch-Schönlein purpura • hiccups • leucopenia • neuroleptic malignant syndrome (associated with abrupt withdrawal) • non-haemolytic anaemia • ocular crisis • paraesthesia • phlebitis • priapism • pupil dilatation • reduced mental acuity • sweating • thrombocytopenia • trismus • urinary incontinence • urinary retention
  • Very rare
    • Angle-closure glaucoma • suicidal ideation
  • Frequency not known
    • Compulsive behaviour

• PREGNANCY
  • Use with caution—toxicity has occurred in animal studies.

• BREAST FEEDING
  • May suppress lactation; present in milk—avoid.

• HEPATIC IMPAIRMENT
  • Use with caution.

• RENAL IMPAIRMENT
  • Use with caution.

• EFFECT ON LABORATORY TESTS
  • False positive tests for urinary ketones have been reported.

• TREATMENT CESSATION
  • Avoid abrupt withdrawal (risk of neuroleptic malignant syndrome and rhabdomyolysis).

• PRESCRIBING AND DISPENSING INFORMATION
  • Co-careldopa is a mixture of carbidopa and levodopa; the proportions are expressed in the form x/y where x and y are the strengths in milligrams of carbidopa and levodopa respectively.

  When transferring patients from another levodopa/dopacarboxylase inhibitor preparation, the previous preparation should be discontinued at least 12 hours before.

  Co-careldopa 25/100 provides an adequate dose of carbidopa when low doses of levodopa are needed.

  2 tablets Sinemet® 12.5 mg/50 mg ≡ 1 tablet Sinemet® Plus 25 mg/100 mg.

• MEDICINAL FORMS
  • There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet

CAUTIONARY AND ADVISORY LABELS 10, 14

• CO-CARELDOPA (Non-proprietary)
  • Sinemet (as Carbidopa monohydrate) 10 mg, Levodopa 50 mg
    • Co-careldopa 10mg/100mg tablets | 100 tablet [PS] £10.25
    • Carbidopa (as Carbidopa monohydrate) 25 mg, Levodopa 100 mg
      • Co-careldopa 25mg/100mg tablets | 100 tablet [PS] £26.99
    • Carbidopa (as Carbidopa monohydrate) 25 mg, Levodopa 250 mg
      • Co-careldopa 25mg/250mg tablets | 100 tablet [PS] £35.00
  • Sinemet (as Carbidopa monohydrate) 12.5 mg, Levodopa 50 mg
    • Sinemet 12.5mg/50mg tablets | 90 tablet [PS] £6.28
  • Carbidopa (as Carbidopa monohydrate) 10 mg, Levodopa 100 mg
    • Sinemet 10mg/100mg tablets | 100 tablet [PS] £7.30
  • Carbidopa (as Carbidopa monohydrate) 25 mg, Levodopa 250 mg
    • Sinemet 25mg/250mg tablets | 100 tablet [PS] £18.29
  • Sinemet Plus (Merck Sharp & Dohme Ltd)
    • Carbidopa (as Carbidopa monohydrate) 25 mg, Levodopa 100 mg
      • Sinemet Plus 25mg/100mg tablets | 100 tablet [PS] £12.88
  • Carbidopa (as Carbidopa monohydrate) 25 mg, Levodopa 250 mg
    • Sinemet 25mg/250mg tablets | 100 tablet [PS] £15.83
  • Modified-release tablet

CAUTIONARY AND ADVISORY LABELS 10, 14, 25

• CO-CARELDOPA (Non-proprietary)
  • Sinemet (as Carbidopa monohydrate) 25 mg, Levodopa 100 mg
    • Co-careldopa 25mg/100mg modified-release tablets | 50 tablet [PS] no price available | 60 tablet [PS] no price available
  • Co-careldopa 50mg/200mg modified-release tablets | 60 tablet [PS] no price available
  • Caramet CR (Teva UK Ltd)
    • Carbidopa (as Carbidopa monohydrate) 25 mg, Levodopa 100 mg
      • Caramet 25mg/100mg CR tablets | 60 tablet [PS] £11.47
    • Carbidopa (as Carbidopa monohydrate) 50 mg, Levodopa 200 mg
      • Caramet 50mg/200mg CR tablets | 60 tablet [PS] £11.47

SINEMET® CR

Parkinson’s disease (patients not receiving levodopa/dopacarboxylase inhibitor therapy)

BY MOUTH
  • Adult: Initially 1 tablet twice daily, both dose and interval then adjusted according to response at intervals of not less than 3 days

Parkinson’s disease (patients transferring from immediate-release levodopa/dopacarboxylase inhibitor preparations)

BY MOUTH
  • Adult: 1 tablet twice daily, dose can be substituted for a daily dose of levodopa 300–400 mg in immediate-release Sinemet® tablets (substitute Sinemet® CR to provide approximately 10% more levodopa per day and extend dosing interval by 30–50%); dose and interval then adjusted according to response at intervals of not less than 3 days.

HALF SINEMET® CR

Parkinson’s disease (for fine adjustment of Sinemet® CR dose)

BY MOUTH
  • Adult: (consult product literature)

DUODOPA®

Severe Parkinson’s disease inadequately controlled by other preparations

BY MOUTH
  • Adult: Administered as intestinal gel, for use with enteral tube (consult product literature)
Carbidopa with entacapone and levodopa

The properties listed below are those particular to the combination only. For the properties of the components please consider, entacapone p. 327, co-carbeldopa p. 329.

INDICATIONS AND DOSE

**STALEVO® 75/18.75/200**
Parkinson's disease and end-of-dose motor fluctuations not adequately controlled with levodopa and dopa-decarboxylase inhibitor treatment

**BY MOUTH**
- Adult: 1 tablet for each dose; maximum 10 tablets per day

**STALEVO® 50/12.5/200**
Parkinson's disease and end-of-dose motor fluctuations not adequately controlled with levodopa and dopa-decarboxylase inhibitor treatment

**BY MOUTH**
- Adult: 1 tablet for each dose; maximum 10 tablets per day

**STALEVO® 150/37.5/200**
Parkinson's disease and end-of-dose motor fluctuations not adequately controlled with levodopa and dopa-decarboxylase inhibitor treatment

**BY MOUTH**
- Adult: 1 tablet for each dose; maximum 10 tablets per day

**STALEVO® 200/50/200**
Parkinson's disease and end-of-dose motor fluctuations not adequately controlled with levodopa and dopa-decarboxylase inhibitor treatment

**BY MOUTH**
- Adult: 1 tablet for each dose; maximum 7 tablets per day

**STALEVO® 125/31.25/200**
Parkinson's disease and end-of-dose motor fluctuations not adequately controlled with levodopa and dopa-decarboxylase inhibitor treatment

**BY MOUTH**
- Adult: 1 tablet for each dose; maximum 10 tablets per day

**STALEVO® 175/43.75/200**
Parkinson's disease and end-of-dose motor fluctuations not adequately controlled with levodopa and dopa-decarboxylase inhibitor treatment

**BY MOUTH**
- Adult: 1 tablet for each dose; maximum 8 tablets per day

**PRESCRIBING AND DISPENSING INFORMATION**

Patients receiving standard-release co-carbeldopa or co-beneldopa alone, initiate Stalevo® at a dose that provides similar (or slightly lower) amount of levodopa. Patients with dyskinesia or receiving more than 800 mg levodopa daily, introduce entacapone before transferring to Stalevo® (levodopa dose may need to be reduced by 10–30% initially).

Patients receiving entacapone and standard-release co-carbeldopa or co-beneldopa, initiate Stalevo® at a dose that provides similar (or slightly higher) amount of levodopa.

**PATIENT AND CARER ADVICE**

**Sudden onset of sleep**
Excessive daytime sleepiness and sudden onset of sleep can occur with Stalevo®. Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring. Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS** 10, 14, 25

- **Stalevo** (Orion Pharma (UK) Ltd)
  - Carbidopa 37.5 mg, Entacapone 200 mg, Levodopa 150 mg Stalevo 150mg/37.5mg/200mg tablets | 30 tablet | £20.79 | 100 tablet | £69.31
  - Carbidopa 18.75 mg, Entacapone 200 mg, Levodopa 75 mg Stalevo 75mg/18.75mg/200mg tablets | 30 tablet | £20.79 | 100 tablet | £69.31
  - Carbidopa 50 mg, Entacapone 200 mg, Levodopa 200 mg Stalevo 200mg/50mg/200mg tablets | 30 tablet | £20.79 | 100 tablet | £69.31
  - Carbidopa 43.75 mg, Entacapone 200 mg, Levodopa 175 mg Stalevo 175mg/43.75mg/200mg tablets | 30 tablet | £20.79 | 100 tablet | £69.31
  - Carbidopa 31.25 mg, Entacapone 200 mg, Levodopa 125 mg Stalevo 125mg/31.25mg/200mg tablets | 30 tablet | £20.79 | 100 tablet | £69.31
  - Carbidopa 12.5 mg, Entacapone 200 mg, Levodopa 50 mg Stalevo 50mg/12.5mg/200mg tablets | 30 tablet | £20.79 | 100 tablet | £69.31
  - Carbidopa 25 mg, Entacapone 200 mg, Levodopa 100 mg Stalevo 100mg/25mg/200mg tablets | 30 tablet | £20.79 | 100 tablet | £69.31
- Brands may include Sastravi; Stanek

**DOPAMINE RECEPTOR AGONISTS**

**Amantadine hydrochloride**

**DRUG ACTION**
Amantadine is a weak dopamine agonist with modest antiparkinsonian effects.
MEDICINAL FORMS

INDICATIONS AND DOSE

Parkinson’s disease

BY MOUTH
- Adult: 100 mg daily for 1 week, then increased to 100 mg twice daily, usually administered in conjunction with other treatment. Some patients may require higher doses; maximum 400 mg per day
- Elderly: 100 mg daily, adjusted according to response

Post-herpetic neuralgia

BY MOUTH
- Adult: 100 mg twice daily for 14 days (continued for another 14 days if necessary)

Treatment of influenza A (but not recommended)

BY MOUTH
- Adult: 100 mg daily 4–5 days

Prophylaxis of influenza A (but not recommended)

BY MOUTH
- Adult: 100 mg daily usually for 6 weeks or with influenza vaccination for 2–3 weeks after vaccination

CONTRA-INDICATIONS
- Epilepsy · history of gastric ulceration
- CAUTIONS
- Confused or hallucinatory states · congestive heart disease (may exacerbate oedema) · elderly · tolerance to the effects of amantadine may develop in Parkinson’s disease

INTERACTIONS → Appendix 1 (amantadine).

SIDE-EFFECTS
- Common or very common
  - Anorexia · anxiety · dizziness · dry mouth · gastro-intestinal disturbances · hallucinations · headache · impaired concentration · insomnia · lethargy · livedo reticularis · mood changes · myalgia · palpitation · peripheral oedema · postural hypotension · slurred speech · sweating
  - Uncommon
  - Confusion · movement disorders · neuroleptic malignant syndrome · psychosis · rash · seizure · tremor · urinary incontinence · urinary retention · visual disturbances
- Frequency not known
- Heart failure · leucopenia · photosensitisation
- PREGNANCY
  - Avoid; toxicity in animal studies.
- BREAST FEEDING
  - Avoid; present in milk; toxicity in infant reported.

HEPATIC IMPAIRMENT
  - Use with caution.

RENAL IMPAIRMENT
- Reduce dose. Avoid if eGFR less than 15 mL/minute/1.73 m².

TREATMENT CESSION
- Avoid abrupt withdrawal in Parkinson’s disease.

PATIENT AND CARER ADVICE
- May affect performance of skilled tasks (e.g. driving).

NATIONAL FUNDING/ACCESS DECISIONS
- NICE technology appraisals (TAs)

Oseltamivir, zanamivir, and amantadine for prophylaxis of influenza (September 2008) NICE TA158
- Amantadine is not recommended for prophylaxis of influenza. www.nice.org.uk/TA158

Oseltamivir, zanamivir, and amantadine for treatment of influenza (February 2009) NICE TA168
- Amantadine is not recommended for treatment of influenza. www.nice.org.uk/TA168

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet

Capsule
- AMANTADINE HYDROCHLORIDE (Non-proprietary)
  - Amantadine hydrochloride 100 mg
  - 14 capsule | £7.45–£7.50
  - 56 capsule | £29.80

Oral solution
- AMANTADINE HYDROCHLORIDE (Non-proprietary)
  - Amantadine hydrochloride 10 mg per 1 ml
  - Oral solution sugar free (sugar-free) | 150 ml | PO £89.30–£117.20
  - DT price = £103.25

Apomorphine hydrochloride

INDICATIONS AND DOSE

Refractory motor fluctuations in Parkinson's disease ('off' episodes) inadequately controlled by co-beneldopa or co-careldopa or other dopaminergics (in patients requiring division into more than 10 injections daily) (under expert supervision)

BY SUBCUTANEOUS INJECTION
- Adult: Initially 1 mg, dose to be administered at the first sign of 'off' episode, then 2 mg after 30 minutes, dose to be given if inadequate or no response following initial dose, thereafter increase dose at minimum 40-minute intervals until satisfactory response obtained, this determines threshold dose; usual dose 3–30 mg daily in divided doses (max. per dose 10 mg), subcutaneous infusion may be preferable in those requiring division of injections into more than 10 doses; maximum 100 mg per day

Refractory motor fluctuations in Parkinson's disease ('off' episodes) inadequately controlled by co-beneldopa or co-careldopa or other dopaminergics (in patients requiring division into more than 10 injections daily) (under expert supervision)

BY CONTINUOUS SUBCUTANEOUS INFUSION
- Adult: Initially 1 mg/hour, adjusted according to response, then increased in steps of up to 500 micrograms/hour, dose to be increased at intervals not more often than every 4 hours; usual dose 1–4 mg/hour, alternatively usual dose 15–60 micrograms/kg/hour, change infusion site every 12 hours and give during waking hours only (tolerance may occur unless there is a 4-hour treatment-free period at night—24-hour infusions not recommended unless severe night time symptoms); intermittent bolus doses may be needed; maximum 100 mg per day

Important safety information
- IMPULSE CONTROL DISORDERS
  - Treatment with dopamine-receptor agonists are associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders. There is no evidence that ergot- and non-ergot-derived dopamine-receptor agonists differ in their propensity to cause impulse control disorders, so switching between dopamine-receptor agonists to control these side-effects is not recommended. If the patient develops an impulse control disorder, the dopamine-receptor agonist or levodopa should be withdrawn or the dose reduced until the symptoms resolve.

CONTRA-INDICATIONS
- Avoid if 'on' response to levodopa marred by severe dyskinesia or dystonia · dementia · psychosis · respiratory depression
- CAUTIONS
  - Cardiovascular disease · history of postural hypotension (special care on initiation) · neuropsychiatric conditions · pulmonary disease · susceptibility to QT-interval prolongation

INTERACTIONS → Appendix 1 (apomorphine).

SIDE-EFFECTS
- Common or very common
  - Confusion · drowsiness · hallucinations · nausea · sudden onset of sleep · vomiting · yawning
Uncommon Dyskinesias during ‘on’ periods (may require discontinuation) - dyspnoea - haemolytic anaemia (with levodopa) - postural hypotension - rash - thrombocytopenia (with levodopa)

Rare Eosinophilia

Frequency not known Compulsive behaviour - dizziness - peripheral oedema

ALLERGY AND CROSS-SENSITIVITY Contraindicated if history of hypersensitivity to opioids.

PREGNANCY Avoid unless clearly necessary.

BREAST FEEDING No information available; may suppress lactation.

HEPATIC IMPAIRMENT Avoid.

RENAL IMPAIRMENT Use with caution.

MONITORING REQUIREMENTS
- Monitor hepatic, haemopoietic, renal, and cardiovascular function.
- With concomitant levodopa test initially and every 6 months for haemolytic anaemia and thrombocytopenia (development calls for specialist haematological care with dose reduction and possible discontinuation).

TREATMENT CESSATION Antiparkinsonian drug therapy should never be stopped abruptly as this carries a small risk of neuroleptic malignant syndrome.

PATIENT AND CARER ADVICE
- Sudden onset of sleep Excessive daytime sleepiness and sudden onset of sleep can occur with dopamine-receptor agonists. Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.
- Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.

Drugs and driving Prescribers and other healthcare professionals should advise patients if treatment is likely to affect their ability to perform skilled tasks (e.g. driving). This applies especially to drugs with sedative effects; patients should be warned that these effects are increased by alcohol. General information about a patient’s fitness to drive is available from the Driver and Vehicle Licensing Agency at www.dvla.gov.uk. 2015 legislation regarding driving whilst taking certain drugs, may also apply to apomorphine, see Drugs and driving under Guidance on prescribing p. 1.

Hypotensive reactions Hypotensive reactions can occur in some patients taking dopamine-receptor agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery.

MEdICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, solution for infusion

Solution for infusion

CAUTIONARY AND ADVISORY LABELS 10
EXCIPIENTS: May contain Sulphites

APO-go PFS (Britannia Pharmaceuticals Ltd)
Apomorphine hydrochloride 5 mg per 1 ml APO-go PFS 50mg/10ml solution for infusion pre-filled syringes | 5 pre-filled disposable injection \[POM\] £73.11

APO-go Pen (Britannia Pharmaceuticals Ltd)
Apomorphine hydrochloride 10 mg per 1 ml APO-go PEN 30mg/3ml solution for injection | 5 pre-filled disposable injection \[POM\] £123.91

Solution for injection

CAUTIONARY AND ADVISORY LABELS 10
EXCIPIENTS: May contain Sulphites

APO-go (Britannia Pharmaceuticals Ltd)
Apomorphine hydrochloride 10 mg per 1 ml APO-go 50mg/5ml solution for injection ampoules | 5 ampoule \[POM\] £17.96

APO-go 20mg/2ml solution for injection ampoules | 5 ampoule \[POM\] £17.96

Bromocriptine

DRUG ACTION Bromocriptine is a stimulant of dopamine receptors in the brain; it also inhibits release of prolactin by the pituitary.

INDICATIONS AND DOSE

Prevention of lactation

BY MOUTH
- Adult: Initially 2.5 mg daily for 1 day, then 2.5 mg twice daily for 14 days

Suppression of lactation

BY MOUTH
- Adult: Initially 2.5 mg daily for 2–3 days, then 2.5 mg twice daily for 14 days

Hypogonadism | Galactorrhoea | Infertility

BY MOUTH
- Adult: Initially 1–1.25 mg daily, dose to be taken at bedtime, increase dose gradually; usual dose 7.5 mg daily in divided doses, increased if necessary up to 30 mg daily, usual dose in infertility without hyperprolactinaemia is 2.5 mg twice daily

Acromegaly

BY MOUTH
- Adult: Initially 1–1.25 mg daily, dose to be taken at bedtime, then increased to 5 mg every 6 hours, increase dose gradually

Prolactinoma

BY MOUTH
- Adult: Initially 1–1.25 mg daily, dose to be taken at bedtime, then increased to 5 mg every 6 hours, increase dose gradually. Occasionally patients may require up to 30 mg daily

Parkinson’s disease

BY MOUTH
- Adult: Initially 1–1.25 mg daily for 1 week, dose to be taken at night, then 2–2.5 mg daily for 1 week, dose to be taken at night, then 2.5 mg twice daily for 1 week, then 2.5 mg 3 times a day for 1 week, then increased in steps of 2.5 mg every 3–14 days, adjusted according to response; maintenance 10–30 mg daily

Important safety information

FIBROTIC REACTIONS
Bromocriptine has been associated with pulmonary, retroperitoneal, and pericardial fibrotic reactions. Exclude cardiac valvulopathy with echocardiography before starting treatment with these ergot derivatives for Parkinson’s disease or chronic endocrine disorders (excludes suppression of lactation); it may also be appropriate to measure the erythrocyte sedimentation rate and serum creatinine to obtain a chest X-ray. Patients should be monitored for dyspnoea, persistent cough, chest pain, cardiac failure, and abdominal pain or tenderness. If long-term treatment is expected, then lung-function tests may also be helpful.

IMPULSE CONTROL DISORDERS
Treatment with dopamine-receptor agonists are associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders.
There is no evidence that ergot- and non-ergot-derived dopamine-receptor agonists differ in their propensity to cause impulse control disorders, so switching between dopamine-receptor agonists to control these side-effects is not recommended. If the patient develops an impulse control disorder, the dopamine-receptor agonist should be withdrawn or the dose reduced until the symptoms resolve.

**CONTRA-INDICATIONS** Avoid in pre-eclampsia - cardiac valvulopathy (exclude before treatment) - hypertension in postpartum women or in puerperium

**CONTRA-INDICATIONS, FURTHER INFORMATION**

Postpartum or puerperium Should not be used postpartum or in puerperium in women with high blood pressure, coronary artery disease, or symptoms (or history) of serious mental disorder; monitor blood pressure carefully (especially during first few days) in postpartum women. Very rarely hypertension, myocardial infarction, seizures or stroke (both sometimes preceded by severe headache or visual disturbances), and mental disorders have been reported in postpartum women given bromocriptine for lactation suppression—caution with antihypertensive therapy and avoid other ergot alkaloids. Discontinue immediately if hypertension, unmitting headache, or signs of CNS toxicity develop.

**CAUTIONS** Acute porphyrias p. 864 - cardiovascular disease - history of peptic ulcer (particularly in acromegalic patients) - history of serious mental disorders (especially psychotic disorders) - Raynaud’s syndrome

**CAUTIONS, FURTHER INFORMATION**

Hyperprolactinemic patients In hyperprolactinaemic patients, the source of the hyperprolactinaemia should be established (i.e. exclude pituitary tumour before treatment).

**INTERACTIONS** → Appendix 1 (bromocriptine).

Tolerance may be reduced by alcohol.

**SIDE-EFFECTS**

- **Common or very common** Constipation - headache - nasal congestion - nausea
- **Uncommon** Confusion (particularly with high doses) - dizziness - dry mouth - fatigue - hallucinations (particularly with high doses) - postural hypotension - psychomotor excitation (particularly with high doses) - vomiting
- **Rare** Abdominal pain - arrhythmia - bradycardia - diarrhoea - gastric ulcer - gastrointestinal bleeding - insomnia - paraesthesia - psychosis - tachycardia - tinnitus - visual disturbances
- **Very rare** Neuroleptic malignant syndrome on withdrawal - vasospasm of fingers and toes (particularly in patients with Raynaud’s syndrome)
- **Frequency not known** Allergic skin reactions - alopecia - cardiac valvulopathy - constriective pericarditis - drowsiness - dyskinesia - hypersexuality - hyponatraemia - hypotension - increased libido - leg cramps - leucopenia - pathological gambling - pericardial effusion - peripheral oedema - pleural effusion - pleural fibrosis - pleuritis - pulmonary fibrosis - retroperitoneal fibrosis - reversible hearing loss - thrombocytopenia - urinary incontinence

**SIDE-EFFECTS, FURTHER INFORMATION**

Gastro-intestinal bleeding Treatment should be withdrawn if gastro-intestinal bleeding occurs.

**ALLERGY AND CROSS-SENSITIVITY** Bromocriptine should not be used in patients with hypersensitivity to ergot alkaloids.

**CONCEPTION AND CONTRACEPTION** Caution—provide contraceptive advice if appropriate (oral contraceptives may increase prolactin concentration).

**BREAST FEEDING** Suppresses lactation; avoid breast feeding for about 5 days if lactation prevention fails.

**HEPATIC IMPAIRMENT** Dose reduction may be necessary.

**MONITORING REQUIREMENTS**

- Specialist evaluation—monitor for pituitary enlargement, particularly during pregnancy; monitor visual field to detect secondary field loss in macroprolactinoma.
- Monitor for fibrotic disease.
- Monitor blood pressure for a few days after starting treatment and following dosage increase.

**TREATMENT CESSATION** Antiparkinsonian drug therapy should never be stopped abruptly as this carries a small risk of neuroleptic malignant syndrome.

**PATIENT AND CARER ADVICE**

**Sudden onset of sleep** Excessive daytime sleepiness and sudden onset of sleep can occur with dopamine-receptor agonists. Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring. Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.

**Hypotensive reactions** Hypotensive reactions can occur in some patients taking dopamine-receptor agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**

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<td>Bromocriptine (as Bromocriptine mesilate) 5 mg</td>
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<td>Bromocriptine (as Bromocriptine mesilate) 10 mg</td>
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**Cabergoline**

**DRUG ACTION** Cabergoline is a stimulant of dopamine receptors in the brain and it also inhibits release of prolactin by the pituitary.

**INDICATIONS AND DOSE**

**Prevention of lactation**

- **BY MOUTH**
  - Adult: 1 mg, to be taken as a single dose on the first day postpartum

**Suppression of established lactation**

- **BY MOUTH**
  - Adult: 250 micrograms every 12 hours for 2 days

**Hyperprolactinaemic disorders**

- **BY MOUTH**
  - Adult: Initially 500 micrograms once weekly, dose may be taken as a single dose or as 2 divided doses on
epigastric pain, gastritis, hallucinations, headache, nausea, syncope

- Rare Digital vasospasm, epistaxis, hot flushes, muscle weakness, palpitation, paraesthesia, transient hemianopia, vomiting.

- Frequency not known Allergic skin reactions, alopecia, cardiac valvulopathy, constrictive pericarditis, drowsiness, dyskinesia, erythromelalgia, hypersexuality, hypotension, increased libido, leg cramps, pathological gambling, pericardial effusion, peripheral oedema, pleural effusion, pleural fibrosis, pleuritis, pulmonary fibrosis, retroperitoneal fibrosis.

**SIDE-EFFECTS, FURTHER INFORMATION**

**Gastro-intestinal bleeding** Treatment should be withdrawn if gastro-intestinal bleeding occurs.

- **ALLERGY AND CROSS-SENSITIVITY** Cabergoline should not be used in patients with hypersensitivity to ergot alkaloids.

- **CONCEPTION AND CONTRACEPTION** Exclude pregnancy before starting and perform monthly pregnancy tests during the amenorrhoeic period. Caution—advise non-hormonal contraception if pregnancy not desired. Discontinue 1 month before intended conception (ovulatory cycles persist for 6 months).

- **PREGNANCY** Discontinue if pregnancy occurs during treatment (specialist advice needed).

- **BREAST FEEDING** Suppresses lactation; avoid breast-feeding if lactation prevention fails.

- **HEPATIC IMPAIRMENT** Reduce dose in severe hepatic impairment.

- **MONITORING REQUIREMENTS**
  - Monitor for fibrotic disease.
  - Monitor blood pressure for a few days after starting treatment and subsequently at 6–12 month intervals.

- **TREATMENT CESSATION** Antiparkinsonian drug therapy should never be stopped abruptly as this carries a small risk of neuroleptic malignant syndrome.

- **PRESCRIBING AND DISPENSING INFORMATION** Dispense in original container (contains desiccant).

- **PATIENT AND CARER ADVICE**

**Sudden onset of sleep** Excessive daytime sleepiness and sudden onset of sleep can occur with dopamine-receptor agonists.

Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.

Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.

**Hypotensive reactions** Hypotensive reactions can occur in some patients taking dopamine-receptor agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery.

- **MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

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**Important safety information**

**FIBROTIC REACTIONS**

Cabergoline has been associated with pulmonary, retroperitoneal, and pericardial fibrotic reactions. Exclude cardiac valvulopathy with echocardiography before starting treatment with these ergot derivatives for Parkinson’s disease or chronic endocrine disorders (excludes suppression of lactation); it may also be appropriate to measure the erythrocyte sedimentation rate and serum creatinine and to obtain a chest X-ray. Patients should be monitored for dyspnoea, persistent cough, chest pain, cardiac failure, and abdominal pain or tenderness. If long-term treatment is expected, then lung-function tests may also be helpful. Patients taking cabergoline should be regularly monitored for cardiac fibrosis by echocardiography (within 3–6 months of initiating treatment and subsequently at 6–12 month intervals).

**IMPALE CONTROL DISORDERS**

Treatment with dopamine-receptor agonists are associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders. There is no evidence that ergot- and non-ergot-derived dopamine-receptor agonists differ in their propensity to cause impulse control disorders, so switching between dopamine-receptor agonists to control these side-effects is not recommended. If the patient develops an impulse control disorder, the dopamine-receptor agonist should be withdrawn or the dose reduced until the symptoms resolve.

- **CONTRA-INDICATIONS** Avoid in pre-eclampsia; cardiac valvulopathy (exclude before treatment); history of pericardial fibrotic disorders; history of puerperal syndrome; history of pulmonary fibrotic disorders; history of retroperitoneal fibrotic disorders.

- **CAUTIONS**
  - Acute porphyria p. 864; cardiovascular disease; history of peptic ulcer (particularly in acromegalic patients); history of serious mental disorders (especially psychotic disorders) — Raynaud’s syndrome.

**CAUTIONS, FURTHER INFORMATION**

Hyperprolactinaemic patients In hyperprolactinaemic patients, the source of the hyperprolactinaemia should be established (i.e. exclude pituitary tumour before treatment).

- **INTERACTIONS** Appendix 1 (cabergoline).

Tolerance may be reduced by alcohol.

- **SIDE-EFFECTS**
  - Common or very common Abdominal pain, angina, breast pain, confusion, constipation, depression, dyspepsia, epigastric pain, gastritis, hallucinations, headache, nausea, syncope.
Pergolide

INDICATIONS AND DOSE

Monotherapy in Parkinson’s disease where dopamine-receptor agonists other than ergot derivative not appropriate

BY MOUTH

- Adult: Initially 50 micrograms once daily for day 1, dose to be taken at bedtime, then 50 micrograms twice daily for days 2–4, then increased in steps of 100–250 micrograms daily, dose to be increased at intervals of 3–4 days, increased to 2.5 mg daily in 3 divided doses at day 28, then increased in steps of up to 250 micrograms every 3–4 days, this increase to be started after day 30; maintenance 2.1–2.5 mg daily; maximum 3 mg per day

Adjunctive therapy with co-beneldopa or co-careldopa in Parkinson’s disease where dopamine-receptor agonists other than ergot derivative not appropriate

BY MOUTH

- Adult: Initially 50 micrograms daily for 2 days, then increased in steps of 100–150 micrograms every 3 days, dose to be adjusted over next 12 days following initial dose and usually given in 3 divided doses, then increased in steps of 250 micrograms every 3 days, during pergolide titration, levodopa dose may be reduced cautiously; maximum 3 mg per day

Important safety information

FIBROTIC REACTIONS

Pergolide has been associated with pulmonary, retroperitoneal, and pericardial fibrotic reactions. Exclude cardiac valvulopathy with echocardiography before starting treatment with pergolide; it may also be appropriate to measure the erythrocyte sedimentation rate and serum creatinine and to obtain a chest X-ray. Patients should be monitored for dyspnoea, persistent cough, chest pain, cardiac failure, and abdominal pain or tenderness. If long-term treatment is expected, then lung-function tests may also be helpful. Patients taking pergolide should be regularly monitored for cardiac fibrosis by echocardiography (within 3–6 months of initiating treatment and subsequently at 6–12 month intervals).

IMPULSE CONTROL DISORDERS

Treatment with dopamine-receptor agonists is associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders. There is no evidence that ergot- and non-ergot-derived dopamine-receptor agonists differ in their propensity to cause impulse control disorders, so switching between dopamine-receptor agonists to control these side-effects is not recommended. If the patient develops an impulse control disorder, the dopamine-receptor agonist or levodopa should be withdrawn or the dose reduced until the symptoms resolve.

CONTRA-INDICATIONS

Cardiac valvulopathy (exclude before treatment) - history of fibrotic disorders

CAUTIONS

Acute porphyrias p. 864 - arhythmias - dyskinesia (may exacerbate) - hallucinations - history of confusion - psychosis - underlying cardiac disease

INTERACTIONS

Appendix 1 (pergolide).

SIDE-EFFECTS


PREGNANCY

Use only if potential benefit outweighs risk.

BRACST FEEDING

May suppress lactation.

TREATMENT CESSATION

Antiparkinsonian drug therapy should never be stopped abruptly as this carries a small risk of neuroleptic malignant syndrome.

PATIENT AND CARER ADVICE

Sudden onset of sleep

Excessive daytime sleepiness and sudden onset of sleep can occur with dopamine-receptor agonists. Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring. Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.

Hypotensive reactions

Hypotensive reactions can occur in some patients taking dopamine-receptor agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS

PERGOLIDE (Non-proprietary)

Pergolide (as Pergolide mesilate) 50 microgram Pergolide 50microgram tablets | 100 tablet [PDR] £33.00 DT price = £32.66

Pergolide (as Pergolide mesilate) 250 microgram Pergolide 250microgram tablets | 100 tablet [PDR] £35.00–£36.00 DT price = £35.92

Pergolide (as Pergolide mesilate) 1 mg Pergolide 1mg tablets | 100 tablet [PDR] £125.00–£140.00 DT price = £131.66

Pramipexole

INDICATIONS AND DOSE

Parkinson’s disease, used alone or as an adjunct to co-beneldopa or co-careldopa

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

- Adult: Initially 88 micrograms 3 times a day, increased if tolerated to 350 micrograms 3 times a day, dose to be increased by doubling dose every 5–7 days, then increased in steps of 180 micrograms 3 times a day if required, dose to be increased at weekly intervals, during dose titration and maintenance, levodopa dose may be reduced, maximum daily dose to be given in 3 divided doses; maximum 3.3 mg per day

BY MOUTH USING MODIFIED-RELEASE MEDICINES

- Adult: Initially 260 micrograms once daily, increased to 1.05 mg once daily, dose to be increased by doubling dose every 5–7 days, then increased in steps of 520 micrograms every 1 week if required, during dose titration and maintenance, levodopa dose may be reduced according to response; maximum 3.15 mg per day
Restless legs syndrome

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

- Adult: Initially 88 micrograms once daily, dose to be taken 2–3 hours before bedtime, dose to be increased by doubling dose every 4–7 days, repeat dose titration if restarting treatment after an interval of more than a few days; maximum 540 micrograms per day

Dose equivalence and conversion

Doses and strengths are stated in terms of pramipexole (base).

Equivalent strengths of pramipexole (base) in terms of pramipexole dihydrochloride monohydrate (salt) for immediate-release preparations are as follows:
- 88 micrograms base = 125 micrograms salt;
- 180 micrograms base = 250 micrograms salt;
- 350 micrograms base = 500 micrograms salt;
- 700 micrograms base = 1 mg salt.

Equivalent strengths of pramipexole (base) in terms of pramipexole dihydrochloride monohydrate (salt) for modified-release preparations are as follows:
- 260 micrograms base = 375 micrograms salt;
- 520 micrograms base = 750 micrograms salt;
- 1.05 mg base = 1.5 mg salt;
- 1.57 mg base = 2.25 mg salt;
- 2.1 mg base = 3 mg salt;
- 2.62 mg base = 3.75 mg salt;
- 3.15 mg base = 4.5 mg salt.

Important safety information

IMPULSE CONTROL DISORDERS

Treatment with dopamine-receptor agonists is associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders. There is no evidence that ergot- and non-ergot-derived dopamine-receptor agonists differ in their propensity to cause impulse control disorders, so switching between dopamine-receptor agonists to control these side-effects is not recommended. If the patient develops an impulse control disorder, the dopamine-receptor agonist should be withdrawn or the dose reduced until the symptoms resolve.

- CAUTIONS
  - Psychotic disorders: risk of visual disorders (ophthalmological testing recommended) - severe cardiovascular disease

- INTERACTIONS
  - Appendix 1 (pramipexole).

- SIDE-EFFECTS
  - Common or very common Confusion, constipation, decreased appetite, dizziness, drowsiness, dyskinesia, hallucinations, headache, hyperkinesia, hypotension, nausea, peripheral oedema, postural hypotension, restlessness, sleep disturbances, sudden onset of sleep, visual disturbances, vomiting, weight changes
  - Uncommon Amnesia, binge eating, cardiac failure, compulsive behaviour, delusion, dysphoria, hiccups, paranoia, pnuemonia, pruritis, rash, syncope

- Frequency not known Paradoxical worsening of restless legs syndrome

- PREGNANCY
  - Use only if potential benefit outweighs risk—no information available.

- BREAST FEEDING
  - May suppress lactation; avoid—present in milk in animal studies.

- RENAL IMPAIRMENT
  - For immediate-release tablets in Parkinson’s disease, initially 88 micrograms twice daily (max. 1.57 mg daily in 2 divided doses) if eGFR 20–50 mL/minute/1.73 m²; initially 88 micrograms once daily (max. 1.1 mg once daily) if eGFR less than 20 mL/minute/1.73 m². If renal function declines during treatment, reduce dose by the same percentage as the decline in eGFR. For immediate-release tablets in restless legs syndrome, reduce dose if eGFR less than 20 mL/minute/1.73 m². For modified-release tablets, initially 260 micrograms on alternate days if eGFR 30–50 mL/minute/1.73 m², increased to 250 micrograms once daily after 1 week, further increased if necessary by 260 micrograms daily at weekly intervals to max. 1.57 mg daily. For modified-release tablets, avoid if eGFR less than 30 mL/minute/1.73 m².

- MONITORING REQUIREMENTS
  - Risk of postural hypotension (especially on initiation)—monitor blood pressure.

- TREATMENT CESSATION
  - Antiparkinsonian drug therapy should never be stopped abruptly as this carries a small risk of neuroleptic malignant syndrome.

- PATIENT AND CARER ADVICE
  - Sudden onset of sleep: Excessive daytime sleepiness and sudden onset of sleep can occur with dopamine-receptor agonists. Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.

  - Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.

  - Hypotensive reactions: Hypotensive reactions can occur in some patients taking dopamine-receptor agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 10

- PRAMPIPEXOLE (Non-proprietary)
  - Pramipexole (as Pramipexole dihydrochloride monohydrate) 88 microgram Pramipexole 88 mg tablet | 30 tablet | £9.54 DT price = £2.28
  - Pramipexole (as Pramipexole dihydrochloride monohydrate) 180 microgram Pramipexole 180 mg tablet | 30 tablet | £17.19 DT price = £1.77 | 100 tablet | £9.09
  - Pramipexole (as Pramipexole dihydrochloride monohydrate) 350 microgram Pramipexole 350 mg tablet | 30 tablet | £38.20 DT price = £3.46 | 100 tablet | £45.53
  - Pramipexole (as Pramipexole dihydrochloride monohydrate) 700 microgram Pramipexole 700 mg tablet | 30 tablet | £76.40 DT price = £2.75 | 100 tablet | £254.69
  - Mirapexin (Boehringer Ingelheim Ltd)
    - Pramipexole (as Pramipexole dihydrochloride monohydrate) 88 microgram Mirapexin 0.088 mg tablet | 30 tablet | £11.24 DT price = £2.28
    - Pramipexole (as Pramipexole dihydrochloride monohydrate) 180 microgram Mirapexin 0.18 mg tablet | 30 tablet | DT price = £2.49 | 100 tablet | £74.95
    - Pramipexole (as Pramipexole dihydrochloride monohydrate) 350 microgram Mirapexin 0.35 mg tablet | 30 tablet | £44.97 DT price = £3.46 | 100 tablet | £149.90
  - Pramipexole (as Pramipexole dihydrochloride monohydrate) 700 microgram Mirapexin 0.7 mg tablet | 30 tablet | £89.94 DT price = £2.75 | 100 tablet | £299.82
  - Brands may include Oprymea

Modified-release tablet

CAUTIONARY AND ADVISORY LABELS 10, 25

- PRAMPIPEXOLE (Non-proprietary)
  - Pramipexole (as Pramipexole dihydrochloride monohydrate) 260 microgram Pramipexole 260 mg modified-release tablet | 30 tablet | £30.87–£32.49 DT price = £32.49
**Pramipexole (as Pramipexole dihydrochloride monohydrate)**

520 microgram Pramipexole 520 microgram modified-release tablets | 30 tablet [Boehringer Ingelheim Ltd] £61.73–£64.98 DT price = £64.98

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**Ropinirole**

**INDICATIONS AND DOSE**

Parkinson's disease, either used alone or as adjunct to co-beneldopa or co-careldopa

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

Adult: Initially 750 micrograms daily in 3 divided doses, then increased in steps of 750 micrograms daily, dose to be increased at weekly intervals, increased to 3 mg daily in 3 divided doses, then increased in steps of 1.5–3 mg daily, adjusted according to response, dose to be increased at weekly intervals; usual dose 4–6 mg daily divided doses, higher doses may be required if used with levodopa, when administered as adjunct to levodopa, concurrent dose of levodopa may be reduced by approx. 30%, if treatment interrupted for 1 day or more, consider re-initiation with immediate-release tablets

**Moderate to severe restless legs syndrome**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

Adult: Initially 250 micrograms once daily for 2 days, increased if tolerated to 500 micrograms once daily for 5 days, then increased if tolerated to 1 mg once daily for 7 days, then increased in steps of 500 micrograms daily, adjusted according to response, dose to be increased at weekly intervals; usual dose 2 mg once daily, doses to be taken at night, repeat dose titration if restarting after interval of more than a few days; maximum 4 mg per day

**Dose adjustments due to interactions**

Dose adjustment may be necessary if smoking started or stopped during treatment.

**UNLICENSED USE**

Doses in the BNF may differ from those in product literature.

**Important safety information**

**IMPULSE CONTROL DISORDERS**

Treatment with dopamine-receptor agonists is associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders. There is no evidence that ergot- and non-ergot-derived dopamine-receptor agonists differ in their propensity to cause impulse control disorders, so switching between dopamine-receptor agonists to control these side-effects is not recommended. If the patient develops an impulse control disorder, the dopamine-receptor agonist should be withdrawn or the dose reduced until the symptoms resolve.

**CAUTIONS**

Elderly • major psychiatric disorders • severe cardiovascular disease (risk of hypotension—monitor blood pressure)

**INTERACTIONS** → Appendix 1 (ropinirole).

**SIDE-EFFECTS**

**Common or very common** Abdominal pain • confusion • constipation • dizziness • dyskinesia • dyspepsia • fatigue • gastro-oesophageal reflux disease • hallucinations • hypotension • nausea • nervousness • peripheral oedema • sudden onset of sleep • syncope • vomiting

**Uncommon** Compulsive behaviour • psychosis

**Very rare** Hepatic disorders

**Frequency not known** Paradoxical worsening of restless legs syndrome

**PREGNANCY** Avoid unless potential benefit outweighs risk—toxicity in animal studies.

**BREAST FEEDING** May suppress lactation—avoid.

**HEPATIC IMPAIRMENT** Avoid—no information available.

**RENAL IMPAIRMENT** Avoid if eGFR less than 30 mL/minute/1.73 m².

**TREATMENT CESSATION** Anti-parkinsonian drug therapy should never be stopped abruptly as this carries a small risk of neuroleptic malignant syndrome.

**PATIENT AND CARER ADVICE**

**Sudden onset of sleep** Excessive daytime sleepiness and sudden onset of sleep can occur with dopamine-receptor agonists. Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of
sleep should refrain from driving or operating machines until these effects have stopped occurring. Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour. Hypotensive reactions Hypotensive reactions can occur in some patients taking dopamine-receptor agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery.

- **NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (June 2006) that rotigotine should be restricted for use in patients with a baseline score of 24 points or more on the International Restless Legs Scale.

- **MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, powder

### Tablet

**CAUTIONARY AND ADVISORY LABELS 10, 21**

#### Rotigotine (Non-proprietary)

- **Ropinirole** (as Ropinirole hydrochloride) 250 microgram [Ropinirole 250microgram tablets | 12 tablet (RoS) £4.13 DT price = £1.69
- **Ropinirole** (as Ropinirole hydrochloride) 500 microgram [Ropinirole 500microgram tablets | 28 tablet (RoS) £15.34 DT price = £2.12
- **Ropinirole** (as Ropinirole hydrochloride) 1 mg [Ropinirole 1mg tablets | 84 tablet (RoS) £49.81 DT price = £3.03
- **Ropinirole** (as Ropinirole hydrochloride) 2 mg [Ropinirole 2mg tablets | 28 tablet (RoS) £2.31→£2.62 DT price = £2.31 | 84 tablet (RoS) £33.35
- **Ropinirole** (as Ropinirole hydrochloride) 5 mg [Ropinirole 5mg tablets | 84 tablet (RoS) £175.60 DT price = £5.65
- **Adartrel** (GlaxoSmithKline UK Ltd)
- **Ropinirole** (as Ropinirole hydrochloride) 250 microgram [Adartrel 250microgram tablets | 12 tablet (RoS) £3.94 DT price = £1.69
- **Ropinirole** (as Ropinirole hydrochloride) 500 microgram [Adartrel 500microgram tablets | 28 tablet (RoS) £15.75 DT price = £2.12
- **Ropinirole** (as Ropinirole hydrochloride) 2 mg [Adartrel 2mg tablets | 28 tablet (RoS) £31.51 DT price = £2.31
- **Requip** (GlaxoSmithKline UK Ltd)
- **Ropinirole** (as Ropinirole hydrochloride) 250 microgram [Requip 250microgram tablets | 21 tablet (RoS) £5.70 | 42 tablet (RoS) no price available
- **Ropinirole** (as Ropinirole hydrochloride) 500 microgram [Requip 500microgram tablets | 42 tablet (RoS) no price available
- **Ropinirole** (as Ropinirole hydrochloride) 1 mg [Requip 1mg tablets | 21 tablet (RoS) no price available | 42 tablet (RoS) no price available | 84 tablet (RoS) £56.71 DT price = £3.03
- **Ropinirole** (as Ropinirole hydrochloride) 2 mg [Requip 2mg tablets | 63 tablet (RoS) no price available | 84 tablet (RoS) £113.44
- **Ropinirole** (as Ropinirole hydrochloride) 5 mg [Requip 5mg tablets | 84 tablet (RoS) £195.92 DT price = £5.65

#### Modified-release tablet

**CAUTIONARY AND ADVISORY LABELS 10, 25**

- **Requip XL** (GlaxoSmithKline UK Ltd)
- **Ropinirole** (as Ropinirole hydrochloride) 2 mg [Requip XL 2mg tablets | 28 tablet (RoS) £12.54 DT price = £2.12
- **Ropinirole** (as Ropinirole hydrochloride) 4 mg [Requip XL 4mg tablets | 28 tablet (RoS) £25.09 DT price = £25.09
- **Ropinirole** (as Ropinirole hydrochloride) 8 mg [Requip XL 8mg tablets | 28 tablet (RoS) £42.11 DT price = £12.11
- **Brands may include Aimpact XL; Epinix XL; Ralnea XL; Raponer XL; Repiniz XL; Spirico XL**

### Important safety information

#### IMPULSE CONTROL DISORDERS

Treatment with dopamine-receptor agonists is associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients and their carers should be informed about the risk of impulse control disorders. There is no evidence that ergot- and non-ergot-derived dopamine-receptor agonists differ in their propensity to cause impulse control disorders, so switching between dopamine-receptor agonists to control these side-effects is not recommended. If the patient develops an impulse control disorder, the dopamine-receptor agonist should be withdrawn or the dose reduced until the symptoms resolve.

#### CAUTIONS

Avoid exposure of patch to heat - remove patch (aluminium-containing) before magnetic resonance imaging or cardioversion.

#### INTERACTIONS

- Appendix 1 (rotigotine).

#### SIDE-EFFECTS

- **Common or very common** Abnormal behaviour - abnormal thinking - aggression - application site reactions - confusion - constipation - dizziness - drowsiness - dry mouth - dyskinesia - dysphoria - hallucinations - headache - hiccups - hypertension - malaise - nausea - palpitation - paroixia - peripheral oedema - postural hypotension - pruritis - psychosis - rash - sleep disturbances - sudden onset of sleep - sweating - syncope - vomiting - weight changes

- **Uncommon** Abdominal pain - atrial fibrillation - erectile dysfunction - hypotension - impulse control disorders - visual disturbances

- **Rare** Irritability - obsessive compulsive disorder - seizures - tachycardia

#### PREGNANCY

Avoid—no information available.

#### BREAST FEEDING

May suppress lactation; avoid—present in milk in animal studies.

#### HEPATIC IMPAIRMENT

Caution in severe impairment—no information available.

#### MONITORING REQUIREMENTS

Ophthalmic testing recommended.

#### TREATMENT CESSATION

Antiparkinsonian drug therapy should never be stopped abruptly as this carries a small risk of neuroleptic malignant syndrome.

#### DIRECTIONS FOR ADMINISTRATION

Apply patch to dry, non-irritated skin on torso, thigh, or upper arm, removing after 24 hours and siting replacement patch on a different area (avoid using the same area for 14 days).
PATIENT AND CARER ADVICE

Sudden onset of sleep Excessive daytime sleepiness and sudden onset of sleep can occur with dopamine-receptor agonists. Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring. Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication. Patients should be counselled on improving sleep behaviour.

Hypotensive reactions Hypotensive reactions can occur in some patients taking dopamine-receptor agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery.

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) Decisions The Scottish Medicines Consortium has advised that Neupro® is accepted for restricted use for the treatment of advanced Parkinson’s disease in combination with levodopa where the transdermal route would facilitate treatment (July 2007). The Scottish Medicines Consortium has advised that Neupro® is accepted as monotherapy for the treatment of early-stage idiopathic Parkinson’s disease (June 2007). The Scottish Medicines Consortium has advised (April 2009) that rotigotine (Neupro®) is accepted for restricted use within NHS Scotland for the symptomatic treatment of moderate to severe idiopathic restless legs syndrome in adults with a baseline score of 15 points or more on the International Restless Legs Scale.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Transdermal patch

| CAUTIONARY AND ADVISORY LABELS | 10 |
| Rotigotine 1 mg per 24 hour | Neupro 1mg/24hours transdermal patches | 28 patch | £7.44 |
| Rotigotine 2 mg per 24 hour | Neupro 2mg/24hours transdermal patches | 7 patch | £19.77 |
| Rotigotine 3 mg per 24 hour | Neupro 3mg/24hours transdermal patches | 28 patch | £102.35 |
| Rotigotine 4 mg per 24 hour | Neupro 4mg/24hours transdermal patches | 7 patch | £223.60 |
| Rotigotine 6 mg per 24 hour | Neupro 6mg/24hours transdermal patches | 28 patch | £149.93 |
| Rotigotine 8 mg per 24 hour | Neupro 8mg/24hours transdermal patches | 7 patch | £149.93 |

MONOAMINE-OXIDASE B INHIBITORS

Rasagiline

DRUG ACTION Rasagiline is a monoamine-oxidase B inhibitor.

INDICATIONS AND DOSE Parkinson’s disease, used alone or as adjunct to co- beneldopa or co-careldopa for ‘end-of-dose’ fluctuations by mouth

Adult: 1 mg daily

INTERACTIONS Appendix 1 (rasagiline).

SIDE-EFFECTS

Common or very common Abnormal dreams • angina • anorexia • arthralgia • conjunctivitis • constipation • depression • dry mouth • dyspepsia • flatulence • hallucinations • headache • influenza-like symptoms • leucopenia • rash • rhinitis • skin carcinoma • urinary urgency • vertigo • weight loss

Uncommon Cerebrovascular accident • myocardial infarction

PREGNANCY Use with caution.

BREAST FEEDING Use with caution—may suppress lactation.

HEPATIC IMPAIRMENT Use with caution in mild impairment. Avoid in moderate to severe impairment.

TREATMENT CESSATION Avoid abrupt withdrawal.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

Tablet

Azilect (Teva UK Ltd)

Rasagiline (as Rasagiline mesilate) 1 mg Azilect 1mg tablets | 28 tablet | £70.72 DT price = £70.72

Selegiline hydrochloride

DRUG ACTION Selegiline is a monoamine-oxidase-B inhibitor.

INDICATIONS AND DOSE Parkinson’s disease, used alone or as adjunct to co- beneldopa or co-careldopa to reduce ‘end of dose’ deterioration | Symptomatic Parkinsonism by mouth using immediate-release medicines

Adult: Initially 5 mg once daily for 2–4 weeks, then increased if tolerated to 10 mg daily, dose to be taken in the morning

BY MOUTH USING ORAL LYPHILISATE

Adult: 1.25 mg once daily, dose to be taken before breakfast

Dose equivalence and conversion

1.25–mg oral lyphilisate is equivalent to 10-mg tablet.

Patients receiving 10 mg conventional selegiline hydrochloride tablets can be switched to oral lyphilisates (Zelapar®) 1.25 mg.

CONTRA-INDICATIONS Active duodenal ulceration • active gastric ulceration • avoid or use with great caution in postural hypotension (when used in combination with levodopa)

CAUTIONS Angina • arrhythmias • avoid in Acute porphyrias p. 864 • duodenal ulceration • gastric ulceration • history of hepatic dysfunction • patients predisposed to confusion and psychosis • psychosis • uncontrolled hypertension

INTERACTIONS Appendix 1 (selegiline). Avoid with drugs that increase blood pressure.

SIDE-EFFECTS

Common or very common Arthralgia • bradycardia • confusion • constipation • depression • diarrhoea • dizziness • dry mouth • fatigue • hair loss • headache • hypertension • hypotension • impaired balance • mouth ulcers • movement disorders • muscle cramps • myalgia • myopathy • nasal congestion • nausea • psychosis • sleeping disorders • stomatitis • sweating • tremor

Uncommon Agitation • angina • ankle oedema • anxiety • arrhythmias • blurred vision • dyspnoea • leucocytopenia • loss of appetite • micturition difficulties • palpitation • postural hypotension • skin reactions • supraventricular tachycardia • thrombocytopenia

Frequency not known Hypersexuality
Nausea and labyrinth disorders

Nausea and labyrinth disorders

Antiemetics should be prescribed only when the cause of vomiting is known because otherwise they may delay diagnosis, particularly in children. Antiemetics are unnecessary and sometimes harmful when the cause can be treated, such as in diabetic ketoacidosis, or in digoxin p. 94 or antiepileptic overdose.

If antiemetic drug treatment is indicated, the drug is chosen according to the aetiology of vomiting. Antihistamines are effective against nausea and vomiting resulting from many underlying conditions. There is no evidence that any one antihistamine is superior to another but their duration of action and incidence of adverse effects (drowsiness and antimuscarinic effects) differ.

The phenothiazines are dopamine antagonists and act centrally by blocking the chemoreceptor trigger zone. They are of considerable value for the prophylaxis and treatment of nausea and vomiting associated with diffuse neoplastic disease, radiation sickness, and the emesis caused by drugs such as opioids, general anaesthetics, and cytotoxics. Prochlorperazine p. 309, perphenazine p. 308, and trifluoperazine p. 310 are less sedating than chlorpromazine hydrochloride p. 304; severe dystonic reactions sometimes occur with phenothiazines, especially in children. Some phenothiazines are available as rectal suppositories, which can be useful in patients with persistent vomiting or with severe nausea; prochlorperazine p. 309 can also be administered as a buccal tablet which is placed between the upper lip and the gum.

Other antipsychotic drugs including haloperidol p. 306 and levomepromazine p. 345 are used for the relief of nausea and vomiting in terminal illness. Metoclopramide hydrochloride p. 347 is an effective antiemetic and its activity closely resembles that of the phenothiazines. Metoclopramide hydrochloride also acts directly on the gastro-intestinal tract and it may be superior to the phenothiazines for emesis associated with gastroduodenal, hepatic, and biliary disease.

Dopaminedone p. 346 acts at the chemoreceptor trigger zone; it is licensed only for the relief of nausea and vomiting. It has the advantage over metoclopramide hydrochloride and the phenothiazines of being less likely to cause central effects such as sedation and dystonic reactions because it does not readily cross the blood–brain barrier. In Parkinson’s disease, it can be used to treat nausea caused by dopaminergic drugs.

Granisetron p. 348 and ondansetron p. 349 are of value in the management of nausea and vomiting in patients receiving cytotoxics and in postoperative nausea and vomiting. Palonosetron p. 350 is licensed for prevention of nausea and vomiting associated with moderately or highly emetogenic cytotoxic chemotherapy.

Dexamethasone p. 581 has antiemetic effects and it is used in vomiting associated with cancer chemotherapy. It can be used alone or with metoclopramide hydrochloride, prochlorperazine p. 309, lorazepam p. 412, or a 5HT₃-receptor antagonist.

Aprepitant p. 351 and fosaprepitant p. 351 are neurokinin 1-receptor antagonists licensed for the prevention of acute and delayed nausea and vomiting associated with cisplatin-based cytotoxic chemotherapy; they are given with dexamethasone p. 581 and a 5HT₃-receptor antagonist.

Nabilone p. 346 is a synthetic cannabinoid with antiemetic properties. It may be used for nausea and vomiting caused by cytotoxic chemotherapy that is unresponsive to conventional antiemetics.

Vomiting during pregnancy

Nausea in the first trimester of pregnancy is generally mild and does not require drug therapy. On rare occasions if vomiting is severe, short-term treatment with an antihistamine, such as promethazine, may be required. Prochlorperazine p. 309 or metoclopramide hydrochloride p. 347 are alternatives. If symptoms do not settle in 24 to 48 hours then specialist opinion should be sought.

Hyperemesis gravidarum is a more serious condition, which requires regular antihistamine therapy, intravenous fluid and electrolyte replacement and sometimes nutritional support. Supplementation with thiamine p. 882 must be considered in order to reduce the risk of Wernicke’s encephalopathy.

Postoperative nausea and vomiting

The incidence of postoperative nausea and vomiting depends on many factors including the anaesthetic used,
Nervous system

Less sedating antihistamine such as cyclizine p. generally better tolerated than hyoscine. If a sedative effect is required, and associated with migraine.

Antiemetics have a role in the management of nausea and vomiting induced by cytotoxic chemotherapy, in palliative care, and during postoperative use of opioids. Therapy to prevent postoperative nausea and vomiting should be based on the assessed risk of postoperative nausea and vomiting in each patient. Drugs used include 5HT3-receptor antagonists, droperidol p. 345, dexamethasone p. 581, some phenothiazines (e.g. prochlorperazine p. 309), and antihistamines (e.g. cyclizine p. 343). A combination of two or more antiemetic drugs that have different mechanisms of action is often indicated in those at high risk of postoperative nausea and vomiting or where postoperative vomiting presents a particular danger (e.g. in some types of surgery). When a prophylactic antiemetic drug has failed, postoperative nausea and vomiting should be treated with one or more drugs from a different class.

Motion sickness

Antiemetics should be given to prevent motion sickness rather than after nausea or vomiting develop. The most effective drug for the prevention of motion sickness is hyoscine hydrobromide p. 344. The sedating antihistamines are slightly less effective against motion sickness, but are generally better tolerated than hyoscine. If a sedative effect is desired promethazine is useful, but generally a slightly less sedating antihistamine such as cyclizine p. 343 or cinnarizine below is preferred. Domperidone p. 346, metoclopramide hydrochloride p. 347, 5HT3-receptor antagonists, and the phenothiazines (except the antihistamine phenothiazine promethazine) are ineffective in motion sickness.

Other vestibular disorders

Management of vestibular diseases is aimed at treating the underlying cause as well as treating symptoms of the balance disturbance and associated nausea and vomiting. Vertigo and nausea associated with Ménière’s disease and middle-ear surgery can be difficult to treat.

Betahistine dihydrochloride p. 352 is an analogue of histamine and is claimed to reduce endolymphatic pressure by improving the microcirculation. Betahistine dihydrochloride is licensed for vertigo, tinnitus, and hearing loss associated with Ménière’s disease.

A diuretic alone or combined with salt restriction may provide some benefit in vertigo associated with Ménière’s disease; antihistamines (such as cinnarizine below), and phenothiazines (such as prochlorperazine p. 309) are also used. Where possible, prochlorperazine should be reserved for the treatment of acute symptoms.

Cytotoxic chemotherapy, palliative care, and migraine

Antiemetics have a role in the management of nausea and vomiting induced by cytotoxic chemotherapy, in palliative care, and associated with migraine.

Drugs used for Nausea and labyrinth disorders not listed below; Chlorpromazine hydrochloride, p. 304 · Haloperidol, p. 306 · Lorazepam, p. 412 · Perphenazine, p. 308 · Prochlorperazine, p. 309 · Promethazine hydrochloride, p. 251 · Promazine teoclante, p. 252 · Trifluoperazine, p. 310
Cinnarizine with dimenhydrinate

The properties listed below are those particular to the combination only. For the properties of the components please consider, cinnarizine.

**INDICATIONS AND DOSE**

**Vertigo**

**BY MOUTH**

- Adult: 1 tablet 3 times a day

**BY RECTUM**

**Nausea and vomiting associated with palliative care**

**BY SUBCUTANEOUS INFUSION**

- Adult: 150 mg, dose to be given over 24 hours

**BY MOUTH**

- Adult: 50 mg up to 3 times a day

**UNLICENSED USE**


**CONTRA-INDICATIONS**

Avoid in Acute porphyrias p. 864 (some antihistamines are thought to be safe) - neonate (due to significant antimuscarinic activity) (in neonates)

**CAUTIONS**

Epilepsy - glaucoma - may counteract haemodynamic benefits of opioids - neuromuscular disorders - increased risk of transient paralysis with intravenous use - prostatic hypertrophy (in adults) - pyloroduodenal obstruction - severe heart failure - may cause fall in cardiac output and associated increase in heart rate, mean arterial pressure and pulmonary wedge pressure - susceptibility to angle-closure glaucoma - urinary retention

**INTERACTIONS**

Appendix 1 (antihistamines).

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- Common or very common Drowsiness

- Rare Anaphylaxis - angioedema - angle-closure glaucoma - arrhythmias - blood disorders - bronchospasm - confusion - convulsions - depression - dizziness - extrapyramidal effects - hypersensitivity reactions - hypotension - liver dysfunction - palpitation - paradoxical stimulation (especially with high doses in children) (in children) - paradoxical stimulation (especially with high doses in the elderly) (in adults) - photosensitivity reactions - rashes - sleep disturbances - tremor


**SPECIFIC SIDE-EFFECTS**

- Rare

- With intravenous use transient paralysis

- Frequency not known

- With subcutaneous use local irritation

**SIDE-EFFECTS, FURTHER INFORMATION**

Children and the elderly are more susceptible to side-effects. Drowsiness is a significant side-effect with most of the older antihistamines although paradoxical stimulation may occur rarely, especially with high doses or in children and the elderly. Drowsiness may diminish after a few days of treatment and is considerably less of a problem with the newer antihistamines.

**PREGNANCY**

Manufacturer advises avoid; however, there is no evidence of teratogenicity. The use of sedating antihistamines in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor.

**BREAST FEEDING**

No information available. Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

**HEPATIC IMPAIRMENT**

Avoid in severe liver disease—increased risk of coma

**DIRECTIONS FOR ADMINISTRATION**

For administration by mouth, tablets may be crushed. Mixing and compatibility for the use of syringe drivers in palliative care Cyclicine may precipitate at concentrations above 10 mg/mL or in the presence of sodium chloride 0.9%
ANTIMUSCARINICS

Hyoscine hydrobromide (Scopolamine hydrobromide)
The properties listed below are those particular to the drug only. For properties common to the class, see Antimuscarinics, Systemic, p. 668.

INDICATIONS AND DOSE
Motion sickness
BY MOUTH
- Child 4–9 years: 75–150 micrograms, dose to be taken up to 30 minutes before the start of journey, then 75–150 micrograms every 6 hours if required; maximum 450 micrograms per day
- Child 10–17 years: 150–300 micrograms, dose to be taken up to 30 minutes before the start of journey, then 150–300 micrograms every 6 hours if required; maximum 900 micrograms per day
- Adult: 150–300 micrograms, dose to be taken up to 30 minutes before the start of journey, then 150–300 micrograms every 6 hours if required; maximum 900 micrograms per day

BY TRANSDERMAL APPLICATION
- Child 10–17 years: Apply 1 patch, apply behind ear 5–6 hours before journey, then apply 1 patch after 72 hours if required, remove old patch and site replacement patch behind the other ear
- Adult: Apply 1 patch, apply behind ear 5–6 hours before journey, then apply 1 patch after 72 hours if required, remove old patch and site replacement patch behind the other ear

Hypersalivation associated with clozapine therapy
BY MOUTH
- Adult: 300 micrograms up to 3 times a day; maximum 900 micrograms per day

Excessive respiratory secretion (in palliative care)
BY SUBCUTANEOUS INJECTION
- Adult: 400 micrograms every 4 hours as required, hourly use is occasionally necessary, particularly in excessive respiratory secretions

BY CONTINUOUS SUBCUTANEOUS INFUSION
- Adult: 1.2–2 mg/24 hours

Bowel colic in palliative care
BY SUBCUTANEOUS INJECTION
- Adult: 400 micrograms every 4 hours as required, hourly use is occasionally necessary

BY SUBCUTANEOUS INFUSION
- Adult: 1.2–2 mg/24 hours

or as the concentration of diamorphine relative to cyclizine increases; mixtures of diamorphine and cyclizine are also likely to precipitate after 24 hours.

- **PATIENT AND CARER ADVICE** Drowsiness may affect performance of skilled tasks (e.g. cycling, driving); effects of alcohol enhanced.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: suppository, oral suspension, oral solution

  **Tablet**
  CAUTIONARY AND ADVISORY LABELS 2
  CYCLIZINE (Non-proprietary)
  Cyclizine hydrochloride 50 mg Cyclizine 50mg tablets | 100 tablet £13.64 DT price = £10.97

  **Solution for injection**
  CYCLIZINE (Non-proprietary)
  Cyclizine lactate 50 mg per 1 ml Cyclizine 50mg/1ml solution for injection ampoules | 5 ampoule £8.65 DT price = £8.65

**ANTIMUSCARINICS**

Hyoscine hydrobromide

**INDICATIONS AND DOSE**

**Motion sickness**

**BY MOUTH**
- Child 4–9 years: 75–150 micrograms, dose to be taken up to 30 minutes before the start of journey, then 75–150 micrograms every 6 hours if required; maximum 450 micrograms per day
- Child 10–17 years: 150–300 micrograms, dose to be taken up to 30 minutes before the start of journey, then 150–300 micrograms every 6 hours if required; maximum 900 micrograms per day
- Adult: 150–300 micrograms, dose to be taken up to 30 minutes before the start of journey, then 150–300 micrograms every 6 hours if required; maximum 900 micrograms per day

**BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION**
- Adult: 200–600 micrograms, to be administered 30–60 minutes before induction of anaesthesia

Bowel colic pain in palliative care

**BY MOUTH**
- Adult: 300 micrograms 3 times a day, Sublingually as Kwells®

Premedication

**BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION**
- Adult: 200–600 micrograms, to be administered 30–60 minutes before induction of anaesthesia

**UNLICENSED USE**
- In children Not licensed for use in excessive respiratory secretions or hypersalivation associated with clozapine therapy.

**Important safety information**
Antimuscarinic drugs used for premedication to general anaesthesia should only be administered by, or under the direct supervision of, personnel experienced in their use.

**CAUTIONS**

**Epilepsy**

**CAUTIONS, FURTHER INFORMATION**

**Anticholinergic syndrome** In some patients, especially children and the elderly, hyoscine may cause the central anticholinergic syndrome (excitement, ataxia, hallucinations, behavioural abnormalities, and drowsiness).

- **PREGNANCY** Use only if potential benefit outweighs risk. Injection may depress neonatal respiration.

- **BREAST FEEDING** Amount too small to be harmful.

- **HEPATIC IMPAIRMENT** Use with caution.

- **RENAL IMPAIRMENT** Use with caution.

**DIRECTIONS FOR ADMINISTRATION**
- With topical use *Patch* applied to hairless area of skin behind ear; if less than whole patch required *either* cut with scissors along full thickness ensuring membrane is not peeled away or cover portion to prevent contact with skin.
- With oral use in children For administration by *mouth*, injection solution may be given orally.

**PRESCRIBING AND DISPENSING INFORMATION** Flavours of chewable tablet formulations may include raspberry.

**PATIENT AND CARER ADVICE**
- With transdermal use Explain accompanying instructions to patient and in particular emphasise advice to wash hands after handling and to wash application site after removing, and to use one patch at a time.

**Driving and skilled tasks**
- With transdermal use Drowsiness may persist for up to 24 hours or longer after removal of patch; effects of alcohol enhanced.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops, oral suspension, oral solution

**Tablet**

CAUTIONARY AND ADVISORY LABELS 2
- **HYOSCINE HYDROBROMIDE (Non-proprietary)**
  Hyoscine hydrobromide 300 microgram Hyoscine hydrobromide 300microgram tablets | 12 tablet £1.67
  Kwell (Bayer Plc)
  Hyoscine hydrobromide 150 microgram Kwells Kids 150microgram tablets | 12 tablet £1.67
  Orbelle hydrobromide 300 microgram Kwells 300microgram tablets | 12 tablet £1.67
  Brands may include Travel Calm
Chewable tablet
CAUTIONARY AND ADVISORY LABELS 2, 24
- Joy-Rides (Forest Laboratories UK Ltd)
Droperidol 150 microgram chewable tablets (sugar-free) | 12 tablet | £1.55

Solution for injection
- HYOSCINE HYDROBROMIDE (Non-proprietary)
Hyoscine hydrobromide 400 microgram per 1 ml | 10 ampoule | £31.06–£31.29 DT price = £31.29

Transdermal patch
CAUTIONARY AND ADVISORY LABELS 19
- Scopoderm (Novartis Consumer Health UK Ltd)
Hyoscine 1 mg per 72 hour | 2 patch | £4.52 DT price = £4.52

ANTIPSYCHOTICS (FIRST-GENERATION)
Droperidol
The properties listed below are those particular to the drug only. For properties common to the class, see Antipsychotics, p. 303.
- DRUG ACTION Droperidol is a butyrophenone, structurally related to haloperidol, which blocks dopamine receptors in the chemoreceptor trigger zone.

INDICATIONS AND DOSE
Prevention and treatment of postoperative nausea and vomiting
BY INTRAVENOUS INJECTION
- Adult: 0.625–1.25 mg, dose to be given 30 minutes before end of surgery, then 0.625–1.25 mg every 6 hours as required
- Elderly: 625 micrograms, dose to be given every 30 minutes before end of surgery, then 625 micrograms every 6 hours as required

Prevention of nausea and vomiting caused by opioid analgesics in postoperative patient controlled analgesia (PCA)
BY INTRAVENOUS INJECTION
- Adult: 15–50 micrograms of droperidol for every 1 mg of morphine in PCA, reduce dose in elderly; maximum 5 mg per day

- CONTRA-INDICATIONS Bradycardia - CNS depression - comatose states - hypokalaemia - hypomagnesaemia - phaeochromocytoma - QT-interval prolongation
- CAUTIONS Chronic obstructive pulmonary disease - electrolyte disturbances - history of alcohol abuse - respiratory failure
- INTERACTIONS Appendix 1 (droperidol). Avoid concomitant administration of drugs that prolong QT interval.
- SIDE-EFFECTS Anxiety - cardiac arrest - hallucinations - inappropriate antiidiuretic hormone secretion
- PREGNANCY Extrapyramidal effects and withdrawal syndrome have been reported occasionally in the neonate when antipsychotic drugs are taken during the third trimester of pregnancy. Following maternal use of antipsychotic drugs in the third trimester, neonates should be monitored for symptoms including agitation, hypertonia, hypotonia, tremor, drowsiness, feeding problems, and respiratory distress.
- BREAST FEEDING Limited information available—avoid repeated administration.
- HEPATIC IMPAIRMENT In postoperative nausea and vomiting, max. 625 micrograms repeated every 6 hours as required. For nausea and vomiting caused by opioid analgesics in postoperative patient-controlled analgesia, reduce dose.

- RENAL IMPAIRMENT In postoperative nausea and vomiting, max. 625 micrograms repeated every 6 hours as required. For nausea and vomiting caused by opioid analgesics in postoperative patient-controlled analgesia, reduce dose.
- MONITORING REQUIREMENTS Continuous pulse oximetry required if risk of ventricular arrhythmia—continue for 30 minutes following administration.
- MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension, capsule
Solution for injection
- Xomolix (ProStrakan Ltd)
Droperidol 2.5 mg per 1 ml | 10 ampoule | £39.40

Levomepromazine
(Methotrimeprazine)
The properties listed below are those particular to the drug only. For properties common to the class, see Antipsychotics, p. 303.

INDICATIONS AND DOSE
Pain in palliative care (reserved for distressed patients with severe pain unresponsive to other measures)
BY CONTINUOUS SUBCUTANEOUS INFUSION OR BY INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INJECTION
- Adult: Seek specialist advice
Restlessness and confusion in palliative care
BY CONTINUOUS SUBCUTANEOUS INFUSION
- Child 1-11 years: 0.35–3 mg/kg, to be administered over 24 hours
- Child 12-17 years: 12.5–200 mg, to be administered over 24 hours
BY MOUTH
- Adult: 6 mg every 2 hours as required
BY SUBCUTANEOUS INJECTION
- Adult: 6.25 mg every 2 hours as required
BY SUBCUTANEOUS INFUSION
- Adult: Initially 12.5–50 mg/24 hours, titrated according to response (doses greater than 100 mg/24 hours should be given under specialist supervision)

Nausea and vomiting in palliative care
BY CONTINUOUS INTRAVENOUS INFUSION OR BY SUBCUTANEOUS INFUSION
- Child 1 month-11 years: 100–400 micrograms/kg, to be administered over 24 hours
- Child 12-17 years: 5–25 mg, to be administered over 24 hours
BY MOUTH
- Adult: 6 mg once daily, dose to be taken at bedtime, increased if necessary to 12.5–25 mg twice daily
BY SUBCUTANEOUS INFUSION
- Adult: 6.25 mg once daily, dose to be given at bedtime, increased if necessary to 12.5–25 mg twice daily
BY SUBCUTANEOUS INFUSION
- Adult: 5–25 mg/24 hours, sedation can limit the dose
Schizophrenia
BY MOUTH
- Adult: Initially 25–50 mg daily in divided doses, dose can be increased as necessary
BY SUBCUTANEOUS INFUSION
- Adult: 5–25 mg/24 hours, sedation can limit the dose

Schizophrenia (bed patients)
BY MOUTH
- Adult: Initially 100–200 mg daily in 3 divided doses, increased if necessary to 1 g daily
RISK OF POSTURAL HYPOTENSION; NOT RECOMMENDED FOR AMBULANT PATIENTS OVER 50 YEARS UNLESS RISK OF HYPTENSIVE REACTION ASSESSED.

SIDE-EFFECTS

RAISED ERYTHROCYTE SEDIMENTATION RATE

PREGNANCY

EXTRAPYRAMIDAL EFFECTS AND WITHDRAWAL SYNDROME HAVE BEEN REPORTED OCCASIONALLY IN THE NEONATE WHEN ANTIPSYCHOTIC DRUGS ARE TAKEN DURING THE THIRD TRIMESTER OF PREGNANCY. FOLLOWING MATERNAL USE OF ANTIPSYCHOTIC DRUGS IN THE THIRD TRIMESTER, NEONATES SHOULD BE MONITORED FOR SYMPTOMS INCLUDING AGITATION, HYPTONIA, HYPOTONIA, TREMOR, DROWSINESS, FEEDING PROBLEMS, AND RESPIRATORY DISTRESS.

BREAST FEEDING

THERE IS LIMITED INFORMATION AVAILABLE ON THE SHORT- AND LONG-TERM EFFECTS OF ANTIPSYCHOTIC DRUGS ON THE BREAST-FED INFANT. ANIMAL STUDIES INDICATE POSSIBLE ADVERSE EFFECTS OF ANTIPSYCHOTIC MEDICINES ON THE DEVELOPING NERVOUS SYSTEM. CHRONIC TREATMENT WITH ANTIPSYCHOTIC DRUGS Whilst BREAST-FEEDING SHOULD BE AVOIDED UNLESS ABSOLUTELY NECESSARY. PHENOTHIAZINE DERIVATIVES ARE SOMETIMES USED IN BREAST-FEEDING WOMEN FOR SHORT-TERM TREATMENT OF NAUSEA AND VOMITING.

HEPATIC IMPAIRMENT

CAN PRECIPITATE COMA; PHENOThIAZINES ARE HEPATOTOXIC.

RENAL IMPAIRMENT

START WITH SMALL DOSES IN SEVERE RENAL IMPAIRMENT BECAUSE OF INCREASED CEREBRAL SENSITIVITY.

DIRECTIONS FOR ADMINISTRATION

WITH SUBCUTANEOUS USE IN CHILDREN FOR ADMINISTRATION BY SUBCUTANEOUS INFUSION DILUTE WITH A SUITABLE VOLUME OF SODIUM CHLORIDE 0.9%.

MEDICINAL FORMS

THERE CAN BE VARIATION IN THE LICENSING OF DIFFERENT MEDICINES CONTAINING THE SAME DRUG. FORMS AVAILABLE FROM SPECIAL-ORDER MANUFACTURERS INCLUDE: ORAL SOLUTION, ORAL SUSPENSION

Tablet

CAUTIONARY AND ADVISORY LABELS 2

Levomepromazine maleate 6 mg | 28 tablet (PO) no price available

Nozinan (Sanofi)

Levomepromazine maleate 25 mg | 84 tablet (PO) £20.26 DT price = £20.26

Solution for injection

LEVOMEPROMAZINE (NON-PROPRIETARY)

Levomepromazine hydrochloride 25 mg/1 ml | 10 ampoule (PO) £20.13 DT price = £20.13

Nozinan (Sanofi)

Levomepromazine hydrochloride 25 mg/1 ml | 10 ampoule (PO) £20.13 DT price = £20.13

CANNABINOIDS

Nabilone

INDICATIONS AND DOSE

NAUSEA AND VOMITING CAUSED BY CYTOXIC CHEMOTHERAPY, UNRESPONSIVE TO CONVENTIONAL ANTIEMETICS (PREFERABLY IN HOSPITAL SETTING) (UNDER CLOSE MEDICAL SUPERVISION) BY MOUTH

Adult: Initially 1 mg twice daily, increased if necessary to 2 mg twice daily throughout each cycle of cytotoxic therapy and, if necessary, for 48 hours after the last dose of each cycle, the first dose should be taken the night before initiation of cytotoxic treatment and the second dose 1–3 hours before the first dose of

CYTOXIC DRUG, DAILY DOSE MAXIMUM SHOULD BE GIVEN IN 3 DIVIDED DOSES; MAXIMUM 6 MG PER DAY

CAUTIONS

ADVERSE EFFECTS ON MENTAL STATE CAN PERSIST FOR 48–72 HOURS AFTER STOPPING. ELDERLY, HEART DISEASE, HISTORY OF PSYCHIATRIC DISORDER, HYPTENSION

SIDE-EFFECTS

COMMON OR VERY COMMON Ataxia, concentration difficulties, drowsiness, dry mouth, dysthria, euphoria, headache, hypotension, nausea, sleep disturbance, vertigo, visual disturbance

FREQUENCY NOT KNOWN Abdominal pain, confusion, decreased appetite, decreased coordination, depression, disorientation, hallucinations, psychosis, tachycardia, tremors

SIDE-EFFECTS, FURTHER INFORMATION

DROWSINESS AND DIZZINESS OCCUR FREQUENTLY WITH STANDARD DOSES.

PREGNANCY

AVOID UNLESS ESSENTIAL.

BREAST FEEDING

AVOID—NO INFORMATION AVAILABLE.

HEPATIC IMPAIRMENT

AVOID IN SEVERE IMPAIRMENT.

PATIENT AND CARER ADVICE

DROWSINESS MAY AFFECT PERFORMANCE OF SKILLED TASKS (E.G. DRIVING). EFFECTS OF ALCOHOL ENHANCED.

For information on 2015 Legislation regarding driving whilst taking certain controlled drugs, including nabilone, see Drugs and driving under Guidance on prescribing p. 1. Behavioural effects Patients should be made aware of possible changes of mood and other adverse behavioural effects.

MEDIcINAL FORMS

THERE CAN BE VARIATION IN THE LICENSING OF DIFFERENT MEDICINES CONTAINING THE SAME DRUG. FORMS AVAILABLE FROM SPECIAL-ORDER MANUFACTURERS INCLUDE: CAPSULE

Capsule

CAUTIONARY AND ADVISORY LABELS 2

Nabilone 250 microgram Nabilone 250 microgram capsules | 20 capsule (PO) £96.11 Schedule 2 (CD)

Nabilone 1 mg Nabilone 1 mg capsules | 20 capsule (PO) £125.84 Schedule 2 (CD)

DOPAMINE RECEPTOR ANTAGONISTS

Domperidone

INDICATIONS AND DOSE

RELIEF OF NAUSEA AND VOMITING BY MOUTH

Child (body-weight up to 35 kg): 250 micrograms/kg up to 3 times a day; maximum 750 micrograms/kg per day

Child 12–17 years (body-weight 35 kg and above): 10 mg up to 3 times a day; maximum 30 mg per day

Adult (body-weight 35 kg and above): 10 mg up to 3 times a day; maximum 30 mg per day

Gastro-intestinal pain in palliative care

BY MOUTH

Adult: 10 mg 3 times a day, before meals

UNLICENSED USE

NOT LICENSED FOR USE IN CHILDREN FOR GASTRO-OESOPHAGEAL REFUX DISEASE.
duration of treatment have been made, and new contra-
indications added:  
- Domperidone should only be used for the relief of the 
symptoms of nausea and vomiting;  
- Domperidone should be used at the lowest effective
dose for the shortest possible duration (max. 
treatment duration should not normally exceed 1 
week);  
- Domperidone is contra-indicated for use in conditions
where cardiac conduction is, or could be, impaired, or 
where there is underlying cardiac disease, when 
administered concomitantly with drugs that prolong
the QT interval or potent CYP3A4 inhibitors, and in 
severe hepatic impairment;  
- The recommended dose in adults and adolescents
over 12 years and over 35 kg is 10 mg up to 3 times
daily;  
- The recommended dose in children under 35 kg is 
250 micrograms/kg up to 3 times daily;  
- Oral liquid formulations should be given via an
appropriately designed, graduated oral syringe to 
ensure dose accuracy. 
This advice does not apply to unlicensed uses of
domperidone (e.g. palliative care).  
- CONTRA-INDICATIONS Cardiac disease • conditions 
where cardiac conduction is, or could be, impaired (in adults) • 
gastro-intestinal haemorrhage (in children) • if increased 
gastrointestinal motility harmful (in adults) • mechanical 
obstruction (in children) • mechanical perforation (in 
children) • predisposition to cardiac conduction disorders
(in children) • prolactinoma  
- CAUTIONS Children • if there are cardiac concerns, obtain
ECG before and during treatment (in children) • patients 
on over 60 years—increased risk of ventricular arrhythmia (in adults)  
- INTERACTIONS → Appendix 1 (domperidone). 
Contra-indicated with concomitant use of drugs that 
prolong the QT interval. Contra-indicated with concomitant use of potent CYP3A4 
inhibitors.  
- SIDE-EFFECTS  
- Common or very common Drowsiness • dry mouth • malaise  
- Uncommon Anxiety • breast pain • decreased libido • 
diarhoea • galactorrhoea • headache • pruritus • rash  
- Frequency not known Agitation • amenorrhoea • 
convulsions • extrapyramidal disorders • gynaecomastia • 
nervousness • oculogyric crisis • QT-interval prolongation • 
sudden cardiac death • urinary retention • ventricular
arrhythmias  
- PREGNANCY Use only if potential benefit outweighs risk.  
- BREAST FEEDING Amount too small to be harmful.  
- HEPATIC IMPAIRMENT Avoid in moderate or severe 
impairment.  
- RENAL IMPAIRMENT Reduce frequency.  
- PATIENT AND CARER ADVICE 
Arrhythmia Patients and their carers should be told how 
to recognise signs of arrhythmia and advised to seek medical 
attention if symptoms such as palpitation or syncope 
develop. 
Medicines for Children leaflet: Domperidone for gastro-
oesophageal reflux www.medicinesforchildren.org.uk/
domperidone-for-gastro-oesophageal-reflux  
- MEDICINAL FORMS 
There can be variation in the licensing of different medicines
containing the same drug. Forms available from special-order
manufacturers include: solution for injection, oral suspension, 
suppository

Tablet 
CAUTIONARY AND ADVISORY LABELS 22  
- DOMPERIDONE (Non-proprietary) ▼ 
| Domperidone (as Domperidone maleate) 10 mg | Domperidone 10mg tablets | 30 tablet (P) £2.71 DT price = £1.75 | 100 tablet (P) £9.04 DT price = £5.83  
- Motilium (Zentiva) ▼ 
| Domperidone (as Domperidone maleate) 10 mg | Motilium 10mg tablets | 30 tablet (P) £2.71 DT price = £1.75 | 100 tablet (P) £9.04 DT price = £5.83  
- Oral suspension 
CAUTIONARY AND ADVISORY LABELS 22  
- DOMPERIDONE (Non-proprietary) ▼ 
| Domperidone 1 mg per 1 ml | Domperidone 5mg/5ml oral suspension sugar free (sugar-free) | 200 ml (P) £13.43 DT price = £13.43

Metoclopramide hydrochloride

INDICATIONS AND DOSE 
Symptomatic treatment of nausea and vomiting including 
that associated with acute migraine | Delayed (but not 
acute) chemotherapy-induced nausea and vomiting | 
Radiotherapy-induced nausea and vomiting | Prevention of 
postoperative nausea and vomiting  
BY MOUTH OR BY INTRAMUSCULAR INJECTION OR BY SLOW 
INTRAVENOUS INJECTION  
- Adult (body-weight up to 60 kg): Up to 500 micrograms/kg 
daily in 3 divided doses, when administered by slow 
intravenous injection, to be given over at least 3 
minutes  
- Adult (body-weight 60 kg and above): 10 mg up to 3 times 
a day, when administered by slow intravenous 
injection, to be given over at least 3 minutes  

Hiccups in palliative care  
BY MOUTH OR BY INTRAMUSCULAR INJECTION OR BY 
SUBLATEOUS INJECTION  
- Adult: 10 mg every 6–8 hours  
Nausea and vomiting in palliative care  
BY MOUTH  
- Adult: 10 mg 3 times a day  
BY SUBCUTANEOUS INJECTION  
- Adult: 30–100 mg/24 hours

Important safety information  
MHRA/CHM ADVICE—METOCLOPRAMIDE: RISK OF 
NEUROLOGICAL ADVERSE EFFECTS—RESTRICTED DOSE AND 
DURATION OF USE (AUGUST 2013) 
The benefits and risks of metoclopramide have been 
reviewed by the European Medicines Agency’s 
Committee on Medicinal Products for Human Use, 
which concluded that the risk of neurological effects 
such as extrapyramidal disorders and tardive dyskinesia 
outweigh the benefits in long-term or high-dose 
treatment. To help minimise the risk of potentially 
serious neurological adverse effects, the following 
restrictions to indications, dose, and duration of use 
have been made:  
- In adults over 18 years, metoclopramide should only 
be used for prevention of postoperative nausea and 
vomiting, radiotherapy-induced nausea and vomiting, 
delayed (but not acute) chemotherapy-induced 
nausea and vomiting, and symptomatic treatment of 
nausea and vomiting, including that associated with 
acute migraine (where it may also be used to improve 
absorption of oral analgesics);  
- Metoclopramide should only be prescribed for short-
term use (up to 5 days);  
- Usual dose is 10 mg, repeated up to 3 times daily; 
max. daily dose is 500 micrograms/kg;
Nervous system

MEDICINAL FORMS

DIRECTIONS FOR ADMINISTRATION

RENAL IMPAIRMENT

BREAST FEEDING

PREGNANCY

INTERACTIONS ➔ Appendix 1 (metoclopramide).

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

Specific side-effects

Very rare

With intravenous use cardiac conduction abnormalities

SIDE-EFFECTS, FURTHER INFORMATION

Metoclopramide can induce acute dystonic reactions involving facial and skeletal muscle spasms and oculogryric crises. These dystonic effects are more common in the young (especially girls and young women) and the very old; they usually occur shortly after starting treatment with metoclopramide and subside within 24 hours of stopping it. Injection of an antiparkinsonian drug such as procyclidine will abort dystonic attacks.

PREGNANCY Not known to be harmful.

BREAST FEEDING Small amount present in milk; avoid.

HEPATIC IMPAIRMENT Reduce dose.

RENAL IMPAIRMENT Avoid or use small dose in severe impairment; increased risk of extrapyramidal reactions.

DIRECTIONS FOR ADMINISTRATION Oral liquid preparation to be given via a graduated oral dosing syringe.

PATIENT AND CARER ADVICE Counselling on use of pipette advised with oral solution.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

Tablet

METOCLOPRAMIDE HYDROCHLORIDE (Non-proprietary)

Metoclopramide hydrochloride 10 mg Metoclopramide 10mg tablets | 28 tablet £1.23 DT price = £0.97

Maxolon (AMCo)

Metoclopramide hydrochloride 10 mg Maxolon 10mg tablets | 84 tablet £5.24

Oral solution

METOCLOPRAMIDE HYDROCHLORIDE (Non-proprietary)

Metoclopramide hydrochloride 1 mg per 1 ml Metoclopramide 5mg/5ml oral solution sugar free (sugar-free) | 150 ml £19.77 DT price = £13.77

Solution for injection

METOCLOPRAMIDE HYDROCHLORIDE (Non-proprietary)

Metoclopramide hydrochloride 5 mg per 1 ml Metoclopramide 10mg/2ml solution for injection ampoules | 5 ampoule £1.31-1.82 | 10 ampoule £3.50 DT price = £3.23

Maxolon (AMCo)

Metoclopramide hydrochloride 5 mg per 1 ml Maxolon 10mg/2ml solution for injection ampoules | 12 ampoule £3.21

Maxolon High Dose 100mg/20ml solution for injection ampoules | 10 ampoule £26.68

5HT3 RECEPTOR ANTAGONISTS

Granisetron

DRUG ACTION Granisetron is a specific 5HT3-receptor antagonist which blocks 5HT3 receptors in the gastrointestinal tract and in the CNS.

INDICATIONS AND DOSE

Nausea and vomiting induced by cytotoxic chemotherapy for planned duration of 3–5 days where oral antiemetics cannot be used

BY TRANSDERMAL APPLICATION USING PATCHES

Adult: Apply 3.1 mg/24 hours, apply patch to clean, dry, non-irritated, non-hairy skin on upper arm (or abdomen if upper arm cannot be used) 24–48 hours before treatment, patch may be worn for up to 7 days; remove at least 24 hours after completing chemotherapy

Prevention of postoperative nausea and vomiting

BY INTRAVENOUS INJECTION

Adult: 1 mg, to be administered before induction of anaesthesia, dose to be diluted to 5 ml and given over 30 seconds

Treatment of postoperative nausea and vomiting

BY INTRAVENOUS INJECTION

Adult: 1 mg, dose to be diluted to 5 ml and given over 30 seconds; maximum 3 mg per day

Management of nausea and vomiting induced by cytotoxic chemotherapy or radiotherapy

BY MOUTH

Adult: 1–2 mg, to be taken within 1 hour before start of treatment, then 2 mg daily in 1–2 divided doses for up to 1 week following treatment, when intravenous route also used, maximum combined total dose 9 mg in 24 hours

BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION

Adult: 10–40 micrograms/kg (max. per dose 3 mg), to be given 5 minutes before start of treatment, dose may be repeated if necessary, further maintenance doses must not be given less than 10 minutes apart, for intravenous injection, each 1 mg granisetron diluted to 5 ml and given over not less than 30 seconds, for intravenous infusion, to be given over 5 minutes; maximum 9 mg per day

CAUTIONS Subacute intestinal obstruction • susceptibility to QT-interval prolongation (including electrolyte disturbances)

INTERACTIONS ➔ Appendix 1 (5HT3-receptor Antagonists). Caution with concomitant use of drugs that prolong QT interval.

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

Common or very common Constipation • diarrhoea • headache • insomnia

Nervous system

MEDICINAL FORMS

DIRECTIONS FOR ADMINISTRATION

RENAL IMPAIRMENT

BREAST FEEDING

PREGNANCY

INTERACTIONS ➔ Appendix 1 (metoclopramide).

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

Specific side-effects

Very rare

With intravenous use cardiac conduction abnormalities

SIDE-EFFECTS, FURTHER INFORMATION

Metoclopramide can induce acute dystonic reactions involving facial and skeletal muscle spasms and oculogryric crises. These dystonic effects are more common in the young (especially girls and young women) and the very old; they usually occur shortly after starting treatment with metoclopramide and subside within 24 hours of stopping it. Injection of an antiparkinsonian drug such as procyclidine will abort dystonic attacks.

PREGNANCY Not known to be harmful.

BREAST FEEDING Small amount present in milk; avoid.

HEPATIC IMPAIRMENT Reduce dose.

RENAL IMPAIRMENT Avoid or use small dose in severe impairment; increased risk of extrapyramidal reactions.

DIRECTIONS FOR ADMINISTRATION Oral liquid preparation to be given via a graduated oral dosing syringe.

PATIENT AND CARER ADVICE Counselling on use of pipette advised with oral solution.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

Tablet

METOCLOPRAMIDE HYDROCHLORIDE (Non-proprietary)

Metoclopramide hydrochloride 10 mg Metoclopramide 10mg tablets | 28 tablet £1.23 DT price = £0.97

Maxolon (AMCo)

Metoclopramide hydrochloride 10 mg Maxolon 10mg tablets | 84 tablet £5.24

Oral solution

METOCLOPRAMIDE HYDROCHLORIDE (Non-proprietary)

Metoclopramide hydrochloride 1 mg per 1 ml Metoclopramide 5mg/5ml oral solution sugar free (sugar-free) | 150 ml £19.77 DT price = £13.77

Solution for injection

METOCLOPRAMIDE HYDROCHLORIDE (Non-proprietary)

Metoclopramide hydrochloride 5 mg per 1 ml Metoclopramide 10mg/2ml solution for injection ampoules | 5 ampoule £1.31-1.82 | 10 ampoule £3.50 DT price = £3.23

Maxolon (AMCo)

Metoclopramide hydrochloride 5 mg per 1 ml Maxolon 10mg/2ml solution for injection ampoules | 12 ampoule £3.21

Maxolon High Dose 100mg/20ml solution for injection ampoules | 10 ampoule £26.68

5HT3 RECEPTOR ANTAGONISTS

Granisetron

DRUG ACTION Granisetron is a specific 5HT3-receptor antagonist which blocks 5HT3 receptors in the gastrointestinal tract and in the CNS.

INDICATIONS AND DOSE

Nausea and vomiting induced by cytotoxic chemotherapy for planned duration of 3–5 days where oral antiemetics cannot be used

BY TRANSDERMAL APPLICATION USING PATCHES

Adult: Apply 3.1 mg/24 hours, apply patch to clean, dry, non-irritated, non-hairy skin on upper arm (or abdomen if upper arm cannot be used) 24–48 hours before treatment, patch may be worn for up to 7 days; remove at least 24 hours after completing chemotherapy

Prevention of postoperative nausea and vomiting

BY INTRAVENOUS INJECTION

Adult: 1 mg, to be administered before induction of anaesthesia, dose to be diluted to 5 ml and given over 30 seconds

Treatment of postoperative nausea and vomiting

BY INTRAVENOUS INJECTION

Adult: 1 mg, dose to be diluted to 5 ml and given over 30 seconds; maximum 3 mg per day

Management of nausea and vomiting induced by cytotoxic chemotherapy or radiotherapy

BY MOUTH

Adult: 1–2 mg, to be taken within 1 hour before start of treatment, then 2 mg daily in 1–2 divided doses for up to 1 week following treatment, when intravenous route also used, maximum combined total dose 9 mg in 24 hours

BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION

Adult: 10–40 micrograms/kg (max. per dose 3 mg), to be given 5 minutes before start of treatment, dose may be repeated if necessary, further maintenance doses must not be given less than 10 minutes apart, for intravenous injection, each 1 mg granisetron diluted to 5 ml and given over not less than 30 seconds, for intravenous infusion, to be given over 5 minutes; maximum 9 mg per day

CAUTIONS Subacute intestinal obstruction • susceptibility to QT-interval prolongation (including electrolyte disturbances)

INTERACTIONS ➔ Appendix 1 (5HT3-receptor Antagonists). Caution with concomitant use of drugs that prolong QT interval.

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

Common or very common Constipation • diarrhoea • headache • insomnia
Ondansetron

**DRUG ACTION**
Ondansetron is a specific 5HT3-receptor antagonist which blocks 5HT, receptors in the gastrointestinal tract and in the CNS.

**INDICATIONS AND DOSE**
Moderately emetogenic chemotherapy or radiotherapy

- **INITIALLY BY MOUTH**
  - Adult: Initially 8 mg, dose to be taken 1–2 hours before treatment, alternatively (by rectum) initially 16 mg, dose to be administered 1–2 hours before treatment, alternatively (by intramuscular injection or by slow intravenous injection) initially 8 mg, dose to be administered immediately before treatment, then (by mouth) 8 mg every 12 hours for up to 5 days, alternatively (by rectum) 16 mg daily for up to 5 days
  - Elderly: Initially 8 mg, dose to be taken 1–2 hours before treatment, alternatively (by rectum) initially 16 mg, dose to be administered 1–2 hours before treatment, alternatively (by intramuscular injection or by intravenous infusion) initially 8 mg, dose to be administered immediately before treatment, intravenous infusion dose to be administered over at least 15 minutes, then (by mouth) 8 mg every 12 hours for up to 5 days, alternatively (by rectum) 16 mg daily for up to 5 days

- **Prevention of postoperative nausea and vomiting**
  - **INITIALLY BY MOUTH**
    - Adult: 16 mg, dose to be taken 1 hour before anaesthesia, alternatively (by intramuscular injection or by slow intravenous injection) 4 mg, dose to be administered at induction of anaesthesia

**TREATMENT OF POSTOPERATIVE NAUSEA AND VOMITING**
BY INTRAMUSCULAR INJECTION OR BY SLOW INTRAVENOUS INJECTION

- Adult: 4 mg for 1 dose

**CONTRA-INDICATIONS**
Congenital long QT syndrome

**CAUTIONS**
Adenotonsillar surgery - subacute intestinal obstruction - susceptibility to QT-interval prolongation (including electrolyte disturbances)

**INTERACTIONS**

- Appendix 1 (5HT3-receptor Antagonists).
Caution with concomitant use of drugs that prolong QT interval.

- **SIDE-EFFECTS**
  - **GENERAL SIDE-EFFECTS**
    - Common or very common: Constipation, flushing, headache, injection site-reactions
    - Uncommon: Arrhythmias, bradycardia, chest pain, hiccup, hypotension, movement disorders, seizures
  - **SPECIFIC SIDE-EFFECTS**
    - Rare
    - With intravenous use: dizziness, transient visual disturbances
    - Very rare
    - With intravenous use: transient blindness
    - Frequency not known
    - With rectal use: rectal irritation

- **PREGNANCY**
  - No information available; avoid unless potential benefit outweighs risk.

- **BREAST FEEDING**
  - Present in milk in animal studies—avoid.

- **HEPATIC IMPAIRMENT**
  - Maximum 8 mg daily in moderate or severe impairment.

- **DIRECTIONS FOR ADMINISTRATION**
  - With intravenous use: For intravenous infusion (Zofran®), give continuously or intermittently in Glucose 5% or Glucose 5% with Potassium chloride 0.3% or Sodium chloride 0.9% or Sodium chloride 0.9% with Potassium chloride 0.3% or Mannitol 10% or Ringers solution; for intermittent infusion, dilute the required dose in 50–100 mL of infusion fluid and give over at least 15 minutes.
  - With oral use: Orodispensible films and lyophylisates should be placed on the tongue, allowed to disperse and swallowed.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Flavours of oral liquid formulations may include strawberry.

- **PATIENT AND CARER ADVICE**
  - Patients or carers should be given advice on how to administer orodispensible films and lyophylisates.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

### Table

<table>
<thead>
<tr>
<th><strong>Tablet</strong></th>
<th><strong>Zofran (Novartis Pharmaceuticals UK Ltd)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron (as Ondansetron hydrochloride) 4 mg</td>
<td>Ondansetron 16 mg</td>
</tr>
<tr>
<td>Ondansetron 4 mg tablets 10 tablet [PO] £25.46 DT price = £1.80</td>
<td>Ondansetron 16 mg tablets 50 tablet [PO] £37.74</td>
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<td>Ondansetron 8 mg tablets 10 tablet [PO] £47.79 DT price = £4.69</td>
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<tr>
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<tr>
<td>Ondansetron (as Ondansetron hydrochloride) 8 mg</td>
<td>Ondansetron (as Ondansetron hydrochloride) 32 mg</td>
</tr>
<tr>
<td>Zofran 4 mg tablets 30 tablet [PO] £80.93 DT price = £4.69</td>
<td>Zofran 16 mg tablets 50 tablet [PO] £191.94 DT price = £4.69</td>
</tr>
<tr>
<td>Ondansetron 8 mg tablets 10 tablet [PO] £80.93 DT price = £8.09</td>
<td>Ondansetron 32 mg tablets 50 tablet [PO] £191.94 DT price = £4.69</td>
</tr>
</tbody>
</table>

- **Oral solution**
  - **Zofran (Novartis Pharmaceuticals UK Ltd)**
    - Ondansetron (as Ondansetron hydrochloride) 800 microgram per 1 mL
      - Ondansetron 4 mg/5 mL oral solution sugar-free (sugar-free) 50 mL [PO] £38.08 DT price = £37.74
      - Ondansetron 8 mg/10 mL oral solution sugar-free (sugar-free) 50 mL [PO] £75.16 DT price = £37.74

### Palonosetron

- **DRUG ACTION**
  - Palonosetron is a specific 5HT3-receptor antagonist which blocks 5HT3 receptors in the gastrointestinal tract and in the CNS.

### Indications and Dose

- **Moderately emetogenic chemotherapy**
  - Initially by mouth
    - Adult: 500 micrograms, dose to be taken 1 hour before treatment, alternatively (by intravenous injection)
    - 250 micrograms for 1 dose, dose to be administered over 30 seconds, 30 minutes before treatment

- **Severely emetogenic chemotherapy**
  - By intravenous injection
    - Adult: 250 micrograms for 1 dose, dose to be administered over 30 seconds, 30 minutes before treatment

- **CAUTIONS**
  - History of constipation, intestinal obstruction, susceptibility to QT-interval prolongation (including electrolyte disturbances)

- **INTERACTIONS**
  - Caution with concomitant use of drugs that prolong QT interval.

- **SIDE-EFFECTS**
  - Common or very common: Constipation, diarrhoea, dizziness, headache
  - Uncommon: Abdominal pain, anorexia, anxiety, arrhythmia, bradycardia, changes in blood pressure, dry mouth, dyspepsia, peripheral neuropathy

- **PREGNANCY**
  - Avoid—no information available.

- **BREAST FEEDING**
  - Avoid—no information available.

- **PATIENT AND CARER ADVICE**
  - Dizziness or drowsiness may affect performance of skilled tasks (e.g. driving).
Fosaprepitant

**DRUG ACTION** Fosaprepitant is a prodrug of aprepitant.

**INDICATIONS AND DOSE**

Adjunct to dexamethasone and a 5HT3-receptor antagonist in preventing nausea and vomiting associated with moderately and highly emetogenic chemotherapy

**BY INTRAVENOUS INFUSION**

- Adult: 150 mg, dose to be administered over 20–30 minutes and given 30 minutes before chemotherapy on day 1 of cycle only, consult product literature for dose of concomitant corticosteroid and 5HT3-receptor antagonist

**CONTRA-INDICATIONS** Acute porphyrias p. 864

**INTERACTIONS** → Appendix 1 (aprepitant).

**SIDE-EFFECTS**

- **Common or very common** Anorexia · asthenia · constipation · diarrhoea · dizziness · dyspepsia · headache · hiccups
- **Uncommon** Abdominal pain · abnormal dreams · acne · anaemia · anxiety · bradycardia · chills · colitis · confusion · conjunctivitis · cough · drowsiness · dry mouth · duodenal ulcer · dysuria · euphoria · flatulence · flushing · haematuria · hyperglycaemia · hyponatraemia · myalgia · neutropenia · oedema · palpitations · pharyngitis · photosensitivity · polyuria · pruritus · rash · sneezing · stomatitis · sweating · taste disturbance · thirst · tinnitus · weight changes

**CONCEPTION AND CONTRACEPTION** Effectiveness of hormonal contraceptives reduced—effective non-hormonal methods of contraception necessary during treatment and for 2 months after stopping fosaprepitant.

**PREGNANCY** Avoid unless potential benefit outweighs risk—no information available.

**BREAST FEEDING** Avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT** Caution in moderate to severe impairment.

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (I vemend®), give intermittently in Sodium chloride 0.9%; reconstitute each 150-mg vial with 5 mL sodium chloride 0.9% gently without shaking to avoid foaming, then dilute in 145 mL infusion fluid; give over 20–30 minutes.

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (January 2011) that fosaprepitant (I vemend®) is accepted for restricted use within NHS Scotland for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based chemotherapy.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**

- I vemend (Merck Sharp & Dohme Ltd) Fosaprepitant (as Fosaprepitant dimeglumine) 150 mg I vemend 150mg powder for solution for infusion vials | 1 vial [PFS] £47.42

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**NEUROKININ RECEPTOR ANTAGONISTS**

Aprepitant

**INDICATIONS AND DOSE**

Adjunct to dexamethasone and a 5HT3-receptor antagonist in preventing nausea and vomiting associated with moderately and highly emetogenic chemotherapy

**BY MOUTH**

- Adult: Initially 125 mg, dose to be taken 1 hour before chemotherapy, then 80 mg once daily for 2 days, consult product literature for dose of concomitant corticosteroid and 5HT3-receptor antagonist

**CONTRA-INDICATIONS** Acute porphyrias p. 864

**INTERACTIONS** → Appendix 1 (aprepitant).

**SIDE-EFFECTS**

- **Common or very common** Anorexia · asthenia · constipation · diarrhoea · dizziness · dyspepsia · headache · hiccups
- **Uncommon** Abdominal pain · abnormal dreams · acne · anaemia · anxiety · bradycardia · chills · colitis · confusion · conjunctivitis · cough · drowsiness · dry mouth · duodenal ulcer · dysuria · euphoria · flatulence · flushing · haematuria · hyperglycaemia · hyponatraemia · myalgia · neutropenia · oedema · palpitations · pharyngitis · photosensitivity · polyuria · pruritus · rash · sneezing · stomatitis · sweating · taste disturbance · thirst · tinnitus · weight changes

**CONCEPTION AND CONTRACEPTION** Effectiveness of hormonal contraceptives reduced—effective non-hormonal methods of contraception necessary during treatment and for 2 months after stopping aprepitant.

**PREGNANCY** Avoid unless potential benefit outweighs risk—no information available.

**BREAST FEEDING** Avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT** Caution in moderate to severe impairment.

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (I vemend®), give intermittently in Sodium chloride 0.9%; reconstitute each 150-mg vial with 5 mL sodium chloride 0.9% gently without shaking to avoid foaming, then dilute in 145 mL infusion fluid; give over 20–30 minutes.

**NATIONAL FUNDING/ACCESS DECISIONS**

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**MEDICINAL FORMS**

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**Powder for solution for infusion**

- I vemend (Merck Sharp & Dohme Ltd) Fosaprepitant (as Fosaprepitant dimeglumine) 150 mg I vemend 150mg powder for solution for infusion vials | 1 vial [PFS] £47.42
4.1 Meniere’s disease

HISTAMINE ANALOGUES

Betahistine dihydrochloride

INDICATIONS AND DOSE
Vertigo, tinnitus and hearing loss associated with Ménière’s disease
BY MOUTH
• Adult: Initially 16 mg 3 times a day, dose preferably taken with food; maintenance 24–48 mg daily

CONTRA-INDICATIONS
Phaeochromocytoma

CAUTIONS
Asthma - history of peptic ulcer

INTERACTIONS
→ Appendix 1 (betahistine).

SIDE-EFFECTS
Gastro-intestinal disturbances - headache - pruritus - rashes

PREGNANCY
Avoid unless clearly necessary — no information available.

BREAST FEEDING
Use only if potential benefit outweighs risk — no information available.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

Table

| CAUTIONARY AND ADVISORY LABELS | 21 |
| BETAHISTINE DIHYDROCHLORIDE (Non-proprietary) |
| Betahistine dihydrochloride 8 mg | Betahistine 8mg tablets |
| 84 tablet | £0.50 DT price = £1.66 |
| Betahistine dihydrochloride 16 mg | Betahistine 16mg tablets |
| 84 tablet | £1.19 DT price = £2.00 |
| Serco (BGP Products Ltd) |
| Betahistine dihydrochloride 8 mg | Serco 8mg tablets |
| 120 tablet | £0.94 |
| Betahistine dihydrochloride 16 mg | Serco 16mg tablets |
| 84 tablet | £1.65 DT price = £2.00 |

5 Pain

Analgesics

The non-opioid drugs, paracetamol p. 354 and aspirin p. 104 (and other NSAIDs), are particularly suitable for pain in musculoskeletal conditions, whereas the opioid analgesics are more suitable for moderate to severe pain, particularly of visceral origin.

Pain in sickle-cell disease

The pain of mild sickle-cell crises is managed with paracetamol p. 354, a NSAID, codeine phosphate p. 360, or dihydrocodeine tartrate p. 362. Severe crises may require the use of morphine p. 367 or diamorphine hydrochloride p. 361; concomitant use of a NSAID may potentiate analgesia and allow lower doses of the opioid to be used. Pethidine hydrochloride p. 372 should be avoided if possible because accumulation of a neurotoxic metabolite can precipitate seizures; the relatively short half-life of pethidine hydrochloride necessitates frequent injections.

Dental and orofacial pain

Analgesics should be used judiciously in dental care as a temporary measure until the cause of the pain has been dealt with.

Dental pain of inflammatory origin, such as that associated with pulpitis, apical infection, localised osteitis or pericoronitis is usually best managed by treating the infection, providing drainage, restorative procedures, and other local measures. Analgesics provide temporary relief of pain (usually for about 1 to 7 days) until the causative factors have been brought under control. In the case of pulpitis, intra-osseous infection or abscess, reliance on analgesics alone is usually inappropriate.

Similarly the pain and discomfort associated with acute problems of the oral mucosa (e.g. acute herpetic gingivostomatitis, erythema multiforme) may be relieved by benzylamine hydrochloride p. 993 mouthwash or spray until the cause of the mucosal disorder has been dealt with. However, where a patient is febrile, the antipyretic action of paracetamol p. 354 or ibuprofen p. 927 is often helpful.

The choice of an analgesic for dental purposes should be based on its suitability for the patient. Most dental pain is relieved effectively by non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs that are used for dental pain include ibuprofen p. 927, diclofenac sodium p. 921, and aspirin p. 104. Paracetamol p. 354 has analgesic and antipyretic effects but no anti-inflammatory effect.

Opioid analgesics such as dihydrocodeine tartrate p. 362 act on the central nervous system and are traditionally used for moderate to severe pain. However, opioid analgesics are relatively ineffective in dental pain and their side-effects can be unpleasant. Paracetamol, ibuprofen, or aspirin are adequate for most cases of dental pain and an opioid is rarely required.

Combining a non-opioid with an opioid analgesic can provide greater relief of pain than either analgesic given alone. However, this applies only when an adequate dose of each analgesic is used. Most combination analgesic preparations have not been shown to provide greater relief of pain than an adequate dose of the non-opioid component given alone. Moreover, combination preparations have the disadvantage of an increased number of side-effects.

Any analgesic given before a dental procedure should have a low risk of increasing postoperative bleeding. In the case of pain after the dental procedure, taking an analgesic before the effect of the local anaesthetic has worn off can improve control. Postoperative analgesia with ibuprofen or aspirin is usually continued for about 24 to 72 hours.

Temporomandibular dysfunction can be related to anxiety in some patients who may clench or grind their teeth (bruxism) during the day or night. The muscle spasm (which appears to be the main source of pain) may be treated empirically with an overlay appliance which provides a free sliding occlusion and may also interfere with grinding. In addition, diazepam p. 267, which has muscle relaxant as well as anxiolytic properties, may be helpful but it should only be prescribed on a short-term basis during the acute phase. Analgesics such as aspirin or ibuprofen may also be required.

Dysmenorrhoea

Use of an oral contraceptive prevents the pain of dysmenorrhoea which is generally associated with ovulatory cycles. If treatment is necessary paracetamol p. 354 or a NSAID will generally provide adequate relief of pain. The vomiting and severe pain associated with dysmenorrhoea in women with endometriosis may call for an antiemetic (in addition to an analgesic). Antispasmodics (such as alverine citrate p. 74) have been advocated for dysmenorrhoea but the antispasmodic action does not generally provide significant relief.

Non-opioid analgesics and compound analgesic preparations

Aspirin p. 104 is indicated for headache, transient musculoskeletal pain, dysmenorrhoea, and pyrexia. In inflammatory conditions, most physicians prefer anti-inflammatory treatment with another NSAID which may be better tolerated and more convenient for the patient. Aspirin is used increasingly for its antiplatelet properties.
Aspirin tablets or dispersible aspirin tablets are adequate for most purposes as they act rapidly. Gastric irritation may be a problem; it is minimised by taking the dose after food. Enteric-coated preparations are available, but have a slow onset of action and are therefore unsuitable for single-dose analgesic use (though their prolonged action may be useful for night pain).

Aspirin interacts significantly with a number of other drugs and its interaction with warfarin sodium is a special hazard.

Paracetamol p. 354 is similar in efficacy to aspirin, but has no demonstrable anti-inflammatory activity; it is less irriant to the stomach and for that reason is now generally preferred to aspirin, particularly in the elderly. Overdosage with paracetamol is particularly dangerous as it may cause hepatic damage which is sometimes not apparent for 4 to 6 days.

Nefopam hydrochloride p. 356 may have a place in the relief of persistent pain unresponsive to other non-opioid analgesics. It causes little or no respiratory depression, but sympathomimetic and antimuscarinic side-effects may be troublesome.

Non-steroidal anti-inflammatory analgesics (NSAIDs) are particularly useful for the treatment of patients with chronic disease accompanied by pain and inflammation. Some of them are also used in the short-term treatment of mild to moderate pain including transient musculoskeletal pain. Some NSAIDs are also used in the short-term treatment of secondary bone tumours, many of which produce lysis of bone and release prostaglandins. Selective inhibitors of cyclo-oxygenase-2 may be used in preference to non-selective NSAIDs for patients at high risk of developing serious gastro-intestinal side-effects. Several NSAIDs are also used for postoperative analgesia.

A non-opioid analgesic administered by intrathecal infusion (ziconotide (Prialt®), available from Eisai) is licensed for the treatment of chronic severe pain; ziconotide can be used by a hospital specialist as an adjunct to opioid analgesics.

Compound analgesic preparations

Compound analgesic preparations that contain a simple analgesic (such as aspirin p. 104 or paracetamol p. 254) with an opioid component reduce the need for effective titration of the individual components in the management of pain of varying intensity.

Compound analgesic preparations containing paracetamol p. 354 or aspirin p. 104 with a low dose of an opioid analgesic (e.g. 8 mg of codeine phosphate per compound tablet) are commonly used, but the advantages have not been substantiated. The low dose of the opioid may be enough to cause opioid side-effects (in particular, constipation) and can complicate the treatment of overdosage yet may not provide significant additional relief of pain.

A full dose of the opioid component (e.g. 60 mg codeine phosphate) in compound analgesic preparations effectively augments the analgesic activity but is associated with the full range of opioid side-effects (including nausea, vomiting, severe constipation, drowsiness, respiratory depression, and risk of dependence on long-term administration).

Important: the elderly are particularly susceptible to opioid side-effects and should receive lower doses.

In general, when assessing pain, it is necessary to weigh up carefully whether there is a need for a non-opioid and an opioid analgesic to be taken simultaneously.

Caffeine is a weak stimulant that is often included, in small doses, in analgesic preparations. It is claimed that the addition of caffeine may enhance the analgesic effect, but the alerting effect, mild habit-forming effect and possible provocation of headache may not always be desirable. Moreover, in excessive dosage or on withdrawal caffeine may itself induce headache.

Co-proxamol tablets (dextropropoxyphene in combination with paracetamol) are no longer licensed because of safety concerns, particularly toxicity in overdose. Co-proxamol tablets (unlicensed) may still be prescribed for patients who find it difficult to change, because alternatives are not effective or suitable.

Opioid analgesics

Opioid analgesics are usually used to relieve moderate to severe pain particularly of visceral origin. Repeated administration may cause dependence and tolerance, but this is no deterrent in the control of pain in terminal illness. Regular use of a potent opioid may be appropriate for certain cases of chronic non-malignant pain; treatment should be supervised by a specialist and the patient should be assessed at regular intervals.

Strong opioids

Morphine p. 367 remains the most valuable opioid analgesic for severe pain although it frequently causes nausea and vomiting. It is the standard against which other opioid analgesics are compared. In addition to relief of pain, morphine also confers a state of euphoria and mental detachment.

Morphine is the opioid of choice for the oral treatment of severe pain in palliative care. It is given regularly every 4 hours (or every 12 or 24 hours as modified-release preparations). Buprenorphine p. 434 has both opioid agonist and antagonist properties and may precipitate withdrawal symptoms, including pain, in patients dependent on other opioids. It has abuse potential and may itself cause dependence. It has a much longer duration of action than morphine and sublingually is an effective analgesic for 6 to 8 hours. Unlike most opioid analgesics, the effects of buprenorphine are only partially reversed by naloxone hydrochloride p. 1133.

Dipipanone hydrochloride used alone is less sedating than morphine but the only preparation available contains an antiemetic and is therefore not suitable for regular regimens in palliative care.

Diamorphine hydrochloride p. 361 (heroin) is a powerful opioid analgesic. It may cause less nausea and hypotension than morphine. In palliative care the greater solubility of diamorphine hydrochloride allows effective doses to be injected in smaller volumes and this is important in the emaciated patient.

Alfentanil p. 357, fentanyl p. 362 and remifentanil p. 1108 are used by injection for intra-operative analgesia; fentanyl is available in a transdermal drug delivery system as a self-adhesive patch which is changed every 72 hours.

Methadone hydrochloride p. 436 is less sedating than morphine and acts for longer periods. In prolonged use, methadone hydrochloride should not be administered more often than twice daily to avoid the risk of accumulation and opioid overdosage. Methadone hydrochloride may be used instead of morphine in the occasional patient who experiences excitement (or exacerbation of pain) with morphine.

Oxycodone hydrochloride p. 369 has an efficacy and side-effect profile similar to that of morphine. It is used primarily for control of pain in palliative care.

Papaveretum p. 371 is rarely used; morphine is easier to prescribe and less prone to error with regard to the strength and dose.

Pentazocine p. 371 has both agonist and antagonist properties and precipitates withdrawal symptoms, including pain in patients dependent on opioids. By injection it is more potent than dihydrocodeine tartrate or codeine phosphate, but hallucinations and thought disturbances may occur. It is not recommended and, in particular, should
be avoided after myocardial infarction as it may increase pulmonary and aortic blood pressure as well as cardiac work.

Pethidine hydrochloride p. 372 produces prompt but short-lasting analgesia; it is less constipating than morphine, but even in high doses is a less potent analgesic. It is not suitable for severe continuing pain. It is used for analgesia in labour; however, other opioids, such as morphine or diamorphine hydrochloride p. 361, are often preferred for obstetric pain.

Tapentadol p. 372 produces analgesia by two mechanisms. It is an opioid-receptor agonist and it also inhibits noradrenaline reuptake. Nausea, vomiting, and constipation are less likely to occur with tapentadol than with other strong opioid analgesics.

Tramadol hydrochloride p. 373 produces analgesia by two mechanisms: an opioid effect and an enhancement of serotonergic and adrenergic pathways. It has fewer of the typical opioid side-effects (notably, less respiratory depression, less constipation and less addiction potential); psychiatric reactions have been reported.

**Weak opioids**

Codeine phosphate p. 360 can be used for the relief of mild to moderate pain where other painkillers such as paracetamol or ibuprofen have proved ineffective. Dihydrocodeine tartrate p. 362 has an analgesic efficacy similar to that of codeine phosphate. Higher doses may provide some additional pain relief but this may be at the cost of more nausea and vomiting.

Meptazinol p. 367 is claimed to have a low incidence of respiratory depression. It has a reported length of action of 2 to 7 hours with onset within 15 minutes.

**Postoperative analgesia**

A combination of opioid and non-opioid analgesics is used to treat postoperative pain. The use of intra-operative opioids affects the prescribing of postoperative analgesics. A postoperative opioid analgesic should be given with care since it may potentiate any residual respiratory depression.

Morphine p. 367 is used most widely. Tramadol hydrochloride p. 373 is not as effective in severe pain as other opioid analogues. Buprenorphine p. 434 may antagonise the analgesic effect of previously administered opioids and is generally not recommended. Pethidine hydrochloride p. 372 is generally not recommended for postoperative pain because it is metabolised to norpethidine which may accumulate, particularly in renal impairment; norpethidine stimulates the central nervous system and may cause convulsions.

Opioids are also given epidurally [unlicensed route] in the postoperative period but are associated with side-effects such as pruritus, urinary retention, nausea and vomiting; respiratory depression can be delayed, particularly with morphine.

Patient-controlled analgesia (PCA) can be used to relieve postoperative pain—consult individual hospital protocols.

**Pain management and opioid dependence**

Although caution is necessary, patients who are dependent on opioids or have a history of drug dependence may be treated with opioid analgesics when there is a clinical need. Treatment with opioid analgesics in this patient group should normally be carried out with the advice of specialists. However, doctors do not require a special licence to prescribe opioid analgesics to patients with opioid dependence for relief of pain due to organic disease or injury.

**Drugs used for Pain not listed below:** Aspirin p. 104; Bupivacaine hydrochloride p. 1113; Buprenorphine with fentanyl p. 362; Diphenhydramine p. 534; Diclofenac potassium p. 920; Fenoprofen p. 926; Ibuprofen p. 927; Levothyroxine, p. 1115; Levetiracetam, p. 345; Mefenamic acid, p. 932; Methadone hydrochloride, p. 436; Nitrous oxide, p. 1096; Ropivacaine hydrochloride, p. 1121

**ANALGESICS**

**Aspirin with codeine**

The properties listed below are those particular to the combination only. For the properties of the components please consider, aspirin p. 104, codeine phosphate p. 360.

**INDICATIONS AND DOSE**

**Mild to moderate pain | Pyrexia**

**BY MOUTH**

- Adult: 1–2 tablets every 4–6 hours as required, dose to be dispersed in water; maximum 8 tablets per day

**PRESCRIBING AND DISPENSING INFORMATION** When co-codaprin tablets or dispersible tablets are prescribed and no strength is stated, tablets or dispersible tablets, respectively, containing codeine phosphate 8 mg and aspirin 400 mg should be dispensed.

**LESS SUITABLE FOR PRESCRIBING** Aspirin with codeine is less suitable for prescribing.

**EXCEPTIONS TO LEGAL CATEGORY** Aspirin with codeine can be sold to the public provided packs contain no more than 32 capsules or tablets; pharmacists can sell multiple packs up to a total quantity of 100 capsules or tablets in justifiable circumstances.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Dispersible tablet**

**CAUTIONARY AND ADVISORY LABELS** 13, 21, 32

- **Codis** (Reckitt Benckiser Healthcare (UK) Ltd)
  - **Aspirin 500 mg, Codeine phosphate 8 mg** Codis 500 dispersible tablets (sugar-free) | 32 tablet [£3.23 Schedule 5 (CD Inv)]
  - **Co-codaprin (Non-proprietary)**
    - **Aspirin 400 mg, Codeine 8 mg** Co-codaprin 8/400 mg dispersible tablets | 100 tablet [P] £37.65 Schedule 5 (CD Inv)

**Paracetamol**

**Acetaminophen**

**INDICATIONS AND DOSE**

**Mild to moderate pain | Pyrexia**

**BY MOUTH**

- Adult: 0.5–1 g every 4–6 hours; maximum 4 g per day

**BY INTRAVENOUS INFUSION**

- Adult (body-weight 10–50 kg): 15 mg/kg every 4–6 hours, dose to be administered over 15 minutes; maximum 60 mg/kg per day
- Adult (body-weight 50 kg and above): 1 g every 4–6 hours, dose to be administered over 15 minutes; maximum 4 g per day

**BY RECTUM**

- Adult: 0.5–1 g every 4–6 hours; maximum 4 g per day
Mild to moderate pain in patients with risk factors for hepatotoxicity

BY INTRAVENOUS INFUSION
- Adult (body-weight 50 kg and above): 1 g every 4–6 hours, dose to be administered over 15 minutes; maximum 3 g per day

Pain | Pyrexia with discomfort

BY MOUTH
- Child 3-5 months: 60 mg every 4–6 hours; maximum 4 doses per day
- Child 6 months-1 year: 120 mg every 4–6 hours; maximum 4 doses per day
- Child 2-3 years: 180 mg every 4–6 hours; maximum 4 doses per day
- Child 4-5 years: 240 mg every 4–6 hours; maximum 4 doses per day
- Child 6-7 years: 240–250 mg every 4–6 hours; maximum 4 doses per day
- Child 8-9 years: 360–375 mg every 4–6 hours; maximum 4 doses per day
- Child 10-11 years: 480–500 mg every 4–6 hours; maximum 4 doses per day
- Child 12-15 years: 480–750 mg every 4–6 hours; maximum 4 doses per day
- Child 16-17 years: 0.5–1 g every 4–6 hours; maximum 4 doses per day

BY RECTUM
- Child 3-11 months: 60–125 mg every 4–6 hours as required; maximum 4 doses per day
- Child 1-4 years: 125–250 mg every 4–6 hours as required; maximum 4 doses per day
- Child 5-11 years: 250–500 mg every 4–6 hours as required; maximum 4 doses per day
- Child 12-17 years: 500 mg every 4–6 hours

Post-immunisation pyrexia in infants

BY MOUTH
- Child 2 months: 60 mg for 1 dose, then 60 mg after 4–6 hours if required

PANADOL OATM

Mild to moderate pain | Pyrexia

BY MOUTH
- Adult: 1 g up to 4 times a day, dose not to be taken more often than every 4 hours

- UNLICENSED USE Paracetamol oral suspension 500 mg/5 mL not licensed for use in children under 16 years. Not licensed for use in children under 2 months by mouth; under 3 months by rectum. Intravenous infusion not licensed in pre-term neonates, or children and neonates with body-weight under 10 kg.

- CAUTIONS Alcohol dependence - before administering, check when paracetamol last administered and cumulative paracetamol dose over previous 24 hours - chronic alcoholism - chronic dehydration - chronic malnutrition - hepatocellular insufficiency

- INTERACTIONS → Appendix 1 (paracetamol).

- SIDE-EFFECTS
  - GENERAL SIDE-EFFECTS
    - Rare: Acute generalised exanthematous pustulosis - malaise - skin reactions - Stevens-Johnson syndrome - toxic epidermal necrolysis
  - Frequency not known: Blood disorders - leucopenia - neutropenia - thrombocytopenia

- SPECIFIC SIDE-EFFECTS
  - Rare
    - With intravenous use: flushing - tachycardia
  - Frequency not known
    - With intravenous use: hypotension

Overdose

Important: liver damage and less frequently renal damage can occur following overdose.

Nausea and vomiting, the only early features of poisoning, usually settle within 24 hours. Persistence beyond this time, often associated with the onset of right subcostal pain and tenderness, usually indicates development of hepatic necrosis.

For specific details on the management of poisoning, see Paracetamol, under Emergency treatment of poisoning p. 1123

- PREGNANCY Not known to be harmful.
- BREAST FEEDING Amount too small to be harmful.
- HEPATIC IMPAIRMENT Dose-related toxicity—avoid large doses.

- RENAL IMPAIRMENT
  - In adults Increase infusion dose interval to every 6 hours if eGFR less than 30 mL/minute/1.73 m².
  - In children Increase infusion dose interval to every 6 hours if estimated glomerular filtration rate less than 30 mL/minute/1.73 m².

- DIRECTIONS FOR ADMINISTRATION
  - For intravenous infusion (Perfalgan®), give in Glucose 5% or Sodium Chloride 0.9%; dilute to a concentration of not less than 1 mg/mL and use within an hour; may also be given undiluted. For children under 33 kg, use 50 mL-vial.

- PRESCRIBING AND DISPENSING INFORMATION
  - BP directs that when Paediatric Paracetamol Oral Suspension or Paediatric Paracetamol Mixture is prescribed Paracetamol Oral Suspension 120 mg/5 mL should be dispensed.
  - PATIENT AND CARER ADVICE
    - In children
      - Medicines for Children leaflet: Paracetamol for mild-to-moderate pain www.medicinesforchildren.org.uk/paracetamol-for-mildtomoderate-pain

- PROFESSION SPECIFIC INFORMATION
  - Dental practitioners’ formulary
    - Paracetamol Tablets may be prescribed. Paracetamol Soluble Tablets 500 mg may be prescribed. Paracetamol Oral Suspension may be prescribed.

- EXCEPTIONS TO LEGAL CATEGORY
  - Paracetamol capsules or tablets can be sold to the public provided packs contain no more than 32 capsules or tablets; pharmacists can sell multiple packs up to a total quantity of 100 capsules or tablets in justifiable circumstances.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: suppository, oral suspension, oral solution

Tablet

CAUTIONARY AND ADVISORY LABELS 29, 30

- PARACETAMOL (Non-proprietary)
  - Paracetamol 500 mg Paracetamol 500mg caplets | 16 tablet GSK £0.43 | 32 tablet P £2.11 DT price = £0.96 | 100 tablet P £3.18 DT price = £3.00
  - Paracetamol 500mg tablets | 16 tablet GSK £0.48 | 30 tablet P £0.78 | 32 tablet P £1.24 DT price = £0.96 | 100 tablet P £3.18 DT price = £3.00 | 1000 tablet P £31.25 | 5000 tablet no price available
  - Panadol (GlaxoSmithKline Consumer Healthcare)
  - Paracetamol 500 mg Panadol Advance 500mg tablets | 16 tablet GSK £1.07 | 32 tablet P £1.74 DT price = £0.96
  - Brands may include Mandanol

Effervescent tablet

- PARACETAMOL (Non-proprietary)
  - Paracetamol 500 mg Paracetamol 500mg soluble tablets | 16 tablet GSK £2.25 | 24 tablet GSK no price available DT price = £1.43 | 60 tablet P no price available | 60 tablet P £3.58–£4.99 | 100 tablet P £5.96 DT price = £5.96 | 100 tablet GSK £8.88 DT price = £5.96 | 100 tablet P no price available DT price = £5.96
Nervous system

Perfalgan
▶ Solution for infusion
Oral solution
Calpol
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Capsule
Disprol
▶ 13, 29, 30
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Pain

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<th>Paracetamol</th>
<th>Paracetamol 10 mg per 1 ml</th>
<th>Paracetamol 120 mg per 1 ml</th>
<th>Paracetamol 325 mg, Tramadol hydrochloride 37.5 mg</th>
<th>Paracetamol 60 mg</th>
<th>Paracetamol 125 mg</th>
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Paracetamol with tramadol

The properties listed below are those particular to the combination only. For the properties of the components please consider, paracetamol p. 354, tramadol hydrochloride p. 373.

INDICATIONS AND DOSE

<table>
<thead>
<tr>
<th>Moderate to severe pain</th>
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<tbody>
<tr>
<td>BY MOUTH</td>
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<tr>
<td>▶ Child 12-17 years: 2 tablets up to every 6 hours; maximum 8 tablets per day</td>
</tr>
<tr>
<td>▶ Adult: 2 tablets up to every 6 hours; maximum 8 tablets per day</td>
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MEDICINAL FORMS

There may be variation in the licensing of different medicines containing the same drug.

Tablet

| CAUTIONARY AND ADVISORY LABELS 2, 25, 29, 30 |
| PARACETAMOL WITH TRAMADOL (Non-proprietary) |
| Paracetamol 325 mg, Tramadol hydrochloride 37.5 mg |
| Tramadol 37.5 mg / Paracetamol 325 mg tablets |
| 60 tablet (P) | £9.20–£9.68 DT price | £9.22 Schedule 3 (CD No Register Exempt Safe Custody) |

Effervescent tablet

| CAUTIONARY AND ADVISORY LABELS 2, 13, 29, 30 |
| ELECTROLYTES: May contain Sodium |
| ▶ Tramacet (Grunenthal Ltd) |
| Paracetamol 325 mg, Tramadol hydrochloride 37.5 mg |
| Tramadol 37.5 mg / 325 mg effervescent tablets (sugar-free) |
| 60 tablet (P) | £9.68 DT price | £9.68 Schedule 3 (CD No Register Exempt Safe Custody) |

Nefopam hydrochloride

INDICATIONS AND DOSE

| Moderate pain |
| BY MOUTH |
| ▶ Adult: Initially 60 mg 3 times a day, adjusted according to response; usual dose 30–90 mg 3 times a day |
**SIDE-EFFECTS, FURTHER INFORMATION**

**Hyperalgesia** Long-term use of opioid analgesics has also been associated with a state of abnormal pain sensitivity (hyperalgesia). Pain associated with hyperalgesia is usually distinct from pain associated with disease progression or breakthrough pain, and is often more diffuse and less defined. Treatment of hyperalgesia involves reducing the dose of opioid medication or switching therapy; cases of suspected hyperalgesia should be referred to a specialist pain team.

**Respiratory depression** Respiratory depression is a major concern with opioid analgesics and it may be treated by artificial ventilation or be reversed by naloxone.

**Dependence and withdrawal** Psychological dependence rarely occurs when opioids are used therapeutically (e.g. for pain relief) but tolerance can develop during long-term treatment.

**Overdose** Opioids (narcotic analgesics) cause coma, respiratory depression, and pinpoint pupils. For details on the management of poisoning, see Opioids, under Emergency treatment of poisoning p. 1123 and consider the specific antidote, naloxone hydrochloride p. 1133.

**PREGNANCY** Respiratory depression and withdrawal symptoms can occur in the neonate if opioid analgesics are used during delivery; also gastric stasis and inhalation pneumonia has been reported in the mother if opioid analgesics are used during labour.

**HEPATIC IMPAIRMENT** Avoid use or reduce dose; may precipitate coma in patients with hepatic impairment.

**RENAL IMPAIRMENT** Avoid abrupt withdrawal after long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms.

**PATIENT AND CARER ADVICE** Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced. Driving at the start of therapy with opioid analgesics, and following dose changes, should be avoided.

For information on 2015 legislation regarding driving whilst taking certain controlled drugs, including opioids, see Drugs and driving under Guidance on prescribing p. 1.

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**Indications and Dose**

**Spontaneous respiration: analgesia and enhancement of anaesthesia for short procedures**

**BY INTRAVENOUS INJECTION**

- Adult: Initially up to 500 micrograms, dose to be administered over 30 seconds; supplemental doses 250 micrograms

**Assisted ventilation: analgesia and enhancement of anaesthesia for short procedures**

**BY INTRAVENOUS INJECTION**

- Adult: Initially 30–50 micrograms/kg, supplemental doses 15 micrograms/kg

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**Alfentanil**

**INDICATIONS AND DOSE**

*Spontaneous respiration: analgesia and enhancement of anaesthesia for short procedures* 

*BY INTRAVENOUS INJECTION* 

- Adult: Initially up to 500 micrograms, dose to be administered over 30 seconds; supplemental doses 250 micrograms

*Assisted ventilation: analgesia and enhancement of anaesthesia for short procedures* 

*BY INTRAVENOUS INJECTION* 

- Adult: Initially 30–50 micrograms/kg, supplemental doses 15 micrograms/kg
**Assisted ventilation: analgesia and enhancement of anaesthesia during maintenance of anaesthesia for longer procedures**

**BY INTRAVENOUS INFUSION**
- Adult: Initially 50–100 micrograms/kg, dose to be administered over 10 minutes or as a bolus, followed by maintenance 30–60 micrograms/kg/hour

**DIRECTIONS FOR ADMINISTRATION**

**BREAST FEEDING**
- Frequency not known
  - Uncommon

**SIDE-EFFECTS**
- **CAUTIONS**
  - **FURTHER INFORMATION**
  - Repeated intra-operative doses
  - Half-life is prolonged in neonates and accumulation is likely with prolonged use. Clearance may be increased in children 1 month–12 years and higher infusion doses might be needed.

**SIDE-EFFECTS, FURTHER INFORMATION**
- **MUSCLE RIGIDITY** Alfentanil can cause muscle rigidity, particularly of the chest wall or jaw; this can be managed by the use of neuromuscular blocking drugs.

**BREAST FEEDING**
- Present in milk— withhold breast-feeding for 24 hours.

**RENA L IMPAIRMENT**
- Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

**DIRECTIONS FOR ADMINISTRATION**
- 5 mg/mL injection to be diluted before use. For continuous or intermittent intravenous infusion dilute in Glucose 5% or Sodium Chloride 0.9%.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, spray

**Solution for injection**
- **ALFENTANIL** (non-proprietary)
  - Alfentanil (as Alfentanil hydrochloride) 500 microgram per 1 ml Alfentanil 1mg/2ml solution for injection ampoules | 10 ampoule (BNF) £7.00 Schedule 2 (CD)
  - Alfentanil 5mg/1ml solution for injection ampoules | 5 ampoule (BNF) £16.00 Schedule 2 (CD)
  - Alfentanil (as Alfentanil hydrochloride) 5 mg per 1 ml Alfentanil 5mg/1ml solution for injection ampoules | 10 ampoule (BNF) £25.00 Schedule 2 (CD)

**Co-codanol**

**INDICATIONS AND DOSE**
- **Mild to moderate pain (using co-codamol 8/500 preparations only)**
  - **BY MOUTH**
  - Adult: 8/500–16/1000 mg every 4–6 hours as required; maximum 64/4000 mg per day

- **Mild to moderate pain (using co-codamol 15/500 preparations only)**
  - **BY MOUTH**
  - Adult: 15/500–30/1000 mg every 4–6 hours as required; maximum 120/4000 mg per day

- **Severe pain (using co-codamol 30/500 preparations only)**
  - **BY MOUTH**
  - Adult: 30/500–60/1000 mg every 4–6 hours as required; maximum 240/4000 mg per day

**SOLPADOL® CAPLETS**
- **Severe pain**
  - **BY MOUTH**
  - Adult: 2 tablets every 4–6 hours as required; maximum 8 tablets per day

**KAPAKE® 15/500**
- **Mild to moderate pain**
  - **BY MOUTH**
  - Adult: 2 tablets every 4–6 hours as required; maximum 8 tablets per day

**SOLPADOL® EFFERVESCENT TABLETS**
- **Severe pain**
  - **BY MOUTH USING EF FERVESCENT TABLETS**
  - Adult: 2 tablets every 4–6 hours as required, tablets to be dispersed in water; maximum 8 tablets per day

**SOLPADOL® CAPSULES**
- **Severe pain**
  - **BY MOUTH**
  - Adult: 2 capsules every 4–6 hours as required; maximum 8 capsules per day

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**Important safety information**

See codeine phosphate p. 360 for MHRA/CHM advice for restrictions on the use of codeine as an analgesic in children.

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**CONTRA-INDICATIONS**
- Acute ulcerative colitis - antibiotic-associated colitis - children under 18 years who undergo the removal of tonsils or adenoids for the treatment of obstructive sleep apnoea - conditions where abdominal distension develops - conditions where inhibition of peristalsis should be avoided - known ultra-rapid codeine metabolisers

**CAUTIONS**
- Acute abdomen - alcohol dependence - avoid abrupt withdrawal after long-term treatment - cardiac arrhythmias - chronic alcoholism - chronic dehydration - chronic malnutrition - convulsive disorders - gallstones - hepatocellular insufficiency

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**CAUTIONS, FURTHER INFORMATION**
- **Variation in metabolism** The capacity to metabolise codeine to morphine can vary considerably between
PRESCRIBING AND DISPENSING INFORMATION

HEPATIC IMPAIRMENT
Considerably in their capacity to metabolise codeine of morphine overdose in infant.

STATED
When co-codamol tablets, dispersible (or effervescent) are the strengths in milligrams of codeine phosphate and proportions are expressed in the form $x/y$, where $x$ and $y$ is a mixture of codeine phosphate and paracetamol; the manufacturers include: oral suspension, oral solution,

Co-codamol is less
8 mg and paracetamol

Dose-related toxicity with

malaise.

Depression (with larger doses)

seizures - thrombocytopenia

Overdose Important: liver damage (and less frequently renal damage) following overdosage with paracetamol.

Important:

CO-CODAMOL (Non-proprietary)

Codeine phosphate 8 mg, Paracetamol 500 mg

- Co-codamol 8mg/500mg effervescent tablets | 32 tablet (£4.51 DT price = £2.52 Schedule 5 (CD Inv) | 60 tablet (£ no price available Schedule 5 (CD Inv) | 100 tablet (£12.97 DT price = £7.88 Schedule 5 (CD Inv)

- Codeine phosphate 30 mg, Paracetamol 500 mg

- Co-codamol 30mg/500mg effervescent tablets | 32 tablet (£5.40 DT price = £2.80 Schedule 5 (CD Inv) | 100 tablet (£19.20 DT price = £8.75 Schedule 5 (CD Inv)

- Tylex (UCB Pharma Ltd)

- Codeine phosphate 30 mg, Paracetamol 500 mg

- Tylex 30mg/500mg effervescent tablets | 100 tablet (£6.06 DT price = £8.75 Schedule 5 (CD Inv)

- Brands may include Codipar; Paracodol; Solpadol

Capsule

CAUTIONARY AND ADVISORY LABELS 2, 29, 30

- Exciipients: May contain Sulfites

LESS SUITABLE FOR PRESCRIBING

Co-codamol is less suitable for prescribing.

EXCEPTIONS TO LEGAL CATEGORY

Co-codamol 8/500 can be sold to the public in certain circumstances; for exemptions see Medicines, Ethics and Practice, London, Pharmaceutical Press (always consult latest edition).

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet

CO-CODAMOL (Non-proprietary)

Codeine phosphate 8 mg, Paracetamol 500 mg Co-codamol 8mg/500mg tablets | 30 tablet (£1.19 DT price = £1.19 Schedule 5 (CD Inv) | 32 tablet (£1.42 Schedule 5 (CD Inv) | 100 tablet (£54.43 DT price = £3.97 Schedule 5 (CD Inv) | 500 tablet (£119.85 Schedule 5 (CD Inv) | 1000 tablet (£393.70 Schedule 5 (CD Inv)

Co-codamol 8mg/500mg caplets | 32 tablet (£0.69 Schedule 5 (CD Inv)

- Codeine phosphate 15 mg, Paracetamol 500 mg Co-codamol 15mg/500mg tablets | 100 tablet (£15.00 DT price = £5.58 Schedule 5 (CD Inv)

Codeine phosphate 30 mg, Paracetamol 500 mg Co-codamol 30mg/500mg tablets | 100 tablet (£30.00 DT price = £5.80 Schedule 5 (CD Inv)

Co-codamol 30mg/500mg tablets | 30 tablet (£2.45 DT price = £1.74 Schedule 5 (CD Inv) | 100 tablet (£11.00 DT price = £5.80 Schedule 5 (CD Inv)

- Kapake (Galen Ltd)

- Codeine phosphate 15 mg, Paracetamol 500 mg Kapake 15mg/500mg tablets | 100 tablet (£7.01 DT price = £5.98 Schedule 5 (CD Inv)

Codeine phosphate 30 mg, Paracetamol 500 mg Kapake 30mg/500mg tablets | 100 tablet (£11.04 DT price = £5.90 Schedule 5 (CD Inv)

- Solpadol (Sanofi)

- Codeine phosphate 30 mg, Paracetamol 500 mg Solpadol 30mg/500mg caplets | 30 tablet (£2.02 DT price = £1.74 Schedule 5 (CD Inv) | 100 tablet (£63.75 DT price = £5.80 Schedule 5 (CD Inv)

- Brands may include Codipar; Migraleve Yellow; Panadol Ultra; Solpadine Max; Zapain

Effervescent tablet

CAUTIONARY AND ADVISORY LABELS 2, 13, 29, 30

- Excipients: May contain Sodium

CO-CODAMOL (Non-proprietary)

Codeine phosphate 8 mg, Paracetamol 500 mg Co-codamol 8mg/500mg effervescent tablets | 32 tablet (£4.51 DT price = £2.52 Schedule 5 (CD Inv) | 60 tablet (£ no price available Schedule 5 (CD Inv) | 100 tablet (£12.97 DT price = £7.88 Schedule 5 (CD Inv)

Codeine phosphate 30 mg, Paracetamol 500 mg Co-codamol 30mg/500mg effervescent tablets | 32 tablet (£5.40 DT price = £2.80 Schedule 5 (CD Inv) | 100 tablet (£19.20 DT price = £8.75 Schedule 5 (CD Inv)

- Tylex (UCB Pharma Ltd)

- Codeine phosphate 30 mg, Paracetamol 500 mg

- Tylex 30mg/500mg effervescent tablets | 100 tablet (£6.06 DT price = £8.75 Schedule 5 (CD Inv)

- Brands may include Codipar; Paracodol; Solpadol

Capsule

CAUTIONARY AND ADVISORY LABELS 2, 29, 30

- Exciipients: May contain Sulfites

CO-CODAMOL (Non-proprietary)

Codeine phosphate 8 mg, Paracetamol 500 mg Co-codamol 8mg/500mg capsules | 32 capsule (£3.68 DT price = £3.68 Schedule 5 (CD Inv) | 100 capsule (£11.50 DT price = £11.50 Schedule 5 (CD Inv)

Codeine phosphate 30 mg, Paracetamol 500 mg Co-codamol 30mg/500mg capsules | 100 capsule (£15.00 DT price = £4.10 Schedule 5 (CD Inv)

- Codipar (AMCo)

- Codeine phosphate 15 mg, Paracetamol 500 mg Codipar 15mg/500mg capsules | 100 capsule (£7.25 DT price = £17.25 Schedule 5 (CD Inv)

- Kapake (Galen Ltd)

- Codeine phosphate 30 mg, Paracetamol 500 mg Kapake 30mg/500mg capsules | 100 capsule (£6.04 DT price = £4.10 Schedule 5 (CD Inv)

- Solpadol (Sanofi)

- Codeine phosphate 30 mg, Paracetamol 500 mg Solpadol 30mg/500mg capsules | 100 capsule (£6.74 DT price = £4.10 Schedule 5 (CD Inv)

- Tylex (UCB Pharma Ltd)

- Codeine phosphate 30 mg, Paracetamol 500 mg

- Tylex 30mg/500mg capsules | 8 capsule (£0.61 Schedule 5 (CD Inv) | 24 capsule (£1.78 Schedule 5 (CD Inv) | 100 capsule (£7.93 DT price = £4.10 Schedule 5 (CD Inv)

- Zapain (AMCo)

- Codeine phosphate 30 mg, Paracetamol 500 mg

- Zapain 30mg/500mg capsules | 100 capsule (£3.85 DT price = £4.10 Schedule 5 (CD Inv)

Co-dyramol

INDICATIONS AND DOSE

Mild to moderate pain (using co-dyramol 10/500 preparations only)

BY MOUTH

- Adult: 10/500–20/1000 mg every 4–6 hours as required; maximum 80/4000 mg per day

Severe pain (using co-dyramol 20/500 preparations only)

BY MOUTH

- Adult: 20/500–40/1000 mg every 4–6 hours as required; maximum 160/4000 mg per day

Severe pain (using co-dyramol 30/500 preparations only)

BY MOUTH

- Adult: 30/500–60/1000 mg every 4–6 hours as required; maximum 240/4000 mg per day

Dose equivalence and conversion

A mixture of dihydrocodeine tartrate and paracetamol; the proportions are expressed in the form x/y, continued
**Pain**

where x and y are the strengths in milligrams of dihydrocodeine and paracetamol respectively.

- **CAUTIONS** Alcohol dependence - before administering, check when paracetamol last administered and cumulative paracetamol dose over previous 24 hours - chronic alcoholism - chronic dehydration - chronic malnutrition - hepatocellular insufficiency - pancreatitis - severe cor pulmonale

- **INTERACTIONS** → Appendix 1 (paracetamol).

- **SIDE-EFFECTS** Abdominal pain - acute generalised exanthematous pustulosis - blood disorders - leucopenia - malaise - neutropenia - pancreatitis - paraesthesia - paralytic ileus - skin reactions - Stevens-Johnson syndrome - thrombocytopenia - toxic epidermal necrolysis

- **BREAST FEEDING** Codeine should not be used in breast-feeding mothers

- **INTERACTIONS**

- **RENAI IMPAIRMENT**

- **BREAST FEEDING**

- **INTERACTIONS**

- **RENAL IMPAIRMENT** Reduce dose or avoid dihydrocodeine; increased and prolonged effect; increased cerebral sensitivity.

- **PRESCRIBING AND DISPENSING INFORMATION**

- **LESG SUITABLE FOR PRESCRIBING** Co-dyramol is less suitable for prescribing.

- **MILD SUITABLE FOR PRESCRIBING**

- **MEDICINAL FORMS**

- **CAUTIONARY AND ADVISORY LABELS** 2, 29, 30

  - **CO-DYDRAMOL (Non-proprietary)**

- **CODEINE PHOSPHATE**

  **INDICATIONS AND DOSE**

  **Acute diarrhoea**

  **BY MOUTH**

  - Child 12-17 years: 30 mg 3–4 times a day; usual dose 15–60 mg 3–4 times a day
  - Adult: 30 mg 3–4 times a day; usual dose 15–60 mg 3–4 times a day

  **Mild to moderate pain**

  **BY MOUTH**

  - Adult: 30–60 mg every 4 hours if required; maximum 240 mg per day

  **BY INTRAMUSCULAR INJECTION**

  - Adult: 30–60 mg every 4 hours if required

  **Short-term treatment of acute moderate pain**

  **BY MOUTH OR BY INTRAMUSCULAR INJECTION**

  - Child 12-17 years: 30–60 mg every 6 hours if required for maximum 3 days; maximum 240 mg per day

  **CONTRA-INDICATIONS**

  - Acute ulcerative colitis - antibiotic-associated colitis - children under 18 years who undergo the removal of tonsils or adenoids for the treatment of obstructive sleep apnoea - conditions where inhibition of peristalsis should be avoided - known ultra-rapid codeine metabolisers

  - Breastfeeding mothers

  **CAUTIONS**

  - Acute abdomen - cardiac arrhythmias - gallstones - not recommended for adolescents aged 12–18 years with breathing problems

  **CAUTIONS, FURTHER INFORMATION**

  **Variation in metabolism** The capacity to metabolise codeine to morphine can vary considerably between individuals; there is a marked increase in morphine toxicity in patients who are ultra-rapid codeine
metabolisers (CYP2D6 ultra-rapid metabolisers) and a reduced therapeutic effect in poor codeine metabolisers.

**SIDE-EFFECTS** Abdominal pain - anorexia - antidiuretic effect - hypothermia - malaise - muscle fasciculation - pancreatitis - seizures

**BREAST FEEDING** Avoid - although amount usually too small to be harmful, mothers vary considerably in their capacity to metabolise codeine - risk of morphine overdose in infant.

**RENAL IMPAIRMENT** Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

**PRESCRIBING AND DISPENSING INFORMATION** BP directs that when Diabetic Codeine Linctus is prescribed, Codeine Linctus formulated with a vehicle appropriate for administration to diabetics, whether or not labelled 'Diabetic Codeine Linctus', shall be dispensed or supplied.

**PATIENT AND CARER ADVICE**

*Medicines for Children leaflet: Codeine phosphate for pain* www.medicinesforchildren.org.uk/codeine-phosphate-pain-0

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: suppository, solution for injection, oral suspension, oral solution

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 2**

▶ **CODEINE PHOSPHATE (Non-proprietary)**

**Codeine phosphate 15 mg** Codeine 15mg tablets | 28 tablet (Pb) £1.90 DT price = £1.26 Schedule 5 (CD Inv) | 50 tablet (Pb) no price available Schedule 5 (CD Inv) | 100 tablet (Pb) £6.60 DT price = £4.46 Schedule 5 (CD Inv) | 500 tablet (Pb) no price available Schedule 5 (CD Inv)

**Codeine phosphate 30 mg** Codeine 30mg tablets | 28 tablet (Pb) £2.50 DT price = £1.52 Schedule 5 (CD Inv) | 50 tablet (Pb) no price available Schedule 5 (CD Inv) | 100 tablet (Pb) £5.68 DT price = £3.43 Schedule 5 (CD Inv) | 500 tablet (Pb) £44.00 Schedule 5 (CD Inv)

**Codeine phosphate 60 mg** Codeine 60mg tablets | 28 tablet (Pb) £5.95 DT price = £2.70 Schedule 5 (CD Inv)

**Oral solution**

**CAUTIONARY AND ADVISORY LABELS 2**

▶ **CODEINE PHOSPHATE (Non-proprietary)**

**Codeine phosphate 3 mg per 1 ml** Codeine 15mg/5ml linctus sugar free (sugar-free) | 200 ml (P) £3.06 DT price = £1.69 Schedule 5 (CD Inv) (sugar-free) | 2000 ml (P) £16.90 Schedule 5 (CD Inv)

Codeine 15mg/5ml linctus | 200 ml (Pb) £1.79 DT price = £1.79 Schedule 5 (CD Inv) | 2000 ml (P) no price available Schedule 5 (CD Inv)

**Codeine phosphate 5 mg per 1 ml** Codeine 25mg/5ml oral solution | 500 ml (Pb) £6.53 DT price = £6.53 Schedule 5 (CD Inv)

▶ **Galcodeine (Thornton & Ross Ltd)**

**Codeine phosphate 3 mg per 1 ml** Galcodeine 15mg/5ml linctus (sugar-free) | 2000 ml (P) £9.90 Schedule 5 (CD Inv)

**Solution for injection**

▶ **CODEINE PHOSPHATE (Non-proprietary)**

**Codeine phosphate 60 mg per 1 ml** Codeine 60mg/1ml solution for injection ampoules | 10 ampoule (Pb) £23.70–25.00 Schedule 2 (CD)

**Diamorphine hydrochloride (Heroin hydrochloride)**

**INDICATIONS AND DOSE**

Acute pain

**BY INTRAMUSCULAR INJECTION OR BY SUBCUTANEOUS INJECTION**

▶ Adult: 5 mg every 4 hours if required

**BY SLOW INTRAVENOUS INJECTION**

▶ Adult: 1.25–2.5 mg every 4 hours if required

**Acute pain (heavier, well-muscled patients)**

**BY INTRAMUSCULAR INJECTION OR BY SUBCUTANEOUS INJECTION**

▶ Adult: Up to 10 mg every 4 hours if required

**BY SLOW INTRAVENOUS INJECTION**

▶ Adult: 2.5–5 mg every 4 hours if required

**Chronic pain not currently treated with a strong opioid analgesic**

**BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION**

▶ Adult: Initially 2.5–5 mg every 4 hours, adjusted according to response

**BY SUBCUTANEOUS INFUSION**

▶ Adult: Initially 5–10 mg, adjusted according to response, dose to be administered over 24 hours

**Acute pulmonary oedema**

**BY SLOW INTRAVENOUS INJECTION**

▶ Adult: 2.5–5 mg, dose to be administered at a rate of 1 mg/minute

**Myocardial infarction**

**BY SLOW INTRAVENOUS INJECTION**

▶ Adult: 5 mg, followed by 2.5–5 mg if required, dose to be administered at a rate of 1–2 mg/minute

**Elderly: 2.5 mg, followed by 1.25–2.5 mg if required, dose to be administered at a rate of 1–2 mg/minute

**Myocardial infarction (frail patients)**

**BY SLOW INTRAVENOUS INJECTION**

▶ Adult: 2.5 mg, followed by 1.25–2.5 mg if required, dose to be administered at a rate of 1–2 mg/minute

**CONTRA-INDICATIONS** Delayed gastric emptying - phaeochromocytoma

**CAUTIONS** CNS depression - severe cor pulmonale - severe diarrhoea - toxic psychosis

**SIDE-EFFECTS** Anorexia - asthenia - myocardial infarction - raised intracranial pressure - syncope - taste disturbance

**BREAST FEEDING** Therapeutic doses unlikely to affect infant; withdrawal symptoms in infants of dependent mothers; breast-feeding not best method of treating dependence in offspring.

**RENAL IMPAIRMENT** Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: powder for solution for injection, suppository, solution for injection, oral solution, capsule, impregnated cigarette

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 2**

▶ **DIAMORPHINE HYDROCHLORIDE (Non-proprietary)**

**Diamorphine hydrochloride 10 mg** Diamorphine 10mg tablets | 100 tablet (Pb) £24.09 DT price = £24.09 Schedule 2 (CD)

**Powder for solution for injection**

▶ **DIAMORPHINE HYDROCHLORIDE (Non-proprietary)**

**Diamorphine hydrochloride 5 mg** Diamorphine 5mg powder for solution for injection ampoules | 5 vial (Pb) £11.89–15.00 Schedule 2 (CD)

Diamorphine 5mg powder for solution for injection ampoules | 5 ampoule (Pb) £11.36 DT price = £11.36 Schedule 2 (CD)

**Diamorphine hydrochloride 10 mg** Diamorphine 10mg powder for solution for injection ampoules | 5 ampoule (Pb) £15.00 DT price = £15.00 Schedule 2 (CD)

Diamorphine 10mg powder for solution for injection ampoules | 5 vial (Pb) £15.99–19.00 Schedule 2 (CD)

**Diamorphine hydrochloride 30 mg** Diamorphine 30mg powder for solution for injection ampoules | 5 vial (Pb) £16.99–21.00 Schedule 2 (CD)

Diamorphine 30mg powder for solution for injection ampoules | 5 ampoule (Pb) £14.02 DT price = £14.02 Schedule 2 (CD)

**Diamorphine hydrochloride 100 mg** Diamorphine 100mg powder for solution for injection ampoules | 5 vial (Pb) £42.99–54.00 Schedule 2 (CD)
Dihydrocodeine tartrate

**INDICATIONS AND DOSE**

**Moderate to severe pain**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

- Child 4–11 years: 0.5–1 mg/kg every 4–6 hours (max. per dose 30 mg)
- Child 12-17 years: 30 mg every 4–6 hours
- Adult: 30 mg every 4–6 hours as required

**BY DEEP SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION**

- Adult: Up to 50 mg every 4–6 hours if required

**Chronic severe pain**

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

- Child 12-17 years: 60–120 mg every 12 hours
- Adult: 60–120 mg every 12 hours

**DF118 FORTE®**

**Severe pain**

**BY MOUTH**

- Child 12-17 years: 40–80 mg 3 times a day; maximum 240 mg per day
- Adult: 40–80 mg 3 times a day; maximum 240 mg per day

**SIDE-EFFECTS**

Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

**PROFESSIONAL INFORMATION**

Dental practitioners’ formulary Dihydrocodeine tablets 30 mg may be prescribed.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

CAUTIONARY AND ADVISORY LABELS

- DIHYDROCODEINE TARTRATE (Non-proprietary)
  - Dihydrocodeine tartrate 30 mg
  - 28 tablet (CD Inv) £1.75 DT price = £1.35 Schedule 5 (CD Inv)
  - 30 tablet (CD Inv) £1.56 Schedule 5 (CD Inv) 100 tablet (CD Inv) £6.81 DT price = £4.82 Schedule 5 (CD Inv)
  - 500 tablet (CD Inv) £24.11 Schedule 5 (CD Inv)
  - DF 118 (Martintrade Pharmaceuticals Ltd)
  - Dihydrocodeine tartrate 40 mg
  - DF 118 Forte 40mg tablets 100 tablet (CD Inv) £11.51 DT price = £11.51 Schedule 5 (CD Inv)

**Modified-release tablet**

CAUTIONARY AND ADVISORY LABELS

- DMC Continus (Napp Pharmaceuticals Ltd)
  - Dihydrocodeine tartrate 60 mg
  - 56 tablet (CD Inv) £5.20 DT price = £5.20 Schedule 5 (CD Inv)
  - Dihydrocodeine tartrate 90 mg
  - 56 tablet (CD Inv) £8.66 DT price = £8.66 Schedule 5 (CD Inv)
  - Dihydrocodeine tartrate 120 mg
  - 56 tablet (CD Inv) £10.95 DT price = £10.95 Schedule 5 (CD Inv)

**Oral solution**

CAUTIONARY AND ADVISORY LABELS

- DIHYDROCODEINE TARTRATE (Non-proprietary)
  - Dihydrocodeine tartrate 2 mg per 1 ml
  - Dihydrocodeine tartrate 2 mg/5ml oral solution 150 ml (CD Inv) £6.20 Schedule 5 (CD Inv)

**Solution for injection**

- DIHYDROCODEINE TARTRATE (Non-proprietary)
  - Dihydrocodeine tartrate 50 mg per 1 ml

**Dipipanone hydrochloride with cyclizine**

**INDICATIONS AND DOSE**

**Acute pain**

**BY MOUTH**

- Adult: Initially 1 tablet every 6 hours, then increased if necessary up to 3 tablets every 6 hours, dose to be increased gradually

**CAUTIONS**

Diabetes mellitus - palliative care (not recommended) - phaeochromocytoma

**SIDE-EFFECTS**

Psychosis - raised intracranial pressure - restlessness

**BREAST FEEDING**

No information available.

**RENAI IMPAIRMENT**

Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- DIPIPANONE HYDROCHLORIDE WITH CYCLIZINE (Non-proprietary)
  - Cyclizine hydrochloride 30 mg, Dipipanone hydrochloride 10 mg
  - Dipipanone 10mg / Cyclizine 30mg tablets 50 tablet (CD) £181.67 DT price = £181.67 Schedule 2 (CD)

**Fentanyl**

**INDICATIONS AND DOSE**

Chronic intractable pain not currently treated with a strong opioid analgesic

**BY TRANSDERMAL APPLICATION**

- Child 16-17 years: Initially 12 micrograms/hour every 72 hours, alternatively initially 25 micrograms/hour every 72 hours, when starting, evaluation of the analgesic effect should not be made before the system has been worn for 24 hours (to allow for the gradual increase in plasma-fentanyl concentration)—previous analgesic therapy should be phased out gradually from time of first patch application, dose should be adjusted at 48–72 hour intervals in steps of 12–25 micrograms/hour if necessary, more than one patch may be used at a time (but applied at the same time to avoid confusion)—consider additional or alternative analgesic therapy if dose required exceeds 300 micrograms/hour (important: it takes 17 hours or more for the plasma-fentanyl concentration to decrease by 50%—replacement opioid therapy should be initiated at a low dose and increased gradually)
- Adult: Initially 12 micrograms/hour every 72 hours, alternatively initially 25 micrograms/hour every 72 hours, when starting, evaluation of the analgesic effect should not be made before the system has been worn for 24 hours (to allow for the gradual increase in plasma-fentanyl concentration)—previous analgesic

**Price**

- £24.11 Schedule 5 (CD Inv)
therapy should be phased out gradually from time of first patch application, dose should be adjusted at 48–72 hour intervals in steps of 12–25 micrograms/hour if necessary, more than one patch may be used at a time (but applied at the same time to avoid confusion)—consider additional or alternative analgesic therapy if dose required exceeds 300 micrograms/hour (important: it takes 17 hours or more for the plasma-fentanyl concentration to decrease by 50%—replacement opioid therapy should be initiated at a low dose and increased gradually)

**Chronic intractable pain currently treated with a strong opioid analgesic**

**BY TRANSDERMAL APPLICATION**

- Child 2–17 years: Initial dose based on previous 24-hour opioid requirement (consult product literature), for evaluating analgesic efficacy and dose increments, see under *Chronic intractable pain not currently treated with a strong opioid analgesic*, for conversion from long-term oral morphine to transdermal fentanyl, see *Pain management with opioids* under p. 20.
- Adult: Initial dose based on previous 24-hour opioid requirement (consult product literature), for evaluating analgesic efficacy and dose increments, see under *Chronic intractable pain not currently treated with a strong opioid analgesic*, for conversion from long-term oral morphine to transdermal fentanyl, see *Pain management with opioids* under p. 20.

**Spontaneous respiration: analgesia and enhancement of anaesthesia during operation**

**BY SLOW INTRAVENOUS INJECTION**

- Adult: Initially 50–100 micrograms (max. per dose 200 micrograms), dose maximum on specialist advice, then 25–50 micrograms as required
- INTRAVENOUS INFUSION
  - Adult: 3–4.8 micrograms/kg/hour, adjusted according to response

**Assisted ventilation: analgesia and enhancement of anaesthesia during operation**

**BY SLOW INTRAVENOUS INJECTION**

- Adult: Initially 300–3500 micrograms, then 100–200 micrograms as required
- INTRAVENOUS INFUSION
  - Adult: Initially 10 micrograms/kg, dose to be given over 10 minutes, then 6 micrograms/kg/hour, adjusted according to response, may require up to 180 micrograms/kg/hour during cardiac surgery

**Assisted ventilation: analgesia and respiratory depression in intensive care**

**BY SLOW INTRAVENOUS INJECTION**

- Adult: Initially 300–3500 micrograms, then 100–200 micrograms as required
- INTRAVENOUS INFUSION
  - Adult: Initially 10 micrograms/kg, dose to be given over 10 minutes, then 6 micrograms/kg/hour, adjusted according to response, may require up to 180 micrograms/kg/hour during cardiac surgery

**Breakthrough pain in patients receiving opioid therapy for chronic cancer pain**

**INITIALLY BY BUCCAL ADMINISTRATION USING LOZENGES**

- Child 16–17 years: Initially 200 micrograms, dose to be given over 15 minutes, then (by buccal administration) 200 micrograms after 15 minutes if required, no more than 2 dose units for each pain episode; if adequate pain relief not achieved with 1 dose unit for consecutive breakthrough pain episodes, increase the strength of the dose unit until adequate pain relief achieved with 4 lozenges or less daily, if more than 4 episodes of breakthrough pain each day, adjust background analgesia
- Adult: Initially 200 micrograms, dose to be given over 15 minutes, then (by buccal administration) 200 micrograms after 15 minutes if required, no more than 2 dose units for each pain episode; if adequate pain relief not achieved with 1 dose unit for consecutive breakthrough pain episodes, increase the strength of the dose unit until adequate pain relief achieved with 4 lozenges or less daily, if more than 4 episodes of breakthrough pain each day, adjust background analgesia

**BY BUCCAL ADMINISTRATION USING BUCCAL FILMS**

- Adult: Initially 200 micrograms, adjusted according to response, consult product literature for information on dose adjustments, maximum 1.2 mg per episode of breakthrough pain; leave at least 4 hours between treatment of episodes of breakthrough pain, if more than 4 episodes of breakthrough pain each day occur on more than 4 consecutive days, adjust background analgesia

**Doses at extremes of body-weight**

To avoid excessive dosage in obese patients, dose may need to be calculated on the basis of ideal bodyweight.

**Dose equivalence and conversion**

Fentanyl films are not bioequivalent to other fentanyl preparations.

Fentanyl preparations for the treatment of breakthrough pain are not interchangeable; if patients are switched from another fentanyl-containing preparation, a new dose titration is required.

**ABSTRAL®**

**Breakthrough pain in patients receiving opioid therapy for chronic cancer pain**

**BY MOUTH USING SUBLINGUAL TABLETS**

- Adult: Initially 100 micrograms, then 100 micrograms after 15–30 minutes if required, dose to be adjusted according to response—consult product literature, no more than 2 dose units 15–30 minutes apart, for each pain episode; max. 800 micrograms per episode of breakthrough pain; leave at least 2 hours between treatment of episodes of breakthrough pain, if more than 4 episodes of breakthrough pain each day, adjust background analgesia

**RECVIT® SUBLINGUAL TABLETS**

**Breakthrough pain in patients receiving opioid therapy for chronic cancer pain**

**BY MOUTH**

- Adult: Initially 133 micrograms, then 133 micrograms after 15–30 minutes (max. per dose 800 micrograms), dose to be repeated only if necessary: Consult product literature for dose adjustments, no more than 2 dose units, 15–30 minutes apart, for each pain episode, maximum of 800 micrograms per episode of breakthrough pain, if more than 4 episodes of breakthrough pain each day, adjust background analgesia; maximum 4 doses per day

**EFFENTORA®**

**Breakthrough pain in patients receiving opioid therapy for chronic cancer pain**

**BY MOUTH USING SUBLINGUAL TABLETS**

- Adult: Initially 100 micrograms, then 100 micrograms after 30 minutes if required, dose to be adjusted according to response—consult product literature, no more than 2 dose units for each pain episode; max. 800 micrograms per episode of breakthrough pain; leave at least 4 hours between treatment of episodes of breakthrough pain during titration continued
Breakthrough pain in patients receiving opioid therapy for chronic cancer pain

**PECENT®**

Adult: Initially 100 micrograms, adjusted according to response, dose to be administered into one nostril only, maximum 2 sprays for each pain episode and minimum 4 hours between treatment of each pain episode, if more than 4 breakthrough pain episodes daily, adjust background analgesia

**INSTANYL®**

Adult: Initially 50 micrograms, dose to be administered into one nostril, then 50 micrograms after 10 minutes if required, dose to be adjusted according to response, maximum 2 sprays for each pain episode and minimum 4 hours between treatment of each pain episode, if more than 4 breakthrough pain episodes daily, adjust background analgesia

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- Common or very common Abdominal pain • aethesiaphobia • anorexia • anxiety • appetite changes • application-site reactions • diarrhoea • dyspepsia • dysphoria • gastrointestinal reflux disease • hypertension • myocardial infarction • pharyngitis • rhinitis • stomatitis • tremor • vasodilation
- Uncommon Amnesia • arthralgia • blood disorders • chills • depressed level of consciousness • dysgeusia • flatulence • hyperventilation • ileus • impaired concentration • impaired coordination • loss of consciousness • malaise • parosmia • pyrexia • seizures • speech disorder • thirst • thrombocytopenia
- Rare Hiccups
- Very rare Apnoea • arrhythmia • ataxia • bladder pain • delusions • haemoptysis

**SPECIFIC SIDE-EFFECTS**

- Common or very common With intravenous use myoclonic movements
- Uncommon With intravenous use laryngospasm
- Rare With intravenous use astyole • insomia

**FURTHER INFORMATION**

**SIDE-EFFECTS, FURTHER INFORMATION**

**Fever or external heat** Monitor patients using patches for increased side-effects if fever present (increased absorption possible); avoid exposing application site to external heat, for example a hot bath or sauna (may also increase absorption).

**Muscle rigidity** Intravenous fentanyl can cause muscle rigidity, particularly of the chest wall or jaw; this can be managed by the use of neuromuscular blocking drugs.

**CAUTIONS**

**GENERAL CAUTIONS** Cerebral tumour • diabetes mellitus (with Actiq® lozenges) • impaired consciousness

**SPECIFIC CAUTIONS**

- With buccal use mucositis—absorption from oral preparations may be increased, caution during dose titration (in adults)

**CAUTIONS, FURTHER INFORMATION**

**Transdermal preparations** Transdermal fentanyl patches are not suitable for acute pain or in those patients whose analgesic requirements are changing rapidly because the long time to steady state prevents rapid titration of the dose.

- Risk of fatal respiratory depression, particularly in patients not previously treated with a strong opioid and in those patients whose analgesic requirements are changing rapidly because the long time to steady state prevents rapid titration of the dose.

**Repeated intra-operative doses** Repeated intra-operative doses should be given with care since the resulting respiratory depression can persist postoperatively and occasionally it may become apparent for the first time postoperatively when monitoring of the patient might be less intensive.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Fentanyl patches for pain

www.medicinesforchildren.org.uk/fentanyl-patches-for-pain

Medicines for Children leaflet: Fentanyl lozenges for pain

www.medicinesforchildren.org.uk/fentanyl-lozenges-for-pain

With transdermal use Patients and carers should be informed about safe use, including correct administration and disposal, strict adherence to dosage instructions, and the symptoms and signs of opioid overdose. Patches should be removed immediately in case of breathing difficulties, marked drowsiness, confusion, dizziness, or
impaired speech, and patients and carers should seek prompt medical attention.

- With buccal use Patients or carers should be given advice on how to administer fentanyl buccal films or fentanyl lozenges.
- With intranasal use Patients or carers should be given advice on how to administer fentanyl nasal spray.

**ABSTRAL**

Patients should be advised not to eat or drink until the tablet is completely dissolved.

In patients with a dry mouth, the buccal mucosa may be moistened with water before administration of tablet.

**RECVIT SUBLINGUAL TABLETS**

Patients should be advised not to eat or drink until the tablet is completely dissolved; after 30 minutes, if any remnants remain, they may be swallowed. In patients with a dry mouth, the buccal mucosa may be moistened with water before administration of tablet.

**EFFENTORA**

Patients or carers should be given advice on how to administer Effentora buccal tablets. Patients should be advised not to eat or drink until the tablet is completely dissolved; after 30 minutes, if any remnants remain, they may be swallowed with a glass of water. Patients with a dry mouth should be advised to drink water to moisten the buccal mucosa before administration of the tablets; if appropriate effervescence does not occur, a switch of therapy may be advised.

**PECFENT INSTANYL**

Avoid concomitant use of other nasal preparations. Patients or carers should be given advice on how to administer the spray.

### NATIONAL FUNDING/ACCESS DECISIONS

**ABSTRAL**

The Scottish Medicines Consortium has advised (January 2009) that Abstral sublingual tablets should be restricted for use within NHS Scotland for the management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain, when other short-acting opioids are unsuitable.

**EFFENTORA**

The Scottish Medicines Consortium has advised that Effentora buccal tablets should be restricted for the management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain, when other short-acting opioids are unsuitable.

**PECFENT**

The Scottish Medicines Consortium has advised that PecFent nasal spray should be restricted for use within NHS Scotland for the management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain, when other short-acting opioids are unsuitable.

**INSTANYL**

The Scottish Medicines Consortium has advised that Instanyl nasal spray should be restricted for use within NHS Scotland for the management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain, when other short-acting opioids are unsuitable.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, solution for infusion, infusion.

### SUBLINGUAL TABLET

**CAUTIONARY AND ADVISORY LABELS** 2, 26

- **Abstral** (ProStrakan Ltd)
  - Fentanyl (as Fentanyl citrate) 100 microgram
    - Abstral 100microgram sublingual tablets (sugar-free) | 10 tablet PSM £49.99 Schedule 2 (CD) | 30 tablet PSM £149.70 Schedule 2 (CD)
  - Fentanyl (as Fentanyl citrate) 50 microgram
    - Abstral 50microgram sublingual tablets (sugar-free) | 10 tablet PSM £49.99 Schedule 2 (CD) | 30 tablet PSM £149.70 Schedule 2 (CD)
  - Fentanyl (as Fentanyl citrate) 25 microgram
    - Abstral 25microgram sublingual tablets (sugar-free) | 10 tablet PSM £49.99 Schedule 2 (CD) | 30 tablet PSM £149.70 Schedule 2 (CD)

- **Recivit** (Grunenthal Ltd)
  - Fentanyl (as Fentanyl citrate) 133 microgram
    - Recivit 133microgram sublingual tablets (sugar-free) | 30 tablet PSM £127.20 Schedule 2 (CD)
  - Fentanyl (as Fentanyl citrate) 267 microgram
    - Recivit 267microgram sublingual tablets (sugar-free) | 30 tablet PSM £127.20 Schedule 2 (CD)
  - Fentanyl (as Fentanyl citrate) 400 microgram
    - Recivit 400microgram sublingual tablets (sugar-free) | 30 tablet PSM £127.20 Schedule 2 (CD)
  - Fentanyl (as Fentanyl citrate) 533 microgram
    - Recivit 533microgram sublingual tablets (sugar-free) | 30 tablet PSM £127.20 Schedule 2 (CD)

- **Effentora** (Teva UK Ltd)
  - Fentanyl (as Fentanyl citrate) 100 microgram
    - Effentora 100microgram buccal tablets (sugar-free) | 4 tablet PSM £19.96 Schedule 2 (CD) | 28 tablet PSM £139.72 DT price + £139.72 Schedule 2 (CD)
  - Fentanyl (as Fentanyl citrate) 200 microgram
    - Effentora 200microgram buccal tablets (sugar-free) | 4 tablet PSM £19.96 Schedule 2 (CD) | 28 tablet PSM £139.72 DT price + £139.72 Schedule 2 (CD)
  - Fentanyl (as Fentanyl citrate) 400 microgram
    - Effentora 400microgram buccal tablets (sugar-free) | 4 tablet PSM £19.96 Schedule 2 (CD) | 28 tablet PSM £139.72 DT price + £139.72 Schedule 2 (CD)
  - Fentanyl (as Fentanyl citrate) 600 microgram
    - Effentora 600microgram buccal tablets (sugar-free) | 4 tablet PSM £19.96 Schedule 2 (CD) | 28 tablet PSM £139.72 DT price + £139.72 Schedule 2 (CD)
  - Fentanyl (as Fentanyl citrate) 800 microgram
    - Effentora 800microgram buccal tablets (sugar-free) | 4 tablet PSM £19.96 Schedule 2 (CD) | 28 tablet PSM £139.72 DT price + £139.72 Schedule 2 (CD)

**Buccal tablet**

**CAUTIONARY AND ADVISORY LABELS** 2

- **Effentora** (Teva UK Ltd)
  - Fentanyl (as Fentanyl citrate) 100 microgram
    - Effentora 100microgram buccal tablets (sugar-free) | 4 tablet PSM £19.96 Schedule 2 (CD) | 28 tablet PSM £139.72 DT price + £139.72 Schedule 2 (CD)
  - Fentanyl (as Fentanyl citrate) 200 microgram
    - Effentora 200microgram buccal tablets (sugar-free) | 4 tablet PSM £19.96 Schedule 2 (CD) | 28 tablet PSM £139.72 DT price + £139.72 Schedule 2 (CD)
  - Fentanyl (as Fentanyl citrate) 400 microgram
    - Effentora 400microgram buccal tablets (sugar-free) | 4 tablet PSM £19.96 Schedule 2 (CD) | 28 tablet PSM £139.72 DT price + £139.72 Schedule 2 (CD)
  - Fentanyl (as Fentanyl citrate) 600 microgram
    - Effentora 600microgram buccal tablets (sugar-free) | 4 tablet PSM £19.96 Schedule 2 (CD) | 28 tablet PSM £139.72 DT price + £139.72 Schedule 2 (CD)
  - Fentanyl (as Fentanyl citrate) 800 microgram
    - Effentora 800microgram buccal tablets (sugar-free) | 4 tablet PSM £19.96 Schedule 2 (CD) | 28 tablet PSM £139.72 DT price + £139.72 Schedule 2 (CD)

**Buccal film**

**CAUTIONARY AND ADVISORY LABELS** 2

- **Breakyl** (Meda Pharmaceuticals Ltd)
  - Fentanyl (as Fentanyl citrate) 200 microgram
    - Breakyl 200microgram buccal films (sugar-free) | 10 film PSM £49.90 Schedule 2 (CD)
  - Fentanyl (as Fentanyl citrate) 400 microgram
    - Breakyl 400microgram buccal films (sugar-free) | 10 film PSM £49.90 Schedule 2 (CD)
  - Fentanyl (as Fentanyl citrate) 800 microgram
    - Breakyl 800microgram buccal films (sugar-free) | 28 film PSM £139.72 Schedule 2 (CD)
Hydromorphone hydrochloride

INDICATIONS AND DOSE
Severe pain in cancer
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
- Child 12-17 years: 1.3 mg every 4 hours, dose to be increased if necessary according to severity of pain
- Adult: 1.3 mg every 4 hours, dose to be increased if necessary according to severity of pain

BY MOUTH USING MODIFIED-RELEASE MEDICINES
- Child 12-17 years: 4 mg every 12 hours, dose to be increased if necessary according to severity of pain
- Adult: 4 mg every 12 hours, dose to be increased if necessary according to severity of pain

CONTRA-INDICATIONS
- Acute abdomen
- Pancreatitis
- Acute abdomen

CAUTIONS
- Pancreatitis
- Abdominal pain
- Anxiety

SIDE-EFFECTS
- Common or very common: Abdominal pain, anorexia, anxiety
- Uncommon: Agitation, diarrhoea, dysgeusia, dyskinesia, myoclonus, paraesthesia, paralytic ileus, peripheral oedema, seizures, tremor
- No information available.

BREAST FEEDING
Avoid — no information available.

RENAL IMPAIRMENT
Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

DIRECTIONS FOR ADMINISTRATION
For immediate-release capsules, swallow whole capsule or sprinkle contents on soft food. For modified-release capsules, swallow whole or open capsule and sprinkle contents on soft cold food (swallow the pellets within the capsule whole; do not crush or chew).

PATIENT AND CARER ADVICE
Patients or carers should be given advice on how to administer hydromorphone hydrochloride capsules and modified-release capsules.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, oral solution.
Meptazinol

INDICATIONS AND DOSE
Moderate to severe pain, including post-operative and obstetric pain and renal colic
BY MOUTH
Adult: 200 mg every 3–6 hours as required
BY INTRAMUSCULAR INJECTION
Adult: 75–100 mg every 2–4 hours if required
BY SLOW INTRAVENOUS INJECTION
Adult: 50–100 mg every 2–4 hours if required
Obstetric analgesia
BY INTRAMUSCULAR INJECTION
Adult: 2 mg/kg, usual dose 100–150 mg

CONTRA-INDICATIONS
Myocardial infarction - phaeochromocytoma
SIDE-EFFECTS
Abdominal pain - can induce withdrawal symptoms in patients dependent on opioids - diarrhoea - dyspepsia - hypothermia
Overdose: Effects only partially reversed by naloxone.
BREAST FEEDING
Use only if potential benefit outweighs risk.
RENAL IMPAIRMENT
Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
Tablet
CAUTIONARY AND ADVISORY LABELS 2
Meptazinol (as Meptazinol hydrochloride) 200 mg Meptid 200mg tablets | 112 tablet [Pos] £22.11 DT price = £22.11
Solution for injection
Meptazinol (as Meptazinol hydrochloride) 100 mg per 1 ml Meptid 100mg/1ml solution for injection ampoules | 10 ampoule [Pos] £19.21

Morphine

INDICATIONS AND DOSE
Pain
BY SUBCUTANEOUS INJECTION
Child 1–5 months: Initially 100–200 micrograms/kg every 4 hours, adjusted according to response
Child 6 months–1 year: Initially 100–200 micrograms/kg every 4 hours, adjusted according to response
Child 2–11 years: Initially 200 micrograms/kg every 4 hours, adjusted according to response
Child 12–17 years: Initially 2.5–10 mg every 4 hours, adjusted according to response
BY INTRAVENOUS INJECTION
Child 1–5 months: 100 micrograms/kg every 6 hours, adjusted according to response, dose to be administered over at least 5 minutes, alternatively (by intravenous injection) initially 100 micrograms/kg, dose to be administered over at least 5 minutes, followed by (by continuous intravenous infusion) 10–30 micrograms/kg/hour, adjusted according to response
Child 6 months–11 years: 100 micrograms/kg every 4 hours, adjusted according to response, dose to be administered over at least 5 minutes, alternatively (by intravenous injection) initially 100 micrograms/kg, dose to be administered over at least 5 minutes, followed by (by continuous intravenous infusion) 20–30 micrograms/kg/hour, adjusted according to response
Child 12–17 years: 5 mg every 4 hours, adjusted according to response, dose to be administered over at least 5 minutes, alternatively (by intravenous injection) initially 5 mg, dose to be administered over at least 5 minutes, followed by (by continuous intravenous infusion) 20–30 micrograms/kg/hour, adjusted according to response
Child 1–2 months: Initially 50–100 micrograms/kg every 4 hours, adjusted according to response
Child 2–11 months: 200 micrograms/kg every 4 hours, adjusted according to response
Child 1 year: Initially 200–300 micrograms/kg every 4 hours, adjusted according to response
Child 2–11 years: Initially 200–300 micrograms/kg every 4 hours, max. per dose 10 mg, adjusted according to response
Child 12–17 years: Initially 5–10 mg every 4 hours, adjusted according to response

Acute pain
BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION
Adult: Initially 10 mg every 4 hours, adjusted according to response, subcutaneous injection not suitable for oedematous patients, dose can be given more frequently during titration, use dose for elderly in frail patients
Elderly: Initially 5 mg every 4 hours, adjusted according to response, subcutaneous injection not suitable for oedematous patients, dose can be given more frequently during titration
BY SLOW INTRAVENOUS INJECTION
Adult: Initially 5 mg every 4 hours, adjusted according to response, subcutaneous injection not suitable for oedematous patients, dose can be adjusted more frequently during titration, reduced dose recommended in frail and elderly patients

Chronic pain
BY MOUTH OR BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION
Adult: Initially 5–10 mg every 4 hours, adjusted according to response, subcutaneous injection not suitable for oedematous patients
BY RECTUM
Adult: Initially 15–30 mg every 4 hours, adjusted according to response
Pain (with modified-release 12-hourly preparations)
BY MOUTH USING MODIFIED-RELEASE MEDICINES
Adult: Every 12 hours, dose adjusted according to daily morphine requirements, dosage requirements should be reviewed if the brand is altered
**Pain**

<table>
<thead>
<tr>
<th>Pain with modified-release 24-hourly preparations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BY MOUTH USING MODIFIED-RELEASE MEDICINES</strong></td>
</tr>
<tr>
<td>▶ Adult: Every 24 hours, dose adjusted according to daily morphine requirements, dosage requirements should be reviewed if the brand is altered</td>
</tr>
</tbody>
</table>

**Pain in palliative care**

<table>
<thead>
<tr>
<th>BY MOUTH USING IMMEDIATE-RELEASE MEDICINES</th>
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<tbody>
<tr>
<td>▶ Adult: Usual dose 30–200 mg every 4 hours, for management of breakthrough pain and other general advice, see Pain management with opioids under p. 20</td>
</tr>
<tr>
<td>▶ Adult: Usual dose 100–600 mg every 12 hours, for management of breakthrough pain and other general advice, see Pain management with opioids under p. 20</td>
</tr>
</tbody>
</table>

**Pain management in palliative care (starting dose for opioid-naive patients)**

<table>
<thead>
<tr>
<th>BY MOUTH</th>
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</thead>
<tbody>
<tr>
<td>▶ Adult: 20–30 mg daily in divided doses, dose for either immediate-release or a 12-hourly modified-release preparation, for management of breakthrough pain and other general advice, see Pain management with opioids under p. 20</td>
</tr>
<tr>
<td>▶ Adult: 40–60 mg daily in divided doses, for management of breakthrough pain and other general advice, see Pain management with opioids under p. 20</td>
</tr>
</tbody>
</table>

**Cough in terminal disease**

<table>
<thead>
<tr>
<th>BY MOUTH</th>
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</thead>
<tbody>
<tr>
<td>▶ Adult: Initially 5 mg every 4 hours</td>
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</table>

**Premedication**

<table>
<thead>
<tr>
<th>BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION</th>
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<tr>
<td>▶ Adult: Up to 10 mg, dose to be administered 60–90 minutes before operation</td>
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**Patient controlled analgesia (PCA)**

<table>
<thead>
<tr>
<th>BY INTRAVENOUS INFUSION</th>
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<tr>
<td>▶ Adult: (consult local protocol)</td>
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</table>

**Myocardial infarction**

<table>
<thead>
<tr>
<th>BY SLOW INTRavenous INJECTION</th>
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<tbody>
<tr>
<td>▶ Adult: 5–10 mg, followed by 5–10 mg if required, dose to be administered at a rate of 1–2 mg/minute, use dose for elderly in frail patients</td>
</tr>
<tr>
<td>▶ Elderly: 2.5–5 mg, followed by 2.5–5 mg if required, dose to be administered at a rate of 1–2 mg/minute</td>
</tr>
</tbody>
</table>

**Acute pulmonary oedema**

<table>
<thead>
<tr>
<th>BY SLOW INTRavenous INJECTION</th>
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<tbody>
<tr>
<td>▶ Adult: 5–10 mg, dose to be administered at a rate of 2 mg/minute, use dose for elderly in frail patients</td>
</tr>
<tr>
<td>▶ Elderly: 2.5–5 mg, dose to be administered at a rate of 2 mg/minute</td>
</tr>
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**Persistent cyanosis in congenital heart disease when blood glucose less than 3 mmol/litre (following glucose) **

<table>
<thead>
<tr>
<th>BY INTRAVENOUS INJECTION OR BY INTRAMUSCULAR INJECTION</th>
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<tr>
<td>▶ Child: 100 micrograms/kg</td>
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**Dyspnœa in palliative care**

<table>
<thead>
<tr>
<th>BY MOUTH</th>
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<tbody>
<tr>
<td>▶ Adult: Initially 5 mg every 4 hours, to be given in carefully titrated doses</td>
</tr>
</tbody>
</table>

**Dose equivalence and conversion**

The doses stated refer equally to morphine hydrochloride and sulfate.

**UNLICENSED USE**


**CONTRA-INDICATIONS**

Acute abdomen • delayed gastric emptying • heart failure secondary to chronic lung disease • phaeochromocytoma

**CAUTIONS**

Cardiac arrhythmias • pancreatitis • severe cor pulmonale

**SIDE-EFFECTS**

Abdominal pain • agitation • amenorrhœa • anorexia • asthenia • bronchospasm • delirium • disorientation • dyspepsia • exacerbation of pancreatitis • excitation • hypertension • hypothermia • inhibition of cough reflex • malaise • muscle fasciculation • myoclonus • nyctagmus • paraesthesia • paralytic ileus • raised intracranial pressure • restlessness • rhombomolysis • seizures • syncope • taste disturbance

**BREAST FEEDING**

Therapeutic doses unlikely to affect infant.

**RENAL IMPAIRMENT**

Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use in children For continuous intravenous infusion, dilute with Glucose 5% or 10% or Sodium Chloride 0.9%.
- With intravenous use in neonates Neonatal intensive care, dilute 2.5 mg/kg body-weight to a final volume of 50 mL with infusion fluid; an intravenous infusion rate of 0.1 mL/hour provides a dose of 5 micrograms/kg/hour.
- With oral use For modified release capsules—swallow whole or open capsule and sprinkle contents on soft food.

**PRESCRIBING AND DISPENSING INFORMATION**

Prescriptions must also specify the ‘form’.

- With rectal use Both the strength of the suppositories and the morphine salt contained in them must be specified by the prescriber.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Morphine for pain www.medicinesforchildren.org.uk/morphine-for-pain

Patients or carers should be given advice on how to administer morphine modified-release capsules.

**EXCEPTIONS TO LEGAL CATEGORY**

Morphine Oral Solutions Prescription-only medicines or schedule 2 controlled drug. The proportion of morphine hydrochloride may be altered when specified by the prescriber; if above 13 mg per 5 mL the solution becomes a schedule 2 controlled drug. It is usual to adjust the strength so that the dose volume is 5 or 10 mL. Oral solutions of morphine can be prescribed by writing the formula: Morphine hydrochloride 5 mg Chloroform water to 5 mL

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: suppository, solution for injection, solution for infusion, oral solution, gel, capsule, nebuliser liquid, infusion

**Tablet**

**CAUTIONARY AND ADVISORY LABELS** 2

- **Sevredol** (Napp Pharmaceuticals Ltd)
  - Morphine sulfate 10 mg Sevredol 10mg tablets | 56 tablet
  - £3.11 DT price = £5.31 Schedule 2 (CD)
  - Morphine sulfate 20 mg Sevredol 20mg tablets | 56 tablet
  - £10.61 DT price = £10.61 Schedule 2 (CD)
  - Morphine sulfate 50 mg Sevredol 50mg tablets | 56 tablet
  - £28.02 DT price = £28.02 Schedule 2 (CD)
MORPHINE (Non-proprietary)

MST Continus

MODIFIED-RELEASE TABLET

CAUTIONARY AND ADVISORY LABELS

Morphine sulfate 5 mg MST Continus 5 mg tablets | 60 tablet (Pos) £13.29 DT price = £13.29 Schedule 2 (CD)

Morphine sulfate 10 mg MST Continus 10 mg tablets | 60 tablet (Pos) £15.18 DT price = £15.18 Schedule 2 (CD)

Morphine sulfate 15 mg MST Continus 15 mg tablets | 60 tablet (Pos) £19.10 DT price = £19.10 Schedule 2 (CD)

Morphine sulfate 30 mg MST Continus 30 mg tablets | 60 tablet (Pos) £12.47 DT price = £12.47 Schedule 2 (CD)

Morphine sulfate 60 mg MST Continus 60 mg tablets | 60 tablet (Pos) £24.32 DT price = £24.32 Schedule 2 (CD)

Morphine sulfate 100 mg MST Continus 100 mg tablets | 60 tablet (Pos) £38.50 DT price = £38.50 Schedule 2 (CD)

Morphine sulfate 200 mg MST Continus 200 mg tablets | 60 tablet (Pos) £81.34 DT price = £81.34 Schedule 2 (CD)

Brands may include Morphgesic SR

MODIFIED-RELEASE CAPSULE

CAUTIONARY AND ADVISORY LABELS

Morphine sulfate 30 mg MXL 30 mg capsules | 28 capsule (Pos) £10.91 Schedule 2 (CD)

Morphine sulfate 60 mg MXL 60 mg capsules | 28 capsule (Pos) £14.95 Schedule 2 (CD)

Morphine sulfate 90 mg MXL 90 mg capsules | 28 capsule (Pos) £22.04 Schedule 2 (CD)

Morphine sulfate 120 mg MXL 120 mg capsules | 28 capsule (Pos) £29.15 Schedule 2 (CD)

Morphine sulfate 150 mg MXL 150 mg capsules | 28 capsule (Pos) £36.43 Schedule 2 (CD)

Morphine sulfate 200 mg MXL 200 mg capsules | 28 capsule (Pos) £46.15 Schedule 2 (CD)

Brands may include Zomorphp

MODIFIED-RELEASE GRANULES

CAUTIONARY AND ADVISORY LABELS

Morphine sulfate 20 mg MST Continus Suspension 20 mg granules sachets (sugar-free) | 30 sachet (Pos) £24.58 Schedule 2 (CD)

Morphine sulfate 30 mg MST Continus Suspension 30 mg granules sachets (sugar-free) | 30 sachet (Pos) £25.54 Schedule 2 (CD)

Morphine sulfate 60 mg MST Continus Suspension 60 mg granules sachets (sugar-free) | 30 sachet (Pos) £51.09 Schedule 2 (CD)

Morphine sulfate 100 mg MST Continus Suspension 100 mg granules sachets (sugar-free) | 30 sachet (Pos) £85.15 Schedule 2 (CD)

Morphine sulfate 200 mg MST Continus Suspension 200 mg granules sachets (sugar-free) | 30 sachet (Pos) £170.30 Schedule 2 (CD)

ORAL SOLUTION

CAUTIONARY AND ADVISORY LABELS

Morphine (Non-proprietary)

Morphine sulfate 2 mg per 1 ml Morphine sulfate 10 mg/5 ml oral solution | 100 ml (Pos) £1.82 Schedule 5 (CD Inv) | 300 ml (Pos) £5.45 DT price = £5.45 Schedule 5 (CD Inv) | 500 ml (Pos) £9.08 Schedule 5 (CD Inv)

Morphine (Non-proprietary)

Morphine sulfate 2 mg per 1 ml Morphine sulfate 10 mg/5 ml oral solution | 100 ml (Pos) £1.89 Schedule 5 (CD Inv) | 300 ml (Pos) £5.45 DT price = £5.45 Schedule 5 (CD Inv) | 500 ml (Pos) £8.50 Schedule 5 (CD Inv)

Morphine (Non-proprietary)

Morphine sulfate 20 mg per 1 ml Morphine sulfate 100 mg/ml concentrated oral solution (sugar-free) | 30 ml (Pos) £4.98 Schedule 2 (CD) (sugar-free) | 120 ml (Pos) £19.50 DT price = £19.50 Schedule 2 (CD)

SOLUTION FOR INJECTION

Morphine (Non-proprietary)

Morphine sulfate 10 mg per 1 ml Morphine sulfate 10 mg/1 ml solution for injection ampoules | 10 ampoule (Pos) £9.36 DT price = £9.36 Schedule 2 (CD)

Morphine sulfate 15 mg per 1 ml Morphine sulfate 15 mg/1 ml solution for injection ampoules | 10 ampoule (Pos) £9.35 DT price = £9.35 Schedule 2 (CD)

Morphine sulfate 20 mg per 1 ml Morphine sulfate 20 mg/1 ml solution for injection ampoules | 10 ampoule (Pos) £4.74 Schedule 2 (CD)

Morphine sulfate 30 mg per 1 ml Morphine sulfate 30 mg/1 ml solution for injection ampoules | 10 ampoule (Pos) £9.04 DT price = £9.04 Schedule 2 (CD)

Morphine sulfate 60 mg/2 ml solution for injection ampoules | 5 ampoule (Pos) £10.07 Schedule 2 (CD)

SOLUTION FOR INFUSION

Morphine (Non-proprietary)

Morphine sulfate 1 mg per 1 ml Morphine sulfate 50 mg/50 ml solution for infusion vials | 1 vial (Pos) £5.29 Schedule 2 (CD) | 10 vial (Pos) £49.29 no price available Schedule 2 (CD)

Morphine sulfate 2 mg per 1 ml Morphine sulfate 100 mg/50 ml solution for infusion vials | 1 vial (Pos) £5.89 Schedule 2 (CD)

SUPPOSITORY

CAUTIONARY AND ADVISORY LABELS

Morphine (Non-proprietary)

Morphine sulfate 10 mg Morphine sulfate 10 mg suppositories | 12 suppository (Pos) £18.34 Schedule 2 (CD)

Morphine sulfate 15 mg Morphine sulfate 15 mg suppositories | 12 suppository (Pos) £16.48 DT price = £16.48 Schedule 2 (CD)

Morphine sulfate 30 mg Morphine sulfate 30 mg suppositories | 12 suppository (Pos) £18.60 DT price = £18.60 Schedule 2 (CD)

Cyclizine with morphine

The properties listed below are those particular to the combination only. For the properties of the components please consider, cyclizine p. 343, morphine p. 367.

INDICATIONS AND DOSE

CYCLIMORPH-15®

Moderate to severe pain (short-term use only)

BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INJECTION

Adult: 1 ml, do not repeat dose more often than every 4 hours; maximum 3 doses per day

CYCLIMORPH-10®

Moderate to severe pain (short-term use only)

BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INJECTION

Adult: 1 ml, do not repeat dose more often than every 4 hours; maximum 3 doses per day

CAUTIONS

Myocardial infarction (cyclizine may aggravate severe heart failure and counteract the haemodynamic benefits of opioids) - not recommended in palliative care

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion

SOLUTION FOR INJECTION

Cyclimorph (AMCo)

Cyclizine tartrate 50 mg per 1 ml, Morphine tartrate 15 mg per 1 ml Cyclimorph 15 solution for injection 1ml ampoules | 5 ampoule (Pos) £9.12 Schedule 2 (CD)

Cyclizine tartrate 50 mg per 1 ml, Morphine tartrate 10 mg per 1 ml Cyclimorph 10 solution for injection 1ml ampoules | 5 ampoule (Pos) £7.77 Schedule 2 (CD)

Oxycodone hydrochloride

INDICATIONS AND DOSE

Postoperative pain | Severe pain | Moderate to severe pain in palliative care

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

Adult: Initially 5 mg every 4–6 hours, dose to be increased if necessary according to severity of pain, some patients may require higher doses than the maximum daily dose; maximum 400 mg per day BY MOUTH USING MODIFIED-RELEASE MEDICINES

Adult: Initially 10 mg every 12 hours (max. per dose 200 mg every 12 hours), dose to be increased if necessary according to severity of pain, some patients might require higher doses than dose maximum BY SLOW INTRAVENOUS INJECTION

Adult: 1–10 mg every 4 hours as required
Nervous system

370 Pain

BY INTRAVENOUS INFUSION
- Adult: Initially 2 mg/hour, adjusted according to response

BY SUBCUTANEOUS INJECTION
- Adult: Initially 5 mg every 4 hours as required

BY SUBCUTANEOUS INFUSION
- Adult: Initially 7.5 mg/24 hours, adjusted according to response

Patient controlled analgesia (PCA)

Dose equivalence and conversion
2 mg oral oxycodone is approximately equivalent to 1 mg parenteral oxycodone.

CONTRA-INDICATIONS
- Acute abdomen - chronic constipation - cor pulmonale - delayed gastric emptying

CAUTIONS
- Pancreatitis - toxic psychosis

SIDE-EFFECTS
- Common or very common Abdominal pain - anorexia - anxiety - asthenia - bronchospasm - chills - diarrhoea - dyspepsia - dyspnoea - impaired cough reflex

BREAST FEEDING
- Present in milk—avoid.

HEPATIC IMPAIRMENT
- Max. initial dose 2.5 mg every 6 hours in patients not currently treated with an opioid with mild impairment. Avoid in moderate to severe impairment.

RENAL IMPAIRMENT
- Max. initial dose 2.5 mg every 6 hours in patients not currently with an opioid with mild to moderate impairment. Avoid if eGFR less than 10 mL/minute/1.73 m².

Opioid effects increased and prolonged and increased cerebral sensitivity occurs.

DIRECTIONS FOR ADMINISTRATION
- For intravenous infusion (Oxynorm®), give continuously or intermittently in Glucose 5% or Sodium chloride 0.9%; dilute to a concentration of 1 mg/mL.

NATIONAL FUNDING/ACCESS DECISIONS
Scottish Medicines Consortium (SMC) Decision
The Scottish Medicines Consortium has advised (October 2004 and November 2010) that Oxynorm® injection is restricted for use within NHS Scotland for patients with cancer who have difficulty in tolerating morphine or diamorphine.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: suppository, solution for infusion, oral solution

Modified-release tablet

CAUTIONARY AND ADVISORY LABELS

Oxycodeone hydrochloride 80 mg Oxycodone 80mg modified-release tablets | 56 tablet (P) no price available DT price = £200.39 Schedule 2 (CD)
- OxyContin (Napp Pharmaceuticals Ltd)
Oxycodeone hydrochloride 5 mg Oxycodone 5mg modified-release tablets | 28 tablet (P) £12.52 DT price = £12.52 Schedule 2 (CD)
Oxycodeone hydrochloride 10 mg Oxycodone 10mg modified-release tablets | 56 tablet (P) £25.04 DT price = £25.04 Schedule 2 (CD)
Oxycodeone hydrochloride 15 mg Oxycodone 15mg modified-release tablets | 56 tablet (P) £38.12 DT price = £38.12 Schedule 2 (CD)
Oxycodeone hydrochloride 20 mg Oxycodone 20mg modified-release tablets | 56 tablet (P) £50.08 DT price = £50.08 Schedule 2 (CD)
Oxycodeone hydrochloride 30 mg Oxycodone 30mg modified-release tablets | 56 tablet (P) £76.23 DT price = £76.23 Schedule 2 (CD)
Oxycodeone hydrochloride 40 mg Oxycodone 40mg modified-release tablets | 56 tablet (P) £100.19 DT price = £100.19 Schedule 2 (CD)
Oxycodeone hydrochloride 60 mg Oxycodone 60mg modified-release tablets | 56 tablet (P) £152.49 DT price = £152.49 Schedule 2 (CD)
Oxycodeone hydrochloride 80 mg Oxycodone 80mg modified-release tablets | 56 tablet (P) £200.39 DT price = £200.39 Schedule 2 (CD)
Oxycodeone hydrochloride 120 mg Oxycodone 120mg modified-release tablets | 56 tablet (P) £305.02 DT price = £305.02 Schedule 2 (CD)
- Brands may include Oxetrel; Oxylan; Reitebon

Capsule

Oxycodeone hydrochloride 5 mg Oxycodone 5mg capsules | 20 capsule (P) £11.43 DT price = £11.43 Schedule 2 (CD)
Oxycodeone hydrochloride 10 mg Oxycodone 10mg capsules | 20 capsule (P) £22.86 DT price = £22.86 Schedule 2 (CD)
Oxycodeone hydrochloride 20 mg Oxycodone 20mg capsules | 20 capsule (P) £45.71 DT price = £45.71 Schedule 2 (CD)
- Brands may include Lynlor; Stercetone

Oral solution

Oxycodeone hydrochloride 1 mg/5ml oral solution sugar free (sugar-free) | 250 ml (P) £9.71 DT price = £9.71 Schedule 2 (CD)
Oxycodeone hydrochloride 10 mg/100ml oral solution sugar free (sugar-free) | 120 ml (P) £46.63 DT price = £46.63 Schedule 2 (CD)
- OxyNorm (Napp Pharmaceuticals Ltd)
Oxycodeone hydrochloride 1 mg/5ml oral solution sugar free (sugar-free) | 250 ml (P) £9.71 DT price = £9.71 Schedule 2 (CD)
- Oxynorm liquid 5mg/5ml oral solution (sugar-free) | 250 ml (P) £9.71 DT price = £9.71 Schedule 2 (CD)
Oxycodeone hydrochloride 10 mg/100ml concentrate oral solution (sugar-free) | 120 ml (P) £46.63 DT price = £46.63 Schedule 2 (CD)

Solution for injection

Oxycodeone hydrochloride 10 mg/1ml oxycodone 10mg/1ml solution for injection ampoules | 5 ampoule (P) £16.00 DT price = £16.00 Schedule 2 (CD)
Oxycodeone hydrochloride 10 mg/1ml solution for injection ampoules | 5 ampoule (P) £8.00 DT price = £8.00 Schedule 2 (CD)
Oxycodeone hydrochloride 50 mg/1ml oxycodone 50mg/1ml solution for injection ampoules | 5 ampoule (P) £70.10 DT price = £70.10 Schedule 2 (CD)
- Oxynorm (Napp Pharmaceuticals Ltd)
Oxycodeone hydrochloride 10 mg/1ml oxycodone 10mg/1ml solution for injection ampoules | 5 ampoule (P) £8.00 DT price = £8.00 Schedule 2 (CD)
Oxycodeone hydrochloride 50 mg/1ml oxycodone 50mg/1ml solution for injection ampoules | 5 ampoule (P) £70.10 DT price = £70.10 Schedule 2 (CD)

Oxycodone with naloxone
The properties listed below are those particular to the combination only. For the properties of the components please consider, naloxone hydrochloride p. 1133, oxycodone hydrochloride p. 369.
INDICATIONS AND DOSE
Severe pain requiring opioid analgesia in patients not currently treated with opioid analgesics
BY MOUTH
▶ Adult: Initially 10/5 mg every 12 hours (max. per dose 40/20 mg every 12 hours); dose to be increased according to response; patients already receiving opioid analgesics can start with a higher dose

Dose equivalence and conversion
Dose quantities are expressed in the form x/y where x and y are the strengths in milligrams of oxycodone and naloxone respectively.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Modified-release tablet

CAUTIONARY AND ADVISORY LABELS
2, 25
▶ Targinact (Napp Pharmaceuticals Ltd)
Naloxone hydrochloride 2.5 mg, Oxycodone hydrochloride 5 mg Targinact 5mg/2.5mg modified-release tablets | 28 tablet (P) £21.16 DT price = £21.16 Schedule 2 (CD)
Naloxone hydrochloride 5 mg, Oxycodone hydrochloride 10 mg Targinact 10mg/5mg modified-release tablets | 56 tablet (P) £42.32 DT price = £42.32 Schedule 2 (CD)
Naloxone hydrochloride 10 mg, Oxycodone hydrochloride 20 mg Targinact 20mg/10mg modified-release tablets | 56 tablet (P) £84.62 DT price = £84.62 Schedule 2 (CD)
Naloxone hydrochloride 20 mg, Oxycodone hydrochloride 40 mg Targinact 40mg/20mg modified-release tablets | 56 tablet (P) £160.28 Schedule 2 (CD)

Papaveretum

INDICATIONS AND DOSE
Postoperative analgesia | Severe chronic pain
BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION
▶ Adult: 7.7–15.4 mg every 4 hours if required
▶ Elderly: Initially 7.7 mg every 4 hours if required
BY INTRAVENOUS INJECTION
▶ Adult: Use 25 to 50% of the corresponding subcutaneous/intramuscular dose

PREMEDICATION
BY INTRAVENOUS INJECTION
▶ Adult: Use 25 to 50% of the corresponding subcutaneous/intramuscular dose

Important safety information
Do not confuse with papaverine.

CONTRA-INDICATIONS
Heart failure secondary to chronic lung disease · phaeochromocytoma

CAUTIONS
Supraventricular tachycardia

SIDE-EFFECTS
Hypothermia

BREAST FEEDING
Therapeutic doses unlikely to affect infant.

RENAL IMPAIRMENT
Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

PRESCRIBING AND DISPENSING INFORMATION
The name Ommopon was formerly used for papaveretum preparations. Papaveretum is a mixture of 253 parts of morphine hydrochloride, 23 parts of papaverine hydrochloride and 20 parts of codeine hydrochloride.

LESS SUITABLE FOR PRESCRIBING
Papaveretum is less suitable for prescribing.

Pentazocine

INDICATIONS AND DOSE
Moderate to severe pain
BY MOUTH
▶ Adult: 50 mg every 3–4 hours, dose to be taken preferably after food, usual dose 25–100 mg every 3–4 hours; maximum 600 mg per day

Moderate pain
BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION
OR BY INTRAVENOUS INJECTION
▶ Adult: 30 mg every 3–4 hours as required; maximum 360 mg per day

Severe pain
BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION
OR BY INTRAVENOUS INJECTION
▶ Adult: 45–60 mg every 3–4 hours as required; maximum 360 mg per day

CONTRA-INDICATIONS
Acute porphyrias p. 864 · heart failure secondary to chronic lung disease · patients dependent on opioids (can precipitate withdrawal)

CAUTIONS
Arterial hypertension · cardiac arrhythmias · myocardial infarction · pancreatitis · phaeochromocytoma · pulmonary hypertension

SIDE-EFFECTS
Abdominal pain · blood disorders · chills · disorientation · hypertension · hypothermia · myalgia · paraesthesia · raised intracranial pressure · seizures · syncope · toxic epidermal necrolysis · tremor

OVERDOSE
Effects only partially reversed by naloxone.

BREAST FEEDING
Use with caution—limited information available.

RENAL IMPAIRMENT
Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

LESS SUITABLE FOR PRESCRIBING
Pentazocine is less suitable for prescribing.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 2, 21
▶ PENTAZOCINE (Non-proprietary)
Pentazocine hydrochloride 25 mg Pentazocine 25mg tablets | 28 tablet (P) £24.32 DT price = £24.25 Schedule 3 (CD No Register Exempt Safe Custody)

Capsule

CAUTIONARY AND ADVISORY LABELS 2, 21
▶ PENTAZOCINE (Non-proprietary)
Pentazocine hydrochloride 50 mg Pentazocine 50mg capsules | 28 capsule (P) £28.54 Schedule 3 (CD No Register Exempt Safe Custody)

Solution for injection

▶ PENTAZOCINE (Non-proprietary)
Pentazocine (as Pentazocine lactate) 30 mg per 1 ml Pentazocine 60mg/2ml solution for injection ampoules | 10 ampoule (P) £32.14 DT price = £32.14 Schedule 3 (CD No Register Exempt Safe Custody)
Pethidine hydrochloride
(Meperidine)

INDICATIONS AND DOSE

Acute pain
BY MOUTH
- Adult: 50–150 mg every 4 hours
- By subcutaneous injection or by intramuscular injection
- Adult: 25–100 mg, then 25–100 mg after 4 hours, for debilitated patients use dose described for elderly patients
- Elderly: Initially 25 mg, then 25–100 mg after 4 hours

BY SLOW INTRAVENOUS INJECTION
- Adult: 25–50 mg, then 25–50 mg after 4 hours, for debilitated patients use dose described for elderly patients
- Elderly: Initially 25 mg, then 25–50 mg after 4 hours

Obstetric analgesia
BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION
- Adult: 50–100 mg, then 50–100 mg after 1–3 hours if required; maximum 400 mg per day

Premedication
BY INTRAMUSCULAR INJECTION
- Adult: 25–100 mg, dose to be given 1 hour before operation, for debilitated patients use dose described for elderly patients
- Elderly: 25 mg, dose to be given 1 hour before operation

Postoperative pain
BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION
- Adult: 25–100 mg every 2–3 hours if required, for debilitated patients use dose described for elderly patients
- Elderly: Initially 25 mg every 2–3 hours if required

CONTRA-INDICATIONS
Phaeochromocytoma

CAUTIONS
Accumulation of metabolites may result in neurotoxicity · cardiac arrhythmias · not suitable for severe continuing pain · severe cor pulmonale

SIDE-EFFECTS
Hypothermia · restlessness · tremor

Overdose
Convulsions reported in overdosage

BREAST FEEDING
Present in milk but not known to be harmful.

RENAL IMPAIRMENT
Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: suppository, solution for injection, oral solution, capsule.

Tablet
CAUTIONARY AND ADVISORY LABELS 2

- PETHIDINE HYDROCHLORIDE (Non-proprietary)
  - Pethidine hydrochloride 50 mg
    - Pethidine 50mg tablets | 50 tablet | £0.82 DT price = £0.82 Schedule 2 (CD)

- PETHIDINE HYDROCHLORIDE (Non-proprietary)
  - Pethidine hydrochloride 10 mg per 1 ml
    - Pethidine 50mg/5ml solution for injection ampoules | 10 ampoule | £0.91 Schedule 2 (CD)

Solution for injection

- PETHIDINE HYDROCHLORIDE (Non-proprietary)
  - Pethidine hydrochloride 0.5 mg per 1 ml
    - Pethidine 50mg/1ml solution for injection ampoules | 10 ampoule | £0.91 Schedule 2 (CD)

Pethidine hydrochloride 50 mg per 1 ml
- Pethidine 50mg/2ml solution for injection ampoules | 10 ampoule | £0.66 DT price = £0.66 Schedule 2 (CD)

Tapentadol

INDICATIONS AND DOSE

Moderate to severe acute pain which can be managed only with opioid analgesics

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
- Adult: Initially 50 mg every 4–6 hours, adjusted according to response, maximum 700 mg in the first 24 hours, during the first 24 hours of treatment, an additional dose of 50 mg may be taken 1 hour after the initial dose, if pain control not achieved; maximum 600 mg per day

Severe chronic pain

BY MOUTH USING MODIFIED-RELEASE MEDICINES
- Adult: Initially 50 mg every 12 hours, adjusted according to response; maximum 500 mg per day

SIDE-EFFECTS
Abdominal discomfort · anxiety · ataxia · decreased appetite · diarrhoea · dysarthria · dyspepsia · hypoaesthesia · malaise · muscle spasm · paraesthesia · seizures · tremor · weight loss

BREAST FEEDING
Avoid — no information available.

HEPATIC IMPAIRMENT
For immediate-release tablets, initial max. daily dose 150 mg; for modified-release tablets, initial max. daily dose 50 mg.

RENAL IMPAIRMENT
Manufacturer advises no dose adjustment needed in mild or moderate impairment. Avoid in severe impairment. Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (May 2011) that tapentadol (Palexia® SR) is accepted for restricted use within NHS Scotland for the management of severe chronic pain in adult patients, which can be adequately managed only with opioid analgesics, when morphine sulfate modified-release has failed to provide adequate pain control or is not tolerated.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet
CAUTIONARY AND ADVISORY LABELS 2

- Palexia (Grunenthal Ltd)
  - Tapentadol (as Tapentadol hydrochloride) 50 mg
    - Palexia 50mg tablets | 28 tablet | £12.46 DT price = £12.46 Schedule 2 (CD)
    - 56 tablet | £24.91 Schedule 2 (CD)

- Tapentadol (as Tapentadol hydrochloride) 75 mg
  - Palexia 75mg tablets | 28 tablet | £18.68 DT price = £18.68 Schedule 2 (CD)
  - 56 tablet | £37.37 Schedule 2 (CD)

Modified-release tablet
CAUTIONARY AND ADVISORY LABELS 2, 25

- Palexia SR (Grunenthal Ltd)
  - Tapentadol (as Tapentadol hydrochloride) 50 mg
    - Palexia SR 50mg tablets | 28 tablet | £12.46 DT price = £12.46 Schedule 2 (CD)
    - 56 tablet | £24.91 Schedule 2 (CD)

- Tapentadol (as Tapentadol hydrochloride) 100 mg
  - Palexia SR 100mg tablets | 56 tablet | £49.82 DT price = £49.82 Schedule 2 (CD)
  - 28 tablet | £84.92 Schedule 2 (CD)

- Tapentadol (as Tapentadol hydrochloride) 150 mg
  - Palexia SR 150mg tablets | 56 tablet | £74.73 DT price = £74.73 Schedule 2 (CD)

- Tapentadol (as Tapentadol hydrochloride) 200 mg
  - Palexia SR 200mg tablets | 56 tablet | £99.64 DT price = £99.64 Schedule 2 (CD)

- Tapentadol (as Tapentadol hydrochloride) 250 mg
  - Palexia SR 250mg tablets | 56 tablet | £124.55 DT price = £124.55 Schedule 2 (CD)
Tramadol hydrochloride

**INDICATIONS AND DOSE**

Moderate to severe pain

**BY INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INJECTION**

- **Adult:** 50–100 mg every 4–6 hours, intravenous injection to be given over 2–3 minutes

**Moderate to severe acute pain**

**BY MOUTH**

- **Child 12-17 years:** Initially 100 mg, then 50–100 mg every 4–6 hours; maximum 400 mg per day
- **Adult:** Initially 100 mg, then 50–100 mg every 4–6 hours; maximum 400 mg per day

**Moderate to severe chronic pain**

**BY MOUTH**

- **Child 12-17 years:** Initially 50 mg, then adjusted according to response to; maximum 400 mg per day
- **Adult:** Initially 50 mg, then adjusted according to response to; maximum 400 mg per day

**Postoperative pain**

**BY INTRAVENOUS INJECTION**

- **Adult:** Initially 100 mg, then 50 mg per 10–20 minutes if required up to total maximum 250 mg (including initial dose) in first hour, then 50–100 mg every 4–6 hours, intravenous injection to be given over 2–3 minutes; maximum 600 mg per day

**Moderate to severe pain (with modified-release 12-hourly preparations)**

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

- **Child 12-17 years:** 50–100 mg twice daily, increased if necessary to 150–200 mg twice daily, maximum daily dose not usually required; maximum 400 mg per day
- **Adult:** 50–100 mg twice daily, increased if necessary to 150–200 mg twice daily, maximum daily dose not usually required; maximum 400 mg per day

**Moderate to severe pain (with modified-release 24-hourly preparations)**

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

- **Child 12-17 years:** Initially 100–150 mg once daily, increased if necessary up to 400 mg once daily
- **Adult:** Initially 100–150 mg once daily, increased if necessary up to 400 mg once daily

**Zydol® XL**

**Moderate to severe pain**

**BY MOUTH USING MODIFIED-RELEASE TABLETS**

- **Child 12-17 years:** Initially 150 mg once daily, increased if necessary up to 400 mg once daily
- **Adult:** Initially 150 mg once daily, increased if necessary up to 400 mg once daily

- **CONTRA-INDICATIONS** Acute intoxication with alcohol - acute intoxication with analgesics - acute intoxication with hypnotics - acute intoxication with opioids - not suitable for narcotic withdrawal treatment - uncontrolled epilepsy

- **CAUTIONS** Excessive bronchial secretions - history of epilepsy - use tramadol only if compelling reasons - impaired consciousness - not suitable as a substitute in opioid-dependent patients - not suitable in some types of general anaesthesia - susceptibility to seizures - use tramadol only if compelling reasons

**CAUTIONS, FURTHER INFORMATION**

**General anaesthesia** Not recommended for analgesia during potentially light planes of general anaesthesia (possibly increased intra-operative recall reported).

**SIDE-EFFECTS**

- **Common or very common** Malaise
- **Uncommon** Diarrhoea - flatulence - gastritis - retching
- **Rare** Abnormal coordination - anorexia - anxiety - bronchospasm - changes in appetite - delirium - dysphoria - hypertension - muscle weakness - nightmares - paraesthesia - seizures - syncope - tremor - wheezing
- **Frequency not known** Blood disorders - hypoglycaemia - speech disorders

**PREGNANCY** Embryotoxic in animal studies—manufacturers advise avoid.

**BREAST FEEDING** Amount probably too small to be harmful, but manufacturer advises avoid.

**HEPATIC IMPAIRMENT** Caution (avoid for oral drops) in severe impairment.

**RENAL IMPAIRMENT** Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs. Caution (avoid for oral drops) in severe impairment.

**DIRECTIONS FOR ADMINISTRATION**

Tramadol hydrochloride orodispersible tablets should be sucked and then swallowed. May also be dispersed in water. Some tramadol hydrochloride modified-release capsule preparations may be opened and the content swallowed immediately without chewing—check individual preparations. For intravenous infusion, dilute in Glucose 5% or Sodium Chloride 0.9%.

**PRESCRIBING AND DISPENSING INFORMATION** Do not confuse modified-release 12-hourly preparations with 24-hourly preparations.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Tramadol for pain

www.medicinesforchildren.org.uk/tramadol-for-pain

Patients or carers should be given advice on how to administer tramadol hydrochloride orodispersible tablets.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Soluble tablet**

Cautionary and Advisory Labels 2, 13

- **Zydol** (Grunenthal Ltd)
  - Tramadol hydrochloride 50 mg Zydol 50mg soluble tablets (sugar-free) | 20 tablet (POM) £2.79 Schedule 3 (CD No Register Exempt Safe Custody) (sugar-free) | 100 tablet (POM) £13.33 DT price + £13.33 Schedule 3 (CD No Register Exempt Safe Custody)

**Orodispersible tablet**

Cautionary and Advisory Labels 2

- **Tramadol hydrochloride (Non-proprietary)**
  - Tramadol hydrochloride 50 mg Tramadol 50mg orodispersible tablets sugar free (sugar-free) | 60 tablet (POM) £7.12 Schedule 3 (CD No Register Exempt Safe Custody)
  - Tramadol Melt (Meda Pharmaceuticals Ltd)
  - Tramadol hydrochloride 50 mg Tramadol Melt 50mg tablets (sugar-free) | 60 tablet (POM) £13.33 Schedule 3 (CD No Register Exempt Safe Custody)

**Modified-release tablet**

Cautionary and Advisory Labels 2, 25

- **Tramadol hydrochloride (Non-proprietary)**
  - Tramadol hydrochloride 50 mg Tramadol 50mg modified-release tablets | 60 tablet (POM) no price available Schedule 3 (CD No Register Exempt Safe Custody)
  - Tramadol hydrochloride 100 mg Tramadol 100mg modified-release tablets | 60 tablet (POM) £44.80 Schedule 3 (CD No Register Exempt Safe Custody)
Tramadol hydrochloride 150 mg | Tramadol 150mg modified-release tablets | 60 tablet £57.85 Schedule 3 (CD No Register Exempt Safe Custody)

Tramadol hydrochloride 200 mg | Tramadol 200mg modified-release tablets | 30 tablet £60.60 Schedule 3 (CD No Register Exempt Safe Custody)

Tramadol hydrochloride 300 mg | Tramadol 300mg modified-release tablets | 30 tablet £60.60 Schedule 3 (CD No Register Exempt Safe Custody)

Tramadol hydrochloride 400 mg | Tramadol 400mg modified-release tablets | 28 tablet £81.17 Schedule 3 (CD No Register Exempt Safe Custody)

▶ Zydol SR (Grunenthal Ltd)

Tramadol hydrochloride 50 mg | Zydol SR 50mg tablets | 60 tablet £4.60 Schedule 3 (CD No Register Exempt Safe Custody)

Tramadol hydrochloride 100 mg | Zydol SR 100mg tablets | 60 tablet £13.26 Schedule 3 (CD No Register Exempt Safe Custody)

Tramadol hydrochloride 150 mg | Zydol SR 150mg tablets | 60 tablet £21.39 Schedule 3 (CD No Register Exempt Safe Custody)

Tramadol hydrochloride 200 mg | Zydol SR 200mg tablets | 60 tablet £36.52 Schedule 3 (CD No Register Exempt Safe Custody)

▶ Zydol XL (Grunenthal Ltd)

Tramadol hydrochloride 150 mg | Zydol XL 150mg tablets | 30 tablet £12.18 Schedule 3 (CD No Register Exempt Safe Custody)

Tramadol hydrochloride 200 mg | Zydol XL 200mg tablets | 30 tablet £17.98 Schedule 3 (CD No Register Exempt Safe Custody)

Tramadol hydrochloride 300 mg | Zydol XL 300mg tablets | 30 tablet £24.94 Schedule 3 (CD No Register Exempt Safe Custody)

Tramadol hydrochloride 400 mg | Zydol XL 400mg tablets | 30 tablet £32.47 Schedule 3 (CD No Register Exempt Safe Custody)

▶ Brands may include Involid SR; Mabron; Maneo; Marol; Oldslam; Tilidol SR; Tradorec XL; Tramulief SR; Zamadol 24hr; Zeridame SR

Modified-release capsule
CAPTIONARY AND ADVISORY LABELS 2, 25
▶ TRAMADOL HYDROCHLORIDE (Non-proprietary)

Tramadol hydrochloride 50 mg | Tramadol 50mg capsules | 30 capsule £4.71 DT price = £1.20 Schedule 3 (CD No Register Exempt Safe Custody)

Zydol (Grunenthal Ltd)

Tramadol hydrochloride 50 mg | Zydol 50mg capsules | 30 capsule £2.29 DT price = £1.20 Schedule 3 (CD No Register Exempt Safe Custody)

▶ Brands may include Zamadol

5.1 Migraine

Migraine

Treatment of acute migraine

Treatment of a migraine attack should be guided by response to previous treatment and the severity of the attacks. A simple analgesic such as aspirin p. 104, paracetamol p. 354 (preferably in a soluble or dispersible form) or a NSAID is often effective; concomitant antiemetic treatment may be required. If treatment with an analgesic is inadequate, an attack may be treated with a specific antimigraine compound such as a 5HT1-receptor agonist (‘trip坦’). Ergot alkaloids are rarely required now; oral preparations are associated with many side-effects and should be avoided in cerebrovascular or cardiovascular disease. Excessive use of acute treatments for migraine (opioid and non-opioid analgesics, 5HT1-receptor agonists, and ergotamine) is associated with medication-overuse headache (analgesic-induced headache); therefore, increasing consumption of these medicines needs careful management.

Analgesics

Most migraine headaches respond to analgesics such as aspirin p. 104 or paracetamol p. 354 but because peristalsis is often reduced during migraine attacks the medication may not be sufficiently well absorbed to be effective; dispersible or effervescent preparations are therefore preferred. Compound preparations containing analgesics and antiemetics are available.

The NSAID tolfenamic acid p. 381 is licensed specifically for the treatment of an acute attack of migraine; diclofenac potassium p. 920, flurbiprofen p. 927, and ibuprofen p. 927 are also licensed for use in migraine.

SHT1-receptor agonists

A 5HT1-receptor agonist is of considerable value in the treatment of an acute migraine attack. The 5HT1-receptor agonists (‘trip坦’) act on the 5HT (serotonin) 1B/1D receptors and they are therefore sometimes referred to as SHT1/1D-receptor agonists. A 5HT1-receptor agonist may be used during the established headache phase of an attack and is the preferred treatment in those who fail to respond to conventional analgesics.

The SHT1-receptor agonists available for treating migraine are almotriptan p. 377, eletriptan p. 377, frovatriptan p. 378, naratriptan p. 378, rizatriptan p. 379, sumatriptan p. 379, and zolmitriptan p. 380. If a patient does not respond to one 5HT1-receptor agonist, an alternative SHT1-receptor agonist should be tried. For patients who have prolonged attacks that frequently recur despite treatment with a SHT1-receptor agonist, combination therapy with a NSAID such as naproxen can be considered. Sumatriptan or zolmitriptan are also used to treat cluster headache.

Ergot Alkaloids

The value of ergotamine tartrate p. 376 for migraine is limited by difficulties in absorption and by its side-effects, particularly nausea, vomiting, abdominal pain, and
muscular cramps; it is best avoided. The recommended doses of ergotamine tartrate preparations should not be exceeded and treatment should not be repeated at intervals of less than 4 days.

To avoid habituation the frequency of administration of ergotamine tartrate should be limited to no more than twice a month. It should never be prescribed prophylactically but in the management of cluster headache a low dose is occasionally given for 1 to 2 weeks [unlicensed indication].

Antiemetics
Antiemetics, such as metoclopramide hydrochloride p. 347 or domperidone p. 346, or phenothiazine and antihistamine antiemetics, relieve the nausea associated with migraine attacks. Antiemetics may be given by intramuscular injection or rectally if vomiting is a problem.

Metoclopramide hydrochloride and domperidone have the added advantage of promoting gastric emptying and normal peristalsis; a single dose should be given at the onset of symptoms. Oral analgesic preparations containing metoclopramide hydrochloride are a convenient alternative.

Prophylaxis of migraine
Where migraine attacks are frequent, possible provoking factors such as stress, irregular life-style (e.g. lack of sleep), or chemical triggers (e.g. alcohol and nitrates) should be sought; combined oral contraceptives may also provoke migraine.

Preventive treatment for migraine should be considered for patients who:
- suffer at least two attacks a month;
- suffer an increasing frequency of headaches;
- suffer significant disability despite suitable treatment for migraine attacks;
- cannot take suitable treatment for migraine attacks.

Prophylaxis is also necessary in some rare migraine subtypes and those at risk of migraineous infarction. The beta-blockers propranolol hydrochloride p. 146, atenolol p. 141, metoprolol tartrate p. 144, nadolol p. 145, and timolol maleate p. 147 are all effective. Propranolol hydrochloride p. 146 is the most commonly used.

Tricyclic antidepressants [unlicensed indication], topiramate p. 406, sodium valproate p. 403 [unlicensed indication], valproic acid p. 275 [unlicensed indication], and gabapentin p. 392 [unlicensed indication] are also effective for preventing migraine.

Pizotifen p. 376 is an antihistamine and a serotonin-receptor antagonist, structurally related to the tricyclic antidepressants. It is of limited value and may cause weight gain.

Botulinum toxin type A is licensed for the prophylaxis of headaches in adults with chronic migraine.

Cluster headache and the trigeminal autonomic cephalalgias
Cluster headache rarely responds to standard analgesics. Sumatriptan p. 379 given by subcutaneous injection is the drug of choice for the treatment of cluster headache. If an injection is unsuitable, sumatriptan nasal spray or zolmitriptan p. 380 nasal spray [both unlicensed use] may be used. Alternatively, 100% oxygen at a rate of 10–15 litres/minute for 10–20 minutes is useful in aborting an attack.

Prophylaxis of cluster headache is considered if the attacks are frequent, last over 3 weeks, or if they cannot be treated effectively. Verapamil hydrochloride p. 156 or lithium [both unlicensed use] are used for prophylaxis.

Prednisolone p. 585 can be used for short-term prophylaxis of episodic cluster headache [unlicensed use] either as monotherapy, or in combination with verapamil hydrochloride p. 156 during verapamil titration.

Ergotamine tartrate p. 376, used on an intermittent basis is an alternative for patients with short bouts, but it should not be used for prolonged periods.

The other trigeminal autonomic cephalalgias, paroxysmal hemianria (sensitive to indometacin p. 929), and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing, are seen rarely and are best managed by a specialist.

Drugs used for Migraine not listed below: Amitriptyline hydrochloride, p. 292 • Atenolol, p. 141 • Botulinum toxin type A, p. 322 • Clonidine hydrochloride, p. 137 • Diclofenac potassium, p. 920 • Gabapentin, p. 392 • Metoprolol tartrate, p. 144 • Nadolol, p. 145 • Sodium valproate, p. 403 • Timolol maleate, p. 147 • Topiramate, p. 406 • Trifluoperazine, p. 310 • Valproic acid, p. 275

ANALGESICS
Buclizine hydrochloride with codeine phosphate and paracetamol
The properties listed below are those particular to the combination only. For the properties of the components please consider, codeine phosphate p. 360, paracetamol p. 354.

INDICATIONS AND DOSE
MIGRALEVE®
Acute migraine
BY MOUTH
- Child 12–14 years: Initially 1 pink tablet to be taken at onset of attack, or if it is imminent, followed by 1 yellow tablet every 4 hours if required; maximum 1 pink and 3 yellow tablets in 24 hours
- Child 15–17 years: Initially 2 pink tablets to be taken at onset of attack, or if it is imminent, followed by 2 yellow tablets every 4 hours if required; maximum 2 pink and 6 yellow tablets in 24 hours
- Adult: Initially 2 pink tablets to be taken at onset of attack, or if it is imminent, followed by 2 yellow tablets every 4 hours if required; maximum 2 pink and 6 yellow tablets in 24 hours

LESS SUITABLE FOR PRESCRIBING
Migraleve® is less suitable for prescribing.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 2, 17, 30
- Migraleve Pink (McNeil Products Ltd)
  Buclizine hydrochloride 6.25 mg, Codeine phosphate 8 mg, Paracetamol 500 mg
  Migraleve Pink tablets | 8 tablet £ no price available Schedule 5 (CD Inv) | 12 tablet £3.21 Schedule 5 (CD Inv) | 16 tablet £ no price available Schedule 5 (CD Inv) | 24 tablet £5.16 Schedule 5 (CD Inv) | 32 tablet £0.89 Schedule 5 (CD Inv)
  Migraleve (McNeil Products Ltd)
  Migraleve tablets | 12 tablet £3.45 Schedule 5 (CD Inv) | 24 tablet £5.45 Schedule 5 (CD Inv) | 48 tablet £4.75 Schedule 5 (CD Inv)

Migraleve tablets | £0.89 Schedule 5 (CD Inv)

Metoclopramide with paracetamol
The properties listed below are those particular to the combination only. For the properties of the components please consider, metoclopramide hydrochloride p. 347, paracetamol p. 354.
PREGNANCY

Frequency not known
Very rare

▶

Rare
Uncommon

▶

Common or very common

SIDE-EFFECTS

CAUTIONS
Treatment should not exceed 3 months due to risk of tardive dyskinesia

M EDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
CAUTIONARY AND ADVISORY LABELS 17, 30

▶

Paramax (Zentiva)
Metoclopramide hydrochloride 5 mg, Paracetamol 500 mg Paramax tablets  42 tablet (D) £0.64 DT price = £0.64

Effervescent powder
CAUTIONARY AND ADVISORY LABELS 13, 17, 30

▶

Paramax (Zentiva)
Metoclopramide hydrochloride 5 mg, Paracetamol 500 mg Paramax sachets (sugar-free)  42 sachet (D) £12.52 DT price = £12.52

ANTIHISTAMINES

Pizotifen

INDICATIONS AND DOSE
Prevention of vascular headache | Prevention of classical migraine | Prevention of common migraine | Prevention of cluster headache

BY MOUTH

▶

Adult: Initially 500 micrograms at night, increased gradually to 1.5 mg at night, alternatively increased gradually to 1.5 mg daily in 3 divided doses; further increased if necessary up to 4.5 mg daily (but rarely necessary); max. single dose 3 mg

Prophylaxis of migraine

BY MOUTH

▶

Child 5-17 years: Initially 500 micrograms at night, then increased gradually up to 1.5 mg daily in divided doses, max. single dose (at night) 1 mg

UNLICENSED USE

1.5-mg tablets not licensed for use in children.

CAUTIONS
Avoid abrupt withdrawal | history of epilepsy | susceptibility to angle-closure glaucoma | urinary retention

INTERACTIONS
Appendix 1 (pizotifen).

SIDE-EFFECTS

▶

Common or very common
Dizziness | drowsiness | dry mouth | increased appetite | nausea | weight gain

Uncommon
Constipation

Rare
Aggression | anxiety | arthralgia | depression | hallucination | insomnia | myalgia | paraesthesia

Very rare
Rash (in adults) | seizures | urticaria (in adults)

Frequency not known
Hepatitis | jaundice | muscle cramps

PREGNANCY
Avoid unless potential benefit outweighs risk.

Breast feeding
Amount probably too small to be harmful, but manufacturer advises avoid.

HEPATIC IMPAIRMENT
Use with caution.

RENAL IMPAIRMENT
Use with caution.

PATIENT AND CARER ADVICE
Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

Medicines for Children leaflet: Pizotifen to prevent migraine headaches www.medicinesforchildren.org.uk/pizotifen-to-prevent-migraine-headaches

M EDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

Tablet
CAUTIONARY AND ADVISORY LABELS 2

▶

Pizotifen (Non-proprietary)

Pizotifen (as Pizotifen hydrogen malate) 500 microgram Pizotifen 500microgram tablets  28 tablet (D) £0.56 DT price = £1.03

Pizotifen (as Pizotifen hydrogen malate) 1.5 mg Pizotifen 1.5mg tablets  28 tablet (P) £14.74 DT price = £8.10

Sanomigran (Novartis Pharmaceuticals UK Ltd)

Pizotifen (as Pizotifen hydrogen malate) 1.5 mg Sanomigran 1.5mg tablets  28 tablet (P) £3.42 DT price = £8.10

ERGOT ALKALOIDS

Ergotamine tartrate

INDICATIONS AND DOSE
Management of cluster headache

BY MOUTH USING TABLETS

▶

Adult: 1 mg once daily for 6 nights in 7; occasionally given for 1–2 weeks, dose to be taken at night

UNLICENSED USE
Not licensed for the management of cluster headache.

CONTRA-INDICATIONS
Acute porphyrias p. 864 | coronary heart disease | hyperthyroidism | inadequately controlled hypertension | obliterative vascular disease | peripheral vascular disease | Raynaud’s syndrome | sepsis | severe hypertension | temporal arteritis

CAUTIONS
Anaemia | cardiac disease | dependence | elderly | risk of peripheral vasospasm

INTERACTIONS
Appendix 1 (ergot alkaloids).

SIDE-EFFECTS

Common or very common
Abdominal pain | dizziness | nausea | vomiting

Uncommon
Cyanosis | diarrhoea | hypoaesthesia | pain in extremities | paraesthesia | peripheral vasoconstriction | weakness in extremities

Rare
Arrhythmias | bradycardia | dyspnoea | ergotism (including absence of pulse and numbness in extremities) | increased blood pressure | intestinal ischaemia | myalgia | rash | tachycardia | urticaria

Very rare
Gangrene | heart-vent fibrosis | myocardial infarction | myocardial ischaemia

Frequency not known
Anxiety | arthralgia | blood disorders | blurred vision | cerebral ischaemia | confusion | constipation | depression | drowsiness | dry mouth | extrapyramidal effects | hallucinations | renal artery spasm | seizures | sleep disturbances | thrombosis | tremor | urinary retention

PREGNANCY
Avoid: oxytocic effect on the uterus.

Breast feeding
Avoid; ergotism may occur in infant; repeated doses may inhibit lactation.

HEPATIC IMPAIRMENT
Avoid in severe impairment—risk of toxicity increased.

RENAL IMPAIRMENT
Avoid; risk of renal vasoconstriction.
Ergotamine tartrate with caffeine hydrate and cyclizine hydrochloride

The properties listed below are those particular to the combination only. For the properties of the components please consider, cyclizine p. 343, ergotamine tartrate p. 376.

**INDICATIONS AND DOSE**
Treatment of acute migraine and migraine variants unresponsive to analgesics

**BY MOUTH**
- Adult: 1 tablet, to be taken at onset, followed by 0.5–1 tablet after 30 minutes, then 0.5–1 tablet every 30 minutes if required, max. 3 tablets in 24 hours, max. 4 tablets per attack, max. 6 tablets in one week

**PATIENT AND CARER ADVICE**
Patient counselling is advised for cyclizine hydrochloride with caffeine hydrate and ergotamine tartrate tablets (dosage).

**LESS SUITABLE FOR PRESCRIBING**
Cyclizine hydrochloride with caffeine hydrate and ergotamine tartrate (Migril®) is less suitable for prescribing.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- CAUTIONARY AND ADVISORY LABELS 2, 18
  - Migril (Wockhardt UK Ltd)
    - Caffeine hydrate 100 mg, Cyclizine hydrochloride 50 mg, Ergotamine tartrate 2 mg
    - Migral tablets | 100 tablet | £5.00

**SHT1 RECEPTOR AGONISTS**

**Almotriptan**

**INDICATIONS AND DOSE**
Treatment of acute migraine

**BY MOUTH**
- Adult: 12.5 mg, dose to be taken as soon as possible after onset, followed by 12.5 mg after 2 hours if required, dose to be taken only if migraine recurs (patient not responding should not take second dose for same attack); maximum 25 mg per day

**UNLICENSED USE**
Not licensed for use in elderly.

**CONTRA-INDICATIONS**
Coronary vasospasm - ischaemic heart disease - peripheral vascular disease - previous cerebrovascular accident - previous myocardial infarction - previous transient ischaemic attack

**CAUTIONS**
Conditions which predispose to coronary artery disease - elderly

**INTERACTIONS**
Appendix 1 (SHT1 agonists).

**SIDE-EFFECTS**
- Common or very common Drowsiness, transient increase in blood pressure
- Very rare Myocardial infarction - tachycardia
- Frequency not known Dizziness - fatigue - feeling of weakness - flushing - nausea - seizures - vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**
Sensations of tingling, heat, heaviness, pressure, or tightness of any part of the body may occur (including throat and chest—discontinue if intense, may be due to coronary vasoconstriction or to anaphylaxis).

**ALLERGY AND CROSS-SENSITIVITY**
Caution in patients with sensitivity to sulfonamides.

**PREGNANCY**
There is limited experience of using SHT1-receptor agonists during pregnancy; manufacturers advise that they should be avoided unless the potential benefit outweighs the risk.

**BREAST FEEDING**
Present in milk in animal studies— withhold breast-feeding for 24 hours.

**HEPATIC IMPAIRMENT**
Caution in mild to moderate impairment. Avoid in severe impairment.

**RENAL IMPAIRMENT**
Max. 12.5 mg in 24 hours if eGFR less than 30 mL/minute/1.73 m².

**MEDICINAL FORMS**
There are listed in the use of different medicines containing the same drug. Table:

**Tablet**
- CAUTIONARY AND ADVISORY LABELS 3
  - Almotriptan (Non-proprietary)
    - Almotriptan (as Almotriptan hydrogen malate)
      - 12.5 mg Almotriptan 12.5mg tablets | 3 tablet | £9.07 | 6 tablet | £18.14 DT price + £18.14 | 9 tablet | £27.21
  - Almogran (Almirall Ltd)
    - Almotriptan (as Almotriptan hydrogen malate)
      - 12.5 mg Almogran 12.5mg tablets | 3 tablet | £9.07 | 6 tablet | £18.14 DT price + £18.14 | 9 tablet | £27.20

**Eltriptan**

**INDICATIONS AND DOSE**
Treatment of acute migraine

**BY MOUTH**
- Adult: 40 mg, followed by 40 mg after 2 hours if required, dose to be taken only if migraine recurs (patient not responding to initial dose should not take second dose for same attack); increased if necessary to 80 mg, dose to be taken for subsequent attacks if 40 mg dose inadequate; maximum 80 mg per day

**UNLICENSED USE**
Not licensed for use in elderly.

**CONTRA-INDICATIONS**
Arrhythmias - coronary vasospasm - heart failure - ischaemic heart disease - peripheral vascular disease - previous cerebrovascular accident - previous myocardial infarction - previous transient ischaemic attack - Prinmetal's angina - severe hypertension - uncontrolled hypertension

**CAUTIONS**
Conditions which predispose to coronary artery disease - elderly

**INTERACTIONS**
Appendix 1 (SHT1 agonists).

**SIDE-EFFECTS**
- Common or very common Abdominal pain - chills - drowsiness - dry mouth - dyspepsia - headache - myalgia - myasthenia - palpitation - pharyngitis - rhinitis - sweating - tachycardia
- Rare Asthma - bradycardia - constipation - lymphadenopathy - menorrhagia - oesophagitis - syncope
- Frequency not known Dizziness - fatigue - feeling of weakness - flushing - hypertension - ischaemic colitis - nausea - vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**
Sensations of tingling, heat, heaviness, pressure, or tightness of any part of the body may occur (including throat and chest—discontinue if intense, may be due to coronary vasoconstriction or to anaphylaxis).

**ALLERGY AND CROSS-SENSITIVITY**
Caution in patients with sensitivity to sulfonamides.

**PREGNANCY**
There is limited experience of using SHT1-receptor agonists during pregnancy; manufacturers advise that they should be avoided unless the potential benefit outweighs the risk.

**BREAST FEEDING**
Present in milk in animal studies— withhold breast-feeding for 24 hours.

**HEPATIC IMPAIRMENT**
Caution in mild to moderate impairment. Avoid in severe impairment.

**RENAL IMPAIRMENT**
Max. 12.5 mg in 24 hours if eGFR less than 30 mL/minute/1.73 m².

**MEDICINAL FORMS**
There are listed in the use of different medicines containing the same drug. Table:

**Tablet**
- CAUTIONARY AND ADVISORY LABELS 3
  - Almotriptan (Non-proprietary)
    - Almotriptan (as Almotriptan hydrogen malate)
      - 12.5 mg Almotriptan 12.5mg tablets | 3 tablet | £9.07 | 6 tablet | £18.14 DT price + £18.14 | 9 tablet | £27.21
  - Almogran (Almirall Ltd)
    - Almotriptan (as Almotriptan hydrogen malate)
      - 12.5 mg Almogran 12.5mg tablets | 3 tablet | £9.07 | 6 tablet | £18.14 DT price + £18.14 | 9 tablet | £27.20
Nervous system

Frequency not known ▶ Uncommon ▶ Common or very common

INTERACTIONS

CAUTIONS

l UNLICENSED USE

INTERACTIONS

CONTRA-INDICATIONS

CONTRA-INDICATIONS

CAUTIONS

INTERACTIONS

SIDE-EFFECTS

SID EFFECTS

Frequency not known Dizziness - fatigue - feeling of weakness - flushing - nausea - vomiting

SIDE-EFFECTS, FURTHER INFORMATION

Sensations of tingling, heat, heaviness, pressure, or tightness of any part of the body may occur (including throat and chest—discontinue if intense, may be due to coronary vasoconstriction or to anaphylaxis).

PREGNANCY There is limited experience of using 5HT1-receptor agonists during pregnancy; manufacturers advise that they should be avoided unless the potential benefit outweighs the risk.

BREAST FEEDING Present in milk—avoid breast-feeding for 24 hours.

HEPATIC IMPAIRMENT Avoid in severe impairment.

MEDICAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 3

Relpax (as Frovatriptan succinate monohydrate) 2.5 mg

2.5 mg Migard 2.5mg tablets ▶ 6 tablet (P) £22.50 DT price = £22.50

Frovatriptan (as Frovatriptan succinate monohydrate) 20 mg

Relpax 20mg tablets ▶ 6 tablet (P) £22.50 DT price = £22.50

Relpax (as Frovatriptan hydrobromide) 40 mg

Relpax 40mg tablets ▶ 6 tablet (P) £22.50 DT price = £22.50

Not licensed for use in elderly.

Appendix 1 (5HT, agonists).

Dizziness - fatigue - feeling of weakness - flushing - nausea - vomiting

SIDE-EFFECTS, FURTHER INFORMATION

Sensations of tingling, heat, heaviness, pressure, or tightness of any part of the body may occur (including throat and chest—discontinue if intense, may be due to coronary vasoconstriction or to anaphylaxis).

PREGNANCY There is limited experience of using 5HT1-receptor agonists during pregnancy; manufacturers advise that they should be avoided unless the potential benefit outweighs the risk.

BREAST FEEDING Present in milk in animal studies— withhold breast-feeding for 24 hours.

HEPATIC IMPAIRMENT Avoid in severe impairment.

MEDICAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 3

Migard (A. Menarini Farmaceutica Internazionale SRL)

Frovatriptan (as Frovatriptan succinate monohydrate)

2.5 mg

Migard 2.5mg tablets ▶ 6 tablet (P) £16.67 DT price = £16.67

Naratriptan

INDICATIONS AND DOSE

Treatment of acute migraine

By mouth

Adult: 2.5 mg, followed by 2.5 mg after at least 4 hours if required, to be taken only if migraine recurs (patient not responding to initial dose should not take second dose for same attack); maximum 5 mg per day

Unlicensed use Not licensed for use in elderly.

Contra-indications

Coronary vasospasm - ischaemic heart disease - moderate or severe hypertension - peripheral vascular disease - previous cerebrovascular accident - previous myocardial infarction - previous transient ischaemic attack - Prinzmetal’s angina - severe hypertension - uncontrolled hypertension

Caution in patients with sensitivity to sulfonamides.

Rare Bradycardia - palpitation - tachycardia - visual disturbance

Frequency not known Dizziness - fatigue - feeling of weakness - flushing - nausea - vomiting

Sensations of tingling, heat, heaviness, pressure, or tightness of any part of the body may occur (including throat and chest—discontinue if intense, may be due to coronary vasoconstriction or to anaphylaxis).

Allergy and cross-sensitivity

Caution in patients with sensitivity to sulfonamides.

Pregnancy

There is limited experience of using 5HT1-receptor agonists during pregnancy; manufacturers advise that they should be avoided unless the potential benefit outweighs the risk.

Breast feeding

Withhold breast-feeding for 24 hours.

Hepatic impairment

Max. 2.5 mg in 24 hours in moderate impairment. Avoid if severe.

Renal impairment

Max. 2.5 mg in 24 hours. Avoid if eGFR less than 15 mL/minute/1.73 m².

Patient and carer advice

Drowsiness may affect performance of skilled tasks (e.g. driving).

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

INDICATIONS AND DOSE

Treatment of acute migraine

BY MOUTH

Adult: 2.5 mg, followed by 2.5 mg after at least 4 hours if required, to be taken only if migraine recurs (patient not responding to initial dose should not take second dose for same attack); maximum 5 mg per day

Tablet

CAUTIONARY AND ADVISORY LABELS 3

Migard (A. Menarini Farmaceutica Internazionale SRL)

Frovatriptan (as Frovatriptan succinate monohydrate)

2.5 mg

Migard 2.5mg tablets ▶ 6 tablet (P) £16.67 DT price = £16.67

Naratriptan

INDICATIONS AND DOSE

Treatment of acute migraine

BY MOUTH

Adult: 2.5 mg, followed by 2.5 mg after at least 4 hours if required, to be taken only if migraine recurs (patient not responding to initial dose should not take second dose for same attack); maximum 5 mg per day

Unlicensed use Not licensed for use in elderly.

Contra-indications

Coronary vasospasm - ischaemic heart disease - moderate or severe hypertension - peripheral vascular disease - previous cerebrovascular accident - previous myocardial infarction - previous transient ischaemic attack - Prinzmetal’s angina - severe hypertension - uncontrolled hypertension

Caution in patients with sensitivity to sulfonamides.

Rare Bradycardia - palpitation - tachycardia - visual disturbance

Frequency not known Dizziness - fatigue - feeling of weakness - flushing - nausea - vomiting

Sensations of tingling, heat, heaviness, pressure, or tightness of any part of the body may occur (including throat and chest—discontinue if intense, may be due to coronary vasoconstriction or to anaphylaxis).

Allergy and cross-sensitivity

Caution in patients with sensitivity to sulfonamides.

Pregnancy

There is limited experience of using 5HT1-receptor agonists during pregnancy; manufacturers advise that they should be avoided unless the potential benefit outweighs the risk.

Breast feeding

Withhold breast-feeding for 24 hours.

Hepatic impairment

Max. 2.5 mg in 24 hours in moderate impairment. Avoid if severe.

Renal impairment

Max. 2.5 mg in 24 hours. Avoid if eGFR less than 15 mL/minute/1.73 m².

Patient and carer advice

Drowsiness may affect performance of skilled tasks (e.g. driving).

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.
**INDICATIONS AND DOSE**

Treatment of acute migraine

**BY MOUTH**

- Adult: 10 mg, dose to be taken as soon as possible after onset, followed by 10 mg after 2 hours if required, dose to be taken only if migraine recurs (patient not responding to initial dose should not take second dose for same attack); maximum 20 mg per day

- **UNLICENSED USE** Not licensed for use in elderly.
- **CONTRA-INDICATIONS** Coronary vasospasm - ischaemic heart disease - peripheral vascular disease - previous cerebrovascular accident - previous myocardial infarction - previous transient ischaemic attack - Prinzmetal’s angina - severe hypertension - uncontrolled hypertension
- **CAUTIONS** Conditions which predispose to coronary artery disease - elderly
- **INTERACTIONS** → Appendix 1 (SHT1 agonists).

**SIDE-EFFECTS**

- **Common or very common** Decreased alertness - diarrhoea - drowsiness - dry mouth - dysphoria - headache - palpitation - paraesthesia - pharyngeal discomfort - sweating - tachycardia - tremor
- **Uncommon** Arrhythmias - ataxia - blurred vision - confusion - dyspepsia - hypertension - insomnia - muscle weakness - myalgia - nervousness - pruritus - taste disturbances - thirst - urticaria - vertigo
- **Rare** Bradycardia - syncope
- **Frequency not known** Dizziness - fatigue - feeling of weakness - flushing - nausea - seizures - toxic epidermal necrolysis - vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

Sensations of tingling, heat, heaviness, pressure, or tightness of any part of the body may occur (including throat and chest—continue if intense, may be due to coronary vasocstriction or to anaphylaxis).

- **PREGNANCY** There is limited experience of using SHT1 receptor agonists during pregnancy; manufacturers advise that they should be avoided unless the potential benefit outweighs the risk.
- **BREAST FEEDING** Present in milk in animal studies—withhold breast-feeding for 24 hours.
- **HEPATIC IMPAIRMENT** Reduce dose to 5 mg in mild to moderate impairment. Avoid in severe impairment.
- **RENAL IMPAIRMENT** Reduce dose to 5 mg in mild to moderate impairment. Avoid in severe impairment.
- **DIRECTIONS FOR ADMINISTRATION** Rizatriptan orodispersible tablets should be placed on the tongue, allowed to disperse and swallowed. Rizatriptan oral lyophilisates should be placed on the tongue and allowed to dissolve.
- **PATIENT AND CARER ADVICE** Drowsiness may affect performance of skilled tasks (e.g. driving). Patients or carers should be given advice on how to administer rizatriptan orodispersible tablets and oral lyophilisates.
UNLICENSED USE Not licensed for use in elderly.

CONTRA-INDICATIONS
- Coronary vasospasm - ischaemic heart disease - mild uncontrolled hypertension - moderate and severe hypertension - peripheral vascular disease - previous cerebrovascular accident - previous myocardial infarction - previous transient ischaemic attack - Prinzmetal’s angina
- Parkinson-White syndrome

CAUTIONS Conditions which predispose to coronary artery disease - elderly - history of seizures - mild, controlled hypertension - pre-existing cardiac disease - risk factors for seizures

INTERACTIONS → Appendix 1 (SHT, agonists).

GENERAL SIDE-EFFECTS
- Common or very common Dizziness - drowsiness - dyspnoea - fatigue - flushing - myalgia - nausea - sensory disturbances - transient increase in blood pressure - vomiting - weakness

SPECIFIC SIDE-EFFECTS
- Common or very common Zolmitriptan

INDICATIONS AND DOSE
Treatment of acute migraine

BY MOUTH
- Adult: 2.5 mg, followed by 2.5 mg after at least 2 hours if required, dose to be taken only if migraine recurs, then increased if necessary to 5 mg, dose to be taken only for subsequent attacks in patients not achieving satisfactory relief with 2.5 mg dose; maximum 10 mg per day

BY INTRANASAL ADMINISTRATION
- Adult: 5 mg, dose to be administered as soon as possible after onset into one nostril only, followed by 5 mg after at least 2 hours if required, dose to be administered only if migraine recurs; maximum 10 mg per day

Treatment of acute cluster headache

BY INTRANASAL ADMINISTRATION
- Adult: 5 mg, dose to be administered as soon as possible after onset into one nostril only, followed by 5 mg after at least 2 hours if required, dose to be administered only if migraine recurs; maximum 10 mg per day

Dose adjustments due to interactions
Max. 5 mg in 24 hours with concomitant cimetidine, fluvoxamine, moclobemide, or quinolone antibiotics.

Dose equivalence and conversion
1 spray of Zomig™ nasal spray = 5 mg zolmitriptan.


CONTRA-INDICATIONS Arthralgias associated with accessory cardiac conduction pathways - coronary vasospasm - ischaemic heart disease - previous cerebrovascular accident - previous myocardial infarction - Prinzmetal’s angina - severe hypertension - transient ischaemic attack - uncontrolled hypertension - Wolff-Parkinson-White syndrome

CAUTIONS Conditions which predispose to coronary artery disease - elderly - should not be taken within 24 hours of any other SHT, receptor agonist

INTERACTIONS → Appendix 1 (SHT, agonists).
Aspirin with metoclopramide

The properties listed below are those particular to the combination only. For the properties of the components please consider, aspirin p. 104, metoclopramide hydrochloride p. 347.

**INDICATIONS AND DOSE**

<table>
<thead>
<tr>
<th>Acute migraine</th>
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<tbody>
<tr>
<td><strong>BY MOUTH</strong></td>
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<tr>
<td><strong>Adult</strong></td>
</tr>
</tbody>
</table>

**SIDE-EFFECTS**

**CONTRA-INDICATIONS** Active gastro-intestinal bleeding - active gastro-intestinal ulceration - history of gastro-intestinal bleeding related to previous NSAID therapy - history of gastro-intestinal haemorrhage (two or more distinct episodes) - history of gastro-intestinal perforation related to previous NSAID therapy - history of recurrent gastro-intestinal ulceration (two or more distinct episodes) - severe heart failure

**CAUTIONS** Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - cerebrovascular disease - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - elderly (risk of serious side-effects and fatalities) - heart failure - ischaemic heart disease - peripheral arterial disease - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated) - uncontrolled hypertension

**INTERACTIONS** Appendix 1 (NSAIDs).

**SIDE-EFFECTS**

**FREQUENCY not known** Angioedema - blood disorders - bronchospasm - colitis (induction of or exacerbation of) - confusion - Crohn’s disease (induction of or exacerbation of) - depression - diarrhoea - dizziness - drowsiness - dysuria (most commonly in men) - euphoria - fluid retention (rarely precipitating congestive heart failure) - gastro-intestinal bleeding - gastro-intestinal discomfort - gastro-intestinal disturbances - gastro-intestinal ulceration - haematuria - hallucination - headache -
The pain may occur in an area of sensory deficit nerve damage following acute herpes zoster infection and syringomyelia, and central pain.

5.2 Neuropathic pain

Neuropathic pain, which occurs as a result of damage to neural tissue, includes phantom limb pain, compression neuropathies, peripheral neuropathies (e.g. due to Diabetes p. 588, chronic excessive alcohol intake, HIV infection p. 555, chemotherapy, idiopathic neuropathy), trauma, central pain (e.g. pain following stroke, spinal cord injury, and syringomyelia), and postherpetic neuralgia (peripheral nerve damage following acute herpes zoster infection (shingles)). The pain may occur in an area of sensory deficit and is sometimes accompanied by pain that is evoked by a non-noxious stimulus (allodynia).

Trigeminal neuralgia is also caused by dysfunction of neural tissue, but its management is distinct from other forms of neuropathic pain.

Neuropathic pain is generally managed with a tricyclic antidepressant or with certain antiepileptic drugs.

Amitriptyline hydrochloride p. 292 [unlicensed indication] and pregabalin p. 400 are effective treatments for neuropathic pain. Amitriptyline hydrochloride p. 292 and pregabalin can be used in combination if the patient has an inadequate response to either drug at the maximum tolerated dose.

Nortriptyline p. 298 [unlicensed indication] may be better tolerated than amitriptyline hydrochloride.

Gabapentin p. 392 is also effective for the treatment of neuropathic pain.

Neuropathic pain may respond to opioid analgesics. There is evidence of efficacy for tramadol hydrochloride p. 373, morphine p. 367, and oxycodone hydrochloride p. 369; however, treatment with morphine or oxycodone hydrochloride should be initiated only under specialist supervision. Tramadol hydrochloride p. 373 can be prescribed when other treatments have been unsuccessful, while the patient is waiting for assessment by a specialist.

Patients with localised pain who are unable to take oral medicines may benefit from topical local anaesthetic preparations, such as lidocaine hydrochloride p. 1116 medicated plasters, while awaiting specialist review.

Capsaicin p. 383 is licensed for neuropathic pain (but the intense burning sensation during initial treatment may limit use). Capsaicin p. 383 0.075% cream is licensed for the symptomatic relief of postherpetic neuralgia. A self-adhesive patch containing capsaicin p. 383 8% is licensed for the treatment of peripheral neuropathic pain in non-diabetic patients. It should be used under specialist supervision.

A corticosteroid may help to relieve pressure in compression neuropathy and thereby reduce pain.

Neurromodulation by spinal cord stimulation may be of benefit in some patients. Many patients with chronic neuropathic pain require multidisciplinary management, including physiotherapy and psychological support.

Trigeminal neuralgia

Surgery may be the treatment of choice in many patients; a neurological assessment will identify those who stand to benefit. Carbamazepine p. 387 taken during the acute stages of trigeminal neuralgia, reduces the frequency and severity of attacks. It is very effective for the severe pain associated with trigeminal neuralgia and (less commonly) glossopharyngeal neuralgia. Blood counts and electrolytes should be monitored when high doses are given. Small doses should be used initially to reduce the incidence of side-effects e.g. dizziness. Some cases respond to phenytoin p. 398; the drug may be given by intravenous infusion (possibly as fosphenytoin sodium p. 391) in a crisis (specialist use only).

Chronic facial pain

Chronic oral and facial pain including persistent idiopathic facial pain (also termed ‘atypical facial pain’) and temporomandibular dysfunction (previously termed temporomandibular joint pain dysfunction syndrome) may call for prolonged use of analgesics or for other drugs. Tricyclic antidepressants may be useful for facial pain [unlicensed indication], but are not on the Dental Practitioners’ List. Disorders of this type require specialist referral and psychological support to accompany drug treatment. Patients on long-term therapy need to be monitored both for progress and for side-effects.

Drugs used for Neuropathic pain not listed below:

**Capsaicin**

**INDICATIONS AND DOSE**

**AXSAIN®**

Post-herpetic neuralgia

**TO THE SKIN**
- **Adult:** Apply 3–4 times a day, dose to be applied sparingly; **important; after** lesions have healed, not more often than every 4 hours

Painful diabetic neuropathy (under expert supervision)

**TO THE SKIN**
- **Adult:** Apply 3–4 times a day for 8 weeks then review, dose to be applied sparingly, not more often than every 4 hours

**ZACIN®**

Symptomatic relief in osteoarthritis

**TO THE SKIN**
- **Adult:** Apply 4 times a day, dose to be applied sparingly, not more often than every 4 hours

**QUTENZA®**

Peripheral neuropathic pain in non-diabetic patients (under the supervision of a physician)

**TO THE SKIN**
- **Adult:** (consult product literature)

**CAUTIONS**

**GENERAL CAUTIONS**
Avoid contact with broken skin - avoid contact with inflamed skin

**SPECIFIC CAUTIONS:**
- With topical use avoid contact with eyes - avoid hot shower or bath just before or after application (burning sensation enhanced) - avoid inhalation of vapours - not to be used under tight bandages
- With transdermal use avoid contact with the face, scalp or in proximity to mucous membranes - avoid holding near eyes or mucous membranes - recent cardiovascular events - uncontrolled hypertension

**SIDE-EFFECTS**
- Common or very common
  - With topical use transient burning sensation during initial treatment (particularly if too much used or if administered less than 3–4 times daily)
  - With transdermal use application site reactions - erythema - pruritus - transient burning - uncommon
  - With transdermal use burning sensation - cough - dysgeusia - eye irritation - first degree AV block - hypertension - hypoaesthesia - muscle spasm - nausea - pain in extremities - palpitations - peripheral oedema - pruritus - tachycardia - throat irritation
- Rare
  - With topical use cough - eye irritation - sneezing
  - Frequency not known
  - With topical use dyspnœa - exacerbation of asthma

**MONITORING REQUIREMENTS**
- With transdermal use Monitor blood pressure during treatment procedure.
- **HANDLING AND STORAGE**
  - With topical use Wash hands immediately after use (or wash hands 30 minutes after application if hands treated).
  - With transdermal use Nitrile gloves to be worn while handling patches and cleaning treatment areas (latex gloves do not provide adequate protection).

**NATIONAL FUNDING/ACCESS DECISIONS**

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**6 Seizures**

**6.1 Epilepsy**

**Epilepsy**

**Control of the epilepsies**

The object of treatment is to prevent the occurrence of seizures by maintaining an effective dose of one or more antiepileptic drugs. Careful adjustment of doses is necessary, starting with low doses and increasing gradually until seizures are controlled or there are significant adverse effects.

When choosing an antiepileptic drug, the presenting epilepsy syndrome should first be considered. If the syndrome is not clear, the seizure type should determine the choice of treatment. Concomitant medication, comorbidity, age, and sex should also be taken into account.

The dosage frequency is often determined by the plasma-drug half-life, and should be kept as low as possible to encourage adherence with the prescribed regimen. Most antiepileptics, when used in the usual dosage, can be given twice daily. Lamotrigine p. 394, perampanel p. 398, phenobarbital p. 409, and phenytoin p. 398, which have long half-lives, can be given once daily at bedtime. However, with large doses, some antiepileptics may need to be given more frequently to avoid adverse effects associated with high peak plasma-drug concentration.

**Management**

When monotherapy with a first-line antiepileptic drug has failed, monotherapy with a second drug should be tried; the diagnosis should be checked before starting an alternative drug if the first drug showed lack of efficacy. The change from one antiepileptic drug to another should be cautious, slowly withdrawing the first drug only when the new regimen has been established. Combination therapy with two or more antiepileptic drugs may be necessary, but the concurrent use of antiepileptic drugs increases the risk of adverse effects and drug interactions. If combination...
therapy does not bring about worthwhile benefits, revert to the regimen (monotherapy or combination therapy) that provided the best balance between tolerability and efficacy. A single antiepileptic drug should be prescribed wherever possible.

MHRA/CHM advice: Antiepileptic drugs: new advice on switching between different manufacturers’ products for a particular drug (November 2013)

The CHM has reviewed spontaneous adverse reactions received by the MHRA and publications that reported potential harm arising from switching of antiepileptic drugs in patients previously stabilised on a branded product to a generic. The CHM concluded that reports of loss of seizure control and/or worsening of side-effects around the time of switching between products could be explained as chance associations, but that a causal role of switching could not be ruled out in all cases. The following guidance has been issued to help minimise risk:

- Different antiepileptic drugs vary considerably in their characteristics, which influences the risk of whether switching between different manufacturers’ products of a particular drug may cause adverse effects or loss of seizure control;
- Antiepileptic drugs have been divided into three risk-based categories to help healthcare professionals decide whether it is necessary to maintain continuity of supply of a specific manufacturer’s product. These categories are listed below;
- If it is felt desirable for a patient to be maintained on a specific manufacturer’s product this should be prescribed either by specifying a brand name, or by using a generic; Reducing the generic name and name of the manufacturer (otherwise known as the Marketing Authorisation Holder);
- This advice relates only to antiepileptic drug use for treatment of epilepsy; it does not apply to their use in other indications (e.g. mood stabilisation, neuropathic pain);
- Please report on a Yellow Card any suspected adverse reactions to antiepileptic drugs;
- Dispensing pharmacists should ensure the continuity of supply of a particular product when the prescription specifies it. If the prescribed product is unavailable, it may be necessary to dispense a product from a different manufacturer to maintain continuity of treatment of that antiepileptic drug. Such cases should be discussed and agreed with both the prescriber and patient (or carer);
- Usual dispensing practice can be followed when a specific product is not stated.

**Category 1**

Phenytoin p. 398, carbamazepine p. 387, phenobarbital p. 409, primidone p. 401. For these drugs, doctors are advised to ensure that their patient is maintained on a specific manufacturer’s product.

**Category 2**

Valproate, lamotrigine p. 394, perampanel p. 398, retigabine p. 402, rufinamide p. 402, clobazam p. 410, clonazepam p. 411, oxcarbazepine p. 397, eslicarbazepine acetate p. 390, zonisamide p. 408, topiramate p. 406. For these drugs, the need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient and/or carer taking into account factors such as seizure frequency and treatment history.

**Category 3**

Levetiracetam p. 396, lacosamide p. 393, tiagabine p. 406, gabapentin p. 292, pregabalin p. 400, ethosuximide p. 390, vigabatrin p. 407. For these drugs, it is usually unnecessary to ensure that patients are maintained on a specific manufacturer’s product unless there are specific concerns such as patient anxiety, and risk of confusion or dosing errors Interactions.

**Antiepileptic hypersensitivity syndrome**

Antiepileptic hypersensitivity syndrome is a rare but potentially fatal syndrome associated with some antiepileptic drugs (carbamazepine, lacosamide, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, primidone, and rufinamide); rarely cross-sensitivity occurs between some of these antiepileptic drugs. Some other antiepileptics (eslicarbazepine, stiripentol, and zonisamide) have a theoretical risk. The symptoms usually start between 1 and 8 weeks of exposure; fever, rash, and lymphadenopathy are most commonly seen. Other systemic signs include liver dysfunction, haematological, renal, and pulmonary abnormalities, vasculitis, and multi-organ failure. If signs or symptoms of hypersensitivity syndrome occur, the drug should be withdrawn immediately, the patient must not be re-exposed, and expert advice should be sought.

**Interactions**

Interactions between antiepileptics are complex and may increase toxicity without a corresponding increase in antiepileptic effect. Interactions are usually caused by hepatic enzyme induction or inhibition; displacement from protein binding sites is not usually a problem. These interactions are highly variable and unpredictable.

**Withdrawal**

Antiepileptic drugs should be withdrawn under specialist supervision. Avoid abrupt withdrawal, particularly of barbiturates and benzodiazepines, because this can precipitate severe rebound seizures. Reduction in dosage should be gradual and, in the case of barbiturates, withdrawal of the drug may take months.

The decision to withdraw antiepileptic drugs from a seizure-free patient, and its timing, is often difficult and depends on individual circumstances. Even in patients who have been seizure-free for several years, there is a significant risk of seizure recurrence on drug withdrawal. In patients receiving several antiepileptic drugs, only one drug should be withdrawn at a time.

**Driving**

Patients with epilepsy may drive a motor vehicle (but not a large goods or passenger carrying vehicle) provided that they have been seizure-free for one year or, if subject to attacks only while asleep, have established a 5-year period of asleep attacks without awake attacks. Those affected by drowsiness should not drive or operate machinery.

Guidance issued by the Drivers Medical Unit of the Driver and Vehicle Licensing Agency (DVLA) recommends that patients should be advised not to drive during medication changes or withdrawal of antiepileptic drugs, and for 6 months afterwards.

Patients who have had a first or single epileptic seizure must not drive for 6 months (5 years in the case of large goods or passenger carrying vehicles) after the event; driving may then be resumed, provided the patient has been assessed by a specialist as fit to drive because no abnormality was detected on investigation.

**Pregnancy**

Women of child-bearing potential should discuss with a specialist the impact of both epilepsy, and its treatment, on the outcome of pregnancy.

There is an increased risk of teratogenicity associated with the use of antiepileptic drugs (especially if used during the first trimester and particularly if the patient takes two or more antiepileptic drugs). Valproate is associated with the highest risk of major and minor congenital malformations (in particular neural tube defects), and long-term neurodevelopmental effects. There is also an increased risk of teratogenicity with phenytoin, primidone, phenobarbital,
lamotrigine, and carbamazepine. Topiramate carries an increased risk of cleft palate if taken in the first trimester of pregnancy. There is not enough evidence to establish the risk of teratogenicity with other antiepileptic drugs.

Prescribers should also consider carefully the choice of antiepileptic therapy in pre-pubescent girls who may later become pregnant. Women of child-bearing potential who take antiepileptic drugs should be given contraceptive advice. Some antiepileptic drugs can reduce the efficacy of hormonal contraceptives, and the efficacy of some antiepileptics may be affected by hormonal contraceptives.

Women who want to become pregnant should be referred to a specialist for advice in advance of conception. For some women, the severity of seizure or the seizure type may not pose a serious threat, and drug withdrawal may be considered; therapy may be resumed after the first trimester. If treatment with antiepileptic drugs must continue throughout pregnancy, then monotherapy is preferable at the lowest effective dose.

Once an unplanned pregnancy is discovered it is usually too late for changes to be made to the treatment regimen; the risk of harm to the mother and fetus from convulsive seizures outweighs the risk of continued therapy. The likelihood of a woman who is taking antiepileptic drugs having a baby with no malformations is at least 90%, and it is important that women do not stop taking essential treatment because of concern over harm to the fetus. To reduce the risk of neural tube defects, folic acid supplementation is advised before conception and throughout the first trimester.

The concentration of antiepileptic drugs in the plasma can change during pregnancy. Doses of phenytoin, carbamazepine, and lamotrigine should be adjusted on the basis of plasma-drug concentration monitoring; the dose of other antiepileptic drugs should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis. Plasma-drug concentration monitoring during pregnancy is also useful to check compliance. Additionally, in patients taking topiramate or levetiracetam, it is recommended that fetal growth should be monitored. Women who have seizures in the second half of pregnancy should be assessed for eclampsia before any change is made to antiepileptic treatment. Status epilepticus should be treated according to the standard protocol.

Routine injection of vitamin K at birth minimises the risk of neonatal haemorrhage associated with antiepileptics. Withdrawal effects in the newborn may occur with some antiepileptic drugs, in particular benzodiazepines and phenobarbital.

Epilepsy and Pregnancy Register
All pregnant women with epilepsy, whether taking medication or not, should be encouraged to notify the UK Epilepsy and Pregnancy Register (Tel: 0800 389 1248).

Breast-feeding
Women taking antiepileptic monotherapy should generally be encouraged to breast-feed; if a woman is on combination therapy or if there are other risk factors, such as premature birth, specialist advice should be sought.

All infants should be monitored for sedation, feeding difficulties, adequate weight gain, and developmental milestones. Infants should also be monitored for adverse effects associated with the antiepileptic drug particularly with newer antiepileptics, if the antiepileptic is readily transferred into breast-milk causing high infant serum-drug concentrations (e.g. ethosuximide, lamotrigine, primidone, and zonisamide), or if slower metabolism in the infant causes drugs to accumulate (e.g. phenobarbital and lamotrigine). Serum-drug concentration monitoring should be undertaken in breast-fed infants if suspected adverse reactions develop; if toxicity develops it may be necessary to introduce formula feeds to limit the infant’s drug exposure, or to wean the infant off breast-milk altogether.

Primidone, phenobarbital, and the benzodiazepines are associated with an established risk of drowsiness in breast-fed babies and caution is required.

Withdrawal effects may occur in infants if a mother suddenly stops breast-feeding, particularly if she is taking phenobarbital, primidone, or lamotrigine.

Focal seizures with or without secondary generalisation
Carbamazepine p. 387 and lamotrigine p. 394 are first-line options for treating newly diagnosed focal seizures; oxcarbazepine p. 397, sodium valproate p. 403 and levetiracetam p. 396 may be used if carbamazepine or lamotrigine are unsuitable or not tolerated. If monotherapy is unsuccessful with two of these first-line antiepileptic drugs, adjunctive treatment may be considered. Options for adjunctive treatment include carbamazepine, clobazam p. 410, gabapentin p. 392, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, or topiramate p. 406. If adjunctive treatment is ineffective or not tolerated, a tertiary epilepsy specialist should be consulted who may consider eslicarbazepine acetate p. 390, lacosamide p. 393, phenobarbital p. 409, phenytoin p. 398, pregabalin p. 400, tiagabine p. 406, vigabatrin p. 407 and zonisamide p. 408.

Generalised seizures
Tonic-clonic seizures
Sodium valproate p. 403 is the first-line treatment for newly diagnosed generalised tonic-clonic seizures. Lamotrigine p. 394 is the alternative choice if sodium valproate is not suitable, but may exacerbate myoclonic seizures. In those with established epilepsy with generalised tonic-clonic seizures only, lamotrigine or sodium valproate may be prescribed as the first-line treatment. Carbamazepine p. 387 and oxcarbazepine p. 397 may also be considered in newly diagnosed and established tonic-clonic seizures, but may exacerbate myoclonic and absence seizures. Clobazam p. 410, lamotrigine p. 394, levetiracetam p. 396, sodium valproate or topiramate p. 406 may be used as adjunctive treatment if monotherapy is ineffective or not tolerated.

Absence seizures
Ethosuximide p. 390 or sodium valproate p. 403 are the drugs of choice in absence seizures and syndromes; lamotrigine p. 394 is a suitable alternative when ethosuximide and sodium valproate are unsuitable, ineffective or not tolerated. Sodium valproate should be used as the first choice if there is a high risk of generalised tonic-clonic seizures. A combination of any two of these drugs may be used if monotherapy is ineffective. Clobazam p. 410, clonazepam p. 411, levetiracetam p. 396, topiramate p. 406 or zonisamide p. 408 may be considered by a tertiary epilepsy specialist if adjunctive treatment fails. Carbamazepine p. 387, gabapentin p. 392, oxcarbazepine p. 397, phenytoin p. 398, pregabalin p. 400, tiagabine p. 406 and vigabatrin p. 407 are not recommended in absence seizures or syndromes.

Myoclonic seizures
Myoclonic seizures (myoclonic jerks) occur in a variety of syndromes, and response to treatment varies considerably. Sodium valproate p. 403 is the drug of choice in newly diagnosed myoclonic seizures; topiramate p. 406 and levetiracetam p. 396 are alternative options if sodium valproate is unsuitable but consideration should be given to the less favourable side-effect profile of topiramate. A combination of two of these drugs may be used if monotherapy is ineffective or not tolerated. If adjunctive treatment fails, a tertiary epilepsy specialist should be consulted and may consider clobazam p. 410, clonazepam p. 411, zonisamide p. 408 or piracetam p. 321.

Nervous system

Seizure type, age of onset, and EEG characteristics. Syndromes are specific types of epilepsy that are ineffective. Ethosuximide is also licensed for myoclonic treatment for absence seizures when monotherapy is ineffective. Lamotrigine can also be used as adjunctive treatment for the generalised tonic-clonic seizures that coexist with myoclonic seizures, such as lamotrigine p.

Atonic and tonic seizures

Atonic and tonic seizures are usually seen in childhood, in specific epilepsy syndromes, or associated with cerebral damage or mental retardation. They may respond poorly to the traditional drugs. Sodium valproate p. 403 is the drug of choice; lamotrigine p. 394 can be added as adjunctive treatment. If adjunctive treatment is ineffective or not tolerated, a tertiary epilepsy specialist should be consulted, and may consider rufinamide p. 402 or topiramate p. 406. Lamotrigine p. 387, gabapentin p. 392, oxcarbazepine p. 397, pregabalin p. 400, tiagabine p. 406 or vigabatrin p. 407 are not recommended in atonic and tonic seizures.

Epilepsy syndromes

Some drugs are licensed for use in particular epilepsy syndromes, such as lamotrigine p. 394 and rufinamide p. 402 in Lennox-Gastaut syndrome. The epilepsy syndromes are specific types of epilepsy that are characterised according to a number of features including seizure type, age of onset, and EEG characteristics.

Antiepileptic drugs

Carbamazepine and related antiepileptics

Carbamazepine p. 387 is a drug of choice for simple and complex focal seizures and is a first-line treatment option for generalised tonic-clonic seizures. It can be used as adjunctive treatment for focal seizures when monotherapy has been ineffective. It is essential to initiate carbamazepine therapy at a low dose and build this up slowly. Carbamazepine may exacerbate tonic, atonic, myoclonic and absence seizures and is therefore not recommended if these seizures are present.

Oxcarbazepine p. 397 is licensed as monotherapy or adjunctive therapy for the treatment of focal seizures with or without secondary generalised tonic-clonic seizures. It can also be considered for the treatment of primary generalised tonic-clonic seizures [unlicensed]. Oxcarbazepine is not recommended in tonic, atonic, absence or myoclonic seizures due to the risk of seizure exacerbation.

Eslicarbazepine acetate p. 390 is licensed for adjunctive treatment in adults with focal seizures with or without secondary generalisation.

Ethisuximide

Ethisuximide p. 390 is a first-line treatment option for absence seizures. It may also be prescribed as adjunctive treatment for absence seizures when monotherapy is ineffective. Ethisuximide is also licensed for myoclonic seizures.

Gabapentin and pregabalin

Gabapentin p. 392 and pregabalin p. 400 are used for the treatment of focal seizures with or without secondary generalisation. They are not recommended if tonic, atonic, absence or myoclonic seizures are present. Both are also licensed for the treatment of neuropathic pain. Pregabalin is licensed for the treatment of generalised anxiety disorder. Gabapentin is an effective treatment for migraine prophylaxis [unlicensed].

Lamotrigine

Lamotrigine p. 394 is an antiepileptic drug recommended as a first-line treatment for focal seizures and primary and secondary generalised tonic-clonic seizures. It is also licensed for typical absence seizures in children (but efficacy may not be maintained in all children) and is an unlicensed treatment option in adults if first-line treatments have been unsuccessful. Lamotrigine can also be used as adjunctive treatment in atonic or tonic seizures if first-line treatment has failed [unlicensed]. Myoclonic seizures may be exacerbated by lamotrigine and it can cause serious rashes especially in children; dose recommendations should be adhered to closely.

Lamotrigine is used either as sole treatment or as an adjunct to treatment with other antiepileptic drugs. Valproate increases plasma-lamotrigine concentration, whereas the enzyme-inducing antiepileptics reduce it; care is therefore required in choosing the appropriate initial dose and subsequent titration. When the potential for interaction is not known, treatment should be initiated with lower doses, such as those used with valproate.

Levetiracetam

Levetiracetam p. 396 is used for monotherapy and adjunctive treatment of focal seizures with or without secondary generalisation, and for adjunctive treatment of myoclonic seizures in patients with juvenile myoclonic epilepsy and primary generalised tonic-clonic seizures. Levetiracetam may be prescribed alone and in combination for the treatment of myoclonic seizures, and under specialist supervision for absence seizures [both unlicensed].

Phenobarbital and primidone

Phenobarbital p. 409 is effective for tonic-clonic and focal seizures but may be sedative in adults. It may be tried for atypical absence, atonic, and tonic seizures. Rebound seizures may be a problem on withdrawal.

Primidone p. 401 is largely converted to phenobarbital and this is probably responsible for its antiepileptic action. A low initial dose of primidone is essential.

Phenytoin

Phenytoin p. 398 is licensed for tonic-clonic and focal seizures but may exacerbate absence or myoclonic seizures and should be avoided if these seizures are present. It has a narrow therapeutic index and the relationship between dose and plasma-drug concentration is non-linear; small dosage increases in some patients may produce large increases in plasma concentration with acute toxic side-effects. Similarly, a few missed doses or a small change in drug absorption may result in a marked change in plasma-drug concentration. Monitoring of plasma-drug concentration improves dosage adjustment.

When only parenteral administration is possible, fosphenytoin sodium p. 391, a pro-drug of phenytoin, may be convenient to give. Unlike phenytoin (which should only be given intravenously), fosphenytoin sodium may also be given by intramuscular injection.

Rufinamide

Rufinamide p. 402 is licensed for the adjunctive treatment of seizures in Lennox-Gastaut syndrome. It may be considered by a tertiary specialist for the treatment of refractory tonic or atonic seizures [unlicensed].

Topiramate

Topiramate p. 406 can be given alone or as adjunctive treatment in generalised tonic-clonic seizures or focal seizures with or without secondary generalisation. It can be used as adjunctive treatment for seizures associated with Lennox-Gastaut syndrome and for absence, tonic and atonic seizures under specialist supervision [unlicensed]. It can also be considered as an option in myoclonic seizures [unlicensed]. Topiramate is also licensed for prophylaxis of migraine.

Valproate

Sodium valproate p. 403 is effective in controlling tonic-clonic seizures, particularly in primary generalised epilepsy. It is a drug of choice in a primary generalised tonic-clonic seizures, focal seizures, generalised absences and myoclonic seizures, and can be tried in atypical absence seizures. It is recommended as a first-line option in atonic and tonic seizures.
seizures. Sodium valproate has widespread metabolic effects and monitoring of liver function tests and full blood count is essential.

Valproic acid p. 275 (as semisodium valproate) is licensed for acute mania associated with bipolar disorder.

Zonisamide
Zonisamide p. 408 can be used alone for the treatment of focal seizures with or without secondary generalisation in adults with newly diagnosed epilepsy, and as adjunctive treatment for refractory focal seizures with or without secondary generalisation in adults and children aged 6 years and above. It can also be used under the supervision of a specialist for refractory absence and myoclonic seizures [unlicensed indications].

Benzodiazepines
Clobazam p. 410 may be used as adjunctive therapy in the treatment of generalised tonic-clonic and refractory focal seizures. It may be prescribed under the care of a specialist for refractory absence and myoclonic seizures. Clonazepam p. 411 may be prescribed by a specialist for refractory absence and myoclonic seizures, but its sedative side-effects may be prominent.

Other drugs
Acetazolamide p. 965, a carbonic anhydrase inhibitor, has a specific role in treating epilepsy associated with menstruation. Piracetam p. 321 is used as adjunctive treatment for cortical myoclonus.

Status epilepticus
Convulsive status epilepticus
Immediate measures to manage status epilepticus include positioning the patient to avoid injury, supporting respiration including the provision of oxygen, maintaining blood pressure, and the correction of any hypoglycaemia. Parenteral thiamine p. 882 should be considered if alcohol abuse is suspected; pyridoxine hydrochloride p. 882 should be given if the status epilepticus is caused by pyridoxine hydrochloride deficiency.

Seizures lasting longer than 5 minutes should be treated urgently with intravenous lorazepam p. 412 (repeated once after 10 minutes if seizures recur or fail to respond). Intravenous diazepam p. 267 is effective but it carries a high risk of thrombophlebitis (reduced by using an emulsion formulation). Absorption of diazepam p. 267 from intramuscular injection or from suppositories is too slow for treatment of status epilepticus. Patients should be monitored for respiratory depression and hypotension.

Where facilities for resuscitation are not immediately available, diazepam can be administered as a rectal solution or midazolam p. 414 oromucosal solution can be given into the buccal cavity.

Important
If, after initial treatment with benzodiazepines, seizures recur or fail to respond 25 minutes after onset, phenytoin sodium, fosphenytoin sodium p. 391, or phenobarbital sodium should be used; contact intensive care unit if seizures continue. If these measures fail to control seizures 45 minutes after onset, anaesthesia with thiopental sodium p. 412, midazolam p. 414, or a non-barbiturate anaesthetic such as propofol p. 1095 [unlicensed indication], should be instituted with full intensive care support.

Phenytoin sodium can be given by slow intravenous injection, followed by the maintenance dosage if appropriate.

Alternatively, fosphenytoin sodium p. 391 (a pro-drug of phenytoin), can be given more rapidly and when given intravenously causes fewer injection-site reactions than phenytoin sodium. Although it can also be given intramuscularly, absorption is too slow by this route for treatment of status epilepticus. Doses of fosphenytoin sodium p. 391 should be expressed in terms of phenytoin sodium.

Non-convulsive status epilepticus
The urgency to treat non-convulsive status epilepticus depends on the severity of the patient’s condition. If there is incomplete loss of awareness, usual oral antiepileptic therapy should be continued or restarted. Patients who fail to respond to oral antiepileptic therapy or have complete loss of awareness can be treated in the same way as for convulsive status epilepticus, although anaesthesia is rarely needed.

Febrile convulsions
Brief febrile convulsions need no specific treatment; antipyretic medication (e.g. paracetamol p. 354), is commonly used to reduce fever and prevent further convulsions but evidence to support this practice is lacking. Prolonged febrile convulsions (those lasting 5 minutes or longer), or recurrent febrile convulsions without recovery must be treated actively (as for convulsive status epilepticus). Long-term anticonvulsant prophylaxis for febrile convulsions is rarely indicated.

Drugs used for Seizures not listed below; Acetazolamide, p. 965 - Lidocaine hydrochloride, p. 1116 - Magnesium sulfate, p. 858

ANTIEPILEPTICS

Carbamazepine

INDICATIONS AND DOSE
Focal and secondary generalised tonic-clonic seizures | Primary generalised tonic-clonic seizures
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

- Adult: Initially 100–200 mg 1–2 times a day, increased in steps of 100–200 mg every 2 weeks; usual dose 0.8–1.2 g daily in divided doses; increased if necessary up to 1.6–2 g daily in divided doses
- Elderly: Reduce initial dose

BY RECTUM

- Adult: Up to 1 g daily in 4 divided doses for up to 7 days, for short-term use when oral therapy temporarily not possible

Trigeminal neuralgia
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

- Adult: Initially 100 mg 1–2 times a day, some patients may require higher initial dose, increased in steps of 100–200 mg every 2 weeks, adjusted according to response, usual dose 200 mg 3–4 times a day; increased if necessary up to 1.6 g daily

Prophylaxis of bipolar disorder unresponsive to lithium
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

- Adult: Initially 400 mg daily in divided doses, increased in steps of 100–200 mg every 2 weeks until symptoms controlled; usual dose 400–600 mg daily; maximum 1.6 g per day

Treatment of alcohol withdrawal
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

- Adult: Initially 800 mg daily in divided doses, then reduced to 200 mg daily usual treatment duration 7–10 days, dose to be reduced gradually over 5 days

Diabetic neuropathy
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

- Adult: Initially 100 mg 1–2 times a day, increased in steps of 100–200 mg every 2 weeks, adjusted according to response, usual dose 200 mg 3–4 times a day; increased if necessary up to 1.6 g daily

Continued
Focal and generalised tonic-clonic seizures

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

- Child 1 month–11 years: Initially 5 mg/kg once daily, dose to be taken at night, alternatively initially 2.5 mg/kg twice daily, then increased in steps of 2.5–5 mg/kg every 3–7 days as required; maintenance 5 mg/kg 2–3 times a day, increased if necessary up to 20 mg/kg daily
- Child 12–17 years: Initially 100–200 mg 1–2 times a day, then increased to 200–400 mg 2–3 times a day, increased if necessary up to 1.8 g daily, dose should be increased slowly

Dose equivalence and conversion

Suppositories of 125 mg may be considered to be approximately equivalent in therapeutic effect to tablets of 100 mg but final adjustment should always depend on clinical response (plasma concentration monitoring recommended).

CARRBEN® SR

Focal and secondary generalised tonic-clonic seizures | Primary generalised tonic-clonic seizures

BY MOUTH

- Adult: Initially 100–400 mg daily in 1–2 divided doses, increased in steps of 100–200 mg every 2 weeks, usual dose 0.8–1.2 g daily in 1–2 divided doses; increased if necessary up to 1.6–2 g daily in 1–2 divided doses
- Elderly: Reduce initial dose

Trigeminal neuralgia

BY MOUTH

- Adult: Initially 100–200 mg daily in 1–2 divided doses, some patients may require higher initial dose, increased in steps of 100–200 mg every 2 weeks, adjusted according to response, usual dose 600–800 mg daily in 1–2 divided doses; increased if necessary up to 1.6 g daily in 1–2 divided doses
- Child 12 years: Initially 5–10 mg/kg weekly, dose should be increased slowly

Prophylaxis of bipolar disorder unresponsive to lithium

BY MOUTH

- Adult: Initially 400 mg daily in 1–2 divided doses, increased in steps of 100–200 mg every 2 weeks until symptoms controlled; usual dose 400–600 mg daily in 1–2 divided doses; maximum 1.6 g per day

Focal and generalised tonic-clonic seizures | Prophylaxis of bipolar disorder

BY MOUTH

- Child 5–11 years: Initially 5 mg/kg daily in 1–2 divided doses, then increased in steps of 2.5–5 mg/kg every 3–7 days as required; maintenance 10–15 mg/kg daily in 1–2 divided doses, increased if necessary up to 20 mg/kg daily in 1–2 divided doses
- Child 12–17 years: Initially 100–400 mg daily in 1–2 divided doses, then increased to 400–1200 mg daily in 1–2 divided doses, increased if necessary up to 1.8 g daily in 1–2 divided doses, dose should be increased slowly

TEGRETOL® PROLONGED RELEASE

Focal and secondary generalised tonic-clonic seizures | Primary generalised tonic-clonic seizures

BY MOUTH

- Adult: Initially 100–400 mg daily in 2 divided doses, increased in steps of 100–200 mg every 2 weeks, usual dose 0.8–1.2 g daily in 2 divided doses; increased if necessary up to 1.6–2 g daily in 2 divided doses
- Elderly: Reduce initial dose

Trigeminal neuralgia

BY MOUTH

- Child 12–17 years: Initially 100–400 mg daily in 2 divided doses, then increased to 400–1200 mg daily in 2 divided doses, increased if necessary up to 1.8 g daily in 2 divided doses, dose should be increased slowly

Prophylaxis of bipolar disorder unresponsive to lithium

BY MOUTH

- Adult: Initially 400 mg daily in 2 divided doses, increased in steps of 100–200 mg every 2 weeks until symptoms controlled; usual dose 400–600 mg daily in 2 divided doses; maximum 1.6 g per day

- UNLICENSED USE
  - In children Suppositories not licensed for use in trigeminal neuralgia or prophylaxis of bipolar disorder.
  - In adults Use in the treatment of alcohol withdrawal is an unlicensed indication. Use in diabetic neuropathy is an unlicensed indication.

- CONTRA-INDICATIONS
  - Acute porphyrias p. 864 • AV conduction abnormalities (unless paced) • history of bone-marrow depression

- CAUTIONS
  - Cardiac disease • history of haematological reactions to other drugs • may exacerbate absence and myoclonic seizures • skin reactions • susceptibility to angle-closure glaucoma

- CAUTIONS, FURTHER INFORMATION
  - Consider vitamin D supplementation in patients who are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium.

- Blood, hepatic, or skin disorders
  - Carbamazepine should be withdrawn immediately in cases of aggravated liver dysfunction or acute liver disease. Leucopenia that is severe, progressive, or associated with clinical symptoms requires withdrawal (if necessary under cover of a suitable alternative).

- INTERACTIONS → Appendix 1 (carbamazepine).

- SIDE-EFFECTS
  - Common or very common
    - Allergic skin reactions • aplastic anaemia • ataxia • blood disorders • blurring of vision • dermatitis • dizziness • drowsiness • dry mouth • eosinophilia • fatigue • haemolytic anaemia • headache • hypnolatraemia (leading in rare cases to water intoxication) • leucopenia • nausea • oedema • thrombocytopenia • unsteadiness • urticaria • vomiting
  - Uncommon
    - Constipation • diarrhoea • involuntary movements (including nystagmus) • visual disturbances
  - Rare
    - Abdominal pain • aggression • agitation • anorexia • cardiac conduction disorders • confusion • delayed multi-organ hypersensitivity disorder • depression • dysarthria • hallucinations • hepatitis • hypertension • hypotension • jaundice • lymph node enlargement • muscle weakness • paraesthesia • peripheral neuropathy • restlessness • systemic lupus erythematosus • vanishing bile duct syndrome
  - Very rare
    - Arthralgia • muscle spasm • acne • alopecia • alterations in skin pigmentation • angle-closure glaucoma • aseptic meningitis • AV block with syncope • circulatory collapse • conjunctivitis • dyspnoea • exacerbation of coronary artery disease • galactorrhoea • gynaecomastia • hearing disorders • hepatic failure • hirsutism • hypercholesterolaemia • impaired male fertility •
interstitial nephritis • muscle pain • neuroleptic malignant syndrome • osteomalacia • osteoporosis • pancreatitis • photosensitivity • pneumonia • pneumonitis • psychosis • pulmonary hypersensitivity • purpura • renal failure • sexual dysfunction • Stevens-Johnson syndrome • stomatitis • sweating • taste disturbance • thromboembolism • thrombophlebitis • toxic epidermal necrolysis • urinary frequency • urinary retention

▶ Frequency not known Suicidal ideation

SIDE-EFFECTS, FURTHER INFORMATION
Some side-effects (such as headache, ataxia, drowsiness, nausea, vomiting, blurring of vision, dizziness, unsteadiness, and allergic skin reactions) are dose-related, and may be dose-limiting. These side-effects are more common at the start of treatment and in the elderly. Patients should be offered a modified-release preparation to reduce the risk of side-effects; altering the timing of medication may also be beneficial.

Overdose
For details on the management of poisoning, see Active elimination techniques, under Emergency treatment of poisoning p. 1123.

ALLERGY AND CROSS-SENSITIVITY
Antiepileptic hypersensitivity syndrome associated with carbamazepine. See under Epilepsy p. 383 for more information. Caution—cross-sensitivity reported with oxcarbazepine and with phenytoin.

PREGNANCY
Doses should be adjusted on the basis of plasma-drug concentration monitoring.

BREAST FEEDING
Amount probably too small to be harmful. Monitor infant for possible adverse reactions.

HEPATIC IMPAIRMENT
Metabolism impaired in advanced liver disease.

RENAL IMPAIRMENT
Use with caution.

PRE-TREATMENT SCREENING
Test for HLA-B*1502 allele in individuals of Han Chinese or Thai origin (avoid unless no alternative—risk of Stevens-Johnson syndrome in presence of HLA-B*1502 allele).

MONITORING REQUIREMENTS
Plasma concentration for optimum response 4–12 mg/litre (20–50 micromol/litre) measured after 1–2 weeks.

Manufacturer recommends blood counts and hepatic and renal function tests (but evidence of practical value uncertain).

TREATMENT CESSATION
When stopping treatment with carbamazepine for bipolar disorder, reduce the dose gradually over a period of at least 4 weeks.

DIRECTIONS FOR ADMINISTRATION
In children Oral liquid has been used rectally—should be retained for at least 2 hours (but may have laxative effect). Tegretol® Prolonged Release tablets can be halved but should not be chewed.

PRESCRIBING AND DISPENSING INFORMATION
Switching between formulations Different formulations of oral preparations may vary in bioavailability. Patients being treated for epilepsy should be maintained on a specific manufacturer’s product.

PATIENT AND CARER ADVICE
Medicines for Children leaflet Carbamazepine (oral) for preventing seizures www.medicinesforchildren.org.uk/carbamazepine-oral-preventing-seizures-0

Blood, hepatic, or skin disorders Patients or their carers should be told how to recognise signs of blood, liver, or skin disorders, and advised to seek immediate medical attention if symptoms such as fever, rash, mouth ulcers, bruising, or bleeding develop.

PROFESSION SPECIFIC INFORMATION
Dental practitioners’ formulary Carbamazepine Tablets may be prescribed.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

Tablet
CAUTIONARY AND ADVISORY LABELS 3, 8
CARBAMAZEPINE (Non-proprietary)
Carbamazepine 100 mg Carbamazepine 100mg tablets | 28 tablet (£5.95 DT price = £4.81 | 84 tablet (£6.63
Carbamazepine 200 mg Carbamazepine 200mg tablets | 28 tablet (£6.35 DT price = £5.11 | 84 tablet (£6.47
Carbamazepine 400 mg Carbamazepine 400mg tablets | 28 tablet (£5.75 | 56 tablet (£6.18 DT price = £5.02
Carbagen (Mylan Ltd)
Carbamazepine 100 mg Carbagen 100mg tablets | 28 tablet (£5.74 DT price = £4.81 | 56 tablet (£6.18 no price available (Hospital only) | 84 tablet (£6.47 no price available (Hospital only)
Carbamazepine 200 mg Carbagen 200mg tablets | 28 tablet (£4.99 DT price = £5.11 | 56 tablet (£6.18 no price available (Hospital only) | 84 tablet (£6.47 no price available (Hospital only)
Carbamazepine 400 mg Carbagen 400mg tablets | 28 tablet (£4.27 | 56 tablet (£5.02 no price available DT price = £5.02 (Hospital only)

Tegretol (Novartis Pharmaceuticals UK Ltd)
Carbamazepine 100 mg Tegretol 100mg tablets | 84 tablet (£2.07
Carbamazepine 200 mg Tegretol 200mg tablets | 84 tablet (£3.83
Carbamazepine 400 mg Tegretol 400mg tablets | 56 tablet (£5.02 DT price = £5.02

Chewable tablet
CAUTIONARY AND ADVISORY LABELS 3, 8, 21, 24
Tegretol Chewtabs (Novartis Pharmaceuticals UK Ltd)
Carbamazepine 100 mg Tegretol 100mg Chewtabs (sugar-free) | 56 tablet (£3.16 DT price = £3.16

Modified-release tablet
CAUTIONARY AND ADVISORY LABELS 3, 8, 25
CARBAMAZEPINE (Non-proprietary)
Carbamazepine 200 mg Carbamazepine 200mg modified-release tablets | 56 tablet (£2.00 DT price = £1.20
Carbamazepine 400 mg Carbamazepine 400mg modified-release tablets | 56 tablet (£3.00 DT price = £1.20
Carbagen SR (Mylan Ltd)
Carbamazepine 200 mg Carbagen SR 200mg tablets | 56 tablet (£4.16 DT price = £5.20
Carbamazepine 400 mg Carbagen SR 400mg tablets | 56 tablet (£8.20 DT price = £10.24

Tegretol Retard (Novartis Pharmaceuticals UK Ltd)
Carbamazepine 200 mg Tegretol Prolonged Release 200mg tablets | 56 tablet (£5.20 DT price = £5.20
Carbamazepine 400 mg Tegretol Prolonged Release 400mg tablets | 56 tablet (£10.24 DT price = £10.24

Oral suspension
CAUTIONARY AND ADVISORY LABELS 3, 8
CARBAMAZEPINE (Non-proprietary)
Carbamazepine 20 mg per 1 ml Carbamazepine 100mg/5ml oral suspension sugar-free (sugar-free) | 300 ml (£6.12 DT price = £6.12

Tegretol (Novartis Pharmaceuticals UK Ltd)
Carbamazepine 20 mg per 1 ml Tegretol 100mg/5ml liquid (sugar-free) | 300 ml (£6.12 DT price = £6.12

Suppository
CAUTIONARY AND ADVISORY LABELS 3, 8
Tegretol (Novartis Pharmaceuticals UK Ltd)
Carbamazepine 125 mg Tegretol 125mg suppositories | 5 suppository (£9.03
Carbamazepine 250 mg Tegretol 250mg suppositories | 5 suppository (£10.71

BNF 70
Epilepsy 389
Nervous system
Eslicarbazepine acetate

INDICATIONS AND DOSE
Adjuvant treatment in adults with focal seizures with or without secondary generalisation

BY MOUTH
- Adult: Initially 400 mg once daily for 1–2 weeks, then increased to 800 mg once daily (max. per dose 1.2 g)

CONTRA-INDICATIONS Second- or third-degree AV block

CAUTIONS Elderly - hyponatraemia - PR-interval prolongation

INTERACTIONS → Appendix 1 (eslicarbazepine). Caution—avoid concomitant administration of drugs that prolong PR interval.

SIDE-EFFECTS
- Common or very common Dizziness - drowsiness - fatigue - gastrointestinal disturbances - headache - impaired coordination - rash - tremor - visual disturbances
- Very rare Leucopenia - pancreatitis - thrombocytopenia
- Frequency not known PR-interval prolongation - suicidal ideation

ALLERGY AND CROSS-SENSITIVITY Antiepileptic hypersensitivity syndrome theoretically associated with eslicarbazepine. See under Epilepsy p. 383 for more information.

PREGNANCY The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

HEPATIC IMPAIRMENT Avoid in severe impairment—no information available.

Renal IMPAIRMENT Reduce initial dose to 400 mg every other day for 2 weeks then 400 mg once daily if eGFR 30–60 mL/minute/1.73 m², adjusted according to response. Avoid if eGFR less than 30 mL/minute/1.73 m².

PRE-TREATMENT SCREENING Test for HLA-B*1502 allele in individuals of Han Chinese or Thai origin (avoid unless no alternative—risk of Stevens-Johnson syndrome in presence of HLA-B*1502 allele).

MONITORING REQUIREMENTS Monitor plasma-sodium concentration in patients at risk of hyponatraemia and discontinue treatment if hyponatraemia occurs.

PRESCRIBING AND DISPENSING INFORMATION Switching between formulations Care should be taken when switching between oral formulations. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history.

NATIONAL FUNDING/ACCESS DECISIONS
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (October 2010) that eslicarbazepine acetate (Zebinix®) is accepted for restricted use within NHS Scotland as adjuvant therapy in adults with focal seizures with or without secondary generalisation. It is restricted for use in refractory epilepsy.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
CAUTIONARY AND ADVISORY LABELS B
- Ethosuximide (Eisai Ltd)
- Eslicarbazepine acetate 800 mg Zebinix 800mg tablets 30 tablet (Re drastically £136.00)

Ethosuximide

INDICATIONS AND DOSE
Absence seizures | Atypical absence seizures | Myoclonic seizures

BY MOUTH
- Child 1 month-5 years: Initially 5 mg/kg twice daily (max. per dose 125 mg), dose to be increased every 5–7 days; maintenance 10–20 mg/kg twice daily (max. per dose 500 mg), total daily dose may rarely be given in 3 divided doses
- Child 6-17 years: Initially 250 mg twice daily, then increased in steps of 250 mg every 5–7 days; usual dose 500–750 mg twice daily, increased if necessary up to 1 g twice daily
- Adult: Initially 500 mg daily in 2 divided doses, then increased in steps of 250 mg every 5–7 days; usual dose 1–1.5 g daily in 2 divided doses, increased if necessary up to 2 g daily

CAUTIONS Avoid in Acute porphyrias p. 864

INTERACTIONS → Appendix 1 (ethosuximide).

SIDE-EFFECTS
- Common or very common anorexia - abdominal pain - diarrhoea - gastro-intestinal disturbances - nausea - vomiting - weight loss
- Uncommon Aggression - ataxia - dizziness - drowsiness - euphoria - fatigue - headache - hiccups - impaired concentration - irritability
- Rare Depression - dyskinesia - gingival hypertrophy - increased libido - myopia - photophobia - psychosis - rash - sleep disturbances - tongue swelling - vaginal bleeding
- Frequency not known Agranulocytosis - aplastic anaemia - blood disorders - hyperactivity - increase in seizure frequency - leucopenia - pancytopenia - Stevens-Johnson syndrome - suicidal ideation - systemic lupus erythematosus

SIDE-EFFECTS, FURTHER INFORMATION
Blood disorders Blood counts required if features of infection.

PREGNANCY The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

BREAST FEEDING Present in milk. Hyperexcitability and sedation reported.

HEPATIC IMPAIRMENT Use with caution.

RENAL IMPAIRMENT Use with caution.

PATIENT AND CARER ADVICE
Medicines for Children leaflet: Ethosuximide for preventing seizures www.medicinesforchildren.org.uk/ethosuximide-for-preventing-seizures

Blood disorders Patients or their carers should be told how to recognise signs of blood disorders, and advised to seek immediate medical attention if symptoms such as fever, mouth ulcers, bruising, or bleeding develop.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
Fosphenytoin sodium

**Dose equivalence and conversion**

Doses are expressed as phenytoin sodium equivalent (PE); fosphenytoin sodium 1.5 mg = phenytoin sodium 1 mg.

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Fosphenytoin sodium is a pro-drug of phenytoin.

### Indications and dose

#### Status epilepticus

**By intravenous infusion**
- **Adult:** Initially 20 mg(PE)/kg, dose to be administered at a rate of 100–150 mg(PE)/minute, then 4–5 mg (PE)/kg daily in 1–2 divided doses, dose to be adjusted at a rate of 50–100 mg(PE)/minute, dose to be adjusted according to response and trough plasma-phenytoin concentration
- **Elderly:** Consider 10–25% reduction in dose or infusion rate

#### Prophylaxis or treatment of seizures associated with neurosurgery or head injury

**By intramuscular injection or by intravenous infusion**
- **Adult:** Initially 10–15 mg(PE)/kg, intravenous infusion to be administered at a rate of 50–100 mg(PE)/minute, then 4–5 mg(PE)/kg daily in 1–2 divided doses, intravenous infusion to be administered at a rate of 50–100 mg(PE)/minute, dose to be adjusted according to response and trough plasma-phenytoin concentration
- **Elderly:** Consider 10–25% reduction in dose or infusion rate

#### Temporary substitution for oral phenytoin

**By intramuscular injection or by intravenous infusion**
- **Adult:** Intravenous infusion to be administered at a rate of 50–100 mg(PE)/minute, same dose and same dosing frequency as oral phenytoin therapy
- **Elderly:** Consider 10–25% reduction in dose or infusion rate

#### Dose equivalence and conversion

Doses are expressed as phenytoin sodium equivalent (PE); fosphenytoin sodium 1.5 mg = phenytoin sodium 1 mg.
Gabapentin

INDICATIONS AND DOSE

Adjunctive treatment of focal seizures with or without secondary generalisation

BY MOUTH

- Child 6–11 years: Initially 300 mg once daily; then 300 mg twice daily; then 300 mg 3 times a day, divided doses; maximum 6 g daily
- Child 12–17 years: Initially 300 mg once daily; then 300 mg twice daily; then 300 mg 3 times a day; increased in steps of 300 mg every 2 days
- Child 18 years or over: Initially 300 mg once daily; then 300 mg twice daily; then 300 mg 3 times a day; increased in steps of 300 mg every 3–5 days

Monotherapy for focal seizures with or without secondary generalisation

BY MOUTH

- Child 12–17 years: Initially 300 mg once daily; then 300 mg twice daily; then 300 mg 3 times a day; increased in steps of 300 mg every 2–3 days
- Adult: Initially 300 mg once daily; then 300 mg twice daily; then 300 mg 3 times a day; increased in steps of 300 mg every 2–3 days

Neuropathic pain

BY MOUTH

- Adult: Initially 300 mg once daily; then 300 mg twice daily; then 300 mg 3 times a day; increased in steps of 300 mg every 2–3 days

Migraine prophylaxis

BY MOUTH

- Adult: Initially 300 mg daily; then increased to up to 4 g daily in divided doses; adjusted according to response

**UNLICENSED USE**

- In children: Not licensed for use in children under 6 years. Not licensed at doses over 50 mg/kg daily in children under 12 years.
- In adults: Not licensed for migraine prophylaxis.

**CAUTIONS**

- Diabetes mellitus: elderly → high doses of oral solution in adolescents and adults with low body-weight → history of psychotic illness → mixed seizures (including absences)

**INTERACTIONS** → Appendix 1 (gabapentin).

**SIDE-EFFECTS**

- Common or very common: Abdominal pain → abnormal reflexes → abnormal thinking → acne → amnesia → anorexia → anxiety → arthralgia → ataxia → confusion → constipation → convulsions → cough → depression → diarrhoea → dizziness → drowsiness → dry mouth → dry throat → dyspepsia → dyspnha → emotional lability → fever → flatulence → flu syndrome → gingivitis → headache → hostility → hypertension → impotence → increased appetite → insomnia → leucopenia → malaise → movement disorders → myalgia → nausea → nervousness → nyctagmus → oedema → paraesthesia → pharyngitis → pruritus → rash → rhinitis → speech disorder → tremor → twitching → vasodilatation → vertigo → visual disturbances → vomiting → weight gain

- Uncommon: Palpitations

- Frequency not known: Acute renal failure → alopoeia → blood glucose fluctuations in patients with diabetes → breast hypotrophy → gynaecomastia → hallucinations → hepatitis → hypersensitivity syndrome → incontience → pancreatitis → Stevens-Johnson syndrome → suicidal ideation → thrombocytopenia → tinnitus

**PREGNANCY**

The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

**BREAST FEEDING**

Present in milk → manufacturer advises use only if potential benefit outweighs risk.

**RENAL IMPAIRMENT**

- In adults: Reduce dose to 0.6–1.8 g daily in 3 divided doses if eGFR 50–80 mL/minute/1.73 m². Reduce dose to 300–900 mg daily in 3 divided doses if eGFR 30–50 mL/minute/1.73 m². Reduce dose to 300 mg on alternate days (up to max. 600 mg daily) in 3 divided doses if eGFR 15–30 mL/minute/1.73 m². Reduce dose to 300 mg on alternate days (up to max. 300 mg daily) in 3 divided doses if eGFR less than 15 mL/minute/1.73 m² → consult product literature.

- In children: Reduce dose if estimated glomerular filtration rate less than 80 mL/minute/1.73 m²; consult product literature.

**EFFECT ON LABORATORY TESTS**

False positive readings with some urinary protein tests.

**DIRECTIONS FOR ADMINISTRATION**

Capsules can be opened but the bitter taste is difficult to mask.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Gabapentin for neuropathic pain www.medicinesforchildren.org.uk/gabapentin-for-neuropathic-pain

Medicines for Children leaflet: Gabapentin for preventing seizures www.medicinesforchildren.org.uk/gabapentin-for-preventing-seizures

**Important safety information**

The levels of propylene glycol, ascorbate K and saccharin sodium may exceed the recommended WHO daily intake limits if high doses of gabapentin oral solution (Rosemont brand) are given to adolescents or adults with low body-weight (39–50 kg) → consult product literature.
Lacosamide

INDICATIONS AND DOSE

Adjunctive treatment of focal seizures with or without secondary generalisation

BY MOUTH OR BY INTRAVENOUS INFUSION

Child 16-17 years: Initially 50 mg twice daily, infusion to be administered over 15–60 minutes (for up to 5 days), then increased, if tolerated, in steps of 50 mg twice daily, adjusted according to response, dose to be increased in weekly intervals; maintenance 100 mg twice daily (max. per dose 200 mg twice daily).

Adult: Initially 50 mg twice daily, infusion to be administered over 15–60 minutes (for up to 5 days), then increased, if tolerated, in steps of 50 mg twice daily, adjusted according to response, dose to be increased in weekly intervals; maintenance 100 mg twice daily (max. per dose 200 mg twice daily).

Adjunctive treatment of focal seizures with or without secondary generalisation (alternative loading dose regimen when it is necessary to rapidly attain therapeutic plasma concentrations) (under close medical supervision)

BY MOUTH OR BY INTRAVENOUS INFUSION

Child 16-17 years: Loading dose 200 mg, infusion to be administered over 15–60 minutes (for up to 5 days), followed by maintenance 100 mg twice daily, to be given 12 hours after initial dose, then increased, if tolerated, in steps of 50 mg twice daily (max. per dose 200 mg twice daily), adjusted according to response, dose to be increased in weekly intervals

Adult: Loading dose 200 mg, infusion to be administered over 15–60 minutes (for up to 5 days), followed by maintenance 100 mg twice daily, to be

given 12 hours after initial dose, then increased, if tolerated, in steps of 50 mg twice daily (max. per dose 200 mg twice daily), adjusted according to response, dose to be increased in weekly intervals

CONTRA-INDICATIONS Second- or third-degree AV block

CAUTIONS Conduction problems - elderly (in adults) - risk of PR-interval prolongation - severe cardiac disease

INTERACTIONS → Appendix 1 (lacosamide). Caution with concomitant use of drugs that prolong PR interval.

SIDE-EFFECTS

Common or very common Abnormal gait - blurred vision - cognitive disorder - constipation - depression - dizziness - drowsiness - fatigue - flatulence - headache - impaired coordination - nausea - nyctagmus - pruritus - tremor - vomiting

Rare Multi-organ hypersensitivity reaction


ALLERGY AND CROSS-SENSITIVITY Antiepileptic hypersensitivity syndrome associated with lacosamide. See under Epilepsy p. 383 for more information.

PREGNANCY The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

BREAST FEEDING Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT Titrate with caution in mild to moderate impairment if co-existing renal impairment. Caution in severe impairment—no information available.

RENAL IMPAIRMENT Loading dose regimen can be considered in mild to moderate impairment—titrate above 200 mg with caution. Titrate with caution in severe impairment, max. 250 mg daily.

In adults Consult product literature for loading dose if eGFR less than 30 mL/minute/1.73 m².

In children Consult product literature for loading dose if estimated glomerular filtration rate is less than 30 mL/minute/1.73 m².

DIRECTIONS FOR ADMINISTRATION

In children For intravenous infusion, give undiluted or dilute with Glucose 5% or Sodium Chloride 0.9%.

In adults For intravenous infusion (Vimpat® 51), give intermittently in Glucose 5% or Sodium Chloride 0.9%. May be administered undiluted.

PRESCRIBING AND DISPENSING INFORMATION Flavours of syrup may include strawberry.

PATIENT AND CARER ADVICE

Medicines for Children leaflet: Lacosamide for preventing seizures www.medicinesforchildren.org.uk/lacosamide-for-preventing-seizures

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (January 2009) that lacosamide (Vimpat® 29) is accepted for restricted use within NHS Scotland as adjunctive treatment for focal seizures with or without secondary generalisation in patients from 16 years. It is restricted for specialist use in refractory epilepsy.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.
Tablet

**INDICATIONS AND DOSE**

**Monotherapy of focal seizures | Monotherapy of primary and secondary generalised tonic-clonic seizures | Monotherapy of seizures associated with Lennox-Gastaut syndrome**

**BY MOUTH**

- **Child 12-17 years:** Initially 25 mg once daily for 14 days, then increased to 50 mg once daily for further 14 days, then increased in steps of up to 100 mg every 7–14 days; maintenance 100–200 mg daily in 1–2 divided doses; increased if necessary up to 500 mg daily, dose titration should be repeated if restarting after interval of more than 5 days
- **Adult:** Initially 25 mg once daily for 14 days, then increased to 50 mg once daily for further 14 days, then increased in steps of up to 100 mg every 7–14 days; maintenance 100–200 mg daily in 1–2 divided doses; increased if necessary up to 500 mg daily, dose titration should be repeated if restarting after interval of more than 5 days

**Adjunctive therapy of focal seizures with valproate | Adjunctive therapy of primary and secondary generalised tonic-clonic seizures with valproate | Adjunctive therapy of seizures associated with Lennox-Gastaut syndrome with valproate**

**BY MOUTH**

- **Child 2-11 years (body-weight up to 13 kg):** Initially 2 mg once daily on alternate days for first 14 days, then 300 micrograms/kg once daily for further 14 days, then increased in steps of up to 300 micrograms/kg every 7–14 days; maintenance 1–5 mg/kg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days; maximum 200 mg per day
- **Child 2-11 years (body-weight 13 kg and above):** Initially 150 micrograms/kg once daily for 14 days, then 300 micrograms/kg once daily for further 14 days, then increased in steps of up to 300 micrograms/kg every 7–14 days; maintenance 1–5 mg/kg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days; maximum 200 mg per day
- **Child 12-17 years:** Initially 25 mg once daily on alternate days for 14 days, then 25 mg once daily for further 14 days, then increased in steps of up to 50 mg every 7–14 days; maintenance 100–200 mg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days

**Oral solution**

**EXCipients:** May contain Aspartame, propylene glycol

**ELECTROLYTES:** May contain Sodium

**Vimpat (UCB Pharma Ltd)**

Lacosamide 10 mg per 1 ml Vimpat 10mg/ml syrup (sugar-free) | 200 ml (£25.74 DT price = £25.74)

**Solution for infusion**

**ELECTROLYTES:** May contain Sodium

**Vimpat (UCB Pharma Ltd)**

Lacosamide 10 mg per 1 ml Vimpat 200mg/200ml solution for infusion vials | 1 vial (£29.70)

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**Lamotrigine**

1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days

- **Adult:** Initially 25 mg once daily on alternate days for 14 days, then 25 mg once daily for further 14 days, then increased in steps of up to 50 mg every 7–14 days; maintenance 100–200 mg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days

**Adjunctive therapy of focal seizures (with enzyme inducing drugs) without valproate | Adjunctive therapy of primary and secondary generalised tonic-clonic seizures (with enzyme inducing drugs) without valproate | Adjunctive therapy of seizures associated with Lennox-Gastaut syndromes (with enzyme inducing drugs) without valproate**

**BY MOUTH**

- **Child 2-11 years:** Initially 300 micrograms/kg twice daily for 14 days, then 600 micrograms/kg twice daily for further 14 days, then increased in steps of up to 1.2 mg/kg every 7–14 days; maintenance 100–200 mg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days; maximum 400 mg per day
- **Child 12-17 years:** Initially 50 mg once daily for 14 days, then 50 mg twice daily for further 14 days, then increased in steps of up to 100 mg every 7–14 days; maintenance 200–400 mg daily in 2 divided doses, increased if necessary up to 700 mg daily, dose titration should be repeated if restarting after interval of more than 5 days

**Adjunctive therapy of focal seizures (without enzyme inducing drugs) without valproate | Adjunctive therapy of primary and secondary generalised tonic-clonic seizures (without enzyme inducing drugs) without valproate | Adjunctive therapy of seizures associated with Lennox-Gastaut syndromes (without enzyme inducing drugs) without valproate**

**BY MOUTH**

- **Child 2-11 years:** Initially 300 micrograms/kg daily in 1–2 divided doses for 14 days, then 600 micrograms/kg daily in 1–2 divided doses for further 14 days, then increased in steps of up to 600 micrograms/kg every 7–14 days; maintenance 1–10 mg/kg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days; maximum 200 mg per day
- **Child 12-17 years:** Initially 25 mg once daily for 14 days, then increased to 50 mg once daily for further 14 days, then increased in steps of up to 100 mg every 7–14 days; maintenance 200–400 mg daily in 2 divided doses, increased if necessary up to 700 mg daily, dose titration should be repeated if restarting after interval of more than 5 days

**Monotherapy or adjunctive therapy of bipolar disorder (without enzyme inducing drugs) without valproate**

**BY MOUTH**

- **Adult:** Initially 25 mg once daily for 14 days, then increased to 50 mg once daily for further 14 days, then increased in steps of up to 100 mg every 7–14 days; maintenance 200–400 mg daily in 1–2 divided doses, dose titration should be repeated if restarting after interval of more than 5 days

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**Lamotrigine**

- **Lamotrigine**
- **Valproate**
- **Tonic-clonic seizures with valproate**
- **Adjunctive therapy of primary and secondary generalised tonic-clonic seizures (with enzyme inducing drugs) without valproate**
- **Adjunctive therapy of seizures associated with Lennox-Gastaut syndromes (without enzyme inducing drugs) without valproate**
- **Monotherapy of primary and secondary generalised tonic-clonic seizures**
- **Monotherapy of seizures associated with Lennox-Gastaut syndrome**
- **Indications and dose**
- **Tablet**
- **Oral solution**
- **Solution for infusion**
- **EXCipients:** May contain Aspartame, propylene glycol
- **Solution for infusion vials | 1 vial (£29.70)**
- **Lacosamide 10 mg per 1 ml Vimpat 10mg/ml syrup (sugar-free) | 200 ml (£25.74 DT price = £25.74)**
- **Lacosamide 10 mg per 1 ml Vimpat 200mg/200ml solution for infusion vials | 1 vial (£29.70)**
- **£144.16 DT price = £144.16**
- **£32.64 | £56 tablet (£21.62 | £56 tablet (£86.50 DT price = £86.50**
- **£25.74 DT price = £25.74**
- **£10.81 DT price = £10.81**
- **£0.81**
- **£4.50**
- **£864.40**
- **£216.50**
- **£2.50**
- **£21.62**
- **£21.62**
- **£32.64 | £56 tablet (£129.74 DT price = £129.74**
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7 days; maintenance 200 mg daily in 1–2 divided doses, patients stabilised on lamotrigine for bipolar disorder may require dose adjustments if other drugs are added to or withdrawn from their treatment regimen—consult product literature, dose titration should be repeated if restarting after interval of more than 5 days; maximum 400 mg per day

Adju nctive therapy of bipolar disorder with valproate

BY MOUTH

Adult: Initially 25 mg once daily on alternate days for 14 days, then 25 mg once daily for further 14 days, then 50 mg daily in 1–2 divided doses for further 7 days; maintenance 100 mg daily in 1–2 divided doses; patients stabilised on lamotrigine for bipolar disorder may require dose adjustments if other drugs are added to or withdrawn from their treatment regimen—consult product literature, dose titration should be repeated if restarting after interval of more than 5 days; maximum 200 mg per day

Adju nctive therapy of bipolar disorder (with enzyme inducing drugs) without valproate

BY MOUTH

Adult: Initially 50 mg once daily for 14 days, then 50 mg twice daily for further 14 days, then increased to 100 mg twice daily for further 7 days, then increased to 150 mg twice daily for further 7 days; maintenance 200 mg twice daily, patients stabilised on lamotrigine for bipolar disorder may require dose adjustments if other drugs are added to or withdrawn from their treatment regimen—consult product literature, dose titration should be repeated if restarting after interval of more than 5 days

Important safety information
SAFE PRACTICE
Do not confuse the different combinations or indications.

● CAUTIONS Myoclonic seizures (may be exacerbated) - Parkinson’s disease (may be exacerbated) (in adults)

● INTERACTIONS ➔ Appendix 1 (lamotrigine)

● SIDE-EFFECTS

● Common or very common blurred vision, aggression, agitation, ataxia, back pain, diarrhea, diplopia, dizziness, drowsiness, dry mouth, headache, insomnia, nausea, nystagmus, rash, tremor, vomiting

● Rare Conjunctivitis

● Very rare Anaemia, blood disorders, confusion, exacerbation of Parkinson’s disease (in adults), hallucination, hepatic failure, hypersensitivity syndrome, increase in seizure frequency, leucopenia, lupus erythematosus-like reactions, movement disorders, pancreatitis, thrombocytopenia, unsteadiness

● Frequency not known Aseptic meningitis, suicidal ideation

SIDE-EFFECTS, FURTHER INFORMATION

Skin reactions Serious skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have developed (especially in children); most rashes occur in the first 8 weeks. Rash is sometimes associated with hypersensitivity syndrome and is more common in patients with history of allergy or rash from other antiepileptic drugs. Consider withdrawal if rash or signs of hypersensitivity syndrome develop. Factors associated with increased risk of serious skin reactions include concomitant use of valproate, initial lamotrigine dosing higher than recommended, and more rapid dose escalation than recommended.

● ALLERGY AND CROSS-SENSITIVITY Antiepileptic hypersensitivity syndrome associated with lamotrigine. See under Epilepsy p. 383 for more information.

● PREGNANCY Doses should be adjusted on the basis of plasma-drug concentration monitoring.

● BREAST FEEDING Present in milk, but limited data suggest no harmful effect on infant.

● HEPATIC IMPAIRMENT Halve dose in moderate impairment. Quarter dose in severe impairment.

● RENAL IMPAIRMENT Consider reducing maintenance dose in significant impairment. Caution in renal failure; metabolite may accumulate.

● TREATMENT CESSATION Avoid abrupt withdrawal (taper off over 2 weeks or longer) unless serious skin reaction occurs.

● PRESCRIBING AND DISPENSING INFORMATION Patients being treated for epilepsy may need to be maintained on a specific manufacturer’s branded or generic lamotrigine product. Switching between formulations Care should be taken when switching between oral formulations in the treatment of epilepsy. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history.

● PATIENT AND CARER ADVICE

Medicines for Children leaflet: Lamotrigine for preventing seizures www.medicinesforchildren.org.uk/lamotrigine-for-preventing-seizures

Skin reactions Warn patients and carers to see their doctor immediately if rash or signs or symptoms of hypersensitivity syndrome develop. Blood disorders Patients and their carers should be alert for symptoms and signs suggestive of bone-marrow failure, such as anaemia, bruising, or infection. Aplastic anaemia, bone-marrow depression, and pancytopenia have been associated rarely with lamotrigine.

● MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

Tablet

CAUTIONARY AND ADVISORY LABELS 8

LAMOTRIGINE (Non-proprietary)

Lamotrigine 25 mg Lamotrigine 25mg tablets 56 tablet POM £20.41 DT price = £1.45

Lamotrigine 50 mg Lamotrigine 50mg tablets 56 tablet POM £9.00 DT price = £1.70

Lamotrigine 100 mg Lamotrigine 100mg tablets 56 tablet POM £15.00 DT price = £2.36

Lamotrigine 200 mg Lamotrigine 200mg tablets 56 tablet POM £30.00 DT price = £3.48

Lamictal (GlaxoSmithKline UK Ltd)

Lamotrigine 25 mg Lamictal 25mg tablets 56 tablet POM £23.53 DT price = £1.45

Lamotrigine 50 mg Lamictal 50mg tablets 56 tablet POM £40.02 DT price = £1.70

Lamotrigine 100 mg Lamictal 100mg tablets 56 tablet POM £69.04 DT price = £2.36

Lamotrigine 200 mg Lamictal 200mg tablets 56 tablet POM £117.35 DT price = £3.48

Dispersible tablet

CAUTIONARY AND ADVISORY LABELS 8, 13

LAMOTRIGINE (Non-proprietary)

Lamotrigine 5 mg Lamotrigine 5mg dispersible tablets sugar free (sugar-free) 28 tablet POM £8.14 DT price = £1.92

Lamotrigine 25 mg Lamotrigine 25mg dispersible tablets sugar free (sugar-free) 56 tablet POM £20.41 DT price = £3.00

Lamotrigine 100 mg Lamotrigine 100mg dispersible tablets sugar free (sugar-free) 56 tablet POM £14.90 DT price = £4.91

Lamictal (GlaxoSmithKline UK Ltd)

Lamotrigine 2 mg Lamictal 2mg dispersible tablets (sugar-free) 30 tablet POM £12.54 DT price = £12.54

Lamotrigine 5 mg Lamictal 5mg dispersible tablets (sugar-free) 28 tablet POM £9.38 DT price = £1.92
Levetiracetam

**INDICATIONS AND DOSE**

Monotherapy of focal seizures with or without secondary generalisation

BY MOUTH OR BY INTRAVENOUS INFUSION

- **Child 16-17 years:** Initially 250 mg once daily for 1 week, then increased to 250 mg twice daily, then increased in steps of 250 mg twice daily (max. per dose 1.5 g twice daily), adjusted according to response, dose to be increased every 2 weeks

- **Adult:** Initially 250 mg once daily for 1–2 weeks, then increased to 250 mg twice daily, then increased in steps of 250 mg twice daily (max. per dose 1.5 g twice daily), adjusted according to response, dose to be increased every 2 weeks

Adjunctive therapy of focal seizures with or without secondary generalisation

BY MOUTH

- **Child 1-5 months:** Initially 7 mg/kg once daily, then increased in steps of up to 7 mg/kg twice daily (max. per dose 21 mg/kg twice daily), dose to be increased every 2 weeks

- **Child 6 months–17 years (body-weight up to 50 kg):** Initially 10 mg/kg once daily, then increased in steps of up to 10 mg/kg twice daily (max. per dose 30 mg/kg twice daily), dose to be increased every 2 weeks

- **Child 12-17 years (body-weight 50 kg and above):** Initially 250 mg twice daily, then increased in steps of 500 mg twice daily (max. per dose 1.5 g twice daily), dose to be increased every 2–4 weeks

BY INTRAVENOUS INFUSION

- **Child 4-17 years (body-weight up to 50 kg):** Initially 10 mg/kg once daily, then increased in steps of up to 10 mg/kg twice daily (max. per dose 30 mg/kg twice daily), dose to be increased every 2 weeks

- **Child 12-17 years (body-weight 50 kg and above):** Initially 250 mg twice daily, then increased in steps of 500 mg twice daily (max. per dose 1.5 g twice daily), dose to be increased every 2 weeks

- **Adult:** Initially 250 mg twice daily, then increased in steps of 500 mg twice daily (max. per dose 1.5 g twice daily), dose to be increased every 2–4 weeks

Adjunctive therapy of myoclonic seizures and tonic-clonic seizures

BY MOUTH OR BY INTRAVENOUS INFUSION

- **Child 12-17 years (body-weight up to 50 kg):** Initially 10 mg/kg once daily, then increased in steps of up to 10 mg/kg twice daily (max. per dose 30 mg/kg twice daily), dose to be increased every 2 weeks

- **Child 12-17 years (body-weight 50 kg and above):** Initially 250 mg twice daily, then increased in steps of 500 mg twice daily (max. per dose 1.5 g twice daily), dose to be increased every 2 weeks

- **Adult:** Initially 250 mg twice daily, then increased in steps of 500 mg twice daily (max. per dose 1.5 g twice daily), dose to be increased every 2–4 weeks

**SPECIAL CONSIDERATIONS**

- In adults Levetiracetam doses in BNF may differ from those in product literature.

**INTERACTIONS**

Appendix 1 (levetiracetam).

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain - aggression - anorexia - anxiety - ataxia - convulsion - cough - depression - diarrhoea - dizziness - drowsiness - dyspepsia - headache - insomnia - irritability - malaise - nasopharyngitis - nausea - rash - tremor - vertigo - vomiting

- **Uncommon** Agitation - alopecia - amnesia - blurred vision - confusion - diplopia - eczema - impaired attention - leucopenia - myalgia - paraesthesia - pruritus - psychosis - suicidal ideation - thrombocytopenia - weight changes

- **Rare** Agranulocytosis - choreoathetosis - drug reaction with eosinophilia and systemic symptoms (DRESS) - dyskinesia - erythema multiforme - hepatic failure - hyponatraemia - neutropenia - pancreatitis - pancytopenia - Stevens-Johnson syndrome - toxic epidermal necrolysis

**Frequency not known** Completed suicide - pancytopenia - Stevens-Johnson syndrome

**PREGNANCY** The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis. It is recommended that the fetal growth should be monitored.

**BREAST FEEDING** Present in milk—manufacturer advises avoid.

**HEPATIC IMPAIRMENT**

- In adults Halve dose in severe hepatic impairment if eGFR less than 60 mL/minute/1.73 m².

- In children Halve dose in severe hepatic impairment if estimated glomerular filtration rate less than 60 mL/minute/1.73 m².

**RENAL IMPAIRMENT**

- In children Reduce dose if estimated glomerular filtration rate less than 80 mL/minute/1.73 m² (consult product literature).

- In adults Maximum 2 g daily if eGFR 50–80 mL/minute/1.73 m². Maximum 1.5 g daily if eGFR 30–50 mL/minute/1.73 m³. Maximum 1 g daily if eGFR less than 30 mL/minute/1.73 m³.

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use For intravenous infusion, dilute requisite dose with at least 100 mL Glucose 5% or Sodium Chloride 0.9% to give over 15 minutes.

- With oral use For administration of oral solution, requisite dose may be diluted in a glass of water.

**PRESCRIBING AND DISPENSING INFORMATION** If switching between oral therapy and intravenous therapy (for those temporarily unable to take oral medication), the intravenous dose should be the same as the established oral dose.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Levetiracetam for preventing seizures www.medicinesforchildren.org.uk/levetiracetam-for-preventing-seizures

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

CAUTIONARY AND ADVISORY LABELS 8

- **LEVERTIRACETAM (Non-proprietary)**

Levetiracetam 250 mg Levetiracetam 250mg tablets | 60 tablet [PDM] £28.01 DT price = £3.53

Levetiracetam 500 mg Levetiracetam 500mg tablets | 60 tablet [PDM] £49.32 DT price = £4.75

Levetiracetam 750 mg Levetiracetam 750mg tablets | 60 tablet [PDM] £64.02 DT price = £6.88

Levetiracetam 1 g Levetiracetam 1g tablets | 60 tablet [PDM] £95.34 DT price = £8.38
Oxcarbazepine

**INDICATIONS AND DOSE**

Monotherapy for the treatment of focal seizures with or without secondary generalised tonic-clonic seizures

**BY MOUTH**

- Child 6–17 years: Initially 4–5 mg/kg twice daily (max. per dose 300 mg), then increased in steps of up to 5 mg/kg twice daily, adjusted according to response, dose to be adjusted at weekly intervals; maximum 46 mg/kg per day
- Adult: Initially 300 mg twice daily, then increased in steps of up to 600 mg daily, adjusted according to response, dose to be adjusted at weekly intervals; usual dose 0.6–2.4 g daily in divided doses

Adjunctive therapy for the treatment of focal seizures with or without secondary generalised tonic-clonic seizures

**BY MOUTH**

- Child 6–17 years: Initially 4–5 mg/kg twice daily (max. per dose 300 mg), then increased in steps of up to 5 mg/kg twice daily, adjusted according to response, dose to be adjusted at weekly intervals; maintenance 15 mg/kg twice daily; maximum 46 mg/kg per day
- Adult: Initially 300 mg twice daily, then increased in steps of up to 600 mg daily, adjusted according to response, dose to be adjusted at weekly intervals; usual dose 0.6–2.4 g daily in divided doses

**TREATMENT OF PRIMARY GENERALISED TONIC-CLONIC SEIZURES**

**BY MOUTH**

- Adult: Initially 300 mg twice daily, then increased in steps of up to 600 mg daily, adjusted according to response, dose to be increased at weekly intervals; usual dose 0.6–2.4 g daily in divided doses

**DOSE ADJUSTMENTS DUE TO INTERACTIONS**

In adjunctive therapy, the dose of concomitant antiepileptics may need to be reduced when using high doses of oxcarbazepine.

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain, acne, agitation, alopecia, amnesia, asthenia, ataxia, confusion, constipation, depression, diarrhoea, diplopia, dizziness, drowsiness, headache, hyponatraemia, impaired concentration, nausea, nyctagmus, rash, tremor, visual disorders, vomiting
- **Very rare** Ecchymosis, erythema multiforme, erythematous rash, thrombocytopenia, toxic epidermal necrolysis
- **Frequency not known** Aplastic anaemia, bone marrow depression, hypertension, hypothyroidism, neutropenia, osteoporotic bone disorders, pancytopenia, suicidal ideation
- **ALLERGY AND CROSS-SENSITIVITY** Caution in patients with hypersensitivity to carbamazepine. Antiepileptic hypersensitivity syndrome associated with oxcarbazepine. See under Epilepsy p. 383 for more information.
- **PREGNANCY** The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.
- **BREAST FEEDING** Amount probably too small to be harmful but manufacturer advises avoid.
- **HEPATIC IMPAIRMENT** Caution in severe impairment—no information available.
- **RENAI IMPAIRMENT**
  - In adults: Halve initial dose if eGFR less than 30 mL/minute/1.73 m²; increase according to response at intervals of at least 1 week.
  - In children: Halve initial dose if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²; increase according to response at intervals of at least 1 week.
- **PRE-TREATMENT SCREENING** Test for HLA-B*1502 allele in individuals of Han Chinese or Thai origin (avoid unless no alternative—risk of Stevens-Johnson syndrome in presence of HLA-B*1502 allele).
- **MONITORING REQUIREMENTS**
  - Monitor plasma-sodium concentration in patients at risk of hyponatraemia.
  - Monitor body-weight in patients with heart failure.
- **PRESCRIBING AND DISPENSING INFORMATION** Patients may need to be maintained on a specific manufacturer’s branded or generic oxcarbazepine product. Switching between formulations Care should be taken when switching between oral formulations. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with clinicians.
the patient or their carer, taking into account factors such as seizure frequency and treatment history.

**PATIENT AND CARER ADVICE**

Medicines for Children: Oxcarbazepine for preventing seizures www.medicinesforchildren.org.uk/oxcarbazepine-preventing-seizures

Blood, hepatic, or skin disorders Patients or their carers should be told how to recognise signs of blood, liver, or skin disorders, and advised to seek immediate medical attention if symptoms such as lethargy, confusion, muscular twitching, fever, rash, blistering, mouth ulcers, bruising, or bleeding develop.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Tablet

**CAUTIONARY AND ADVISORY LABELS** 3, 8

- **OXCARBAZEPINE (Non-proprietary)**
  - Oxcarbazepine 150 mg Oxcarbazepine 150mg tablets | 50 tablet [PBM] £11.14 DT price = £9.81
  - Oxcarbazepine 300 mg Oxcarbazepine 300mg tablets | 50 tablet [PBM] £22.61 DT price = £19.48
  - Oxcarbazepine 600 mg Oxcarbazepine 600mg tablets | 50 tablet [PBM] £45.19 DT price = £40.23
- **Trileptal** (Novartis Pharmaceuticals UK Ltd)
  - Oxcarbazepine 150 mg Trileptal 150mg tablets | 50 tablet [PBM] £10.30 DT price = £9.81
  - Oxcarbazepine 300 mg Trileptal 300mg tablets | 50 tablet [PBM] £20.40 DT price = £19.48
  - Oxcarbazepine 600 mg Trileptal 600mg tablets | 50 tablet [PBM] £40.80 DT price = £40.23

Oral suspension

**CAUTIONARY AND ADVISORY LABELS** 3, 8

**EXCIPIENTS:** May contain Propylene glycol

- **Trileptal** (Novartis Pharmaceuticals UK Ltd)
  - Oxcarbazepine 60 mg per 1 ml Trileptal 60mg/ml oral suspension (sugar-free) | 250 ml [PBM] £40.80

### Perampanel

**INDICATIONS AND DOSE**

Adjunctive treatment of focal seizures with or without secondary generalised seizures

**BY MOUTH**

- Child 12–17 years: Initially 2 mg once daily, dose to be taken before bedtime, then increased, if tolerated, in steps of 2 mg at least every 2 weeks, adjusted according to response; maintenance 4–8 mg once daily; maximum 12 mg per day
- Adult: Initially 2 mg once daily, dose to be taken before bedtime, then increased, if tolerated, in steps of 2 mg at least every 2 weeks, adjusted according to response; maintenance 4–8 mg once daily; maximum 12 mg per day

Dose adjustments due to interactions

Titrated at intervals of at least 1 week with concomitant carbamazepine, fosphenytoin, oxcarbazepine, or phenytoin.

**INTERACTIONS** Appendix 1 (perampanel).

**SIDE-EFFECTS** Aggression · anxiety · ataxia · back pain · blurred vision · changes in appetite · confusion · diplopia · dizziness · drowsiness · dysarthria · gait disturbance · irritability · malaise · nausea · suicidal behaviour · suicidal ideation · vertigo · weight increase

**PREGNANCY** Manufacturer advises avoid.

The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

**BREAST FEEDING** Avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT** Increase at intervals of at least 2 weeks, up to max. 8 mg daily in mild or moderate impairment. Avoid in severe impairment.

**RENAL IMPAIRMENT** Avoid in moderate or severe impairment.

**PRESCRIBING AND DISPENSING INFORMATION**

Switching between formulations Care should be taken when switching between oral formulations. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history. Patients may need to be maintained on a specific manufacturer’s branded or generic perampanel product.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

Tablet

**CAUTIONARY AND ADVISORY LABELS** 3, 8, 25

- **Fycompa** (Eisai Ltd)
  - Perampanel 2 mg Fycompa 2mg tablets | 7 tablet [PBM] £35.00 | 28 tablet [PBM] £140.00
  - Perampanel 4 mg Fycompa 4mg tablets | 28 tablet [PBM] £140.00
  - Perampanel 6 mg Fycompa 6mg tablets | 28 tablet [PBM] £140.00
  - Perampanel 8 mg Fycompa 8mg tablets | 28 tablet [PBM] £140.00
  - Perampanel 10 mg Fycompa 10mg tablets | 28 tablet [PBM] £140.00

Phenytoin

**INDICATIONS AND DOSE**

**Tonic-clonic seizures | Focal seizures**

**BY MOUTH**

- Child 1 month–11 years: Initially 1.5–2.5 mg/kg twice daily, then adjusted according to response to 2.5–5 mg/kg twice daily (max. per dose 7.5 mg/kg twice daily), dose also adjusted according to plasma-phenytoin concentration; maximum 300 mg per day
- Child 12–17 years: Initially 75–150 mg twice daily, then adjusted according to response to 150–200 mg twice daily (max. per dose 300 mg twice daily), dose also adjusted according to plasma-phenytoin concentration
- Adult: Initially 3–4 mg/kg daily, alternatively 150–300 mg once daily, alternatively 150–300 mg daily in 2 divided doses, then increased to 200–500 mg daily, to be taken preferably with or after food, dose to be increased gradually as necessary (with plasma-phenytoin concentration monitoring), exceptionally, higher doses may be used

Status epilepticus | Acute symptomatic seizures associated with head trauma or neurosurgery

Initially by slow intravenous injection or by intravenous infusion

- Adult: Loading dose 20 mg/kg (max. per dose 2 g), to be given at a rate not exceeding 1 mg/kg/minute (max. 50 mg per minute), to be given with blood pressure and ECG monitoring, then (by intravenous infusion or by slow intravenous injection or by mouth) maintenance 100 mg every 6–8 hours adjusted according to plasma-concentration monitoring, to be given with blood pressure and ECG monitoring, adjusted according to plasma-phenytoin concentration
Status epilepticus | Acute symptomatic seizures associated with trauma or neurosurgery

BY SLOW INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION

► Child 1 month–11 years: Loading dose 20 mg/kg, then 2.5–5 mg/kg twice daily, to be given with blood pressure and ECG monitoring

► Child 12–17 years: Loading dose 20 mg/kg, then up to 100 mg 3–4 times a day, to be given with blood pressure and ECG monitoring

Dose equivalence and conversion
Preparations containing phenytoin sodium are not bioequivalent to those containing phenytoin base (such as Epanutin Infatabs® and Epanutin® suspension); 100 mg of phenytoin sodium is approximately equivalent in therapeutic effect to 92 mg phenytoin base. The dose is the same for all phenytoin products when initiating therapy, however, if switching between these products the difference in phenytoin content may be clinically significant. Care is needed when making changes between formulations and plasma-phenytoin concentration monitoring is recommended.

► UNLICENSED USE
  ► With oral use Licensed for use in children (age range not specified by manufacturer).
  ► With intravenous use Phenytoin doses in BNF publications may differ from those in product literature.

► CONTRA-INDICATIONS
  GENERAL CONTRA-INDICATIONS
  Acute porphyrias p. 864

SPECIFIC CONTRA-INDICATIONS
  ► With intravenous use second- and third-degree heart block · sino-atrial block · sinus bradycardia · Stokes-Adams syndrome
  ► CAUTIONS
  GENERAL CAUTIONS
  Enteral feeding (interrupt feeding for 2 hours before and after dose; more frequent monitoring may be necessary)

SPECIFIC CAUTIONS
  ► With intravenous use heart failure · hypotension · injection solutions alkaline (irritant to tissues) · respiratory depression · resuscitation facilities must be available

CAUTIONS, FURTHER INFORMATION
Consider vitamin D supplementation in patients who are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium. Intramuscular phenytoin should not be used (absorption is slow and erratic).

► INTERACTIONS  Appendix 1 (phenytoin).

► SIDE-EFFECTS
  GENERAL SIDE-EFFECTS
  ► Common or very common Acne · anorexia · coarsening of facial appearance · constipation · dizziness · drowsiness · gingival hypertrophy and tenderness (maintain good oral hygiene) · headache · hirsutism · insomnia · nausea · paraesthesia · rash · transient nervousness · tremor · vomiting
  ► Rare Leucopenia · aplastic anaemia · blood disorders · dyskinesia · hepatotoxicity · lupus erythematosus · lymphadenopathy · megaloblastic anaemia · osteomalacia · peripheral neuropathy · polyanarthropathia nodosa · Stevens-Johnson syndrome · thrombocytopenia · toxic epidermal necrolysis
  ► Frequency not known Hypersensitivity syndrome · interstitial nephritis · pneumonitis · polyarthropathy · suicidal ideation

SPECIFIC SIDE-EFFECTS
  ► Common or very common
  ► With intravenous use Alterations in respiratory function · arrhythmias · cardiovascular collapse · cardiovascular depression (particularly if injection too rapid) · CNS depression (particularly if injection too rapid) · hypotension · respiratory arrest
  ► Frequency not known
  ► With intravenous use Purple glove syndrome · tonic seizures

SIDE-EFFECTS, FURTHER INFORMATION
Rash Discontinue; if mild re-introduce cautiously but discontinue immediately if recurrence.

Hepatotoxicity Discontinue immediately and do not re-administer.

► With intravenous use Reduce rate of administration if bradycardia or hypotension occurs.

Phenytoin may cause coarsening of the facial appearance, acne, hirsutism, and gingival hyperplasia and so may be particularly undesirable in adolescent patients.

Overdose Symptoms of phenytoin toxicity include nystagmus, diplopia, slurred speech, ataxia, confusion, and hyperglycaemia.

► ALLERGY AND CROSS-SENSITIVITY
  Cross-sensitivity reported with carbamazepine. Antiepileptic hypersensitivity syndrome associated with phenytoin. See under Epilepsy p. 383 for more information.

► PREGNANCY
Changes in plasma-protein binding make interpretation of plasma-phenytoin concentrations difficult—monitor unbound fraction. Doses should be adjusted on the basis of plasma-drug concentration monitoring.

► BREAST FEEDING
Small amounts present in milk, but not known to be harmful.

► HEPATIC IMPAIRMENT
Reduce dose to avoid toxicity.

► PRE-TREATMENT SCREENING
HLA* 1502 allele in individuals of Han Chinese or Thai origin—avoid unless essential (increased risk of Stevens-Johnson syndrome).

► MONITORING REQUIREMENTS
  ► In adults The usual total plasma-phenytoin concentration for optimum response is 10–20 mg/litre (or 40–80 micromol/litre). In pregnancy, the elderly, and certain disease states where protein binding may be reduced, careful interpretation of total plasma-phenytoin concentration is necessary; it may be more appropriate to measure free plasma-phenytoin concentration.
  ► In children Therapeutic plasma-phenytoin concentrations reduced in first 3 months of life because of reduced protein binding. Trough plasma concentration for optimum response: neonate–3 months, 6–15 mg/litre (25–60 micromol/litre); child 3 months–18 years, 10–20 mg/litre (40–80 micromol/litre).

Manufacturer recommends blood counts (but evidence of practical value uncertain).

► Monitor ECG and blood pressure with intravenous use.

► DIRECTIONS FOR ADMINISTRATION
  ► With intravenous use in children Before and after administration flush intravenous line with Sodium Chloride 0.9%. For intravenous infusion, give into a large vein at rate not exceeding 1 mg/kg/minute (max. 50 mg/minute). For intravenous infusion, dilute to a concentration not exceeding 10 mg/ml with Sodium Chloride 0.9% and give into a large vein through an in-line filter (0.22–0.50 micron) at a rate not exceeding 1 mg/kg/minute (max. 50 mg/minute); complete administration within 1 hour of preparation.

  ► With intravenous use in adults For intravenous infusion (Epanutin®), give intermittently in Sodium chloride 0.9%. Flush intravenous line with Sodium chloride 0.9% before and after infusion; dilute in 50–100 mL infusion fluid (final concentration not to exceed 10 mg/ml) and give
into a large vein through an in-line filter (0.22–0.50 micron) at a rate not exceeding 1 mg/kg/minute (max. 50 mg/minute); complete administration within 1 hour of preparation. To avoid local venous irritation each injection or infusion should be preceded and followed by an injection of sterile physiological saline through the same needle or catheter.

- **PRESCRIBING AND DISPENSING INFORMATION**
  Switching between formulations. Different formulations of oral preparations may vary in bioavailability. Patients being treated for epilepsy should be maintained on a specific manufacturer’s product.

- **PATIENT AND CARER ADVICE**
  Simple leaflet: Phenytoin for preventing seizures www.medicinesforchildren.org.uk/phenytoin-for-preventing-seizures
  Blood or skin disorders. Patients or their carers should be told how to recognise signs of blood or skin disorders, and advised to seek immediate medical attention if symptoms such as fever, rash, mouth ulcers, bruising, or bleeding develop. Leucopenia that is severe, progressive, or associated with clinical symptoms requires withdrawal (if necessary under cover of a suitable alternative).

- **UNLICENSED USE**
  Pregabalin doses in BNF may differ from those in product literature.

- **CAUTIONS**
  Conditions that may precipitate encephalopathy. • severe congestive heart failure

- **SIDE-EFFECTS**
  Common or very common. • Appetite changes. • blurring vision. • confusion. • constipation. • diplopia. • disturbances in muscle control and movement. • dizziness. • drowsiness. • dry mouth. • euphoria. • fatigue. • impaired attention. • impaired memory. • insomnia. • irritability. • malaise. • oedema. • paraesthesia. • sexual dysfunction. • speech disorder. • visual disturbances. • visual field defects. • vomiting. • weight gain

- **COMMON OR VERY COMMON**
  Abdominal distension. • abnormal dreams. • agitation. • arthralgia. • chills. • cognitive impairment. • depersonalisation. • depression. • dry eye. • dysphagia. • dysuria. • first-degree AV block. • flushing. • gastrointestinal reflux disease. • hallucinations. • hyperacusis. • hypercalcaemia. • hypotension. • hypotension. • lacrimation. • myalgia. • nasal dryness. • nasopharyngitis. • panic attacks. • rash. • stuper. • sweating. • syncope. • tachycardia. • tachypnoea. • taste disturbance. • thirst. • thrombocytopenia. • urinary incontinence

- **RARE**
  Arrhythmia. • ascites. • bradycardia. • breath discharge. • breath hypertrophy. • breast pain. • cold extremities. • cough. • dysphagia. • epistaxis. • hypercalcaemia. • hypokalaemia. • leucopenia. • menstrual disturbances. • neutropenia. • oliguria. • pancreatitis. • parosmia. • renal failure. • rhabdomyolysis. • rhinitis. • urticaria. • weight loss

- **FREQUENTLY NOT KNOWN**
  Aggression. • congestive heart failure. • convulsions. • diarrhoea. • encephalopathy. • headache. • keratitis. • nausea. • pruritus. • QT-interval prolongation. • Stevens-Johnson syndrome. • suicidal ideation. • urinary retention

- **RENAL IMPAIRMENT**
  Initially 75 mg daily and maximum 300 mg daily if eGFR 30–60 mL/minute/1.73 m². Initially 25–50 mg daily and maximum 150 mg daily in 1–2 divided doses if eGFR 15–30 mL/minute/1.73 m². Initially 25 mg once daily and maximum 75 mg once daily if eGFR less than 15 mL/minute/1.73 m².

- **TREATMENT CESSATION**
  Avoid abrupt withdrawal (taper over at least 1 week).

- **PRESCRIBING AND DISPENSING INFORMATION**
  Flavours of oral liquid formulations may include strawberry.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  Scottish Medicines Consortium (SMC) Decisions
  The Scottish Medicines Consortium has advised (July 2007) that pregabalin (Lyrica®) is not recommended for the treatment of central neuropathic pain. The Scottish Medicines Consortium has advised (April 2009) that pregabalin (Lyrica®) is accepted for restricted use within NHS Scotland for the treatment of peripheral neuropathic pain.
neuropathic pain in adults who have not achieved adequate pain relief with, or have not tolerated, first- or second-line treatments; discontinue treatment if sufficient benefit is not achieved within 8 weeks of reaching the maximum tolerated dose.

- **MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension, powder

**Capsule**

**CAUTIONARY AND ADVISORY LABELS**

- **Oral solution**

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<th><strong>PREGABALIN (Non-proprietary)</strong></th>
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**SIDE-EFFECTS**

- **Common or very common**
  - Agranulocytosis
  - Allergic skin reactions
  - Ataxia
  - Behavioural disturbances
  - Cholestasis
  - Depression
  - Drowsiness
  - Hallucinations
  - Hepatitis
  - Hyperactivity
  - Hyperactivity in children
  - Hyperactivity particularly in the elderly
  - Hypotension
  - Impaired cognition
  - Impaired memory
  - Irritability
  - Limb contracture
  - Megaloblastic anaemia
  - Megaloblastic anaemia (may be treated with folic acid)
  - Nausea
  - Nystagmus
  - Osteomalacia
  - Paradoxical excitement
  - Respiratory depression
  - Thrombocytopenia
  - Visual disturbances

- **Uncommon**
  - Dizziness
  - Headache
  - Vomiting

- **Rare**
  - Arthralgia
  - Lupus erythematosus
  - Psychosis

- **Very rare**
  - Antiepileptic hypersensitivity syndrome

**NEXT**

- **Allergy and Cross-Sensitivity**
  - Antiepileptic hypersensitivity syndrome associated with primidone. See under Epilepsy p. 383 for more information.

**PREGNANCY**

- The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

**HEPATIC IMPAIRMENT**

- Reduce dose. May precipitate coma.

**RENAL IMPAIRMENT**

- Use with caution.

**MONITORING REQUIREMENTS**

- Monitor plasma concentrations of derived phenobarbital; plasma concentration for optimum response is 15–40 mg/litre (60–180 micromol/litre).

**TREATMENT CESSATION**

- Avoid abrupt withdrawal (dependence with prolonged use).

**PRESCRIBING AND DISPENSING INFORMATION**

- Switching between formulations. Different formulations of oral preparations may vary in bioavailability. Patients being treated for epilepsy should be maintained on a specific manufacturer’s product.

**CAUTIONS**

- Avoid in acute porphyria
- Children
- Debilitated
- Elderly
- History of alcohol abuse
- History of drug abuse
- Respiratory depression (avoid if severe)

- **CAUTIONS, FURTHER INFORMATION**

- Consider vitamin D supplementation in patients who are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium.

- **INTERACTIONS**

  - Appendix 1 (primidone).

**DRUG INTERACTIONS**

- Common or very common
- Agranulocytosis
- Allergic skin reactions
- Ataxia
- Behavioural disturbances
- Cholestasis
- Depression
- Drowsiness
- Hallucinations
- Hepatitis
- Hyperactivity
- Hyperactivity in children
- Hyperactivity particularly in the elderly
- Hypotension
- Impaired cognition
- Impaired memory
- Irritability
- Limb contracture
- Megaloblastic anaemia
- Megaloblastic anaemia (may be treated with folic acid)
- Nausea
- Nystagmus
- Osteomalacia
- Paradoxical excitement (in adults)
- Respiratory depression
- Thrombocytopenia
- Visual disturbances

- Uncommon
- Dizziness
- Headache
- Vomiting

- Rare
- Arthralgia
- Lupus erythematosus
- Psychosis

- Very rare
- Antiepileptic hypersensitivity syndrome
- Stevens-Johnson syndrome
- Suicidal ideation
- Toxic epidermal necrolysis

- **DISPENSING INFORMATION**

- Switching between formulations. Different formulations of oral preparations may vary in bioavailability. Patients being treated for epilepsy should be maintained on a specific manufacturer’s product.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, capsule

**Tablet**

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<th><strong>PHARMACOLOGY</strong></th>
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**Primidone**

**INDICATIONS AND DOSE**

**All forms of epilepsy except typical absence seizures**

**BY MOUTH**

- Child 1 month–1 year: Initially 125 mg daily, dose to be taken at bedtime, then increased in steps of 125 mg every 3 days, adjusted according to response; maintenance 125–250 mg twice daily

- Child 2-4 years: Initially 125 mg once daily, dose to be taken at bedtime, then increased in steps of 125 mg every 3 days, adjusted according to response; maintenance 250–375 mg twice daily

- Child 5–8 years: Initially 125 mg once daily, dose to be taken at bedtime, then increased in steps of 125 mg every 3 days, adjusted according to response; maintenance 375–500 mg twice daily

- Child 9–17 years: Initially 125 mg once daily, dose to be taken at bedtime, then increased in steps of 125 mg every 3 days, increased to 250 mg twice daily, then increased in steps of 250 mg every 3 days (max. per dose 750 mg twice daily), adjusted according to response.

- Adult: Initially 125 mg once daily, dose to be taken at bedtime, then increased in steps of 125 mg every 3 days, increased to 500 mg daily in 2 divided doses, then increased in steps of 250 mg every 3 days, adjusted according to response; maintenance 0.75–1.5 g daily in 2 divided doses

**Essential tremor**

**BY MOUTH**

- Adult: Initially 50 mg daily, then adjusted according to response to up to 750 mg daily, dose to be increased over 2–3 weeks

**CAUTIONS**

- Avoid in acute porphyria
- Children
- Debilitated
- Elderly
- History of alcohol abuse
- History of drug abuse
- Respiratory depression (avoid if severe)

**TREATMENT CESSATION**

- Avoid abrupt withdrawal (dependence with prolonged use).

**PRESCRIBING AND DISPENSING INFORMATION**

- Switching between formulations. Different formulations of oral preparations may vary in bioavailability. Patients being treated for epilepsy should be maintained on a specific manufacturer’s product.
Retigabine

INDICATIONS AND Dose
Adjunctive treatment of drug-resistant focal seizures with or without secondary generalisation when other appropriate drug combinations have proved inadequate or have not been tolerated

BY MOUTH
- Adult: Initially up to 300 mg daily in 3 divided doses, then increased in steps of up to 150 mg every 1 week, adjusted according to response; maintenance 0.6–1.2 g daily
- Elderly: Initially 150 mg daily in 3 divided doses, then increased in steps of up to 150 mg every 1 week, adjusted according to response; maximum 900 mg per day

CAUTIONS
Known QT-interval prolongation - risk of urinary retention

CAUTIONS, FURTHER INFORMATION
QT-interval prolongation Patients with known QT-interval prolongation, or with the following risk factors for QT interval prolongation, should be carefully monitored while taking retigabine: cardiac failure, ventricular hypertrophy, electrolyte abnormalities, or concomitant treatment with drugs that can prolong QT interval.

INTERACTIONS
- Appendix 1 (retigabine).

SIDE-EFFECTS
- Common or very common Amnesia • anxiety • blurred vision • confusion • constipation • diplopia • discoloration of lips • discoloration of nails • discoloration of ocular tissue • discolouration of skin • dizziness • drowsiness • dry mouth • dysuria • haematuria • impaired attention • impaired coordination • impaired speech • increased appetite • malaise • myoclonus • nausea • paraesthesia • peripheral oedema • psychosis • tremor • vertigo • visual impairment • weight gain
- Uncommon Dyspepsia • dysphagia • hypokinesia • nephrolithiasis • rash • suicidal ideation • sweating • urinary retention

PREGNANCY
The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

HEPATIC IMPAIRMENT
Reduce dose by 50% in moderate to severe impairment; increase by 50 mg every week according to response up to maximum 600 mg daily (450 mg in elderly).

RENAL IMPAIRMENT
Reduce dose by 50% if eGFR less than 50 mL/minute/1.73 m²; increase by 50 mg every week according to response up to maximum 600 mg daily (450 mg in elderly).

MONITORING REQUIREMENTS
- Ophthalmological monitoring A comprehensive ophthalmological examination (including visual acuity test, slit-lamp examination, and dilated fundoscopy) should be performed at initiation of treatment and at least every 6 months thereafter during treatment. Changes in vision or retinal pigment should lead to re-assessment of the benefits and risks of continuing treatment—discontinue unless no other treatment options are available. Monitoring should be increased if treatment is continued.
- Monitor for discoloration of ocular tissue and visual impairment.
- Monitor for blue-grey discoloration of nails, lips and skin—continue treatment only if potential benefit outweighs risk.

PRESCRIBING AND DISPENSING INFORMATION
Switching between formulations Care should be taken when switching between oral formulations. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history. Patients may need to be maintained on a specific manufacturer’s branded or generic retigabine product.

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)
- Retigabine for the adjunctive treatment of partial onset seizures in epilepsy (July 2011) NICE TA232
Retigabine is recommended as an option for the adjunctive treatment of partial onset seizures with or without secondary generalisation in adults aged 18 years and older with epilepsy, only when previous treatment with carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, and topiramate has not provided an adequate response, or has not been tolerated. www.nice.org.uk/TA232

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (June 2011) that retigabine (Trobalt®) is accepted for restricted use within NHS Scotland as adjunctive therapy in adults with focal seizures with or without secondary generalisation. It is restricted use for refractory epilepsy.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
CAUTIONARY AND ADVISORY LABELS 8, 14, 25
- Trobalt (GlaxoSmithKline UK Ltd) ▼
- Retigabine 50 mg Trobalt 50mg tablets | 21 tablet £4.87 | 84 tablet £19.46
- Retigabine 100 mg Trobalt 100mg tablets | 21 tablet £3.73 | 42 tablet no price available | 84 tablet £18.93
- Retigabine 200 mg Trobalt 200mg tablets | 84 tablet £77.96
- Retigabine 300 mg Trobalt 300mg tablets | 84 tablet £116.78
- Retigabine 400 mg Trobalt 400mg tablets | 84 tablet £127.68
- Trobalt (GlaxoSmithKline UK Ltd) ▼
- Trobalt tablets starter pack | 63 tablet £24.33

Rufinamide

INDICATIONS AND Dose
Adjunctive treatment of seizures in Lennox-Gastaut syndrome

BY MOUTH
- Child 4-17 years (body-weight up to 30 kg): Initially 100 mg twice daily, then increased in steps of 100 mg twice daily (max. per dose 500 mg twice daily), adjusted according to response, dose to be increased at intervals of not less than 2 days
- Child 4-17 years (body-weight 30-50 kg): Initially 200 mg twice daily, then increased in steps of 200 mg twice daily (max. per dose 900 mg twice daily), adjusted according to response, dose to be increased at intervals of not less than 2 days
- Adult (body-weight 30-50 kg): Initially 200 mg twice daily, then increased in steps of 200 mg twice daily (max. per dose 900 mg twice daily), adjusted according to response, dose to be increased at intervals of not less than 2 days
- Child 4-17 years (body-weight 50-70 kg): Initially 200 mg twice daily, then increased in steps of 200 mg twice daily (max. per dose 1.2 g twice daily), adjusted according to response, dose to be increased at intervals of not less than 2 days
- Adult (body-weight 50-70 kg): Initially 200 mg twice daily, then increased in steps of 200 mg twice daily (max. per dose 1.2 g twice daily), adjusted according to response, dose to be increased at intervals of not less than 2 days
Adjunctive treatment of seizures in Lennox-Gastaut syndrome with valproate

BY MOUTH

- Child 4–17 years (body-weight up to 30 kg): Initially 100 mg twice daily, then increased in steps of 100 mg twice daily (max. per dose 300 mg twice daily), adjusted according to response, dose to be increased at intervals of not less than 2 days

Rufinamide 400 mg Inovelon 400mg tablets | 60 tablet £102.96

Oral suspension

CAUTIONARY AND ADVISORY LABELS 8, 21

EXCipients: May contain Propylene glycol

- Inovel (Eisai Ltd)

Rufinamide 40 mg per 1 ml Inovelon 40mg/ml oral suspension (sugar-free) 460 ml £94.71

Sodium valproate

INDICATIONS AND DOSE

All forms of epilepsy

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

- Child 1 month–11 years: Initially 10–15 mg/kg daily in 1–2 divided doses (max. per dose 600 mg); maintenance 25–30 mg/kg daily in 2 divided doses, doses up to 60 mg/kg daily in 2 divided doses may be used in infantile spasms; monitor clinical chemistry and haematological parameters if dose exceeds 40 mg/kg daily

- Child 12–17 years: Initially 600 mg daily in 1–2 divided doses, increased in steps of 150–200 mg every 3 days; maintenance 1–2 g daily in 2 divided doses; maximum 2.5 g per day

- Adult: Initially 600 mg daily in 1–2 divided doses, then increased in steps of 150–300 mg every 3 days; maintenance 1–2 g daily, alternatively maintenance 20–30 mg/kg daily; maximum 2.5 g per day

Initiation of valproate treatment

INITIALLY BY INTRAVENOUS INJECTION

- Adult: Initially 10 mg/kg, (usually 400–800 mg), followed by (by intravenous infusion or by intravenous injection) up to 2.5 g daily in 2–4 divided doses, alternatively (by continuous intravenous infusion) up to 2.5 g daily; usual dose 1–2 g daily, (20–30 mg/kg daily), intravenous injection to be administered over 3–5 minutes

Continuation of valproate treatment

BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION OR BY CONTINUOUS INTRAVENOUS INFUSION

- Adult: If switching from oral therapy to intravenous therapy give current oral daily dose, give over 3–5 minutes by intravenous injection or in 2–4 divided doses by intravenous infusion

EPILIM CHRONO®

All forms of epilepsy

BY MOUTH

- Adult: Total daily dose to be given in 1–2 divided doses (consult product literature)

EPIVAL®

All forms of epilepsy

BY MOUTH

- Adult: Total daily dose to be given in 1–2 divided doses (consult product literature)

EPISENTA® CAPSULES

All forms of epilepsy

BY MOUTH

- Adult: Total daily dose to be given in 1–2 divided doses (consult product literature)

Mania

BY MOUTH

- Adult: Initially 750 mg daily in 1–2 divided doses, adjusted according to response, usual dose 1–2 g daily in 1–2 divided doses, doses greater than 45 mg/kg daily require careful monitoring
### EPISODENT® GRANULES

**All forms of epilepsy**

**BY MOUTH**

- **Adult:** Total daily dose to be given in 1–2 divided doses (consult product literature)

**Mania**

**BY MOUTH**

- **Adult:** Initially 750 mg daily in 1–2 divided doses, adjusted according to response. Usual dose 1–2 g daily in 1–2 divided doses, doses greater than 45 mg/kg daily require careful monitoring

**EPISODENT CHRONOSPHERE®**

**All forms of epilepsy**

**BY MOUTH**

- **Adult:** Total daily dose to be given in 1–2 divided doses (consult product literature)

**Migraine prophylaxis**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

- **Adult:** Initially 200 mg twice daily, then increased if necessary to 1.2–1.5 g daily in divided doses

### UNLICENSED USE

- In adults Not licensed for migraine prophylaxis.

### CONTRA-INDICATIONS

- Family history of severe hepatic dysfunction - known mitochondrial disorders (higher rate of acute liver failure and liver-related deaths) - personal or family history of severe hepatic dysfunction - porphyria - suspected mitochondrial disorders (higher rate of acute liver failure and liver-related deaths)

### CAUTIONS

- Systemic lupus erythematosus

### CAUTIONS, FURTHER INFORMATION

**Liver toxicity**

Liver dysfunction (including fatal hepatic failure) has occurred in association with valproate (especially in children under 3 years and in those with metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation) usually in first 6 months and usually involving multiple antiepileptic therapy. Raised liver enzymes during valproate treatment are usually transient but patients should be reassessed clinically and liver function (including prothrombin time) monitored until return to normal—discontinue if abnormally prolonged prothrombin time (particularly in association with other relevant abnormalities).

Consider vitamin D supplementation in patients that are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium.

### INTERACTIONS

- Appendix 1 (sodium valproate)

### SIDE-EFFECTS

- **Common or very common** Aggression · anaemia · confusion · convulsion · deafness · diarrhea · extrapyramidal disorders · gastric irritation · haemorrhage · headache · hypoglycaemia · memory impairment · menstrual disturbance · nausea · nystagmus · somnolence · stupor · thrombocytopenia · transient hair loss (regrowth may be curly) · tremor · weight gain

- **Uncommon** Angioedema · ataxia · coma · encephalopathy · increased alertness · lethargy · leucopenia · pancytopenia · paraesthesia · peripheral oedema · rash · reduced bone mineral density · syndrome of inappropriate secretion of antidiuretic hormone · vasculitis

- **Rare** Behavioural disturbance · blood disorders · bone marrow failure · dementia (in adults) · drowsiness · drug rash with eosinophilia and systemic symptoms (DRESS) syndrome · enuresis · Fanconi’s syndrome · hallucinations · hearing loss · hyperactivity · hyperammonaemia · hypothyroidism · learning disorders · male infertility · myelodysplastic syndrome · polycystic ovaries · Stevens-Johnson syndrome · systemic lupus erythematosus · toxic epidermal necrolysis

- **Very rare** Acne · gynaecomastia · hepatic dysfunction · hirsutism · increase in bleeding time · pancreatitis

- **Frequency not known** Hypersensitivity reactions · suicidal ideation

### SIDE-EFFECTS, FURTHER INFORMATION

**Hepatic dysfunction**

Withdraw treatment immediately if persistent vomiting and abdominal pain, anorexia, jaundice, oedema, malaise, drowsiness, or loss of seizure control.

**CONCEPTION AND CONTRACEPTION**

Valproate is associated with teratogenic risks and should not be used in women of child-bearing potential unless there is no safer alternative—this should be fully considered and discussed before prescribing for women of child-bearing age. Effective contraception advised in women of child-bearing potential.

**PREGNANCY**

Valproate is associated with the highest risk of major and minor congenital malformations (in particular neural tube defects), and long-term neurodevelopmental effects. Valproate should not be used during pregnancy or in women of child-bearing potential unless there is no safer alternative and only after a careful discussion of the risks. If valproate is to be used during pregnancy, the lowest effective dose should be prescribed in divided doses or as modified-release tablets to avoid peaks in plasma-valproate concentrations; doses greater than 1 g daily are associated with an increased risk of teratogenicity. Avoid use in the treatment of epilepsy and bipolar disorder unless there is no safer alternative and only after a careful discussion of the risks—effective contraception advised in women of child-bearing potential. Avoid use for the prophylaxis of migraine (unlicensed) — exclude pregnancy before treatment and ensure effective contraception is used during treatment. Neonatal bleeding (related to hypofibrinogenemia) reported. Neonatal hepatotoxicity also reported. Specialist prenatal monitoring should be instigated when valproate has been taken in pregnancy. The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

**BREAST FEEDING**

Present in milk—risk of haematological disorders in breast-fed newborns and infants.

**HEPATIC IMPAIRMENT**

Avoid if possible—hepatotoxicity and hepatic failure may occasionally occur (usually in first 6 months). Avoid in active liver disease.

**RENAL IMPAIRMENT**

Reduce dose.

**MONITORING REQUIREMENTS**

- Plasma—valproate concentrations are not a useful index of efficacy, therefore routine monitoring is unhelpful.

- Monitor liver function before therapy and during first 6 months especially in patients most at risk.

- Measure full blood count and ensure no undue potential for bleeding before starting and before surgery.

**EFFECT ON LABORATORY TESTS**

False-positive urine tests for ketones.

**DIRECTIONS FOR ADMINISTRATION**

- With rectal use in children For rectal administration, sodium valproate oral solution may be given rectally and retained for 15 minutes (may require dilution with water to prevent rapid expulsion).

- With intravenous use in children For intravenous injection, may be diluted in Glucose 5% or Sodium Chloride 0.9% and given over 3–5 minutes. For intravenous infusion, dilute injection solution with Glucose 5% or Sodium Chloride 0.9%.

- With intravenous use in adults For intravenous infusion (Epilim®, Episenta®), give continuously or intermittently in Glucose 5% or Sodium Chloride 0.9%. Reconstitute Epilim® with solvent provided then dilute with infusion fluid.
EPIVAL® Tablets may be halved but not crushed or chewed.

EPISENTA® CAPSULES Contents of capsule may be mixed with cold soft food or drink and swallowed immediately without chewing.

EPISENTA® GRANULES Granules may be mixed with cold soft food or drink and swallowed immediately without chewing.

EPILIM® CHRONOSPHERE® Granules may be mixed with soft food or drink that is cold or at room temperature, and swallowed immediately without chewing.

EPILIM® ORAL SOLUTION May be diluted, preferably in Syrup BP; use within 14 days.

SODIUM VALPROATE (Non-proprietary) ▼
Sodium valproate 100 mg Epilim 100 mg modified-release tablets | 100 tablet (P dip) £1.00
Sodium valproate 100 mg Epilim 200 mg gastro-resistant tablets | 100 tablet (P dip) £1.99 DT price = £8.56

Gastro-resistant tablet

CAUTIONARY AND ADVISORY LABELS 5, 8, 10, 21, 25 ▼
SODIUM VALPROATE (Non-proprietary) ▼
Sodium valproate 300 mg Epilim 300 mg gastro-resistant tablets | 100 tablet (P dip) £4.49
Sodium valproate 300 mg Epilim 300 mg gastro-resistant tablets | 100 tablet (P dip) £4.49
Sodium valproate 500 mg Epilim 500 mg gastro-resistant tablets | 100 tablet (P dip) £11.99 DT price = £8.56

Switching between formulations

CAUTIONARY AND ADVISORY LABELS 5, 8, 10, 21, 25 ▼
SODIUM VALPROATE (Non-proprietary) ▼
Sodium valproate 300 mg Epilim 300 mg gastro-resistant tablets | 100 tablet (P dip) £4.49
Sodium valproate 300 mg Epilim 300 mg gastro-resistant tablets | 100 tablet (P dip) £4.49
Sodium valproate 500 mg Epilim 500 mg gastro-resistant tablets | 100 tablet (P dip) £11.99 DT price = £8.56

Modified-release capsule

CAUTIONARY AND ADVISORY LABELS 5, 8, 10, 21, 25 ▼
SODIUM VALPROATE (Non-proprietary) ▼
Sodium valproate 500 mg Epilim 500 mg gastro-resistant tablets | 100 tablet (P dip) £11.99 DT price = £8.56
Sodium valproate 500 mg Epilim 500 mg gastro-resistant tablets | 100 tablet (P dip) £11.99 DT price = £8.56

Modified-release granules

CAUTIONARY AND ADVISORY LABELS 5, 8, 10, 21, 25 ▼
SODIUM VALPROATE (Non-proprietary) ▼
Sodium valproate 40 mg per 1 ml Epilim 400 mg/5ml oral solution £4.95 DT price = £5.07

Sodium valproate 40 mg per 1 ml Epilim 400 mg/5ml liquid (sugar-free) | 300 ml (P dip) £7.78 DT price = £5.07
Epilim 200mg/5ml syrup | 300 ml (P dip) £9.33 DT price = £9.33

SODIUM VALPROATE (Non-proprietary) ▼
Sodium valproate 100 mg Epilim 100 mg/5ml oral solution | 300 ml (P dip) £5.07

Sodium valproate 200 mg Epilim 200 mg/5ml oral solution | 300 ml (P dip) £5.07

Solution for injection

SODIUM VALPROATE (Non-proprietary) ▼
Sodium valproate 100 mg Epilim 100 mg/5ml oral solution | 1 ampoule (P dip) £5.07

Sodium valproate 100 mg Epilim 100 mg/5ml oral solution | 1 ampoule (P dip) £5.07

Powder and solvent for solution for injection

SODIUM VALPROATE (Non-proprietary) ▼
Sodium valproate 400 mg Epilim Intravenous 400mg powder and solvent for solution for injection vials | 1 vial (P dip) £13.32
## Tiagabine

**INDICATIONS AND DOSE**

Adjunctive treatment for focal seizures with or without secondary generalisation that are not satisfactorily controlled by other antiepileptics (with enzyme-inducing drugs)

**BY MOUTH**

- Child 12-17 years: Initially 5–10 mg daily in 1–2 divided doses, then increased in steps of 5–10 mg/24 hours every 1 week; maintenance 30–45 mg daily in 2–3 divided doses
- Adult: Initially 5–10 mg daily in 1–2 divided doses, then increased in steps of 5–10 mg/24 hours every 1 week; maintenance 30–45 mg daily in 2–3 divided doses

Adjunctive treatment for focal seizures with or without secondary generalisation that are not satisfactorily controlled by other antiepileptics (without enzyme-inducing drugs)

**BY MOUTH**

- Child 12-17 years: Initially 5–10 mg daily in 1–2 divided doses, then increased in steps of 5–10 mg/24 hours every 1 week; maintenance 15–30 mg daily in 2–3 divided doses
- Adult: Initially 5–10 mg daily in 1–2 divided doses, then increased in steps of 5–10 mg/24 hours every 1 week; maintenance 15–30 mg daily in 2–3 divided doses

### CAUTIONS

Avoid in Acute porphyrias p. 864

**CAUTIONS, FURTHER INFORMATION**

Tiagabine should be avoided in absence, myoclonic, tonic and atonic seizures due to risk of seizure exacerbation.

**INTERACTIONS** → Appendix 1 (tiagabine).

**SIDE-EFFECTS**

- **Common or very common** Diarrhoea - dizziness - emotional lability - impaired concentration - nervousness - speech impairment - tiredness - tremor
- **Rare** Bruising - confusion - depression - drowsiness - non-convulsive status epilepticus - psychosis - suicidal ideation - visual disturbances
- **Frequency not known** Leucopenia

**PREGNANCY**

The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

**HEPATIC IMPAIRMENT**

In mild to moderate impairment reduce dose, prolong the dose interval, or both. Avoid in severe impairment.

**PATIENT AND CARER ADVICE**

May impair performance of skilled tasks (e.g. driving).

Medicines for Children leaflet: Tiagabine for preventing seizures [www.medicinesforchildren.org.uk/tiagabine-for-preventing-seizures](http://www.medicinesforchildren.org.uk/tiagabine-for-preventing-seizures)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS 21**
- **Gabitril** (Teva UK Ltd)
- Tiagabine (as Tiagabine hydrochloride monohydrate) 5 mg Gabitril 5mg tablets | 100 tablet (PhR) £52.04
- Tiagabine (as Tiagabine hydrochloride monohydrate) 10 mg Gabitril 10mg tablets | 100 tablet (PhR) £104.09
- Tiagabine (as Tiagabine hydrochloride monohydrate) 15 mg Gabitril 15mg tablets | 100 tablet (PhR) £156.13

## Topiramatate

**INDICATIONS AND DOSE**

Monotherapy of generalised tonic-clonic seizures or focal seizures with or without secondary generalisation

**BY MOUTH**

- Child 6-17 years: Initially 0.5–1 mg/kg once daily (max. per dose 25 mg) for 1 week, dose to be taken at night, then increased in steps of 25–50 mg weekly by 25–50 mg twice daily, dose to be increased by a maximum of 25 mg twice daily at intervals of 1–2 weeks; usual dose 50 mg twice daily (max. per dose 75 mg/kg twice daily), if child cannot tolerate titration regimen, then smaller steps or longer interval between steps may be used; maximum 500 mg per day
- Adult: Initially 25 mg once daily for 1 week, dose to be taken at night, then increased in steps of 25–50 mg every 1–2 weeks, dose to be taken in 2 divided doses; usual dose 100–200 mg daily in 2 divided doses, adjusted according to response, doses of 1 g daily have been used in refractory epilepsy; maximum 500 mg per day

Adjunctive treatment of generalised tonic-clonic seizures or focal seizures with or without secondary generalisation | Adjunctive treatment for seizures associated with Lennox-Gastaut syndrome

**BY MOUTH**

- Child 2-17 years: Initially 1–3 mg/kg once daily (max. per dose 25 mg) for 1 week, dose to be taken at night, then increased in steps of 0.5–1.5 mg/kg twice daily, dose to be increased by a maximum of 25 mg twice daily at intervals of 1–2 weeks; usual dose 2.5–4.5 mg/kg twice daily (max. per dose 7.5 mg/kg twice daily), if child cannot tolerate recommended titration regimen, then smaller steps or longer interval between steps may be used; maximum 400 mg per day
- Adult: Initially 25–50 mg once daily for 1 week, dose to be taken at night, then increased in steps of 25–50 mg every 1–2 weeks, dose to be taken in 2 divided doses; usual dose 200–400 mg daily in 2 divided doses; maximum 400 mg per day

**Migraine prophylaxis**

**BY MOUTH**

- Adult: Initially 25 mg once daily for 1 week, dose to be taken at night, then increased in steps of 25 mg every 1 week; usual dose 50–100 mg daily in 2 divided doses; maximum 200 mg per day

**UNLICENSED USE**

Not licensed for use in children for migraine prophylaxis.

**CAUTIONS**

Avoid in Acute porphyrias p. 864 • risk of metabolic acidosis • risk of nephrolithiasis—ensure adequate hydration (especially in strenuous activity or warm environment)

**INTERACTIONS** → Appendix 1 (topiramatate).

**SIDE-EFFECTS**

- **Uncommon** Abdominal distension - altered sense of smell - blepharospasm - blood disorders - bradycardia - dry eye -
flatulence · flushing · gingival bleeding · glossodynia · haematuria · halitosis · hearing loss · hypokalaemia · hypotension · increased lacrimation · influenza-like symptoms · leucopenia · metabolic acidosis · mydriasis · neutropenia · palpitation · pancreatitis · panic attack · peripheral neuropathy · photophobia · postural hypotension · psychosis · reduced sweating · salivation · sexual dysfunction · skin discoloration · suicidal ideation · thirst · thrombocytopenia · urinary calculus

- **Rare** Abnormal skin odour · calcinosis · hepatic failure · hepatitis · periportal oedema · Raynaud’s syndrome · Stevens-Johnson syndrome · unilateral blindness
- **Very rare** Angle-closure glaucoma
- **Frequency not known** Encephalopathy · hyperammonaemia · maculopathy · toxic epidermal necrolysis

**SIDE-EFFECTS, FURTHER INFORMATION**

**Acute myopia with secondary angle-closure glaucoma** Topiramate has been associated with acute myopia with secondary angle-closure glaucoma, typically occurring within 1 month of starting treatment. Choroidal effusions resulting in anterior displacement of the lens and iris have also been reported. If raised intraocular pressure occurs:
- seek specialist ophthalmological advice;
- use appropriate measures to reduce intraocular pressure;
- stop topiramate as rapidly as feasible

**PREGNANCY** Increased risk of cleft palate if taken in the first trimester of pregnancy. The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis. It is recommended that the fetal growth should be monitored.

**BREAST FEEDING** Manufacturer advises avoid—present in milk.

**HEPATIC IMPAIRMENT** Use with caution in moderate to severe impairment—clearance may be reduced.

**RENAL IMPAIRMENT**
- in adults: Half usual starting and maintenance dose if eGFR less than 70 mL/minute/1.73 m²—reduced clearance and longer time to steady-state plasma concentration.
- in children: Half usual starting and maintenance dose if estimated glomerular filtration less than 70 mL/minute/1.73 m²—reduced clearance and longer time to steady-state plasma concentration.

**DIRECTIONS FOR ADMINISTRATION** Topiramate® Sprinkle capsules can either be swallowed whole or the contents of the capsule can be sprinkled on soft food and swallowed immediately without chewing.

**TOPAMAX® CAPSULES** Swallow whole or sprinkle contents of capsule on soft food and swallow immediately without chewing.

**PRESCRIBING AND DISPENSING INFORMATION** Switching between formulations Care should be taken when switching between oral formulations in the treatment of epilepsy. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history.

Patients being treated for epilepsy may need to be maintained on a specific manufacturer’s branded or generic topiramate product.

**PATIENT AND CARER ADVICE**

**Medicines for Children leaflet: Topiramate for preventing seizures** www.medicinesforchildren.org.uk/topiramate-for-preventing-seizures

Patients should be counselled on the administration of Topiramate® Sprinkle capsules.

Patients or carers should be given advice on how to administer Topamax® capsules.

**INDICATIONS AND DOSE**

Adjunctive treatment of focal seizures with or without secondary generalisation not satisfactorily controlled with other antiepileptics (under expert supervision)

**BY MOUTH**
- **Child 1 month–2 years:** Initially 15–20 mg/kg twice daily (max. per dose 250 mg/kg twice daily), to be increased over 2–3 weeks to usual maintenance dose, usual maintenance 30–40 mg/kg twice daily (max. per dose 75 mg/kg twice daily)
- **Child 2–11 years:** Initially 15–20 mg/kg twice daily (max. per dose 250 mg/kg twice daily), to be increased over 2–3 weeks to usual maintenance dose, usual maintenance 30–40 mg/kg twice daily (max. per dose 1.5 g twice daily)
- **Child 12–17 years:** Initially 250 mg twice daily, to be increased over 2–3 weeks to usual maintenance dose, usual maintenance 1–1.5 g twice daily
- **Adult:** Initially 1 g once daily, alternatively initially 1 g daily in 2 divided doses, then increased in steps of 500 mg every 1 week, adjusted according to response; usual dose 2–3 g daily; maximum 3 g per day

**BY RECTUM**
- **Child 1 month–1 year:** Initially 15–20 mg/kg twice daily (max. per dose 250 mg/kg twice daily), to be increased over 2–3 weeks to usual maintenance dose, usual maintenance 30–40 mg/kg twice daily (max. per dose 75 mg/kg twice daily) continued→
Nervous system

With rectal use

MONITORING REQUIREMENTS

▶ In children

CAUTIONS

UNLICENSED USE

Granules not licensed for rectal use.

Tablets not licensed to be crushed and dispersed in liquid.

Vigabatrin doses in BNF publications may differ from those in product literature.

CONTRA-INDICATIONS

Visual field defects

CAUTIONS, FURTHER INFORMATION

Vigabatrin may worsen absence, myoclonic, tonic and atonic seizures.

Visual field defects

Vigabatrin is associated with visual field defects. The onset of symptoms varies from 1 month to several years after starting. In most cases, visual field defects have persisted despite discontinuation, and further deterioration after discontinuation cannot be excluded. Product literature advises visual field testing before treatment and at 6-month intervals. Patients and their carers should be warned to report any new visual symptoms that develop and those with symptoms should be referred for an urgent ophthalmological opinion.

Gradual withdrawal of vigabatrin should be considered.

INTERACTIONS → Appendix 1 (vigabatrin).

SIDE-EFFECTS

▶ Common or very common


▶ Uncommon

Ataxia - mania - occasional increase in seizure frequency (especially if myoclonic) - psychosis - rash

▶ Rare

Peripheral retinal neuropathy - retinal disorders - suicidal ideation

▶ Very rare

Hepatitis - optic atrophy - optic neuritis

▶ Frequency not known

Movement disorders in infantile spasms

SIDE-EFFECTS, FURTHER INFORMATION

Visual field defects

About one-third of patients treated with vigabatrin have suffered visual field defects; counselling and careful monitoring for this side-effect are required.

Encephalopathic symptoms including marked sedation, stupor, and confusion with non-specific slow wave EEG can occur rarely—reduce dose or withdraw.

PREGNANCY

The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

BREAST FEEDING

Present in milk—manufacturer advises avoid.

RENAL IMPAIRMENT

▶ In adults

Consider reduced dose or increased dose interval if eGFR less than 60 mL/minute/1.73 m².

▶ In children

Consider reduced dose or increased dose interval if estimated glomerular filtration rate less than 60 mL/minute/1.73 m².

monitor weight throughout treatment (fatal cases of weight loss reported in children) - metabolic acidosis—monitor serum bicarbonate concentration in children and those with other risk factors (consider dose reduction or discontinuation if metabolic acidosis develops) - risk factors for renal stone formation (particularly predisposition to nephrolithiasis)

Zonisamide

INDICATIONS AND DOSE

Monotherapy for treatment of focal seizures with or without secondary generalisation in adults with newly diagnosed epilepsy

BY MOUTH

▶ Adult: Initially 100 mg once daily for 2 weeks, then increased in steps of 100 mg every 2 weeks, usual maintenance dose 300 mg once daily; maximum 500 mg per day

Adjunctive treatment for refractory focal seizures with or without secondary generalisation

BY MOUTH

▶ Child 6–17 years (body-weight 20–54 kg): Initially 1 mg/kg once daily for 7 days, then increased in steps of 1 mg/kg every 7 days (max. per dose 500 mg once daily), usual maintenance 6–8 mg/kg once daily, dose to be increased at 2-week intervals in patients who are not receiving concomitant carbamazepine, phenytoin, phenobarbital or other potent inducers of cytochrome P450 enzyme CYP3A4

▶ Child 6–17 years (body-weight 55 kg and above): Initially 1 mg/kg once daily for 7 days, then increased in steps of 1 mg/kg every 7 days, usual maintenance 300–500 mg once daily, dose to be increased at 2-week intervals in patients who are not receiving concomitant carbamazepine, phenytoin, phenobarbital or other potent inducers of cytochrome P450 enzyme CYP3A4

▶ Adult: Initially 50 mg daily in 2 divided doses for 7 days, then increased to 100 mg daily in 2 divided doses, then increased in steps of 100 mg every 7 days, usual maintenance 300–500 mg daily in 1–2 divided doses, dose to be increased at 2-week intervals in patients who are not receiving concomitant carbamazepine, phenytoin, phenobarbital or other potent inducers of cytochrome P450 enzyme CYP3A4

▶ Child 2–11 years: Initially 15–20 mg/kg twice daily (max. per dose 250 mg twice daily), to be increased over 2–3 weeks to usual maintenance dose, usual maintenance 30–40 mg/kg twice daily (max. per dose 1.5 g twice daily)

▶ Child 12–17 years: Initially 250 mg twice daily, to be increased over 2–3 weeks to usual maintenance dose, usual maintenance 1–1.5 g twice daily

The contents of a sachet should be dissolved in water or a soft drink immediately before taking. Tablets may be crushed and dispersed in liquid.

PATIENT AND CARER ADVICE

Medicines for Children leaflet: Vigabatrin for preventing seizures www.medicinesforchildren.org.uk/vigabatrin-for-preventing-seizures

Patients and their carers should be warned to report any new visual symptoms that develop.

MEDITINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

Tablet

CAUTIONARY AND ADVISORY LABELS 3, 8

Sabril (Sanofi) Vigabatrin 500 mg Sabril 500mg tablets | 100 tablet £37.01 DT price = £37.01

Powder

CAUTIONARY AND ADVISORY LABELS 3, 8, 13

Sabril (Sanofi) Vigabatrin 500 mg Sabril 500mg oral powder sachets (sugar-free) | 50 sachet £20.50 DT price = £20.50
CAUTIONS, FURTHER INFORMATION
Avoid overheating and ensure adequate hydration especially in children, during strenuous activity or if in warm environment (fatal cases of heat stroke reported in children).

INTERACTIONS → Appendix 1 (zonisamide).
- In adults Caution with concomitant use of drugs that increase risk of hyperthermia, metabolic acidosis, or nephrolithiasis.
- In children Caution with concomitant use of drugs that increase risk of nephrolithiasis. Contraindicated with use of drugs that increase risk of hyperthermia or metabolic acidosis.

SIDE-EFFECTS
Common or very common Abdominal pain - agitation - alopecia - anorexia - ataxia - confusion - constipation - depression - diarrhoea - diplopia - dizziness - drowsiness - ecchymosis - fatigue - impaired attention - impaired memory - insomnia - irritability - nausea - nystagmus - paraesthesia - peripheral oedema - pruritus - psychosis - pyrexia - rash (consider withdrawal) - speech disorder - tremor - weight loss
- Uncommon Aggression - cholecystitis - cholelithiasis - dyspepsia - hypokalaemia - pneumonia - seizures - suicidal ideation - urinary calculus - urinary tract infection - vomiting

ALLERGY AND CROSS-SENSITIVITY Contraindicated in sulfonamide hypersensitivity. Antiepileptic hypersensitivity syndrome theoretically associated with zonisamide. See under Epilepsy p. 383 for more information.

CONCEPTION AND CONTRACEPTION Manufacturer advises women of childbearing potential should use adequate contraception during treatment and for 4 weeks after last dose.

PREGNANCY The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

BREAST FEEDING Manufacturer advises avoid for 4 weeks after last dose.

HEPATIC IMPAIRMENT Initially increase dose at 2-week intervals if mild or moderate impairment. Avoid in severe impairment.

RENAL IMPAIRMENT Initially increase dose at 2-week intervals; discontinue if renal function deteriorates.

TREATMENT CESSION Avoid abrupt withdrawal (consult product literature for recommended withdrawal regimens in children).

PRESCRIBING AND DISPENSING INFORMATION Switching between formulations Care should be taken when switching between oral formulations. The need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with the patient or their carer, taking into account factors such as seizure frequency and treatment history. Patients may need to be maintained on a specific manufacturer’s branded or generic zonisamide product.

PATIENT AND CARER ADVICE Medicines for Children leaflet: Zonisamide for preventing seizures www.medicinesforchildren.org.uk/zonisamide-for-preventing-seizures
Children and their carers should be made aware of how to prevent and recognise overheating and dehydration.

NATIONAL FUNDING/ACCESS DECISIONS
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (February 2014) that zonisamide (Zonegran®) is accepted for restricted use within NHS Scotland as adjunctive treatment of focal seizures, with or without secondary generalisation, in adolescents and children aged 6 years and above. It is restricted to use on advice from specialists in paediatric neurology or epilepsy.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

Capsule
CAUTIONARY AND ADVISORY LABELS 3, 8, 10
- zonisamide (Eisai Ltd)
  - Zonisamide 25 mg Zonegran 25mg capsules | 14 capsule £8.82 DT price = £8.82
  - Zonisamide 50 mg Zonegran 50mg capsules | 56 capsule £47.04 DT price = £47.04
  - Zonisamide 100 mg Zonegran 100mg capsules | 56 capsule £62.72 DT price = £62.72

BARBITURATES
Phenobarbital
(Phenobarbital

INDICATIONS AND DOSE
All forms of epilepsy except typical absence seizures
BY MOUTH
- Child 1 month-11 years: Initially 1–1.5 mg/kg twice daily, then increased in steps of 2 mg/kg daily as required; maintenance 2.5–4 mg/kg 1–2 times a day
- Child 12-17 years: 60–180 mg once daily, dose to be taken at night
- Adult: 60–180 mg once daily, dose to be taken at night

Status epilepticus
BY INTRAVENOUS INJECTION
- Adult: 10 mg/kg (max. per dose 1 g), dose to be administered at a rate not more than 100 mg/minute, injection to be diluted 1 in 10 with water for injections
- Child 11 years: Initially 20 mg/kg, dose to be administered at a rate no faster than 1 mg/kg/minute, then 2.5–5 mg/kg 1–2 times a day
- Child 12-17 years: Initially 20 mg/kg, dose to be administered at a rate no faster than 1 mg/kg/minute, then 2.5–5 mg/kg 1–2 times a day
- Child 17 years: Initially 20 mg/kg (max. per dose 1 g), dose to be administered at a rate no faster than 1 mg/kg/minute, then 100 mg twice daily

Dose equivalence and conversion
For therapeutic purposes phenobarbital and phenobarbital sodium may be considered equivalent in effect.

CAUTIONS Avoid in Acute porphyrias p. 654 - children - debilitated - elderly - history of alcohol abuse - history of drug abuse - respiratory depression (avoid if severe)

CAUTIONS, FURTHER INFORMATION
Consider vitamin D supplementation in patients who are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium.

INTERACTIONS → Appendix 1 (phenobarbital).

SIDE-EFFECTS
Common or very common Agranulocytosis - allergic skin reactions - ataxia - behavioural disturbances - cholostasis - depression - drowsiness - hallucinations - hepatitis - hyperactivity particularly in the elderly and in children - hypotension - impaired cognition - impaired memory -
irritability · lethargy · megaloblastic anaemia (may be treated with folic acid) · myasthenia · osteomalacia · paradoxical excitement (in adults) · respiratory depression · thrombocytopenia

- Very rare Antiepileptic Hypersensitivity Syndrome · Stevens-Johnson syndrome · suicidal ideation · toxic epidermal necrolysis
- Frequency not known Hyperkinesia (in children)

Overdose For details on the management of poisoning, see Active elimination techniques, under Emergency treatment of poisoning p. 1123.

**ALLERGY AND CROSS-SENSITIVITY** Antiepileptic hypersensitivity syndrome associated with phenobarbital. See under Epilepsy p. 383 for more information.

**PREGNANCY** The dose should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

**BREAST FEEDING** Avoid if possible; drowsiness may occur.

**HEPATIC IMPAIRMENT** May precipitate coma. Avoid in severe impairment.

**RENAL IMPAIRMENT** Use with caution.

**MONITORING REQUIREMENTS**
- Plasma-phenobarbital concentration for optimum response is 15–40 mg/litre (60–180 μg/ml); however, monitoring the plasma-drug concentration is less useful than with other drugs because tolerance occurs.

**TREATMENT CESSATION** Avoid abrupt withdrawal (dependence with prolonged use).

**DIRECTIONS FOR ADMINISTRATION** Solution for injection must be diluted before intravenous administration.
- With intravenous use in children For intravenous injection, dilute to a concentration of 20 mg/ml with Water for Injections; give over 20 minutes (no faster than 1 mg/kg/minute).
- With oral use in children For administration by mouth, tablets may be crushed.

**PRESCRIBING AND DISPENSING INFORMATION**
Switching between formulations Different formulations of oral preparations may vary in bioavailability. Patients should be maintained on a specific manufacturer’s product. Some hospitals supply alcohol-free formulations of varying phenobarbital strengths.

**PATIENT AND CARER ADVICE**
Medicines for Children leaflet: Phenobarbital for preventing seizures www.medicinesforchildren.org.uk/phenobarbital-for-preventing-seizures

**MEDICINE FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension, tablet, capsule

### Tablet

**CAUTIONARY AND ADVISORY LABELS** 2, 8

- **PHENOBARBITAL (Non-proprietary)**
  - Phenobarbital 15 mg Phenobarbital 15mg tablets | 28 tablet £24.95 DT price + £24.61 Schedule 3 (CD No Register Phenobarbital)
  - Phenobarbital 30 mg Phenobarbital 30mg tablets | 28 tablet £5.99 DT price + £0.97 Schedule 3 (CD No Register Phenobarbital)
  - Phenobarbital 60 mg Phenobarbital 60mg tablets | 28 tablet £7.99 DT price + £6.58 Schedule 3 (CD No Register Phenobarbital)

**Oral solution**

**CAUTIONARY AND ADVISORY LABELS** 2, 8

- **PHENOBARBITAL (Non-proprietary)**
  - Phenobarbital 3 mg per 1 ml Phenobarbital 15mg/5ml elixir | 500 ml £83.00 DT price + £83.00 Schedule 3 (CD No Register Phenobarbital)

**BENZODIAZEPINES**

**Clobazam**

The properties listed below are those particular to the drug only. For properties common to the class, see Benzodiazepines, p. 266.

**INDICATIONS AND DOSE**

**Adjunct in epilepsy**

**BY MOUTH**

- Child 6–17 years: Initially 5 mg daily, dose to be increased if necessary at intervals of 5 days, maintenance 0.3–1 mg/kg daily, daily doses of up to 30 mg may be given as a single dose at bedtime; higher doses should be divided; maximum 60 mg per day
- Adult: 20–30 mg daily, then increased if necessary up to 60 mg daily

**Anxiety (short-term use)**

**BY MOUTH**

- Adult: 20–30 mg daily in divided doses, alternatively 20–30 mg once daily, dose to be taken at bedtime; increased if necessary up to 60 mg daily in divided doses, dose only increased in severe anxiety (in hospital patients), for debilitated patients, use elderly dose
- Elderly: 10–20 mg daily

**UNLICENSED USE** Not licensed for use in children under 6 years. Not licensed as monotherapy.

**CONTRA-INDICATIONS** Chronic psychosis (in adults) · hyperkinesia · not for use alone to treat anxiety associated with depression (in adults) · obsessive states · phobic states · respiratory depression

**CAUTIONS** Muscle weakness · organic brain changes · personality disorder (within the fearful group—dependent, avoidant, obsessive-compulsive) may increase risk of dependence

**CAUTIONS, FURTHER INFORMATION**
The effectiveness of clobazam may decrease significantly after weeks or months of continuous therapy.

**SIDE-EFFECTS**

- Common or very common Amnesia · ataxia (especially in the elderly) · confusion (especially in the elderly) · dependence · drowsiness the next day · lightheadedness the next day · muscle weakness · paradoxical increase in aggression
- Uncommon Changes in libido (in adults) · dizziness · dysarthria · gastro-intestinal disturbances · gynaecomastia · headache (in adults) · hypotension (in adults) · incontinence · salivation changes · slurred speech (in adults) · tremor · urinary retention (in adults) · vertigo (in adults) · visual disturbances
- Rare Apnoea · blood disorders · changes in libido (in children) · headache (in children) · hypotension (in children) · jaundice · respiratory depression · skin reactions · urinary retention (in children) · vertigo (in children)

- Frequency not known Delusions (in children) · excitement (in children) · hallucinations (in children) · irritability (in children) · psychosis (in children) · restlessness (in children)

**BREAST FEEDING** Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding. All infants should be monitored for sedation, feeding difficulties, adequate weight gain, and developmental milestones.

**HEPATIC IMPAIRMENT** Start with smaller initial doses or reduce dose. Can precipitate coma. Avoid in severe impairment.
**INDICATIONS AND DOSE**

**All forms of epilepsy**

**BY MOUTH**

- Child 1-11 months: Initially 250 micrograms once daily for 4 nights, dose to be increased over 2–4 weeks, usual dose 0.5–1 mg daily, dose to be taken at night; may be given in 3 divided doses if necessary
- Child 1-4 years: Initially 250 micrograms once daily for 4 nights, dose to be increased over 2–4 weeks, usual dose 1–3 mg daily, dose to be taken at night; may be given in 3 divided doses if necessary
- Child 5-11 years: Initially 500 micrograms once daily for 4 nights, dose to be increased over 2–4 weeks, usual dose 4–8 mg daily, adjusted according to response, dose usually taken at night; may be given in 3–4 divided doses if necessary
- Child 12-17 years: Initially 1 mg once daily for 4 nights, dose to be increased over 2–4 weeks, usual dose 4–8 mg daily, adjusted according to response, dose usually taken at night; may be given in 3–4 divided doses if necessary
- Adult: Initially 1 mg once daily for 4 nights, dose to be increased over 2–4 weeks, usual dose 4–8 mg daily, adjusted according to response, dose usually taken at night; may be given in 3–4 divided doses if necessary
- Elderly: Initially 500 micrograms once daily for 4 nights, dose to be increased over 2–4 weeks, usual dose 4–8 mg daily, adjusted according to response, dose usually taken at night; may be given in 3–4 divided doses if necessary

**SIDE-EFFECTS**

- Rare Aggression - anxiety - blood disorders - dysarthria - gastro-intestinal symptoms - headache - paradoxical effects - pruritus - respiratory depression - reversible hair loss - sexual dysfunction - skin pigmentation changes - suicidal ideation (in adults) - urinary incontinence - urticaria - visual disturbances on long-term treatment
- Very rare Increase in seizure frequency

**BREAST FEEDING** Present in milk, and should be avoided if possible during breast-feeding. All infants should be monitored for sedation, feeding difficulties, adequate weight gain, and developmental milestones.

**HEPATIC IMPAIRMENT** Start with smaller initial doses or reduce dose. Can precipitate coma. Avoid in severe impairment.

**RENAL IMPAIRMENT** Start with small doses in severe impairment.

**MONITORING REQUIREMENTS** Routine measurement of plasma concentrations of antiepileptic drugs is not
usually justified, because the target concentration ranges
are arbitrary and often vary between individuals.
However, plasma drug concentrations may be measured in
children with worsening seizures, status epilepticus,
suspected noncompliance, or suspected toxicity.
Similarly, haematological and biochemical monitoring
should not be undertaken unless clinically indicated.

- **PRESCRIBING AND DISPENSING INFORMATION**
  Switching between formulations Care should be taken when
  switching between oral formulations in the treatment of
  epilepsy. The need for continued supply of a particular
  manufacturer’s product should be based on clinical
  judgement and consultation with the patient or their carer,
taking into account factors such as seizure frequency and
treatment history.

Patients being treated for epilepsy may need to be
maintained on a specific manufacturer’s branded or
generic oral clonazepam product.

- **PATIENT AND CARER ADVICE**
  Medicines for Children leaflet: Clonazepam for preventing
  seizures www.medicinesforchildren.org.uk/clonazepam-
  preventing-seizures-0

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines
  containing the same drug. Forms available from special-order
  manufacturers include: oral suspension, oral drops, oral
  solution, orodispersible tablet

**Tablet**
- CAUTIONARY AND ADVISORY LABELS 2, 8
  - CLONAZEPAM (Non-proprietary)
    Clonazepam 500 microgram (Clonazepam 500microgram tablets) £1.08
    100 tablet (PO) £6.80 DT price = £6.70 Schedule 4 (CD Benz)
  - Clonazepam 2 mg Clonazepam 2mg tablets 100 tablet (PO) £9.94
    DT price = £8.93 Schedule 4 (CD Benz)

**Oral solution**
- CAUTIONARY AND ADVISORY LABELS 2, 8
  - EXCIPIENTS: May contain Ethanol
  - CLONAZEPAM (Non-proprietary)
    Clonazepam 100 microgram per 1 ml Clonazepam
    500micrograms/5ml oral solution sugar free (sugar-free) 120 ml (PO) £6.50
    DT price = £6.70 Schedule 4 (CD Benz)
  - Clonazepam 400 microgram per 1 ml Clonazepam 2mg/5ml oral
    solution sugar free (sugar-free) 150 ml (PO) £10.36 DT price = £10.85
    Schedule 4 (CD Benz)

**6.2 Status epilepticus**

**Drugs used for Status epilepticus not listed below:**
Diazepam, p. 267 · Phosphenytoin sodium, p. 391 ·
Phenobarbital, p. 409 · Phenytoin, p. 398

**BARBITURATES**

Thiopental sodium
(Thiopentone sodium)

**INDICATIONS AND DOSE**
Status epilepticus (only if other measures fail)

- **BY SLOW INTRAVENOUS INJECTION**
  - Adult: 75–125 mg for 1 dose, to be administered as a
    2.5% (25 mg/mL) solution

Induction of anaesthesia

- **BY SLOW INTRAVENOUS INJECTION**
  - Adult: Initially 100–150 mg, to be administered over
    10–15 seconds usually as a 2.5% (25 mg/mL) solution,
    followed by 100–150 mg after 0.5–1 minute if
    required, dose to be given in fit and premedicated
    adults; debilitated patients or adults over 65 years may
    require a lower dose or increased administration time,
    alternatively initially up to 4 mg/kg (max. per dose
    500 mg)

**Anaesthesia of short duration**

- **BY SLOW INTRAVENOUS INJECTION**
  - Adult: Initially 100–150 mg, to be administered over
    10–15 seconds usually as a 2.5% (25 mg/mL) solution,
    followed by 100–150 mg after 0.5–1 minute if
    required, dose to be given in fit and premedicated
    adults; debilitated patients or adults over 65 years may
    require a lower dose or increased administration time,
    alternatively initially up to 4 mg/kg (max. per dose
    500 mg)

**Reduction of raised intracranial pressure if ventilation**
controlled

- **BY SLOW INTRAVENOUS INJECTION**
  - Adult: 1.5–3 mg/kg, repeated if necessary

**Important safety information**
Thiopental sodium should only be administered by, or
under the direct supervision of, personnel experienced
in its use, with adequate training in anaesthesia and
airway management, and when resuscitation equipment
is available.

- **CONTRA-INDICATIONS** Acute porphyrias p. 864 · myotonic
dystrophy
- **CAUTIONS** Acute circulatory failure (shock) · avoid intra-
arterial injection · cardiovascular disease · elderly · fixed
cardiac output · hypovolaemia · reconstituted solution is
highly alkaline (extravasation causes tissue necrosis and
severe pain)
- **INTERACTIONS** Appendix 1 (anaesthetics, general).
- **SIDE-EFFECTS** Arrhythmias · cough · headache ·
hypersensitivity reactions · hypotension · laryngeal spasm ·
myocardial depression · rash · sneezing
- **PREGNANCY** May depress neonatal respiration when used
during delivery.
- **BREAST FEEDING** Breast-feeding can be resumed as soon
as mother has recovered sufficiently from anaesthesia.
- **HEPATIC IMPAIRMENT** Use with caution—reduce dose.
- **RENAL IMPAIRMENT** Caution in severe impairment.
- **PATIENT AND CARER ADVICE**
  Driving and skilled tasks
Patients given sedatives and analgesics during minor
outpatient procedures should be very carefully warned
about the risk of driving or undertaking skilled tasks
afterwards. For a short general anaesthetic the risk
extends to at least 24 hours after administration.
Responsible persons should be available to take patients
home. The dangers of taking alcohol should also be
emphasised.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines
  containing the same drug. Forms available from special-order
  manufacturers include: solution for injection

**Powder for solution for injection**

- THIOPENTAL SODIUM (Non-proprietary)
  Thiopental sodium 500 mg Thiopental 500mg powder for solution
  for injection vials 25 vial (PO) £1.43

**BNF 70**

Lorazepam

The properties listed below are those particular to the drug
only. For properties common to the class, see
Benzo diazepines, p. 266.
### INSTRUCTIONS AND DOSE

**Status epilepticus | Febrile convulsions | Convulsions caused by poisoning**

#### BY SLOW INTRAVENOUS INJECTION INTO LARGE VEIN
- Child 1 month–11 years: 100 micrograms/kg (max. per dose 4 mg) for 1 dose, then 100 micrograms/kg after 10 minutes (max. per dose 4 mg) if required for 1 dose
- Child 12–17 years: 4 mg for 1 dose, then 4 mg after 10 minutes if required for 1 dose
- Adult: 4 mg for 1 dose, then 4 mg after 10 minutes if required for 1 dose

#### Short-term use in anxiety

**BY MOUTH**
- Adult: 1–4 mg daily in divided doses, for debilitated patients, use elderly dose
- Elderly: 0.5–2 mg daily in divided doses

#### Short-term use in insomnia associated with anxiety

**BY MOUTH**
- Adult: 1–2 mg daily, to be taken at bedtime

#### Acute panic attacks

**BY INTRAMUSCULAR INJECTION OR BY SLOW INTRAVENOUS INJECTION**
- Adult: 25–30 micrograms/kg every 6 hours if required; usual dose 1.5–2.5 mg every 6 hours if required, intravenous injection to be administered into a large vein, only use intramuscular route when oral and intravenous routes not possible

#### Conscious sedation for procedures

**BY MOUTH**
- Adult: 2–3 mg, to be taken the night before operation; 2–4 mg, to be taken 1–2 hours before operation

**BY SLOW INTRAVENOUS INJECTION**
- Adult: 50 micrograms/kg, to be administered 30–45 minutes before operation

**BY INTRAMUSCULAR INJECTION**
- Adult: 50 micrograms/kg, to be administered 60–90 minutes before operation

### UNLICENSED USE


### Important safety information

**ANAESTHESIA**

Benzodiazepines should only be administered for anaesthesia by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management.

**CONTRA-INDICATIONS**

Avoid injections containing benzyl alcohol in neonates - chronic psychosis (in adults) - CNS depression - compromised airway - hyperkinesia - not for use alone to treat depression (or anxiety associated with depression) (in adults) - obsessional states - phobic states - respiratory depression

**CAUTIONS**

Muscle weakness - organic brain changes - parenteral administration - personality disorder (within the fearful group—dependent, avoidant, obsessive-compulsive) may increase risk of dependence

### CAUTIONS, FURTHER INFORMATION

**Special precautions for parenteral administration**

When given parenterally, facilities for managing respiratory depression with mechanical ventilation must be available. Close observation required until full recovery from sedation.

**Paradoxical effects**

A paradoxical increase in hostility and aggression may be reported by patients taking benzodiazepines. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects.

#### SIDE-EFFECTS

- **Common or very common** Amnesia - ataxia (in children) - ataxia (especially in the elderly) (in adults) - confusion (in children) - confusion (especially in the elderly) (in adults) - dependence - drowsiness the next day - lightheadedness the next day - muscle weakness - paradoxical increase in aggression

- **Uncommon** Changes in libido (in adults) - dizziness - dysarthria - gastro-intestinal disturbances - gynaecomastia - headache (in adults) - hypotension (in adults) - incontinence - salivation changes - slurred speech (in adults) - tremor - urinary retention (in adults) - vertigo (in adults) - visual disturbances

- **Rare** Apnoea - blood disorders - changes in libido (in children) - headache (in children) - hypotension (in children) - jaundice - respiratory depression - skin reactions - urinary retention (in children) - vertigo (in children)

- **Frequency not known** Delusions (in children) - excitement (in children) - hallucinations (in children) - irritability (in children) - marked respiratory depression, particularly with high dose and intravenous use (facilities for its treatment are essential) - pain (on intravenous injection) - psychosis (in children) - restlessness (in children) - thrombophlebitis (on intravenous injection)

**PREGNANCY**

Women who have seizures in the second half of pregnancy should be assessed for eclampsia before any change is made to antiepileptic treatment. Status epilepticus should be treated according to the standard protocol. All pregnant women with epilepsy, whether taking medication or not, should be encouraged to notify the UK Epilepsy and Pregnancy Register (Tel: 0800 389 1248).

**BREAST FEEDING**

Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding.

**HEPATIC IMPAIRMENT**

Can precipitate coma. Start with smaller initial doses or reduce dose. If treatment is necessary, benzodiazepines with shorter half-lives are safer. Avoid in severe impairment.

**RENAL IMPAIRMENT**

Start with small doses in severe impairment.

### DIRECTIONS FOR ADMINISTRATION

- **In children** For intravenous injection, dilute with an equal volume of Sodium Chloride 0.9% (for neonates, dilute injection solution to a concentration of 100 micrograms/mL). Give over 3–5 minutes; max. rate 50 micrograms/kg over 3 minutes.

- **In adults** For intramuscular injection, solution for injection should be diluted with an equal volume of water for injections or sodium chloride 0.9% (but only use when oral and intravenous routes not possible). For slow intravenous injection, solution for injection should preferably be diluted with an equal volume of water for injections or sodium chloride 0.9%.
PATIENT AND CARER ADVICE
May impair judgement and increase reaction time, and so affect ability to drive or operate machinery; they increase the effects of alcohol. Moreover the hangover effects of a night dose may impair driving on the following day.

Patients given sedatives and analgesics during minor outpatient procedures should be very carefully warned that these drugs may impair judgement and reaction time, and so affect ability to drive or operate machinery; they increase the effects of alcohol. Moreover the hangover effects of a night dose may impair driving on the following day. For intravenous benzodiazepines the risk extends to at least 24 hours after administration. Responsible persons should be available to take patients home afterwards. The dangers of taking alcohol should be emphasised.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, oral solution, oral suspension

Tablet

CAUTIONARY AND ADVISORY LABELS: 2, 19

Adult:

▶ Elderly:

▶ Adult:

▶ Elderly:

▶ Elderly:

▶ Elderly:

BY SUBCUTANEOUS INFUSION

Adult: 20–60 minutes before administration

BY INTRAVENOUS INJECTION

Adult: 10–20 mg; 4 hours, adjusted according to response; usual dose 20–60 mg; 24 hours

Convolusions in palliative care

Adult: Initially 20–40 mg/24 hours

Midazolam

The properties listed below are those particular to the drug only. For properties common to the class, see Benzodiazepines, p. 266.

INDICATIONS AND DOSE

Status epilepticus | Febrile convulsions

BY BUCAL ADMINISTRATION

Child 1-2 months: 300 micrograms/kg (max. per dose 2.5 mg), then 300 micrograms/kg (max. per dose 2.5 mg) if required

Child 3-11 months: 2.5 mg, then 2.5 mg after 10 minutes if required

Child 1-4 years: 5 mg, then 5 mg after 10 minutes if required

Child 5-9 years: 7.5 mg, then 7.5 mg after 10 minutes if required

Adult: 10 mg, then 10 mg after 10 minutes if required

Conscious sedation for procedures

BY SLOW INTRAVENOUS INJECTION

Adult: Initially 2–2.5 mg, to be administered

5–10 minutes before procedure at a rate of approximately 2 mg/minute, increased in steps of 1 mg if required, usual total dose is 3.5–5 mg; maximum 7.5 mg per course

Elderly: Initially 0.5–1 mg, to be administered

5–10 minutes before procedure at a rate of approximately 2 mg/minute, increased in steps of 0.5–1 mg if required; maximum 3.5 mg per course

Sedative in combined anaesthesia

INITIALLY BY INTRAVENOUS INJECTION

Adult: 30–100 micrograms/kg, repeated if necessary, alternatively (by continuous intravenous infusion) 30–100 micrograms/kg/hour

Elderly: Lower doses needed

PREMEDICATION

BY DEEP INTRAVASCULAR INJECTION

Adult: 70–100 micrograms/kg, to be administered

20–60 minutes before induction, for debilitated patients, use elderly dose

Elderly: 25–50 micrograms/kg, to be administered

20–60 minutes before induction

BY INTRAVENOUS INJECTION

Adult: 1–2 mg, repeated if necessary, to be administered

5–30 minutes before procedure, for debilitated patients, use elderly dose

Elderly: 0.5 mg, repeated if necessary, to be administered

5–30 minutes before procedure, repeat dose slowly as required

INDUCTION OF ANAESTHESIA (BUT RARELY USED)

BY SLOW INTRAVENOUS INJECTION

Adult: 150–200 micrograms/kg daily in divided doses (max. per dose 5 mg), dose to be given at intervals of 2 minutes, maximum total dose 600 micrograms/kg, for debilitated patients, use elderly dose

Elderly: 50–150 micrograms/kg daily in divided doses (max. per dose 5 mg), dose to be given at intervals of 2 minutes, maximum total dose 600 micrograms/kg

Sedation of patient receiving intensive care

INITIALLY BY SLOW INTRAVENOUS INJECTION

Adult: Initially 30–300 micrograms/kg, dose to be given in steps of 1–2.5 mg every 2 minutes, then (by slow intravenous injection or by continuous intravenous infusion) 30–200 micrograms/kg/hour, reduce dose (or reduce or omit initial dose) in hypovolaemia, vasoconstriction, or hypothermia, lower doses may be adequate if opioid analgesic also used

Confusion and restlessness in palliative care

BY SUBCUTANEOUS INFUSION

Adult: Initially 10–20 mg/24 hours, adjusted according to response; usual dose 20–60 mg/24 hours

Convolusions in palliative care

BY CONTINUOUS SUBCUTANEOUS INFUSION

Adult: Initially 20–40 mg/24 hours

UNLICENSED USE

Oromucosal solution not licensed for use in children under 3 months. Oromucosal solution not licensed for use in adults over 18 years. Unlicensed oromucosal formulations are also available and may have different doses—refer to product literature. Injection not licensed for use in status epilepticus or febrile convulsions.


Important safety information

ANAESTHESIA

Benzodiazepines should only be administered for anaesthesia by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management.

PRESCRIBING OF MIDAZOLAM IN PALLIATIVE CARE

The use of high-strength midazolam (5 mg/mL in 2 mL and 10 mL ampoules, or 2 mg/mL in 5 mL ampoules) should be considered in palliative care and other situations where a higher strength may be more appropriate to administer the prescribed dose, and where the risk of overdose has been assessed. It is advised that flumazenil is available when midazolam is used, to reverse the effects if necessary.

CONTRA-INDICATIONS

CNS depression · compromised airway · severe respiratory depression
• **CAUTIONS** Cardiac disease - children (particularly if cardiovascular impairment) - concentration of midazolam in children under 15 kg to not exceed 1 mg/mL - debilitated patients (reduce dose) - hypothermia - hypovolaemia (risk of severe hypotension) - neonates - risk of airways obstruction and hypoventilation in children under 6 months (monitor respiratory rate and oxygen saturation) - vasoconstriction

**CAUTIONS, FURTHER INFORMATION**

**Recovery when used for sedation** Midazolam has a fast onset of action, recovery is faster than for other benzodiazepines such as diazepam, but may be significantly longer in the elderly, in patients with a low cardiac output, or after repeated dosing.

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

Amnesia - anaphylaxis - ataxia - blood disorders - bronchospasm - cardiac arrest - changes in libido (in adults) - confusion - convulsions (more common in neonates) - depression of consciousness - dizziness - drowsiness - dry mouth - dysarthria - euphoria - fatigue (in children) - gastro-intestinal disturbances - hallucinations - headache - heart rate changes - hiccups - hypotension - incontinence - increased appetite - injection-site reactions - involuntary movements - jaundice - laryngospasm - muscle weakness - paradoxical aggression (especially in children and elderly) - paradoxical excitement (especially in children and elderly) - respiratory arrest (particularly with high doses or on rapid injection) - respiratory depression (may be severe with sedative and peri-operative use—facilities for its treatment are essential) - respiratory depression (particularly with high doses or on rapid injection) - restlessness (with sedative and peri-operative use) (in children) - salivation changes - severe disinhibition (with sedative and peri-operative use) (in children) - skin reactions - thrombosis - urinary retention - vertigo - visual disturbances

**SPECIFIC SIDE-EFFECTS**

• With intranasal use - burning sensation (in children) - laceration (in children) - severe irritation of nasal mucosa (in children)

**SIDE-EFFECTS, FURTHER INFORMATION**

**Sedation** Midazolam is associated with profound sedation when high doses are given or when it is used with certain other drugs. Midazolam is not recommended for prolonged sedation in neonates; drug accumulation is likely to occur.

**Overdose** There have been reports of overdosage when high strength midazolam has been used for conscious sedation. The use of high-strength midazolam (5 mg/mL in 2 mL and 10 mL ampoules, or 2 mg/mL in 5 mL ampoules) should be restricted to general anaesthesia, intensive care, palliative care, or other situations where the risk has been assessed. It is advised that flumazenil is available when midazolam is used, to reverse the effects if necessary.

**PREGNANCY** Women who have seizures in the second half of pregnancy should be assessed for eclampsia before any change is made to antiepileptic treatment. Status epilepticus should be treated according to the standard protocol. All pregnant women with epilepsy, whether taking medication or not, should be encouraged to notify the UK Epilepsy and Pregnancy Register (Tel: 0800 389 1248).

**BREAST FEEDING** Small amount present in milk—avoid breast-feeding for 24 hours after administration (although amount probably too small to be harmful after single doses).

**HEPATIC IMPAIRMENT** Use with caution particularly in sedative doses; can precipitate coma. For status epileptics and febrile convulsions: use with caution in mild to moderate impairment; avoid in severe impairment.

**RENAL IMPAIRMENT** Use with caution in chronic renal failure.

**DIRECTIONS FOR ADMINISTRATION**

For **intravenous infusion** (Hypnovel®), give continuously in Glucose 5% or Sodium chloride 0.9%. For neonate and children under 15 kg dilute to a maximum concentration of 1 mg/mL.

• With intravenous use in children For **intravenous injection** in status epilepticus and febrile convulsions, dilute with Glucose 5% or Sodium Chloride 0.9%; rapid intravenous injection (less than 2 minutes) may cause seizure-like myoclonus in preterm neonate.

• With intravenous use in neonates Neonatal intensive care, dilute 15 mg/kg body-weight to a final volume of 50 mL with infusion fluid; an intravenous infusion rate of 0.1 mL/hour provides a dose of 30 micrograms/kg/hour.

• With oral use in children For administration by mouth for sedation and premedication, injection solution may be diluted with apple or black currant juice, chocolate sauce, or cola.

• With rectal use in children For rectal administration of the injection solution for sedation and premedication, attach a plastic applicator onto the end of a syringe; if the volume to be given rectally is too small, dilute with Water for Injections.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Midazolam for stopping seizures www.medicinesforchildren.org.uk/midazolam-for-stopping-seizures

Patients or carers should be given advice on how to administer midazolam oromucosal solution.

Patients given sedatives and analgescis during minor outpatient procedures should be very carefully warned about the risks of undertaking skilled tasks (e.g. driving) afterwards. For intravenous benzodiazepines the risk extends to at least 24 hours after administration.

Responsible persons should be available to take patients home afterwards. The dangers of taking alcohol should be emphasised.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, solution for injection, oral suspension, solution for infusion, oral solution, oromucosal solution, infusion

**Oromucosal solution**

**CAUTIONARY AND ADVISORY LABELS**

2

**Buccolam** (ViSPharma Ltd)

Midazolam (as Midazolam hydrochloride) 5 mg per 1 ml

Buccolam 10mg/2ml oromucosal solution pre-filled oral syringes | 4 unit dose (£81.50 DT price = £91.50 Schedule 3 (CD No Register Exempt Safe Custody))

Buccolam 75mg/1.5ml oromucosal solution pre-filled oral syringes | 4 unit dose (£89.00 DT price = £99.00 Schedule 3 (CD No Register Exempt Safe Custody))

Buccolam 5mg/1ml oromucosal solution pre-filled oral syringes | 4 unit dose (£85.50 DT price = £95.50 Schedule 3 (CD No Register Exempt Safe Custody))

Buccolam 2.5mg/0.5ml oromucosal solution pre-filled oral syringes | 4 unit dose (£82.00 DT price = £92.00 Schedule 3 (CD No Register Exempt Safe Custody))

**Solution for injection**

**MIDAZOLAM (Non-proprietary)**

Midazolam (as Midazolam hydrochloride) 1 mg per 1 ml

Midazolam 1mg/1ml oromucosal solution pre-filled oral syringes | 10 ampoules (£16.00 Schedule 3 (CD No Register Exempt Safe Custody))

Midazolam 2mg/2ml solution for injection ampoules | 10 ampoules (£5.00 Schedule 3 (CD No Register Exempt Safe Custody))

Midazolam (as Midazolam hydrochloride) 2 mg per 1 ml

Midazolam 10mg/5ml solution for injection ampoules |
Sleep disorders

7 Insomnia

Hypnotics and anxiolytics

Most hypnotics (‘sedatives’) will induce sleep when given at night and most hypnotics will sedate when given during the day. Prescribing of these drugs is widespread but dependence (both physical and psychological) and tolerance occur. This may lead to difficulty in withdrawing the drug after the patient has been taking it regularly for more than a few weeks. Hypnotics and anxiolytics should therefore be reserved for short courses to alleviate acute conditions after causal factors have been established.

Benzodiazepines are the most commonly used anxiolytics and hypnotics; they act at benzodiazepine receptors which are associated with gamma-aminobutyric acid (GABA) receptors. Older drugs such as meprobamate p. 265 and barbiturates are not recommended—they have more side-effects and interactions than benzodiazepines and are much more dangerous in overdose.

Benzodiazepine indications

- Benzodiazepines are indicated for the short-term relief (two to four weeks only) of anxiety that is severe, disabling, or causing the patient unacceptable distress, occurring alone or in association with insomnia or short-term psychosomatic, organic, or psychotic illness.
- The use of benzodiazepines to treat short-term ‘mild’ anxiety is inappropriate.
- Benzodiazepines should be used to treat insomnia only when it is severe, disabling, or causing the patient extreme distress.

Dependence and withdrawal

Withdrawal of a benzodiazepine should be gradual because abrupt withdrawal may produce confusion, toxic psychosis, convulsions, or a condition resembling delirium tremens. The benzodiazepine withdrawal syndrome may develop at any time up to 3 weeks after stopping a long-acting benzodiazepine, but may occur within a day in the case of a short-acting one. It is characterised by insomnia, anxiety, loss of appetite and of body-weight, tremor, perspiration, tinnitus, and perceptual disturbances. Some symptoms may be similar to the original complaint and encourage further prescribing; some symptoms may continue for weeks or months after stopping benzodiazepines.

Benzodiazepine withdrawal should be flexible and carried out at a reduction rate that is tolerable for the patient. The rate should depend on the initial dose of benzodiazepine, duration of use, and the patient’s clinical response. Short-term users of benzodiazepines (2–4 weeks only) can usually taper off within 2–4 weeks. However, long-term users should be withdrawn over a much longer period of several months or more.

A suggested protocol for withdrawal of prescribed long-term benzodiazepine patients is as follows:
- Transfer patient stepwise, one dose at a time over about a week, to an equivalent daily dose of diazepam preferably taken at night.
- Reduce diazepam dose, usually by 1–2 mg every 2–4 weeks (in patients taking high doses of benzodiazepines, initially it may be appropriate to reduce the dose by up to one-tenth every 1–2 weeks). If uncomfortable withdrawal symptoms occur, maintain this dose until symptoms lessen.
- Reduce diazepam dose further, if necessary in smaller steps; steps of 500 micrograms may be appropriate towards the end of withdrawal. Then stop completely.
- For long-term patients, the period needed for complete withdrawal may vary from several months to a year or more.

Approximate equivalent doses, diazepam 5 mg
- alprazolam 250 micrograms
- clonazepam 10 mg
- clonazepam 250 micrograms
- flurazepam 7.5–15 mg
- chloridiazepoxide 12.5 mg
- loprazolam 0.5–1 mg
- lorazepam 500 micrograms
- lormetazepam 0.5–1 mg
- nitrazepam 5 mg
- oxazepam 10 mg
- temazepam 10 mg

Withdrawal symptoms for long-term users usually resolve within 6–18 months of the last dose. Some patients will recover more quickly, others may take longer. The addition of beta-blockers, antidepressants and antipsychotics should be avoided where possible.

Counselling can be of considerable help both during and after the taper.

Hypnotics

Before a hypnotic is prescribed the cause of the insomnia should be established and, where possible, underlying factors should be treated. However, it should be noted that some patients have unrealistic sleep expectations, and others underestimate their alcohol consumption which is often the cause of the insomnia. Short-acting hypnotics are preferable in patients with sleep onset insomnia, when sedation the following day is undesirable, or when prescribing for elderly patients. Long-acting hypnotics are indicated in patients with poor sleep maintenance (e.g. early morning waking) that causes daytime effects, when an anxiolytic effect is needed during the day, or when sedation the following day is acceptable.

Transient insomnia may occur in those who normally sleep well and may be due to extraneous factors such as noise, shift work, and jet lag. If a hypnotic is indicated one that is rapidly eliminated should be chosen, and only one or two doses should be given.

Short-term insomnia is usually related to an emotional problem or serious medical illness. It may last for a few weeks and may recur; a hypnotic can be useful but should not be given for more than three weeks (preferably only one week). Intermittent use is desirable with omission of some doses. A short-acting drug is usually appropriate.
Chronic insomnia is rarely benefited by hypnotics and is sometimes due to mild dependence caused by injudicious prescribing of hypnotics. Psychiatric disorders such as anxiety, depression, and abuse of drugs and alcohol are common causes. Sleep disturbance is very common in depressive illness and early wakening is often a useful pointer. The underlying psychiatric complaint should be treated, adapting the drug regimen to alleviate insomnia. For example, clomipramine hydrochloride p. 294 or mirtazapine p. 291 prescribed for depression will also help to promote sleep if taken at night. Other causes of insomnia include daytime cat-napping and physical causes such as pain, pruritus, and dyspnoea.

Hypnotics should **not** be prescribed indiscriminately and routine prescribing is undesirable. They should be reserved for short courses in the acutely distressed. Tolerance to routine prescribing is undesirable. They should be reserved for patients because of its freedom from hangover but, as with all hypnotics, routine administration is undesirable and recommended for patients. Zolpidem tartrate and zopiclone have a short duration of action; zaleplon is very short acting. Benzodiazepines and the Z drugs, but they act at the benzodiazepine receptor. They are not licensed for long-term use; dependency occurs.

Where prolonged administration is unavoidable hypnotics should be discontinued as soon as feasible and the patient warned that sleep may be disturbed for a few days before normal rhythm is re-established; broken sleep with vivid dreams may persist for several weeks.

**Elderly**

Benzodiazepines and the Z-drugs should be avoided in the elderly, because the elderly are at greater risk of becoming ataxic and confused, leading to falls and injury.

**Dental patients**

Some anxious patients may benefit from the use of hypnotics during dental procedures such as temazepam p. 420 or diazepam p. 267. Temazepam p. 420 is preferred when it is important to minimise any residual effect the following day.

**Benzodiazepines**

Benzodiazepines used as hypnotics include nitrazepam p. 419 and flurazepam p. 418 which have a prolonged action and may give rise to residual effects on the following day; repeated doses tend to be cumulative.

Lorazepam p. 418, lorormetazepam p. 419, and temazepam p. 420 act for a shorter time and they have little or no hangover effect. Withdrawal phenomena are more common with the short-acting benzodiazepines.

If insomnia is associated with daytime anxiety then the use of a long-acting benzodiazepine anxiolytic such as diazepam p. 267 given as a single dose at night may effectively treat both symptoms.

**Zaleplon, zolpidem, and zopiclone**

Zaleplon p. 422, zolpidem tartrate p. 423 and zopiclone p. 423 are non-benzodiazepine hypnotics (sometimes referred to as Z-drugs), but they act at the benzodiazepine receptor. They are not licensed for long-term use; dependence has been reported in a small number of patients. Zolpidem tartrate and zopiclone have a short duration of action; zaleplon is very short acting.

**Chloral and derivatives**

There is no convincing evidence that they are particularly useful in the elderly and their role as hypnotics is now very limited.

**Clomethiazole**

Clomethiazole p. 421 may be a useful hypnotic for elderly patients because of its freedom from hangover but, as with all hypnotics, routine administration is undesirable and dependence occurs.

**Antihistamines**

Some antihistamines such as promethazine hydrochloride p. 291 are on sale to the public for transient insomnia; their prolonged duration of action can often cause drowsiness the following day. The sedative effect of antihistamines may diminish after a few days of continued treatment; antihistamines are associated with headache, psychomotor impairment and antimuscarinic effects.

**Alcohol**

Alcohol is a poor hypnotic because the diuretic action interferes with sleep during the latter part of the night. Alcohol also disturbs sleep patterns, and so can worsen sleep disorders.

**Melatonin**

Melatonin p. 422 is a pineal hormone; it is licensed for the short-term treatment of insomnia in adults over 55 years.

**Anxiolytics**

Benzodiazepines anxiolytics can be effective in alleviating anxiety states. Although these drugs are sometimes prescribed for stress-related symptoms, unhappiness, or minor physical disease, their use in such conditions is inappropriate. Benzodiazepine anxiolytics should not be used as sole treatment for chronic anxiety, and they are not appropriate for treating depression or chronic psychosis. In bereavement, psychological adjustment may be inhibited by benzodiazepines.

Anxiolytic benzodiazepine treatment should be limited to the lowest possible dose for the shortest possible time. Dependence is particularly likely in patients with a history of alcohol or drug abuse and in patients with marked personality disorders.

Some antidepressant drugs are licensed for use in anxiety and related disorders. Some antipsychotic drugs, in low doses, are also sometimes used in severe anxiety for their sedative action, but long-term use should be avoided because of the risk of adverse effects. The use of antihistamines (e.g. hydroxyzine hydrochloride p. 248) for their sedative effect in anxiety is not appropriate.

**Beta-adrenoceptor blocking drugs**

Beta-blockers do not affect psychological symptoms of anxiety, such as worry, tension, and fear, but they do reduce autonomic symptoms, such as palpitation and tremor; they do not reduce non-autonomic symptoms, such as muscle tension. Beta-blockers are therefore indicated for patients with predominantly somatic symptoms; this, in turn, may prevent the onset of worry and fear.

**Benzodiazepines**

Benzodiazepines are indicated for the short-term relief of severe anxiety; long-term use should be avoided. Diazepam p. 267, alprazolam p. 266, clorazepate hydrochloride p. 267, and clobazam p. 410 have a sustained action. Shorter-acting compounds such as lorazepam p. 412 and oxazepam p. 420 may be preferred in patients with hepatic impairment but they carry a greater risk of withdrawal symptoms.

In panic disorders (with or without agoraphobia) resistant to antidepressant therapy, a benzodiazepine may be used; alternatively, a benzodiazepine may be used as short-term adjunctive therapy at the start of antidepressant treatment to prevent the initial worsening of symptoms.

Diazepam p. 267 or lorazepam p. 412 are very occasionally administered intravenously for the control of panic attacks. This route is the most rapid but the procedure is not without risk and should be used only when alternative measures have failed. The intramuscular route has no advantage over the oral route.

**Buspirone**

Buspirone hydrochloride p. 269 is thought to act at specific serotonin (5HT1A) receptors. Response to treatment may take up to 2 weeks. It does not alleviate the symptoms of benzodiazepine withdrawal. Therefore a patient taking a benzodiazepine still needs to have the benzodiazepine withdrawn gradually; it is advisable to do this before starting buspirone hydrochloride. The dependence and abuse potential of buspirone hydrochloride is low; it is,
however, licensed for short-term use only (but specialists occasionally use it for several months).

**Meprobamate**
Meprobamate p. 265 is less effective than the benzodiazepines, more hazardous in overdosage, and can also induce dependence. It is not recommended.

**Barbiturates**
The intermediate-acting barbiturates have a place only in the treatment of severe intractable insomnia in patients already taking barbiturates; they should be avoided in the elderly. Intermediate-acting barbiturate preparations containing amobarbital sodium, butobarbital, and secobarbital sodium are available on a named patient basis. The long-acting barbiturate phenobarbital is still sometimes of value in epilepsy but its use as a sedative is unjustified.

The very short-acting barbiturate thiopental sodium p. 412 is used in anaesthesia. Increased hostility and aggression after barbiturates and alcohol usually indicates intoxication.

**Flurazepam**

**BENZODIAZEPINES**

**INDICATIONS AND DOSE**

**Insomnia (short-term use)**

**BY MOUTH**

- **Adult:** 15–30 mg once daily, dose to be taken at bedtime, for debilitated patients, use elderly dose
- **Elderly:** 15 mg once daily, dose to be taken at bedtime

**CONTRA-INDICATIONS** Not for use alone to treat chronic psychosis - not for use alone to treat depression (or anxiety associated with depression) - respiratory depression

**CAUTIONS**

Acute porphyrias p. 864 - hypoalbuninaemia - marked personality disorder - muscle weakness

**CAUTIONS, FURTHER INFORMATION**

**Paradoxical effects** A paradoxical increase in hostility and aggression may be reported by patients taking benzodiazepines. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects.

**SIDE-EFFECTS**

- Common or very common: Amnesia, ataxia (especially in the elderly) - confusion (especially in the elderly) - dependence - drowsiness the next day - lightheadedness the next day - muscle weakness - paradoxical increase in aggression
- Rare: Apnoea - blood disorders - jaundice - respiratory depression - skin reactions

**BREAST FEEDING**

Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding.

**HEPATIC IMPAIRMENT** Avoid in severe impairment. Start with smaller initial doses or reduce dose. Can precipitate coma. If treatment is necessary, benzodiazepines with shorter half-lives (such as temazepam or oxazepam) are safer.

**RENAL IMPAIRMENT** Start with small doses in severe impairment.

**PATIENT AND CARER ADVICE** May impair judgement and increase reaction time, and so affect ability to drive or operate machinery; they increase the effects of alcohol. Moreover the hangover effects of a night dose may impair driving on the following day.

**NATIONAL FUNDING/ACCESS DECISIONS**

**MEDICAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

*CAUTIONARY AND ADVISORY LABELS 19*

- Dalmane (Meda Pharmaceuticals Ltd)
- Flurazepam (as Flurazepam hydrochloride) 15 mg Dalmane 15mg capsules | 30 capsule (CD Benz)
- Flurazepam (as Flurazepam hydrochloride) 30 mg Dalmane 30mg capsules | 30 capsule (CD Benz)

**Loprazolam**

The properties listed below are those particular to the drug only. For properties common to the class, see Benzodiazepines, p. 266.

**INDICATIONS AND DOSE**

**Insomnia (short-term use)**

**BY MOUTH**

- **Adult:** 1 mg once daily, then increased to 1.5–2 mg once daily if required, dose to be taken at bedtime, for debilitated patients, use elderly dose
- **Elderly:** 0.5–1 mg once daily, dose to be taken at bedtime

**CONTRA-INDICATIONS** Not for use alone to treat chronic psychosis - not for use alone to treat depression (or anxiety associated with depression) - respiratory depression

**CAUTIONS**

Acute porphyrias p. 864 - hypoalbuminaemia - marked personality disorder - muscle weakness

**CAUTIONS, FURTHER INFORMATION**

**Paradoxical effects** A paradoxical increase in hostility and aggression may be reported by patients taking benzodiazepines. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects.

**SIDE-EFFECTS**

- Common or very common: Amnesia, ataxia (especially in the elderly) - confusion (especially in the elderly) - dependence - drowsiness the next day - lightheadedness the next day - muscle weakness - paradoxical increase in aggression
- Rare: Apnoea - blood disorders - jaundice - respiratory depression - skin reactions

**BREAST FEEDING**

Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding.

**HEPATIC IMPAIRMENT**

If treatment is necessary, benzodiazepines with shorter half-lives (such as temazepam or oxazepam) are safer. Start with smaller
initial doses or reduce dose. Can precipitate coma. Avoid in severe impairment.

- **RENAL IMPAIRMENT** Start with small doses in severe impairment.

- **PATIENT AND CARER ADVICE** May impair judgement and increase reaction time, and so affect ability to drive or operate machinery; they increase the effects of alcohol. Moreover the hangover effects of a night dose may impair driving on the following day.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**

  CAUTIONARY AND ADVISORY LABELS 19
  - LORPRAZOLAM (non-proprietary) Loprazolam 1 mg Loprazolam 1mg tablets | 28 tablet (POT) £18.00 D1 price = £18.00 Schedule 4 (CD Benz)
  - Lormetazepam 500 mg Lormetazepam 500mgmicrogram tablets | 30 tablet (POT) £20.00 D1 price = £20.04 Schedule 4 (CD Benz)
  - Lormetazepam 1mg tablets | 30 tablet (POT) £125.00 D1 price = £120.92 Schedule 4 (CD Benz)

- **NITRAZEPAM**

  The properties listed below are those particular to the drug only. For properties common to the class, see Benzodiazepines, p. 266.

  **INDICATIONS AND DOSE**

  **Insomnia (short-term use)**

  **BY MOUTH**
  - Adult: 0.5–1.5 mg once daily, dose to be taken at bedtime, for debilitated patients, use elderly dose
  - Elderly: 500 micrograms once daily, dose to be taken at bedtime

  **CONTRA-INDICATIONS** Not for use alone to treat chronic psychosis, not for use alone to treat depression (or anxiety associated with depression), respiratory depression

  **CAUTIONS** Acute porphyrias p. 864, hypoalbuminaemia, marked personality disorder, muscle weakness

  **CAUTIONS, FURTHER INFORMATION**

  **Paradoxical effects** A paradoxical increase in hostility and aggression may be reported by patients taking benzodiazepines. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects.

  **SIDE-EFFECTS**
  - **Common or very common** Amnesia, ataxia (especially in the elderly), confusion (especially in the elderly), dependence, drowsiness the next day, lightheadedness the next day, muscle weakness, paradoxical increase in aggression
  - **Uncommon** Changes in libido, dizziness, dysarthria, gastrointestinal disturbances, gynaecomastia, headache, hypotension, incontinence, salivation changes, slurred speech, tremor, urinary retention, vertigo, visual disturbances
  - **Rare** Apnoea, blood disorders, jaundice, respiratory depression, skin reactions

  **BREAST FEEDING** Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding.

  **HEPATIC IMPAIRMENT** If treatment is necessary, benzodiazepines with shorter half-lives (such as temazepam or oxazepam) are safer. Start with smaller initial doses or reduce dose. Can precipitate coma. Avoid in severe impairment.

  **PATIENT AND CARER ADVICE** May impair judgement and increase reaction time, and so affect ability to drive or operate machinery; they increase the effects of alcohol.
Moreover the hangover effects of a night dose may impair driving on the following day.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

  **Tablet**
  CAUTIONARY AND ADVISORY LABELS 19
  - NITRAZEPAM (Non-proprietary)
  - Nitrazepam 5 mg Nitrazepam 5mg tablets | 28 tablet (P) £10.55
  - DT price = £1.84 Schedule 4 (CD Benz) | 500 tablet (P) £125.00
  - Brands may include Mogadon

  **Oral suspension**
  CAUTIONARY AND ADVISORY LABELS 19
  - NITRAZEPAM (Non-proprietary)
  - Nitrazepam 500 microgram per 1 ml Nitrazepam 2.5mg/5ml oral suspension | 150 ml (P) £10.60 DT price = £10.60 Schedule 4 (CD Benz)

### Oxazepam

The properties listed below are those particular to the drug only. For properties common to the class, see Benzodiazepines, p. 266.

#### INDICATIONS AND DOSE

**Anxiety (short-term use)**

BY MOUTH
- Adult: 15–30 mg 3–4 times a day, for debilitated patients, use elderly dose
- Elderly: 10–20 mg 3–4 times a day

**Insomnia associated with anxiety**

BY MOUTH
- Adult: 15–25 mg once daily (max. per dose 50 mg), dose to be taken at bedtime

- CONTRA-INDICATIONS
  Chronic psychosis · hyperkinesia · not for use alone to treat depression (or anxiety associated with depression) · obessional states · phobic states · respiratory depression

- CAUTIONS
  Muscle weakness · organic brain changes · personality disorder (within the fearful group—dependent, avoidant, obsessive-compulsive) may increase risk of dependence

- CAUTIONS, FURTHER INFORMATION
  Paradoxical effects A paradoxical increase in hostility and aggression may be reported by patients taking benzodiazepines. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects.

- SIDE-EFFECTS
  - Common or very common
    Amnesia · ataxia (especially in the elderly) · confusion (especially in the elderly) · dependence · drowsiness the next day · lightheadedness the next day · muscle weakness · paradoxical increase in aggression
  - Uncommon
    Changes in libido · dizziness · dysarthria · gastrointestinal disturbances · gynaecomastia · headache · hypotension · incontinence · salivation changes · slurred speech · tremor · urinary retention · vertigo · visual disturbances
  - Rare
    Apnoea · blood disorders · jaundice · respiratory depression · skin reactions

- BREAST FEEDING
  Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding.

- HEPATIC IMPAIRMENT
  If treatment is necessary, benzodiazepines with shorter half-lives are safer. Start with smaller initial doses or reduce dose. Can precipitate coma. Avoid in severe impairment.

- RENAL IMPAIRMENT
  Start with small doses in severe impairment.

- PATIENT AND CARER ADVICE
  May impair judgement and increase reaction time, and so affect ability to drive or operate machinery; they increase the effects of alcohol. Moreover the hangover effects of a night dose may impair driving on the following day.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

  **Tablet**
  CAUTIONARY AND ADVISORY LABELS 2
  - OXAZEPAM (Non-proprietary)
  - Oxazepam 10 mg Oxazepam 10mg tablets | 28 tablet (P) £13.00
  - DT price = £11.53 Schedule 4 (CD Benz)
  - Oxazepam 15 mg Oxazepam 15mg tablets | 28 tablet (P) £14.50
  - DT price = £11.54 Schedule 4 (CD Benz)

### Temazepam

The properties listed below are those particular to the drug only. For properties common to the class, see Benzodiazepines, p. 266.

#### INDICATIONS AND DOSE

**Insomnia (short-term use)**

BY MOUTH
- Adult: 10–20 mg once daily, alternatively 30–40 mg once daily, higher dose range only to be administered in exceptional circumstances, dose to be taken at bedtime, for debilitated patients, use elderly dose
- Elderly: 10 mg once daily, alternatively 20 mg once daily, higher dose only to be administered in exceptional circumstances, dose to be taken at bedtime

**Conscious sedation for dental procedures**

BY MOUTH
- Adult: 15–30 mg, to be administered 30–60 minutes before procedure

**Premedication before surgery or investigatory procedures**

BY MOUTH
- Adult: 10–20 mg, to be taken 1–2 hours before procedure, alternatively 30 mg, to be taken 1–2 hours before procedure, higher alternate dose only administered in exceptional circumstances
- Elderly: 10 mg, to be taken 1–2 hours before procedure, alternatively 20 mg, to be taken 1–2 hours before procedure, higher alternate dose only administered in exceptional circumstances

- **UNLICENSED USE**
  Temazepam doses in BNF may differ from those in product literature. Not licensed for conscious sedation for dental procedures.

- CONTRA-INDICATIONS
  CNS depression · compromised airway · hyperkinesia · not for use alone to treat chronic psychosis · not for use alone to treat depression (or anxiety associated with depression) · obessional state · phobic states · respiratory depression

- CAUTIONS
  Hypoaalbuminaemia · muscle weakness · organic brain changes · personality disorder (within the fearful group—dependent, avoidant, obsessive-compulsive)—may increase risk of dependence

- CAUTIONS, FURTHER INFORMATION
  Paradoxical effects A paradoxical increase in hostility and aggression may be reported by patients taking benzodiazepines. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects.
**SIDE-EFFECTS**

- **Common or very common** Amnesia - ataxia (especially in the elderly) - confusion (especially in the elderly) - dependence - drowsiness the next day - lightheadedness the next day - muscle weakness - paradoxical increase in aggression
- **Uncommon** Changes in libido - dizziness - dysarthria - gastro-intestinal disturbances - gynaecomastia - headache - hypotension - incontinence - salivation changes - slurred speech - tremor - urinary retention - vertigo - visual disturbances
- **Rare** Apnoea - blood disorders - jaundice - skin reactions
- **Frequency not known** Respiratory depression (may be marked when used for sedation; facilities for its treatment are essential)

**BREAST FEEDING** Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding.

**HEPATIC IMPAIRMENT** If treatment is necessary, benzodiazepines with shorter half-lives are safer. Start with smaller initial doses or reduce dose. Can precipitate coma. Avoid in severe impairment.

**RENAL IMPAIRMENT** Start with small doses in severe impairment.

**PATIENT AND CARER ADVICE** May impair judgement and increase reaction time, and so affect ability to drive or operate machinery; they increase the effects of alcohol. Moreover the hangover effects of a night dose may impair driving on the following day. Patients given sedatives and analgesics during minor outpatient procedures should be very carefully warned afterwards. Responsible persons should be available to take patients home afterwards. The dangers of taking alcohol should be emphasised.

**PROFESSION SPECIFIC INFORMATION**

Dental practitioners' formulary. Temazepam Tablets may be prescribed. Temazepam Oral Solution may be prescribed.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: suppository, oral suspension, oral solution, enema

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS 19</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TEMAZEPAM</strong> (Non-proprietary)</td>
</tr>
<tr>
<td>Temazepam 10 mg</td>
</tr>
<tr>
<td>500 tablet (Pack) £62.42 Schedule 3 (CD No Register)</td>
</tr>
<tr>
<td>Temazepam 20 mg</td>
</tr>
<tr>
<td>250 tablet (Pack) £307.94 Schedule 3 (CD No Register)</td>
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</tbody>
</table>

**Oral solution**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS 19</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TEMAZEPAM</strong> (Non-proprietary)</td>
</tr>
<tr>
<td>Temazepam 2 mg per 1 ml</td>
</tr>
</tbody>
</table>

**CNS DEPRESSANTS**

**Chloral hydrate**

**INDICATIONS AND DOSE**

**Insomnia (short-term use)**

- **BY MOUTH USING ORAL SOLUTION**
  - Adult: 0.5–2 g daily, dose to be taken at bedtime

**WELLDOM® ELIXIR**

**Insomnia (short-term use)**

- **BY MOUTH**
  - Adult: 15–45 mL, alternatively 0.4–1.3 g, dose to be taken with water or milk at bedtime; maximum 70 mL per day; maximum 2 g per day

**CONTRA-INDICATIONS**

Acute porphyrias p. 864 · gastritis · severe cardiac disease

**CAUTIONS**

Avoid contact with mucous membranes · avoid contact with skin · avoid prolonged use (and abrupt withdrawal thereafter) · reduce dose in debilitated · reduce dose in elderly

**INTERACTIONS**

→ Appendix 1 (anxiolytics and hypnotics).

**SIDE-EFFECTS**

Abdominal distention · delirium (especially on abrupt withdrawal) · dependence · excitement · flatulence · gastrointestinal irritation · headache · ketonuria · nausea · rash · tolerance · vomiting

**PREGNANCY**

Avoid.

**BREAST FEEDING** Risk of sedation in infant—avoid.

**HEPATIC IMPAIRMENT** Reduce dose in mild to moderate impairment.

Can precipitate coma. Avoid in severe impairment.

**RENAL IMPAIRMENT** Avoid in severe impairment.

**DIRECTIONS FOR ADMINISTRATION**

- With oral use For administration by mouth dilute liquid with plenty of water or juice to mask unpleasant taste.

**PRESCRIBING AND DISPENSING INFORMATION**

Flavours of oral liquid formulations may include blackcurrant. When prepared extemporaneously, the BP states Chloral Mixture, BP 2000 consists of chloral hydrate 500 mg/5 mL in a suitable vehicle.

**PATIENT AND CARER ADVICE**

Drowsiness may persist the next day and affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

**LESS SUITABLE FOR PRESCRIBING**

Chloral hydrate is less suitable for prescribing in insomnia.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: suppository, oral suspension, oral solution, enema

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS 19, 27</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHLORAL HYDRATE</strong> (Non-proprietary)</td>
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<tr>
<td>Cloral betaine 707 mg</td>
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</table>

**Oral solution**

<table>
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<th>CAUTIONARY AND ADVISORY LABELS 1, 19, 27</th>
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<tbody>
<tr>
<td><strong>CHLORAL HYDRATE</strong> (Non-proprietary)</td>
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<tr>
<td>Chloral hydrate 28.66 mg per 1 ml</td>
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**Crystals**

<table>
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<tr>
<th><strong>CHLORAL HYDRATE</strong> (Non-proprietary)</th>
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</thead>
<tbody>
<tr>
<td>Chloral hydrate 1 mg per 1 ml</td>
</tr>
</tbody>
</table>

**Clomethiazole**

(Chlormethiazole)

**INDICATIONS AND DOSE**

Severe insomnia (short-term use)

**BY MOUTH USING CAPSULES**

- Elderly: 192–384 mg daily, dose to be taken at bedtime

**BY MOUTH USING ORAL SOLUTION**

- Elderly: 5–10 mL daily, dose to be taken at bedtime

Restlessness and agitation

**BY MOUTH USING CAPSULES**

- Elderly: 192 mg 3 times a day

**BY MOUTH USING ORAL SOLUTION**

- Elderly: 5 mL 3 times a day

**Alcohol withdrawal**

**INITIALLY BY MOUTH USING CAPSULES**

- Adult: Initially 2–4 capsules, to be repeated if necessary after some hours, then (by mouth) continued →
### 422 Sleep disorders

#### Nervous system

**Melatonin**

**PATIENT AND CARER ADVICE**

- **HEPATIC IMPAIRMENT**
- **BREAST FEEDING**
- **PREGNANCY**
- **SIDE-EFFECTS**
- **INTERACTIONS**

**INDICATIONS AND DOSE**

- **Adult 55 years and over:**
  - Clomethiazole 192 mg capsule contains 192 mg of clomethiazole base.
  - Melatonin 2 mg CIRCADIN
  - DT price = £39

**SIDE-EFFECTS**

- **CONTRA-INDICATIONS**
- **CAUTIONS**
- **INTERACTIONS**
  - **Appendix 1 (anxiolytics and hypnotics).**

**INTERACTIONS**

- **CONTRA-INDICATIONS**
- **CAUTIONS**
- **INTERACTIONS**
  - **Appendix 1 (anxiolytics and hypnotics).**

**MEDICINAL FORMS**

- **Capsule**
  - Clomethiazole (Non-proprietary)
  - Clomethiazole 192 mg
  - Clomethiazole 192mg capsules 60 capsule pack £22.00 DT price = £20.00

- **Oral solution**
  - Clomethiazole (as Clomethiazole edisilate) 50 mg per 1 ml Clomethiazole 31.5mg/ml oral solution sugar free (sugar-free) 300 ml pack £20.00–£22.00

**SIDE-EFFECTS**

- **CONTRA-INDICATIONS**
- **CAUTIONS**
- **INTERACTIONS**
  - **Appendix 1 (anxiolytics and hypnotics).**

**SIDE-EFFECTS, FURTHER INFORMATION**

- **Frequency not known**
  - Paradoxical effects  A paradoxical increase in hostility and aggression may be reported. The effects range from

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**Zaleplon**

**INDICATIONS AND DOSE**

- **Insomnia (short-term use)**
- **BY MOUTH**
  - **Adult:** 10 mg daily for up to 2 weeks, dose to be taken at bedtime or after going to bed if difficulty falling asleep
  - **Elderly:** 5 mg daily for up to 2 weeks, dose to be taken at bedtime or after going to bed if difficulty falling asleep

**SIDE-EFFECTS**

- **CONTRA-INDICATIONS**
- **CAUTIONS**
- **INTERACTIONS**
  - **Appendix 1 (anxiolytics and hypnotics).**

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**Melatonin**

**INDICATIONS AND DOSE**

- **Insomnia (short-term use)**
- **BY MOUTH USING MODIFIED-RELEASE TABLETS**
  - **Adult 55 years and over:**
    - 2 mg once daily for up to 13 weeks, dose to be taken 1–2 hours before bedtime
talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects. Increased hostility and aggression after barbiturates and alcohol usually indicates intoxication.

- **Pregnancy** Use only if necessary and restrict to occasional short-term use. Risk of withdrawal symptoms in neonate if used in late pregnancy.
- **Breast Feeding** Present in milk but amount probably too small to be harmful.
- **Hepatic Impairment** Reduce dose to 5 mg. Can precipitate coma. Avoid if severe impairment.
- **Renal Impairment** Avoid in severe impairment.
- **Patient and Carer Advice** Patients should be advised not to take a second dose during a single night.

**National Funding/Access Decisions**

- **NICE Technology Appraisals (TAs)**
  - Zaleplon, zolpidem, and zopiclone for the short-term management of insomnia (April 2004) NICE TA77
  - Zolpidem is recommended for the short-term management of severe insomnia that interferes with normal daily life, and should be prescribed for short periods of time only. www.nice.org.uk/TA77

**Medicinal Forms**

There can be variation in the licensing of different medicines containing the same drug.

- **Capsule**
  - **Cautionary and Advisory Labels 2**
    - Zaleplon 5 mg Sonata 5mg capsules | 14 capsule **PO** £3.12 DT price = £3.12 Schedule 4 (CD Benz)
    - Zaleplon 10 mg Sonata 10mg capsules | 14 capsule **PO** £3.76 Schedule 4 (CD Benz)

**Zolpidem Tartrate**

**Indications and Dose**

**Insomnia (short-term use)**

**By Mouth**

- Adult: 10 mg daily for up to 4 weeks, dose to be taken at bedtime, for debilitated patients, use elderly dose
- Elderly: 5 mg daily for up to 4 weeks, dose to be taken at bedtime

- **Contra-Indications** Acute respiratory depression • marked neuromuscular respiratory weakness • obstructive sleep apnoea • psychotic illness • severe respiratory depression • unstable myasthenia gravis
- **Cautions** Avoid prolonged use (and abrupt withdrawal thereafter) • depression • elderly • history of alcohol abuse • history of drug abuse • muscle weakness • myasthenia gravis
- **Interactions** Appendix (anxiolytics and hypnotics).
- **Side-Effects** Agitation • amnesia • asthenia • ataxia • changes in libido • confusion • depression • dependence • diarrhoea • diplopia • diziness • drowsiness • falls • hallucination • headache • memory disturbances • muscular weakness • nausea • nightmares • paradoxical effects • perceptual disturbances • skin reactions • sleep-walking • tremor • vomiting

**Side-Effects, Further Information**

Paradoxical effects A paradoxical increase in hostility and aggression may be reported. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects. Increased hostility and aggression after barbiturates and alcohol usually indicates intoxication.

- **Pregnancy** Avoid regular use (risk of neonatal withdrawal symptoms); high doses during late pregnancy or labour may cause neonatal hypothermia, hypotonia, and respiratory depression.
- **Breast Feeding** Small amounts present in milk—avoid.
- **Hepatic Impairment** Reduce dose to 5 mg. Can precipitate coma. Avoid if severe impairment.
- **Renal Impairment** Use with caution.
- **Patient and Carer Advice** Drowsiness may persist the next day—leave at least 8 hours between taking zolpidem and performing skilled tasks (e.g. driving, or operating machinery); effects of alcohol and other CNS depressants enhanced.

**National Funding/Access Decisions**

- **NICE Technology Appraisals (TAs)**
  - Zaleplon, zolpidem, and zopiclone for the short-term management of insomnia (April 2004) NICE TA77
  - Zolpidem is recommended for the short-term management of severe insomnia that interferes with normal daily life, and should be prescribed for short periods of time only. www.nice.org.uk/TA77

**Medicinal Forms**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: powder

**Tablet**

**Cautionary and Advisory Labels 19**

- **Zolpidem Tartrate (Non-proprietary)**
  - Zolpidem tartrate 5 mg Zolpidem 5mg tablets | 28 tablet **PO** £3.08 DT price = £3.75 Schedule 4 (CD Benz)
  - Zolpidem tartrate 10 mg Zolpidem 10mg tablets | 28 tablet **PO** £4.48 DT price = £1.57 Schedule 4 (CD Benz)
  - Zolpidem tartrate 10 mg Stilnoct 10mg tablets | 28 tablet **PO** £1.00 DT price = £1.57 Schedule 4 (CD Benz)

**Zopiclone**

**Indications and Dose**

**Insomnia (short-term use)**

**By Mouth**

- Adult: 7.5 mg once daily for up to 4 weeks, dose to be taken at bedtime
- Elderly: Initially 3.75 mg once daily for up to 4 weeks, dose to be taken at bedtime, increased if necessary to 7.5 mg daily

**Insomnia (short-term use) in patients with chronic pulmonary insufficiency**

**By Mouth**

- Adult: Initially 3.75 mg once daily for up to 4 weeks, dose to be taken at bedtime, increased if necessary to 7.5 mg daily

- **Contra-Indications** Marked neuromuscular respiratory weakness • respiratory failure • severe sleep apnoea syndrome • unstable myasthenia gravis
- **Cautions** Avoid prolonged use (risk of tolerance and withdrawal symptoms) • chronic pulmonary insufficiency (increased risk of respiratory depression) • elderly • history of drug abuse • muscle weakness • myasthenia gravis (avoid if unstable) • psychiatric illness

**Interactions** Appendix (anxiolytics and hypnotics).

**Side-Effects**

- **Common or Very Common** Taste disturbance
Nervous system

Narcolepsy

7.2 Narcolepsy

Drugs used for Narcolepsy not listed below:
Dexamfetamine sulfate, p. 270 · Methylphenidate hydrochloride, p. 273

CNS STIMULANTS

Modafinil

INDICATIONS AND DOSE
Excessive sleepiness associated with narcolepsy with or without cataplexy

BY MOUTH
- Adult: Initially 200 mg daily in 2 divided doses, dose to be taken in the morning and at noon, alternatively initially 200 mg once daily, dose to be taken in the morning, adjusted according to response to 200–400 mg daily in 2 divided doses, alternatively adjusted according to response to 200–400 mg once daily
- Elderly: Initially 100 mg daily

- CONTRA-INDICATIONS Arhythmia · history of clinically significant signs of CNS stimulant-induced mitral valve prolapse (including ischaemic ECG changes, chest pain and arrhythmias) · history of cor pulmonale · history of left ventricular hypertrophy · moderate uncontrolled hypertension · severe uncontrolled hypertension

- CAUTIONS History of alcohol abuse · history of depression · history of drug abuse · history of mania · history of psychosis · possibility of dependence

- INTERACTIONS → Appendix 1 (modafinil).

- SIDE-EFFECTS
  - Common or very common Abdominal pain · anxiety · appetite changes · asthenia · chest pain · confusion · constipation · depression · diarrhoea · dizziness · drowsiness · dry mouth · dyspepsia · gastrointestinal disturbances · headache · nausea · palpitation · paraesthesia · sleep disturbances · tachycardia · vasodilatation · visual disturbances
  - Uncommon Abnormal dreams · acne · aggression · agitation · amnesia · arhythmia · arthralgia · bradycardia · decreased libido · dry eye · dyskinesia · dysphagia · dyspnoea · emotional lability · eosinophilia · epistaxis · flattulence · glossitis · hypercholesterolaemia · hyperglycaemia · hypertension · hypertonia · hypotension · leucopenia · menstrual disturbances · migraine · mouth ulcers · muscle cramps · myalgia · myasthenia · peripheral oedema · pruritis · rash · reflux · rhabdomyolysis · sinusitis · suicidal ideation · sweating · taste disturbance · thirst · tremor · urinary frequency · vomiting · weight changes

- Rare Hallucinations · mania · psychosis
  - Frequency not known Multi-organ hypersensitivity reaction · psychiatric symptoms · Stevens-Johnson syndrome · toxic epidermal necrolysis

SIDE-EFFECTS, FURTHER INFORMATION

Rash Discontinue treatment if rash develops.
Psychiatric symptoms Discontinue treatment if psychiatric symptoms develop.

- PREGNANCY Avoid.

- BREAST FEEDING Avoid—present in milk in animal studies.

- HEPATIC IMPAIRMENT Halve dose in severe impairment.

- RENAL IMPAIRMENT Use with caution—limited information available.

- PRE-TREATMENT SCREENING ECG required before initiation.

- MONITORING REQUIREMENTS Monitor blood pressure and heart rate in hypertensive patients.

- MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

Uncommon Dizziness · drowsiness · dry mouth · headache · nauasea · vomiting

Rare Amnesia · confusion · depression · hallucinations · nightmares

Very rare Incoordination · light headedness

Frequency not known Paradoxical effects · sleep-walking

SIDE-EFFECTS, FURTHER INFORMATION

Paradoxical effects A paradoxical increase in hostility and aggression may be reported. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects. Increased hostility and aggression after barbiturates and alcohol usually indicates intoxication.

PREGNANCY Not recommended (risk of neonatal withdrawal symptoms). Use during late pregnancy or labour may cause neonatal hypothermia, hypotonia, and respiratory depression.

BREAST FEEDING Present in milk—avoid.

HEPATIC IMPAIRMENT Reduce dose to 3.75 mg in mild to moderate impairment, dose can be increased with caution if necessary. Avoid in severe impairment—can precipitate encephalopathy.

RENAL IMPAIRMENT Start with reduced dose of 3.75 mg. Increased cerebral sensitivity.

PATIENT AND CARER ADVICE

Drowsiness may persist the next day and affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

NATIONAL FUNDING/ACCESS DECISIONS

PATIENT AND CARER ADVICE

HEPATIC IMPAIRMENT

Reduce dose to 3.75 mg in mild to moderate impairment, dose can be increased with caution if necessary. Avoid in severe impairment—can precipitate encephalopathy.

RENAL IMPAIRMENT

Start with reduced dose of 3.75 mg. Increased cerebral sensitivity.

NATIONAL FUNDING/ACCESS DECISIONS

PATIENT AND CARER ADVICE

Drowsiness may persist the next day and affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

Zaleplon, zolpidem and zopiclone for the short-term management of insomnia (April 2004) NICE TA77

Zopiclone is recommended for the short-term management of severe insomnia that interferes with normal daily life, and should be prescribed for short periods of time only. www.nice.org.uk/TA77

TABLET

CAUTIONARY AND ADVISORY LABELS 19, 25

> Zopiclone (Non-proprietary)

Zopiclone 3.75 mg Zopiclone 3.75mg tablets | 28 tablet | £2.50 DT price = £1.68 Schedule 4 (CD Benz)

Zopiclone 7.5 mg Zopiclone 7.5mg tablets | 28 tablet | £3.75 DT price = £1.67 Schedule 4 (CD Benz)

Zimovane (Sanofi)

Zopiclone 3.75 mg Zimovane LS 3.75mg tablets | 28 tablet | £2.24 DT price = £1.68 Schedule 4 (CD Benz)

Zopiclone 7.5 mg Zimovane 7.5mg tablets | 28 tablet | £3.26 DT price = £1.67 Schedule 4 (CD Benz)
## CNS DEPRESSANTS

### Sodium oxybate

- **Drug action**: A central nervous system depressant.

#### INDICATIONS AND DOSE

**Narcolepsy with cataplexy (under expert supervision)**

**By mouth**

- **Adult**: Initially 2.25 g daily, dose to be taken on retiring and 2.25 g after 2.5–4 hours, then increased in steps of 1.5 g daily in 2 divided doses; dose adjusted according to response at intervals of 1–2 weeks; dose titration should be repeated if restarting after interval of more than 14 days, maximum 9 g daily in 2 divided doses

- **Contra-indications**: Major depression · succinic semialdehyde dehydrogenase deficiency

- **Caution**: Body mass index of 40 kg/m² or greater (higher risk of sleep apnoea) · elderly · epilepsy · heart failure (high sodium content) · history of drug abuse · hypertension (high sodium content) · respiratory disorders · risk of discontinuation effects including rebound cataplexy and withdrawal symptoms

- **Interactions**: Appendix 1 (sodium oxybate). If sodium oxybate and sodium valproate or valproic acid used concomitantly, reduce initial dose of sodium oxybate to 1.8 g on retiring and repeat 2.5–4 hours later.

- **Side-effects**: Common or very common: Abdominal pain · anorexia · anxiety · arthralgia · asthma · back pain · blurred vision · confusion · depression · diarrhoea · disorientation · dizziness · drowsiness · dysphonia · headache · hypertension · hypoesthesia · impaired attention · muscle spasm · nasal congestion · nausea · nocturnal enuresis · palpitation · paraesthesia · peripheral oedema · rash · sleep disorders · sleep paralysis · sleep walking · sweating · taste disturbance · tremor · urinary incontinence · vertigo · vomiting

- **Uncommon**: Agitation · amnesia · faecal incontinence · hallucination · myoclonus · paraesthesia · psychosis · restless legs syndrome · suicidal behaviour

- **Frequency not known**: Dependence · euphoria · respiratory depression · seizures · sleep apnoea · suicidal ideation · urticaria

- **Pregnancy**: Avoid.

- **Breastfeeding**: No information available.

- **Hepatic impairment**: Halve initial dose.

- **Renal impairment**: Caution—contains 3.96 mmol Na⁺ per mL.

- **Directions for administration**: Dilute each dose with 60 mL water; prepare both doses before retiring. Observe the same time interval (2–3 hours) each night between the last meal and the first dose.

- **Patient and carer advice**: Leave at least 6 hours between taking sodium oxybate and performing skilled tasks (e.g. driving or operating machinery); effects of alcohol and other CNS depressants enhanced.

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### Substance dependence

Patients or carers should be given advice on how to administer sodium oxybate oral solution.

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

#### Oral solution

**CAUTIONARY AND ADVISORY LABELS**: 13, 19 **ELECTROLYTES**: May contain Sodium

- **Provigil** (Teva UK Ltd)

**Sodium oxybate 500 mg per 1 ml**

<table>
<thead>
<tr>
<th>Strength</th>
<th>BNF Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 mg/ml</td>
<td>2 (CD)</td>
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</tbody>
</table>

**DT price = £105.21**

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### 8 Substance dependence

**Substance dependence**


**Alcohol dependence**

Excessive drinking of alcoholic beverages over a prolonged period of time can result in an alcohol withdrawal syndrome on abrupt cessation of, or marked reduction in, drinking. The presence and severity of alcohol dependence can be assessed by The Severity of Alcohol Dependence Questionnaire (SADQ); other assessment questionnaires are also available.

**Acute alcohol withdrawal**

People with moderate dependence can generally be treated in a community setting unless they are under 18 years of age, or are at high-risk of severe reactions or treatment failure. People with severe dependence should undergo withdrawal in an inpatient setting; withdrawal in severely dependent patients without medical support may lead to seizures, delirium tremens, and death. Long-acting benzodiazepines, usually clomethiazole p. 267, are used to attenuate alcohol withdrawal symptoms. In primary care, fixed-dose reducing regimens are usually used, whilst a symptom-triggered flexible regimen is used in hospital or other settings where continued assessment and monitoring is carried out for 24–48 hours, usually followed by a fixed 5-day reducing dose schedule (sometimes it may be necessary to continue treatment for up to 10 days). Patients with uncomplicated liver disease should be treated under specialist supervision.

Carbamazepine p. 387 [unlicensed indication] is sometimes used as an alternative treatment in acute alcohol withdrawal when benzodiazepines are contra-indicated or not tolerated. Clomethiazole p. 421 is licensed for use in acute alcohol withdrawal, but benzodiazepines are preferred. It should only be used in an inpatient setting and should not be prescribed if the patient is liable to continue drinking alcohol.

Patients with marked agitation or hallucinations and those at risk of delirium tremens (characterised by delirium, hallucinations, tremor, and disorientation) may be prescribed antipsychotic drugs, such as haloperidol p. 306 or olanzapine p. 315 [unlicensed indication], as adjunctive therapy to benzodiazepines; antipsychotics should not be used alone because they do not treat alcohol withdrawal and may lower the seizure threshold. Delirium tremens is a medical emergency that requires specialist inpatient care.

If a patient taking a benzodiazepine as part of a withdrawal regimen develops alcohol withdrawal seizures, a fast-acting benzodiazepine (such as intravenous lorazepam p. 412 [unlicensed indication] or rectal diazepam p. 267) should be prescribed; thereafter an increase in the dose of
oral benzodiazepine should be considered to prevent further seizures from occurring.

**Alcohol dependence**

Acamprosate calcium p. 429 and naltrexone hydrochloride p. 430 are effective treatments for relapse prevention in patients with alcohol dependence; disulfiram p. 428 is an alternative. Disulfiram should only be used in patients in whom acamprosate calcium and naltrexone hydrochloride are not suitable, or if the patient prefers disulfiram. Nalmefene p. 429 is licensed for the reduction of alcohol consumption in patients with alcohol dependence who have a high drinking risk level, without physical withdrawal symptoms, and who do not require immediate detoxification.

Patients with alcohol dependence are at risk of developing Wernicke’s encephalopathy; patients at high-risk are those who are malnourished, at risk of malnourishment, or have decompensated liver disease. Parenteral thiamine p. 882 (as **Pabrinex**<sup>®</sup>) should be prescribed for treatment of suspected or confirmed Wernicke’s encephalopathy, and for prophylaxis in alcohol dependent patients attending hospital for acute treatment (including treatment unrelated to alcohol dependence); parenteral prophylaxis may also be considered for high-risk patients being treated in primary care. High-dose oral thiamine p. 882 should be prescribed following parenteral treatment until cognitive function is maximised. In primary care, prophylactic high-dose oral thiamine should be prescribed during acute withdrawal of alcohol, before planned withdrawal, and for patients not undergoing withdrawal but who are at high-risk of developing Wernicke’s encephalopathy.

Patients with chronic alcohol-related pancreatitis who have symptoms of steatorrhoea or who have poor nutritional status due to exocrine pancreatic insufficiency should be prescribed **pancreatic enzyme supplements**; supplements are not indicated when pain is the only symptom. **Corticosteroids** are used in patients with severe acute alcohol-related hepatitis.

**Drugs used in alcohol dependence**

**Acamprosate**

Acamprosate calcium p. 429, in combination with counselling, may be helpful for maintaining abstinence in alcohol-dependent patients. It is useful for patients who are concerned that strong cravings will result in relapse. It should be initiated as soon as possible after abstinence has been achieved and continued for 1 year; treatment should be maintained if the patient has a temporary relapse but stopped if the patient returns to regular or excessive drinking that persists 4–6 weeks after starting treatment. Acamprosate calcium p. 429 is not effective in all patients, so efficacy should be regularly assessed.

**Disulfiram**

Disulfiram p. 428 gives rise to an extremely unpleasant systemic reaction after the ingestion of even a small amount of alcohol because it causes accumulation of acetaldehyde in the body; it is only effective if taken daily. Symptoms can occur within 10 minutes of ingesting alcohol and include flushing of the face, throbbing headache, palpitation, tachycardia, nausea, vomiting, and, with large doses of alcohol, arrhythmias, hypotension, and collapse; these reactions can last several hours. Small amounts of alcohol such as those included in many oral medicines may be sufficient to precipitate a reaction—even toiletries and mouthwashes that contain alcohol should be avoided.

**Nalmefene**

Nalmefene p. 429 should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption. Nalmefene p. 429 is not recommended for patients aiming to achieve immediate abstinence.

**Naltrexone**

Naltrexone hydrochloride p. 430 is an opioid-receptor antagonist, but is useful as an adjunct in the treatment of alcohol dependence after a successful withdrawal. Treatment should be initiated by a specialist and continued under specialist supervision. Naltrexone hydrochloride p. 430 should be stopped if drinking continues for 4–6 weeks after starting treatment.

**Nicotine dependence**

Smoking cessation interventions are a cost-effective way of reducing ill health and prolonging life. Smokers should be advised to stop and offered help with follow-up when appropriate. If possible, smokers should have access to smoking cessation services for behavioural support. Therapy to aid smoking cessation is chosen according to the smoker’s likely adherence, availability of counselling and support, previous experience of smoking-cessation aids, contra-indications and adverse effects of the preparations, and the smoker’s preferences. **Nicotine replacement therapy**, bupropion hydrochloride p. 433, and varenicline p. 432 are effective aids to smoking cessation. The use of nicotine replacement therapy in an individual who is already accustomed to nicotine introduces few new risks and it is widely accepted that there are no circumstances in which it is safer to smoke than to use nicotine replacement therapy.

Some patients benefit from having more than one type of nicotine replacement therapy prescribed, such as a combination of transdermal and oral preparations. The combination of nicotine replacement therapy with varenicline or bupropion hydrochloride is not recommended.

**Concomitant medication**

Cigarette smoking increases the metabolism of some medicines by stimulating the hepatic enzyme CYP1A2. When smoking is discontinued, the dose of these drugs, in particular theophylline, cinacalcet, ropinirole, and some antipsychotics (including clozapine, olanzapine, chlorpromazine hydrochloride, and haloperidol), may need to be reduced. Regular monitoring for adverse effects is advised.

Bupropion hydrochloride p. 433 has been used as an antidepressant. Its mode of action in smoking cessation is not clear and may involve an effect on noradrenaline and dopamine neurotransmission.

**Nicotine replacement therapy**

Nicotine replacement therapy can be used in place of cigarettes after abrupt cessation of smoking, or alternatively to reduce the amount of cigarettes used in advance of making a quit attempt. Nicotine replacement therapy can also be used to minimise passive smoking, and to treat cravings and reduce compensatory smoking after enforced abstinence in smoke-free environments. Smokers who find it difficult to achieve abstinence should consult a healthcare professional for advice.

**Choice**

Nicotine patches are a prolonged-release formulation and are applied for 16 hours (with the patch removed overnight) or for 24 hours. If patients experience strong cravings for cigarettes on waking, a 24-hour patch may be more suitable. Immediate-release nicotine preparations (gum, lozenges, sublingual tablets, inhalator, nasal spray, and oral spray) are used whenever the urge to smoke occurs or to prevent cravings.

The choice of nicotine replacement preparation depends largely on patient preference, and should take into account what preparations, if any, have been tried before. Patients with a high level of nicotine dependence, or who have failed with nicotine replacement therapy previously, may benefit from nicotine replacement therapy prescribed for treatment of suspected Wernicke’s encephalopathy; patients at high-risk are those who are malnourished, at risk of malnourishment, or have decompensated liver disease. Parenteral thiamine p. 882 (as **Pabrinex**<sup>®</sup>) should be prescribed for treatment of suspected or confirmed Wernicke’s encephalopathy, and for prophylaxis in alcohol dependent patients attending hospital for acute treatment (including treatment unrelated to alcohol dependence); parenteral prophylaxis may also be considered for high-risk patients being treated in primary care. High-dose oral thiamine p. 882 should be prescribed following parenteral treatment until cognitive function is maximised. In primary care, prophylactic high-dose oral thiamine should be prescribed during acute withdrawal of alcohol, before planned withdrawal, and for patients not undergoing withdrawal but who are at high-risk of developing Wernicke’s encephalopathy.

Patients with chronic alcohol-related pancreatitis who have symptoms of steatorrhoea or who have poor nutritional status due to exocrine pancreatic insufficiency should be prescribed **pancreatic enzyme supplements**; supplements are not indicated when pain is the only symptom. **Corticosteroids** are used in patients with severe acute alcohol-related hepatitis.

**Drugs used in alcohol dependence**

**Acamprosate**

Acamprosate calcium p. 429, in combination with counselling, may be helpful for maintaining abstinence in alcohol-dependent patients. It is useful for patients who are concerned that strong cravings will result in relapse. It should be initiated as soon as possible after abstinence has been achieved and continued for 1 year; treatment should be maintained if the patient has a temporary relapse but stopped if the patient returns to regular or excessive drinking that persists 4–6 weeks after starting treatment. Acamprosate calcium p. 429 is not effective in all patients, so efficacy should be regularly assessed.

**Disulfiram**

Disulfiram p. 428 gives rise to an extremely unpleasant systemic reaction after the ingestion of even a small amount of alcohol because it causes accumulation of acetaldehyde in the body; it is only effective if taken daily. Symptoms can occur within 10 minutes of ingesting alcohol and include flushing of the face, throbbing headache, palpitation, tachycardia, nausea, vomiting, and, with large doses of alcohol, arrhythmias, hypotension, and collapse; these reactions can last several hours. Small amounts of alcohol such as those included in many oral medicines may be sufficient to precipitate a reaction—even toiletries and mouthwashes that contain alcohol should be avoided.

**Nalmefene**

Nalmefene p. 429 should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption. Nalmefene p. 429 is not recommended for patients aiming to achieve immediate abstinence.
from using a combination of an immediate-release preparation and patches to achieve abstinence.

**Side-effects of specific nicotine preparations**

Mild local reactions at the beginning of treatment are common because of the irritant effect of nicotine. Oral preparations and inhalation cartridges can cause irritation of the throat, gum, lozenges, and oral spray can cause increased salivation, and patches can cause minor skin irritation. The nasal spray commonly causes coughing, nasal irritation, epistaxis, sneezing, and watery eyes; the oral spray can cause watery eyes and blurred vision.

Gastro-intestinal disturbances are common and may be caused by swallowed nicotine. Nausea, vomiting, dyspepsia, and hiccup occur most frequently. Ulcerative stomatitis has also been reported. Dry mouth is a common side-effect of lozenges, patches, oral spray, and sublingual tablets. Lozenges cause diarrhoea, constipation, dysphagia, oesophagitis, gastritis, mouth ulcers, bloating, flatulence, and less commonly, taste disturbance, thirst, gingival bleeding, and halitosis. The oral spray may also cause abdominal pain, flatulence, and taste disturbance.

Palpitations may occur with nicotine replacement therapy and rarely patches and oral spray can cause arrhythmia. Patch, lozenges, and oral spray can cause chest pain. The inhalator can very rarely cause reversible atrial fibrillation.

Parasthesia is a common side-effect of oral spray. Abnormal dreams can occur with patches; removal of the patch before bed may help. Lozenges and oral spray may cause rash and hot flushes. Sweating and myalgia can occur with patches and oral spray; the patches can also cause arthralgia.

**Opioid dependence**

The management of opioid dependence requires medical, social, and psychological treatment; access to a multidisciplinary team is recommended. Treatment for opioid dependence should be initiated under the supervision of an appropriately qualified prescriber. Untreated heroin dependence shows early withdrawal symptoms within 8 hours, with peak symptoms at 36–72 hours; symptoms subside substantially after 5 days. Methadone hydrochloride p. 436 or buprenorphine p. 434 withdrawal occurs later, with longer-lasting symptoms.

**Opioid substitution therapy**

Methadone hydrochloride and buprenorphine are used as substitution therapy in opioid dependence. Substitute medication should be commenced with a short period of stabilisation, followed by either a withdrawal regimen or by maintenance treatment. Maintenance treatment enables patients to achieve stability, reduces drug use and crime, and improves health; it should be regularly reviewed to ensure the patient continues to derive benefit. The prescriber should monitor for signs of toxicity, and the patient should be told to be aware of warning signs of toxicity on initiation and during titration.

A withdrawal regimen after stabilisation with methadone hydrochloride or buprenorphine should be attempted only after careful consideration. Enforced withdrawal is ineffective for sustained abstinence, and it increases the risk of patients relapsing and subsequently overdosing because of loss of tolerance. Complete withdrawal from opioids usually takes up to 4 weeks in an inpatient or residential setting, and up to 12 weeks in a community setting. If abstinence is not achieved, illicit drug use is resumed, or the patient cannot tolerate withdrawal, the withdrawal regimen should be stopped and maintenance therapy should be resumed at the optimal dose. Following successful withdrawal treatment, further support and monitoring to maintain abstinence should be provided for a period of at least 6 months.

**Missed doses**

Patients who miss 3 days or more of their regular prescribed dose of opioid maintenance therapy are at risk of overdose because of loss of tolerance. Consider reducing the dose in these patients.

If the patient misses 5 or more days of treatment, an assessment of illicit drug use is also recommended before restarting substitution therapy; this is particularly important for patients taking buprenorphine p. 434 because of the risk of precipitated withdrawal.

**Buprenorphine**

Buprenorphine p. 434 is preferred by some patients because it is less sedating than methadone hydrochloride p. 436; for this reason it may be more suitable for employed patients or those undertaking other skilled tasks such as driving. Buprenorphine is safer than methadone hydrochloride when used in conjunction with other sedating drugs, and has fewer drug interactions. Dose reductions may be easier than with methadone hydrochloride because the withdrawal symptoms are milder, and patients generally require fewer adjunctive medications; there is also a lower risk of overdose. Buprenorphine can be given on alternate days in higher doses and it requires a shorter drug-free period than methadone hydrochloride before induction with naloxone hydrochloride p. 430 for prevention of relapse.

Patients dependent on high doses of opioids may be at increased risk of precipitated withdrawal. Precipitated withdrawal can occur in any patient if buprenorphine is administered when other opioid agonist drugs are in circulation. Precipitated opioid withdrawal, if it occurs, starts within 1–3 hours of the first buprenorphine dose and peaks at around 6 hours. Non-opioid adjunctive therapy, such as lofexidine hydrochloride, may be required if symptoms are severe.

To reduce the risk of precipitated withdrawal, the first dose of buprenorphine should be given when the patient is exhibiting signs of withdrawal, or 6–12 hours after the last use of heroin (or other short-acting opioid), or 24–48 hours after the last dose of methadone hydrochloride. It is possible to titrate the dose of buprenorphine within one week—more rapidly than with methadone hydrochloride therapy—but care is still needed to avoid toxicity or precipitated withdrawal; dividing the dose on the first day may be useful.

A combination preparation containing buprenorphine with naloxone p. 436 (Suboxone®) can be prescribed for patients when there is a risk of dose diversion for parenteral administration; the naloxone hydrochloride p. 1133 component precipitates withdrawal if the preparation is injected, but it has little effect when the preparation is taken sublingually.

**Methadone**

Methadone hydrochloride p. 436, a long-acting opioid agonist, is usually administered in a single daily dose as methadone hydrochloride oral solution 1 mg/mL. Patients with a long history of opioid misuse, those who typically abuse a variety of sedative drugs and alcohol, and those who experience increased anxiety during withdrawal of opioids may prefer methadone hydrochloride to buprenorphine because it has a more pronounced sedative effect.

Methadone hydrochloride is initiated at least 8 hours after the last heroin dose, provided that there is objective evidence of withdrawal symptoms. A supplementary dose on the first day may be considered if there is evidence of persistent opioid withdrawal symptoms. Because of the long half-life, plasma concentrations progressively rise during initial treatment even if the patient remains on the same daily dose (it takes 3–10 days for plasma concentrations to reach steady-state in patients on a stable dose); a dose tolerated on the first day of treatment may become a toxic dose on the third day as cumulative toxicity develops. Thus,
titation to the optimal dose in methadone hydrochloride maintenance treatment may take several weeks.

**Opioid substitution during pregnancy**

Acute withdrawal of opioids should be avoided in pregnancy because it can cause fetal death. Opioid substitution therapy is recommended during pregnancy because it carries a lower risk to the fetus than continued use of illicit drugs. If a woman who is stabilised on methadone hydrochloride or buprenorphine for treatment of opioid dependence becomes pregnant, therapy should be continued [buprenorphine is not licensed for use in pregnancy]. Many pregnant patients choose a withdrawal regimen, but withdrawal during the first trimester should be avoided because it is associated with an increased risk of spontaneous miscarriage. Withdrawal of methadone hydrochloride or buprenorphine should be undertaken gradually during the second trimester, with dose reductions made every 3–5 days. If illicit drug use occurs, the patient should be re-stabilised at the optimal maintenance dose and consideration should be given to stopping the withdrawal regimen.

Further withdrawal of methadone hydrochloride or buprenorphine in the third trimester is not recommended because maternal withdrawal, even if mild, is associated with fetal distress, stillbirth, and the risk of neonatal mortality. Drug metabolism can be increased in the third trimester; it may be necessary to either increase the dose of methadone hydrochloride or change to twice-daily consumption (or a combination of both strategies) to prevent withdrawal symptoms from developing.

The neonate should be monitored for respiratory depression and signs of withdrawal if the mother is prescribed high doses of opioid substitute. Signs of neonatal withdrawal from opioids usually develop 24–72 hours after delivery but symptoms may be delayed for up to 14 days, so monitoring may be required for several weeks. Symptoms include a high-pitched cry, rapid breathing, hungry but ineffective sucking, and excessive wakefulness; severe, but rare symptoms include hypertonicity and convulsions.

**Opioid substitution during breastfeeding**

Doses of methadone and buprenorphine should be kept as low as possible in breast-feeding mothers. Increased sleepiness, breathing difficulties, or limpness in breast-fed babies of mothers taking opioid substitutes should be reported urgently to a healthcare professional.

**Adjunctive therapy and symptomatic treatment**

Adjunctive therapy may be required for the management of opioid withdrawal symptoms. Loperamide hydrochloride p. 56 may be used for the control of diarrhoea; mebeverine hydrochloride p. 75 for controlling stomach cramps; paracetamol p. 354 and non-steroidal anti-inflammatory drugs for muscular pains and headaches; metoclopramide hydrochloride p. 347 or prochlorperazine p. 309 may be useful for nausea or vomiting. Topical rubefacients can be helpful for relieving muscle pain associated with methadone hydrochloride p. 436 withdrawal. If a patient is suffering from insomnia, short-acting benzodiazepines or zopiclone p. 423 may be prescribed, but because of the potential for abuse, prescriptions should be limited to a short course of a few days only. If anxiety or agitation is severe, specialist advice should be sought.

**Lofexidine**

Lofexidine hydrochloride p. 434 may alleviate some of the physical symptoms of opioid withdrawal by attenuating the increase in adrenergic neurotransmission that occurs during opioid withdrawal. Lofexidine hydrochloride can be prescribed as an adjuvant to opioid substitution therapy, initiated either at the same time as the opioid substitute or during withdrawal of the opioid substitute. Alternatively, lofexidine hydrochloride may be prescribed instead of an opioid substitute in patients who have mild or uncertain dependence (including young people), and those with a short history of illicit drug use.

**Opioid-receptor antagonists**

Patients dependant on opioids can be given a supply of naloxone hydrochloride p. 1133 to be used in case of accidental overdose. Naltrexone hydrochloride p. 430 precipitates withdrawal symptoms in opioid-dependent subjects. Because the effects of opioid-receptor agonists are blocked by naltrexone hydrochloride, it is prescribed as an aid to prevent relapse in formerly opioid-dependent patients.

**Opioid dependence in children**

In younger patients (under 18 years), the harmful effects of drug misuse are more often related to acute intoxication than to dependence, so substitution therapy is usually inappropriate. Maintenance treatment with opioid substitution therapy is therefore controversial in young people; however, it may be useful for the older adolescent who has a history of opioid use to undergo a period of stabilisation with buprenorphine or methadone hydrochloride before starting a withdrawal regimen.

### 8.1 Alcohol dependence

#### ALDEHYDE DEHYDROGENASE INHIBITORS

**Disulfiram**

**INDICATIONS AND DOSE**

Adjunct in the treatment of alcohol dependence (under expert supervision)

**BY MOUTH**

- Adult: 200 mg daily, increased if necessary up to max. 500 mg daily

- **UNLICENSED USE** Disulfiram doses in BNF may differ from those in product literature.
- **CONTRA-INDICATIONS** Cardiac failure - coronary artery disease - history of cerebrovascular accident - hypertension - psychosis - severe personality disorder - suicide risk
- **CAUTIONS** Alcohol challenge not recommended on routine basis (if considered essential—specialist units only with resuscitation facilities) - avoid in Acute porphyrias p. 864 - diabetes mellitus - epilepsy - respiratory disease
- **INTERACTIONS** Appendix 1 (disulfiram).

Disulfiram gives rise to an extremely unpleasant systemic reaction after the ingestion of even a small amount of alcohol. Ensure that alcohol is not consumed for at least 24 hours before initiating treatment and should be avoided for at least 1 week after stopping treatment.

- **SIDE-EFFECTS**
  - Common or very common Drowsiness - fatigue - halitosis - nausea - reduced libido - vomiting
  - Rare Allergic dermatitis - depression - hepatic cell damage - mania - paranoia - peripheral neuritis - psychotic reactions - schizophrenia
- **PREGNANCY** High concentrations of acetaldehyde which occur in presence of alcohol may be teratogenic; avoid in first trimester.
- **BREAST FEEDING** Avoid—no information available.
- **HEPATIC IMPAIRMENT** Use with caution.
- **RENA L IMPAIRMENT** Use with caution.
PRE-TREATMENT SCREENING  Before initiating disulfiram, prescribers should evaluate the patient’s suitability for treatment, because some patient factors, for example memory impairment or social circumstances, make compliance to treatment or abstinence from alcohol difficult.

MONITORING REQUIREMENTS  During treatment with disulfiram, patients should be monitored at least every 2 weeks for the first 2 months, then each month for the following 4 months, and at least every 6 months thereafter.

PATIENT AND CARER ADVICE  Patient counselling is advised (alcohol reaction).

MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug.

Table

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS 2</th>
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<tr>
<td>Antabuse (Actavis UK Ltd)</td>
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Disulfiram 200 mg Antabuse 200mg tablets | 50 tablet | P (DT price = £31.00

GAMMA-AMINOBUTYRIC ACID ANALOGUES AND DERIVATIVES

Acamprosate calcium

INDICATIONS AND DOSE

Maintenance of abstinence in alcohol-dependent patients

BY MOUTH

- Adult 18–65 years (body-weight up to 60 kg): 666 mg once daily, dose to be taken with breakfast and 333 mg twice daily, dose to be taken at midday and at night
- Adult 18–65 years (body-weight 60 kg and above): 666 mg 3 times a day

CAUTIONS  Continued alcohol abuse (risk of treatment failure)

SIDE-EFFECTS

- Common or very common  Abdominal pain · diarrhoea · fluctuation in libido · maculopapular rash · nausea · pruritus · vomiting
- Rare  Bullous skin reactions
- PREGNANCY  Avoid.
- BREAST FEEDING  Avoid.
- HEPATIC IMPAIRMENT  Avoid if severe.
- RENAL IMPAIRMENT  Avoid if serum-creatinine greater than 120 micromol/litre.
- PRESCRIBING AND DISPENSING INFORMATION

Acamprosate sodium has been used for the maintenance of abstinence in alcohol dependence in children aged 16 years and over [unlicensed].

MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug.

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<th>CAUTIONARY AND ADVISORY LABELS 2</th>
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<tr>
<td>Gastro-resistant tablet</td>
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Disulfiram, patients should be monitored at least every 21, 25

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<tr>
<th>ELECTROLYTES: May contain Calcium</th>
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<tr>
<td>Campral EC (Merck Serono Ltd)</td>
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Acamprosate calcium 333 mg Campral EC 333mg tablets | 168 tablet | P (DT price = £28.80

PRESCRIPTIONS

CONTRA-INDICATIONS  Recent history of acute alcohol withdrawal syndrome · recent or current opioid use

CAUTIONS  Continued treatment for more than 1 year · history of seizure disorders (including alcohol withdrawal seizures) · psychiatric illness

INTERACTIONS  Appendix 1 (nalmefene). Avoid concomitant use of opioids—discontinue treatment 1 week before anticipated use of opioids; if emergency analgesia is required during treatment, an increased dose of opioid analgesic may be necessary (monitor for opioid intoxication).

SIDE-EFFECTS

- Common or very common  Confusion · decreased appetite · decreased libido · disturbance in attention · dizziness · dry mouth · headache · hyperhidrosis · hypoaesthesia · malaise · muscle spasms · nausea · palpitation · paraesthesia · restlessness · sleep disorders · somnolence · tachycardia · tremor · vomiting · weight loss
- Frequency not known  Dissociation · hallucinations

PREGNANCY  Manufacturer advises avoid—toxicity in animal studies.

BREAST FEEDING  Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT  Use with caution—avoid in severe impairment.

RENAI IMPAIRMENT  Use with caution—avoid in severe impairment.

PRE-TREATMENT SCREENING  Before initiating treatment, prescribers should evaluate the patient’s clinical status, alcohol dependence, and level of alcohol consumption. Nalmefene should only be prescribed for patients who continue to have a high drinking risk level two weeks after the initial assessment.

MONITORING REQUIREMENTS  During treatment, patients should be monitored regularly and the need for continued treatment assessed.

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

- Nalmefene for reducing alcohol consumption in people with alcohol dependence (November 2014) NICE TA325

Nalmefene is recommended within its marketing authorisation, as an option for reducing alcohol consumption, for patients with alcohol dependence:

- who have a high drinking risk level (defined as alcohol consumption of more than 60 g per day for men and more than 40 g per day for women, according to the World Health Organization’s drinking risk levels) without physical withdrawal symptoms, and
- who do not require immediate detoxification.

The marketing authorisation states that nalmefene should:
Naltrexone hydrochloride

**INDICATIONS AND DOSE**

Adjunct to prevent relapse in formerly opioid-dependent patients (who have remained opioid-free for at least 7-10 days) (initiated under specialist supervision)

**BY MOUTH**
- Adult: Initially 25 mg daily, then increased to 50 mg daily, total weekly dose may be divided and given on 3 days of the week for improved compliance (e.g. 100 mg on Monday and Wednesday, and 150 mg on Friday); maximum 350 mg per week

Adjunct to prevent relapse in formerly alcohol-dependent patients (initiated under specialist supervision)

**INDICATIONS AND DOSE**

**BY MOUTH**
- Adult: 25 mg once daily on the first day, then increased if tolerated to 50 mg daily

**UNLICENSED USE**

Unlicensed for use in children under 18 years. 25 mg dose for adjunct to prevent relapse in formerly alcohol-dependent patients is an unlicensed dose.

**CONTRA-INDICATIONS**

Patients currently dependent on opioids

**INTERACTIONS**

Avoid concomitant use of opioids but increased dose of opioid analgesic may be required for pain (monitor for opioid intoxication).

**SIDE-EFFECTS**
- Common or very common: joint and muscle pain, abdominal pain, anxiety, chest pain, chills, constipation, decreased potency, delayed ejaculation, diarrhoea, dizziness, headache, increased energy, increased lacrimation, increased sweating, increased thirst, irritability, mood swings, nausea, rash, reduced appetite, sleep disorders, urinary retention, vomiting
- Rare: Depression, hepatic dysfunction, speech disorders, suicidal ideation, tinnitus
- Very rare: Exanthema, hallucinations, idiopathic thrombocytopenia, tremor

**PREGNANCY**

Use only if benefit outweighs risk.

**BREAST FEEDING**

Avoid—potential toxicity.

**HEPATIC IMPAIRMENT**

Avoid in acute hepatitis, hepatic failure, or severe impairment.

**RENAL IMPAIRMENT**

Avoid in severe impairment.

**PRE-TREATMENT SCREENING**

Test for opioid dependence with naloxone before treatment.

**MONITORING REQUIREMENTS**

Liver function tests needed before and during treatment.

**PATIENT AND CARER ADVICE**

Patients should be warned that an attempt to overcome the blockade of opioid receptors by overdosing could result in acute opioid intoxication.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**
- Naltrexone for the management of opioid dependence (January 2007) NICE TA115

Naltrexone is recommended for the prevention of relapse in formerly opioid-dependent patients who are motivated to remain in a supportive care abstinence programme. Naltrexone should be administered under supervision and its effectiveness in preventing opioid misuse reviewed regularly. www.nice.org.uk/TA115

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension, capsule

**Tablet**
- SELINCRON (Lundbeck Ltd)
  - Nalmefene (as Nalmefene hydrochloride) 18 mg tablets | 14 tablet | £42.42 DT price = £42.42 | 28 tablet | £84.84

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**Nicotine**

**INDICATIONS AND DOSE**

Nicotine replacement therapy in individuals who smoke fewer than 20 cigarettes each day

**BY MOUTH USING CHEWING GUM**
- Adult: 2 mg as required, chew 1 piece of gum when the urge to smoke occurs or to prevent cravings, if attempting smoking cessation, treatment should continue for 3 months before reducing the dose

**BY SUBLINGUAL ADMINISTRATION USING SUBLINGUAL TABLETS**
- Adult: 1 tablet every 1 hour, increased to 2 tablets every 1 hour if required, if attempting smoking cessation, treatment should continue for up to 3 months before reducing the dose; maximum 40 tablets per day

Nicotine replacement therapy in individuals who smoke more than 20 cigarettes each day or who require more than 15 pieces of 2-mg strength gum each day

**BY MOUTH USING CHEWING GUM**
- Adult: 4 mg as required, chew 1 piece of gum when the urge to smoke occurs or to prevent cravings, patients should not exceed 15 pieces of 4-mg strength gum daily, if attempting smoking cessation, treatment should continue for 3 months before reducing the dose

Nicotine replacement therapy in individuals who smoke more than 20 cigarettes each day

**BY SUBLINGUAL ADMINISTRATION USING SUBLINGUAL TABLETS**
- Adult: 2 tablets every 1 hour, if attempting smoking cessation, treatment should continue for up to 3 months before reducing the dose; maximum 40 tablets per day

Nicotine replacement therapy

**BY INHALATION USING INHALATOR**
- Adult: As required, the cartridges can be used when the urge to smoke occurs or to prevent cravings, patients should not exceed 12 cartridges of the 10-mg
Nicotine dependence

When used by inhalation bronchospastic disease - chronic throat disease - obstructive lung disease

CAUTIONS, FURTHER INFORMATION
Most warnings for nicotine replacement therapy also apply to continued cigarette smoking, but the risk of continued smoking outweighs any risks of using nicotine preparations.

Specific cautions for individual preparations are usually related to the local effect of nicotine.

INTERACTIONS → Appendix 1 (nicotine).

SIDE-EFFECTS
- Common or very common Bloating - blurred vision - constipation - coughing - diarrhoea - dry mouth - dyspepsia - dysphagia - epistaxis - flatulence - gastritis - gastrointestinal disturbances (may be caused by swallowed nicotine) - hiccup - increased salivation - irritation of the throat - mild local reactions at the beginning of treatment are common because of the irritant effect of nicotine.
- Minor skin irritation - mouth ulcers - nasal irritation - nausea - oesophagitis - paraesthesia - sneezing - vomiting - watery eyes
- Uncommon Gingival bleeding - halitosis - thirst
- Rare Arrhythmia
- Very rare Reversible atrial fibrillation
- Frequency not known Abdominal pain - abnormal dreams (may occur with patches, removal of the patch before bed may help) - arthralgia - chest pain - flatulence - hot flushes - myalgia - palpitations - rash - sweating - taste disturbance - ulcerative stomatitis

SIDE-EFFECTS, FURTHER INFORMATION
Side-effects listed have been reported with use of various nicotine replacement therapy preparations. See Substance dependence p. 425. Nicotine replacement therapy for specific side-effects of individual preparations.

Nicotine withdrawal Some systemic effects occur on initiation of therapy, particularly if the patient is using high-strength preparations; however, the patient may confuse side-effects of the nicotine-replacement preparation with nicotine withdrawal symptoms.

Common symptoms of nicotine withdrawal include malaise, headache, dizziness, sleep disturbance, coughing, influenza-like symptoms, depression, irritability, increased appetite, weight gain, restlessness, anxiety, drowsiness, aphthous ulcers, decreased heart rate, and impaired concentration.

PREGNANCY The use of nicotine replacement therapy in pregnancy is preferable to the continuation of smoking, but should be used only if smoking cessation without nicotine replacement fails. Intermittent therapy is preferable to patches but avoid liquorice-flavoured nicotine products. Patches are useful, however, if the patient is experiencing pregnancy-related nausea and vomiting. If patches are used, they should be removed before bed.

BREAST FEEDING Nicotine is present in milk; however, the amount to which the infant is exposed is small and less hazardous than second-hand smoke. Intermittent therapy is preferred.

HEPATIC IMPAIRMENT Use with caution in moderate to severe hepatic impairment.

RENAL IMPAIRMENT Use with caution in severe renal impairment.

DIRECTIONS FOR ADMINISTRATION Acidic beverages, such as coffee or fruit juice, may decrease the absorption of nicotine through the buccal mucosa and should be avoided for 15 minutes before the use of oral nicotine replacement therapy.

Administration by transdermal patch Patches should be applied on waking to dry, non-hairy skin on the hip, trunk, or upper arm and held in position for 10–20 seconds to ensure
adhesion; place next patch on a different area and avoid using the same site for several days.
Administration by nasal spray Initially 1 spray should be used in both nostrils but when withdrawing from therapy, the dose can be gradually reduced to 1 spray in 1 nostril.
Administration by oral spray The oral spray should be released into the mouth, holding the spray as close to the mouth as possible and avoiding the lips. The patient should not inhale while spraying and avoid swallowing for a few seconds after use. If using the oral spray for the first time, or if unit not used for 2 or more days, prime the unit before administration.
Administration by sublingual tablet Each tablet should be placed under the tongue and allowed to dissolve. Administration by lozenge Slowly allow each lozenge to dissolve in the mouth; periodically move the lozenge from one side of the mouth to the other. Lozenges last for 10–30 minutes, depending on their size.

Administration by inhalation Insert the cartridge into the device and draw in air through the mouthpiece; each session can last for approximately 5 minutes. The amount of nicotine from 1 puff of the cartridge is less than that from a cigarette, therefore it is necessary to inhale more often than when smoking a cigarette. A single 10 mg cartridge lasts for approximately 20 minutes of intense use; a single 15 mg cartridge lasts for approximately 40 minutes of intense use. Administration by medicated chewing gum Chew the gum until the taste becomes strong, then rest it between the cheek and gum; when the taste starts to fade, repeat this process. One piece of gum lasts for approximately 30 minutes.

PRESCRIBING AND DISPENSING INFORMATION Flavours of chewing gum and lozenges may include mint, freshfruit, freshmint, icy white, or cherry.

PATIENT AND CARER ADVICE Patient or carers should be given advice on how to administer nicotine chewing gum, inhalators, lozenges, sublingual tablets, oral spray, nasal spray and patches.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Sublingual tablet

CAUTIONARY AND ADvisory LAbELS 26

Nicorette (McNeil Products Ltd) Nicorette Microtab 2mg sublingual tablets (sugar-free) 100 tablet GSK £13.12 DT price = £13.12

Orodispersible film

NiQuitin (GlaxoSmithKline Consumer Healthcare) Nicotine 2.5 mg NiQuitin Strips Mint 2.5mg oral films (sugar-free) 15 film GSK £3.51 (sugar-free) 60 film GSK £10.85

Lozenge

EXCIPiENTS: May contain Aspartame
ELECTROLYTES: May contain Sodium

NiQuitin (GlaxoSmithKline Consumer Healthcare) Nicotine 1.5 mg NiQuitin Minis Mint 1.5mg lozenges (sugar-free) 20 lozenge GSK £3.50 (sugar-free) 60 lozenge GSK £9.56 DT price = £8.93

NiQuitin Minis Cherry 1.5mg lozenges (sugar-free) 20 lozenge GSK £3.18 (sugar-free) 60 lozenge GSK £8.93 DT price = £8.93

NiQuitin Minis Orange 1.5mg lozenges (sugar-free) 20 lozenge GSK £3.18 (sugar-free) 60 lozenge GSK £8.93 DT price = £8.93

Nicotine 2 mg NiQuitin Mint 2mg lozenges (sugar-free) 36 lozenge GSK £5.12 (sugar-free) 72 lozenge GSK £9.97 DT price = £9.97

Nicotine 4 mg NiQuitin Mint 4mg lozenges (sugar-free) 36 lozenge GSK £5.12 (sugar-free) 72 lozenge GSK £9.97 DT price = £9.97

NiQuitin Minis Mint 4mg lozenges (sugar-free) 20 lozenge GSK £3.50 (sugar-free) 60 lozenge GSK £9.56

NiQuitin Pre-Quit Mint 4mg lozenges (sugar-free) 36 lozenge GSK £5.12

NiQuitin 4mg lozenges original menthol mint (sugar-free) 36 lozenge GSK £5.12 (sugar-free) 72 lozenge GSK £9.97 DT price = £9.97

Nicorette (McNeil Products Ltd) Nicotine 2 mg Nicorette Cools 2mg lozenges (sugar-free) 20 lozenge GSK £3.18 (sugar-free) 80 lozenge GSK £11.48

Nicotine 4 mg Nicorette Cools 4mg lozenges (sugar-free) 36 lozenge GSK £11.48

Nicotinell (Novartis Consumer Health UK Ltd) Nicotine (as Nicotine bitartrate) 1 mg Nicotinell 1mg lozenges (sugar-free) 12 lozenge GSK £1.59 (sugar-free) 36 lozenge GSK £4.27 (sugar-free) 72 lozenge GSK £8.03 (sugar-free) 96 lozenge GSK £9.12 DT price = £9.12 (sugar-free) 144 lozenge GSK £13.59

Nicotine (as Nicotine bitartrate) 2 mg Nicotinell 2mg lozenges (sugar-free) 36 lozenge GSK £4.95 (sugar-free) 72 lozenge GSK £9.41 (sugar-free) 96 lozenge GSK £10.60 (sugar-free) 144 lozenge GSK £15.88

Medicated chewing-gum

NICOTINE (Non-proprietary)

Nicotine 2 mg Boots NicAssist Minty Fresh 2mg medicated chewing gum (sugar-free) 30 piece GSK no price available (sugar-free) 105 piece GSK no price available (sugar-free)

Nicotine 4 mg Boots NicAssist Minty Fresh 4mg medicated chewing gum (sugar-free) 105 piece GSK no price available (sugar-free)

Brands may include NiQuitin, Nicorette, Nicorette Icy White, Nicotinell

Inhalation vapour

Nicorette (McNeil Products Ltd)

Nicotine 15 mg Nicorette 15mg inhalator 4 cartridge GSK £4.27 DT price = £4.27 20 cartridge GSK £15.11 DT price = £15.11 36 cartridge GSK £24.03 DT price = £24.03

Transdermal patch

NICOTINE (Non-proprietary)

Nicotine 5 mg per 16 hour Boots NicAssist 5mg patches 7 patch GSK no price available

Nicotine 7 mg per 24 hour Nicotine 7mg/24hours transdermal patches 7 patch GSK no price available

Nicotine 10 mg per 16 hour Boots NicAssist 10mg patches 7 patch GSK no price available DT price = £10.37

Nicotine 15 mg per 16 hour Boots NicAssist 15mg patches 7 patch GSK no price available DT price = £10.37

Brands may include NiQuitin, Nicorette Clear, Nicorette Invisi, Nicotinell TTS

Spray

EXCIPiENTS: May contain Ethanol

Nicorette (McNeil Products Ltd)

Nicotine 500 microgram per 1 actuation Nicorette 500micrograms/dose nasal spray 10 ml GSK £13.80 DT price = £13.80

Nicorette QuickMist (McNeil Products Ltd)

Nicotine 1 mg per 1 actuation Nicorette QuickMist 1mg/dose mouthspray (sugar-free) 13.2 ml GSK £12.12 DT price = £12.12 (sugar-free) 26.4 ml GSK £13.14

Varenicline

DRUG ACTION Varenicline is a selective nicotine-receptor partial agonist.

INDICATIONS AND DOSE

To aid smoking cessation

BY MOUTH

Adult: Initially 500 micrograms once daily for 3 days, increased to 500 micrograms twice daily for 4 days, then 1 mg twice daily for 11 weeks; reduced if not tolerated to 500 micrograms twice daily, usually to be started 1–2 weeks before target stop date but can be started up to a maximum of 5 weeks before target stop date, 12-week course can be repeated in abstinent individuals to reduce risk of relapse

Important safety information

MHRA/CHM ADVICE: SUICIDAL BEHAVIOUR AND VARENICLINE

Patients should be advised to discontinue treatment and seek prompt medical advice if they develop agitation,
Medicinal forms

Varenicline for smoking cessation (July 2011 NICE)

- National funding/access decisions
  
  - NICE technology appraisals (TAs)
    
    Varenicline for smoking cessation (July 2007) NICE TAI23
    
    Varenicline is recommended, within its licensed indications, as an option for smokers who have expressed a desire to quit smoking; it should normally be prescribed only as part of a programme of behavioural support. www.nice.org.uk/TAI23

- Medicinal forms
  
  There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**
  
  **CAUTIONARY AND ADVISORY LABELS 3**
  
  > Champix (Pfizer Ltd) ▼
  
  Varenicline (as Varenicline tartrate) 500 microgram
  
  Champix 0.5mg tablets | 11 tablet pack no price available | 56 tablet pack £54.60 DT price = £54.60
  
  Varenicline (as Varenicline tartrate) 1 mg
  
  Champix 1mg tablets | 14 tablet pack no price available | 28 tablet pack £27.30 DT price = £27.30 | 56 tablet pack £54.60
  
  > Champix (Pfizer Ltd) ▼
  
  Champix titration pack | 25 tablet pack £27.30

Serpentine and noradrenaline re-uptake inhibitors

**Butropion hydrochloride**

(Amfebutamone hydrochloride)

- Indications and dose
  
  **To aid smoking cessation in combination with motivational support in nicotine-dependent patients**
  
  **BY MOUTH**
  
  - Adult: Initially 150 mg daily for 6 days, then 150 mg twice daily (max. per dose 150 mg), minimum 8 hours between doses; period of treatment 7–9 weeks, start treatment 1–2 weeks before target stop date, discontinue if abstinence not achieved at 7 weeks, consider maximum 150 mg daily in patients with risk factors for seizures; maximum 300 mg per day
  
  - Elderly: 150 mg daily for 7–9 weeks, start treatment 1–2 weeks before target stop date, discontinue if abstinence not achieved at 7 weeks; maximum 150 mg per day

- Contra-indications
  
  - Acute alcohol withdrawal - acute benzodiazepine withdrawal - bipolar disorder - CNS tumour - eating disorders - history of seizures - severe hepatic cirrhosis
  
  - Alcohol abuse - diabetes - elderly - history of head trauma - predisposition to seizures (prescribe only if benefit clearly outweighs risk)

- Interactions
  
  - Appendix 1 (bupropion).
  
  Caution with concomitant use of drugs that lower seizure threshold.

- Side-effects
  
  - Common or very common Agitation - anxiety - depression - dizziness - dry mouth - fever - gastrointestinal disturbances - headache - impaired concentration - insomnia (reduced by avoiding dose at bedtime) - pruritus - rash - sexual dysfunction - sweating - tachycardia - thirst - tinnitus - tremor - vaginal discharge - visual disturbances - weight gain
  
  - Rare Cerebrovascular accident
  
  - Frequency not known Aggression - diabetes mellitus - hyperglycaemia - irritability - myoclonic infarction - psychosis - sleep-walking - Stevens-Johnson syndrome - suicidal ideation

- Pregnancy
  
  Avoid — toxicity in animal studies.

- Breast feeding
  
  Avoid — present in milk in animal studies.

- Renal impairment
  
  If eGFR less than 30 mL/minute/1.73 m², initial dose 500 micrograms once daily, increased after 3 days to 1 mg once daily.

- Treatment cessation
  
  Risk of relapse, irritability, depression, and insomnia on discontinuation; consider dose tapering on completion of 12-week course.

- National funding/access decisions
  
  - NICE technology appraisals (TAs)
    
    Varenicline for smoking cessation (July 2007) NICE TAI23
    
    Varenicline is recommended, within its licensed indications, as an option for smokers who have expressed a desire to quit smoking; it should normally be prescribed only as part of a programme of behavioural support. www.nice.org.uk/TAI23

- Medicinal forms
  
  There can be variation in the licensing of different medicines containing the same drug.

  Modified-release tablet
  
  **CAUTIONARY AND ADVISORY LABELS 25**
  
  > Zyban (GlaxosmithKline UK Ltd)
  
  Bupropion hydrochloride 150 mg
  
  Zyban 150 mg modified-release tablets | 60 tablet pack £41.76 DT price = £41.76
8.3 Opioid dependence

**ALPHA₂ ADRENOCEPTOR AGONISTS**

**Lofexidine hydrochloride**

- **DRUG ACTION** Lofexidine is an alpha₂-adrenergic agonist.

**INDICATIONS AND DOSE**

Management of symptoms of opioid withdrawal

- **BY MOUTH**
  - Adult: Initially 800 micrograms daily in divided doses, increased in steps of 400–800 micrograms daily (max. per dose 800 micrograms) as required for 7–10 days if no opioid use (but longer may be required); maximum 2.4 mg per day

- **CAUTIONS** Bradycardia · cerebrovascular disease · depression · history of QT prolongation · hypotension (monitor pulse rate and blood pressure) · metabolic disturbances · recent myocardial infarction · severe coronary insufficiency

- **INTERACTIONS** → Appendix 1 (lofexidine).

- **SIDE-EFFECTS** Bradycardia · dizziness · drowsiness · dry mucous membranes · hypotension · QT-interval prolongation

- **PREGNANCY** Use only if benefit outweighs risk—no information available.

- **BREAST FEEDING** Use only if benefit outweighs risk—no information available.

- **RENAI IMPAIRMENT** Caution in chronic impairment.

- **MONITORING REQUIREMENTS** Monitoring of blood pressure and pulse rate is recommended on initiation, for at least 72 hours or until a stable dose is achieved, and on discontinuation.

- **PRESCRIBING AND DISPENSING INFORMATION** Lofexidine has been used in children over 12 years for the management of symptoms of opioid withdrawal

- **TREATMENT CESSATION** Treatment should be withdrawn gradually over 2–4 days (or longer) to reduce the risk of rebound hypertension and associated symptoms.

- **PATIENT AND CARER ADVICE** The patient should take part of the dose at bedtime to offset insomnia associated with opioid withdrawal.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>BritLofex (Britannia Pharmaceuticals Ltd)</td>
</tr>
<tr>
<td>Lofexidine hydrochloride 200 microgram BritLofex 200microgram tablets 60 tablet</td>
</tr>
</tbody>
</table>

**OPIOIDS**

**Buprenorphine**

The properties listed below are those particular to the drug only. For properties common to the class, see opioids, p. 357.

- **DRUG ACTION** Buprenorphine is an opioid-receptor partial agonist (it has opioid agonist and antagonist properties).

**INDICATIONS AND DOSE**

- **Moderate to severe pain**
  - **BY SUBLINGUAL ADMINISTRATION**
    - Child (body-weight 16–25 kg): 100 micrograms every 6–8 hours
    - Child (body-weight 25–37.5 kg): 100–200 micrograms every 6–8 hours
  - **BY TRANSDERMAL APPLICATION USING PATCHES**
    - Adult: Patients who have not previously received strong opioid analgesics initially 35 micrograms/hour up to every 72 hours; patients who have received strong opioid analgesic, initial dose based on previous 24-hour opioid requirement, consult product literature, dose adjustment—when starting, analgesic effect should not be evaluated until the system has been worn for 24 hours (to allow for gradual increase in plasma-buprenorphine concentration)—if necessary, dose should be adjusted at intervals of no longer than 72 hours using a patch of the next strength or using 2 patches of the same strength (applied at same time to avoid confusion). Maximum 2 patches can be used at any one time, for breakthrough pain, consider 200–400 micrograms buprenorphine sublingually

**PHARMACOKINETICS**

It may take approximately 25 hours for the plasma-buprenorphine concentration to decrease by 50% after patch is removed.

**TRANSTEC**

- **Moderate to severe chronic cancer pain | Severe pain unresponsive to non-opioid analgesics**

**BY SUBLINGUAL ADMINISTRATION**

- Adult: Patients who have not previously received strong opioid analgesics, initially 35 micrograms/hour up to every 96 hours; patients who have received strong opioid analgesic, initial dose based on previous 24-hour opioid requirement, consult product literature, dose adjustment—when starting, analgesic effect should not be evaluated until the system has been worn for 24 hours (to allow for gradual increase in plasma-buprenorphine concentration)—if necessary, dose should be adjusted at intervals of no longer than 72 hours using a patch of the next strength or using 2 patches of the same strength (applied at same time to avoid confusion). Maximum 2 patches can be used at any one time, for breakthrough pain, consider 200–400 micrograms buprenorphine sublingually
in plasma-buprenorphine concentration)—if necessary, dose should be adjusted at intervals of no longer than 96 hours using a patch of the next strength or using 2 patches of the same strength (applied at same time to avoid confusion). Maximum 2 patches can be used at any one time, for breakthrough pain, consider 200–400 micrograms buprenorphine sublingually

**PHARMACOKINETICS**
It may take approximately 30 hours for the plasma-buprenorphine concentration to decrease by 50% after patch is removed.

**BUTRANS®**
Moderate, non-malignant pain unresponsive to non-opioid analgesics

**BY TRANSDERMAL APPLICATION USING PATCHES**
> Adult: Initially 5 micrograms/hour up to every 7 days, dose adjustments—when starting, analgesic effect should not be evaluated until the system has been worn for 72 hours (to allow for gradual increase in plasma-buprenorphine concentration)—if necessary, dose should be adjusted at intervals of at least 3 days using a patch of the next strength or a combination of 2 patches applied in different places (applied at same time to avoid confusion). Maximum 2 patches can be used at any one time

**UNLICENSED USE**
Sublingual tablets not licensed for use in children under 6 years. Injection not licensed for use in children under 6 months.

**CAUTIONS**
**GENERAL CAUTIONS**
Impaired consciousness

**SPECIFIC CAUTIONS**
> With transdermal use other opioids should not be administered within 24 hours of patch removal (long duration of action) (in adults)
> When used for adjunct in the treatment of opioid dependence hepatitis B infection (in adults) - hepatitis C infection (in adults) - pre-existing liver enzyme abnormalities (in adults)

**INTERACTIONS**
Caution with concomitant use of hepatotoxic drugs.

**SIDE-EFFECTS**
> Common or very common Abdominal pain - agitation - anorexia - anxiety - asthenia - diarrhoea - dyspepsia - dryness - fatigue - mild withdrawal symptoms in patients dependent on opioids - paraesthesia - vasodilatation
> Rare Divertercitis (in children) - dysphagia - impaired concentration - paralytic ileus - psychosis
> Very rare Hiccups - hyperventilation - muscle fasciculation - retching
> Frequency not known Hepatic necrosis - hepatitis

**SIDE-EFFECTS, FURTHER INFORMATION**

**Fever or external heat**
Monitor patients using patches for increased side-effects if fever present (increased absorption possible); avoid exposing application site to external heat (may also increase absorption).

**Overdose**
The effects of buprenorphine are only partially reversed by naloxone.

**HAPOCTASIN®**
In view of the long duration of action, patients who have severe side-effects should be monitored for up to 25 hours after removing patch.

**TRANSTEC®**
In view of the long duration of action, patients who have severe side-effects should be monitored for up to 30 hours after removing patch.

**BREAST FEEDING**
Present in low levels in breast milk.

**RENAL IMPAIRMENT**
Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

**PRE-TREATMENT SCREENING**
Documentation of viral hepatitis status is recommended before commencing therapy for opioid dependence.

**MONITORING REQUIREMENTS**
Monitor liver function; when used in opioid dependence baseline liver function test is recommended before commencing therapy, and regular liver function tests should be performed throughout treatment.

**DIRECTIONS FOR ADMINISTRATION**
> With sublingual use in children For administration by mouth, tablets may be halved.

**HAPOCTASIN®**
Apply patch to dry, non-irritated, non-hairy skin on upper torso, removing after no longer than 72 hours and siting replacement patch on a different area (avoid same area for at least 7 days).

**TRANSTEC®**
Apply patch to dry, non-irritated, non-hairy skin on upper torso, removing after no longer than 96 hours and siting replacement patch on a different area (avoid same area for at least 6 days).

**BUTRANS®**
Apply patch to dry, non-irritated, non-hairy skin on upper torso, removing after 7 days and siting replacement patch on a different area (avoid same area for at least 3 weeks).

**PRESCRIBING AND DISPENSING INFORMATION**
Transdermal buprenorphine patches are not suitable for acute pain or in those patients whose analgesic requirements are changing rapidly because the long time to steady state prevents rapid titration of the dose.

**PATIENT AND CARER ADVICE**
HAPOCTASIN® TRANSTEC® BUTRANS®
Patients or carers should be given advice on how to administer buprenorphine transdermal patches.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**
> Methadone and buprenorphine for the management of opioid dependence (January 2007) NICE TA114

Oral methadone and buprenorphine are recommended for maintenance therapy in the management of opioid dependence. Patients should be committed to a supportive care programme including a flexible dosing regimen administered under supervision for at least 3 months, until compliance is assured. Selection of methadone or buprenorphine should be made on a case-by-case basis, but methadone should be prescribed if both drugs are equally suitable. www.nice.org.uk/TA114

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Sublingual tablet**

**CAUTIONARY AND ADVISORY LABELS 2, 26**
> BUPRENORPHINE (Non-proprietary)

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Strength</th>
<th>UK Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine (as Buprenorphine hydrochloride) 200 microgram</td>
<td>Buprenorphine 200 microgram sublingual tablets sugar free (sugar-free)</td>
<td>£5.04 DT price = £5.04 Schedule 3 (CD No Register)</td>
</tr>
<tr>
<td>Buprenorphine (as Buprenorphine hydrochloride) 400 microgram</td>
<td>Buprenorphine 400 microgram sublingual tablets sugar free (sugar-free)</td>
<td>£10.07 Schedule 3 (CD No Register)</td>
</tr>
</tbody>
</table>
Buprenorphine (as Buprenorphine hydrochloride) 2 mg
Buprenorphine 2mg sublingual tablets sugar free (sugar-free) | 7 tablet (POT) £16.50 DT price = £2.14 Schedule 3 (CD No Register)
Buprenorphine (as Buprenorphine hydrochloride) 8 mg
Buprenorphine 8mg sublingual tablets sugar free (sugar-free) | 7 tablet (POT) £52.00 DT price = £3.85 Schedule 3 (CD No Register)
> Gabup (Martindale Pharmaceuticals Ltd)
Buprenorphine (as Buprenorphine hydrochloride) 400 microgram
Gabup 0.4mg sublingual tablets (sugar-free) | 7 tablet (POT) £1.60 DT price = £1.60 Schedule 3 (CD No Register)
Buprenorphine (as Buprenorphine hydrochloride) 1 mg
Gabup 1mg sublingual tablets (sugar-free) | 7 tablet (POT) £2.00 Schedule 3 (CD No Register)
Buprenorphine (as Buprenorphine hydrochloride) 2 mg
Gabup 2mg sublingual tablets (sugar-free) | 7 tablet (POT) £2.14 DT price = £2.14 Schedule 3 (CD No Register)
Buprenorphine (as Buprenorphine hydrochloride) 4 mg
Gabup 4mg sublingual tablets (sugar-free) | 7 tablet (POT) £3.90 Schedule 3 (CD No Register)
Buprenorphine (as Buprenorphine hydrochloride) 6 mg
Gabup 6mg sublingual tablets (sugar-free) | 7 tablet (POT) £4.10 Schedule 3 (CD No Register)
Buprenorphine (as Buprenorphine hydrochloride) 8 mg
Gabup 8mg sublingual tablets (sugar-free) | 7 tablet (POT) £3.85 DT price = £3.85 Schedule 3 (CD No Register)
> Temgesic (RB Pharmaceuticals Ltd)
Buprenorphine (as Buprenorphine hydrochloride) 200 microgram
Temgesic 200microgram sublingual tablets (sugar-free) | 50 tablet (POT) £5.04 DT price = £5.04 Schedule 3 (CD No Register)
Buprenorphine (as Buprenorphine hydrochloride) 400 microgram
Temgesic 400microgram sublingual tablets (sugar-free) | 50 tablet (POT) £10.07 DT price = £10.07 Schedule 3 (CD No Register)
> Brands may include Natzon; Prelfin; Subutex; Tephine

Solution for injection
> Temgesic (RB Pharmaceuticals Ltd)
Buprenorphine (as Buprenorphine hydrochloride) 300 microgram per 1 ml
Temgesic 300micrograms/1ml solution for injection ampoules | 5 ampoule (POT) £2.46 Schedule 3 (CD No Register)

Transdermal patch

> BUPRENORPHINE (Non-proprietary)
Buprenorphine 35 microgram per 1 hour
Buprenorphine 35micrograms/hour transdermal patches | 4 patch (POT) £15.80 DT price = £15.80 Schedule 3 (CD No Register)
Buprenorphine 5.25 microgram per 1 hour
Buprenorphine 5.25micrograms/hour transdermal patches | 4 patch (POT) £31.60 DT price = £31.60 Schedule 3 (CD No Register)
> BuTrans (Napp Pharmaceuticals Ltd)
Buprenorphine 5 microgram per 1 hour
Buprenorphine 5micrograms/hour transdermal patches | 4 patch (POT) £17.60 DT price = £17.60 Schedule 3 (CD No Register)
Buprenorphine 10 microgram per 1 hour
Buprenorphine 10micrograms/hour transdermal patches | 4 patch (POT) £31.55 DT price = £31.55 Schedule 3 (CD No Register)
Buprenorphine 20 microgram per 1 hour
Buprenorphine 20micrograms/hour transdermal patches | 4 patch (POT) £57.46 Schedule 3 (CD No Register)
> Hapocatin (Actavis UK Ltd)
Buprenorphine 35 microgram per 1 hour
Buprenorphine 35micrograms/hour transdermal patches | 4 patch (POT) £9.48 DT price = £9.48 Schedule 3 (CD No Register)
Buprenorphine 5.25 microgram per 1 hour
Buprenorphine 5.25micrograms/hour transdermal patches | 4 patch (POT) £14.23 DT price = £14.23 Schedule 3 (CD No Register)
> Transte (Napp Pharmaceuticals Ltd)
Buprenorphine 35 microgram per 1 hour
Buprenorphine 35micrograms/hour transdermal patches | 4 patch (POT) £15.80 DT price = £15.80 Schedule 3 (CD No Register)

Buprenorphine 5.25 microgram per 1 hour Transte
Buprenorphine 5.25micrograms/hour transdermal patches | 4 patch (POT) £23.71 DT price = £23.71 Schedule 3 (CD No Register)
Buprenorphine 70 microgram per 1 hour Transte
Buprenorphine 70micrograms/hour transdermal patches | 4 patch (POT) £31.60 DT price = £31.60 Schedule 3 (CD No Register)

Buprenorphine with naloxone

The properties listed below are those particular to the combination only. For the properties of the components please consider, buprenorphine p. 434, naloxone hydrochloride p. 1133.

INDICATIONS AND DOSE
Adjunct in the treatment of opioid dependence (dose expressed as buprenorphine)

BY SUBLINGUAL ADMINISTRATION
> Adult: Initially 2–4 mg once daily, an additional dose of 2–4 mg may be administered on day 1 depending on the individual patient’s requirement, increased in steps of 2–8 mg, adjusted according to response, total weekly dose may be divided and given on alternate days or 3 times weekly; maximum 24 mg per day

NATIONAL FUNDING/ACCESS DECISIONS
Scottish Medicines Consortium (SMC) Decisions The Scottish Medicines Consortium has advised (February 2007) that Suboxone® should be restricted for use in patients in whom methadone is not suitable.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Sublingual tablet

CAUTIONARY AND ADVISORY LABELS 2, 26
> Suboxone (RB Pharmaceuticals Ltd)
Buprenorphine (as Buprenorphine hydrochloride) 2 mg
Naloxone (as Naloxone hydrochloride) 1 mg
Suboxone 2mg/1mg tablets (sugar-free) | 28 tablet (POT) £25.40 DT price = £25.40 Schedule 3 (CD No Register)
Buprenorphine (as Buprenorphine hydrochloride) 8 mg
Naloxone (as Naloxone hydrochloride) 2 mg
Suboxone 8mg/2mg tablets (sugar-free) | 28 tablet (POT) £76.19 DT price = £76.19 Schedule 3 (CD No Register)

Methadone hydrochloride

The properties listed below are those particular to the drug only. For properties common to the class, see opioids, p. 357.

INDICATIONS AND DOSE
Severe pain
BY MOUTH OR BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION
> Adult: 5–10 mg every 6–8 hours, adjusted according to response, on prolonged use not to be given more frequently than every 12 hours
Adjunct in treatment of opioid dependence
BY MOUTH USING ORAL SOLUTION
> Adult: Initially 10–30 mg daily, increased in steps of 5–10 mg daily if required until no signs of withdrawal nor evidence of intoxication, dose to be increased in the first week, then increased every few days as necessary up to usual dose, maximum weekly dose increase of 30 mg; usual dose 60–120 mg daily
Adjunct in treatment of opioid dependence if tolerance low or not known
BY MOUTH USING ORAL SOLUTION
> Adult: Initially 10–20 mg daily, increased in steps of 5–10 mg daily if required until no signs of withdrawal nor evidence of intoxication, dose to be increased in the first week, then increased every few days as necessary up to usual dose, maximum weekly dose increase of 30 mg; usual dose 60–120 mg daily
the first week, then increased every few days as necessary up to usual dose, maximum weekly dose increase of 30 mg; usual dose 60–120 mg daily

**Adjunct in treatment of opioid dependence if tolerance high** (under expert supervision)

- **MOUTH USING ORAL SOLUTION**
  - Adults: Initially up to 40 mg daily, increased in steps of 5–10 mg daily if required until no signs of withdrawal nor evidence of intoxication, dose to be increased in the first week, then increased every few days as necessary up to usual dose, maximum weekly dose increase of 30 mg; usual dose 60–120 mg daily

**Cough in terminal disease**

- **INITIALLY BY MOUTH USING LINCTUS**
- Adults: 1–2 mg every 4–6 hours, (by mouth) reduced to 1–2 mg twice daily, use twice daily frequency if prolonged use

**Dose equivalence and conversion**

See p. 434 for dose adjustments in opioid substitution therapy, for patients taking methadone who want to switch to buprenorphine.

- **UNLICENSED USE** Methadone hydrochloride doses for opioid dependence in the BNF may differ from those in the product literature.

**Important safety information**

Methadone oral solution 1 mg/mL is 2½ times the strength of Methadone Linctus (2 mg/mL). Many preparations of Methadone oral solution are licensed for opioid drug addiction only but some are also licensed for analgesia in severe pain.

- **CONTRA-INDICATIONS** Phaeochromocytoma
- **CAUTIONS** Family history of sudden death (ECG monitoring recommended) - history of cardiac conduction abnormalities

**CAUTIONS, FURTHER INFORMATION**

- **Q1 interval prolongation** Patients with the following risk factors for QT-interval prolongation should be carefully monitored while taking methadone: heart or liver disease, electrolyte abnormalities, or concomitant treatment with drugs that can prolong QT interval; patients requiring more than 100 mg daily should also be monitored.

- **SIDE-EFFECTS** Dry eyes - dysmenorrhoea - hyperprolactinaemia - hypothermia. QT interval prolongation - raised intracranial pressure - restlessness - torsade de pointes

**SIDE-EFFECTS, FURTHER INFORMATION**

Methadone is a long-acting opioid therefore effects may be cumulative. Methadone, even in low doses is a **special hazard** for children; non-dependent adults are also at risk of toxicity; dependent adults are at risk if tolerance is incorrectly assessed during induction.

**Overdose** Methadone has a very long duration of action; patients may need to be monitored for long periods following large overdoses.

**BREAST FEEDING** Withdrawal symptoms in infant; breast-feeding permissible during maintenance but dose should be as low as possible and infant monitored to avoid sedation (high doses of methadone carry an increased risk of sedation and respiratory depression in the neonate).

**RENAI IMPAIRMENT** Avoid use or reduce dose; opioid effects increased and prolonged and increased cerebral sensitivity occurs.

**TREATMENT CETSSION** Avoid abrupt withdrawal.

**DIRECTIONS FOR ADMINISTRATION** Syrup preserved with hydroxybenzoate (parabens) esters may be incompatible with methadone hydrochloride.

**PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid formulations may include tolu.

**METHADOSE® ORAL SOLUTION**

The final strength of the methadone mixture to be dispensed to the patient must be specified on the prescription.

**Important** — care is required in prescribing and dispensing the **correct strength** since any confusion could lead to an overdose; this preparation should be dispensed only **after dilution** as appropriate with Methadose® Diluent (life of diluted solution 3 months) and is for drug dependent persons.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Methadone and buprenorphine for the management of opioid dependence (January 2007) NICE TA114

Oral methadone and buprenorphine are recommended for maintenance therapy in the management of opioid dependence. Patients should be committed to a supportive care programme including a flexible dosing regimen administered under supervision for at least 3 months, until compliance is assured. Selection of methadone or buprenorphine should be made on a case-by-case basis, but methadone should be prescribed if both drugs are equally suitable. [www.nice.org.uk/TA114](http://www.nice.org.uk/TA114)

**LESS SUITABLE FOR PRESCRIBING** Methadone linctus is less suitable for prescribing for cough in terminal disease (has a tendency to accumulate).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, suppository, solution for injection, oral suspension, oral solution, capsule, impregnated cigarette

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 2**

- Phystephe (Martindale Pharmaceuticals Ltd)
  - Methadone hydrochloride 5 mg Phystephe 5mg tablets [© 50 tablet | £3.39 DT price = £3.39 Schedule 2 (CD)]

**Oral solution**

**CAUTIONARY AND ADVISORY LABELS 2**

- **METHADONE HYDROCHLORIDE (Non-proprietary)**
  - Methadone hydrochloride 1 mg per 1 ml Methadone 1mg/ml oral solution 100 ml [© £1.25–1.38 DT price = £1.38 Schedule 2 (CD) | 500 ml | £6.90 DT price = £6.90 Schedule 2 (CD) | 2500 ml | £32.10–34.50 Schedule 2 (CD)]
  - Methadone 1mg/ml oral solution sugar free (sugar-free) | 50 ml [© £1.04 DT price = £1.04 Schedule 2 (CD) (sugar-free)]
  - 100 ml [© £2.08 DT price = £2.08 Schedule 2 (CD) (sugar-free)]
  - 500 ml [© £6.30 DT price = £6.30 Schedule 2 (CD) (sugar-free)]
  - 2500 ml [© £31.50–32.50 Schedule 2 (CD)]

- Methadose (Rosemont Pharmaceuticals Ltd)
  - Methadone hydrochloride 10 mg per 1 ml Methadose 10mg/ml oral solution concentrate (sugar-free) | 150 ml [© £12.01 Schedule 2 (CD)]
  - Methadone hydrochloride 20 mg per 1 ml Methadose 20mg/ml oral solution concentrate (sugar-free) | 150 ml [© £24.02 Schedule 2 (CD)]

- Brands may include Methadose; Phystephe

**Solution for injection**

- **METHADONE HYDROCHLORIDE (Non-proprietary)**
  - Methadone hydrochloride 10 mg per 1 ml Methadone 50mg/5ml solution for injection ampoules | 10 ampoule [© £18.94 DT price = £16.33 Schedule 2 (CD)]
  - Methadone 35mg/3.5ml solution for injection ampoules | 10 ampoule [© £13.92 DT price = £15.14 Schedule 2 (CD)]
  - Methadone hydrochloride 25 mg per 1 ml Methadone 50mg/2ml solution for injection ampoules | 10 ampoule [© no price available Schedule 2 (CD)]
  - Methadone hydrochloride 50 mg per 1 ml Methadone 50mg/1ml solution for injection ampoules | 10 ampoule [© no price available Schedule 2 (CD)]

- Brands may include Phystephe; Synastone
Chapter 5
Infection

1  Amoebic infection

Drugs used for Amoebic infection not listed below; Metronidazole, p. 475  Tinidazole, p. 476

Diloxanide furoate

INDICATIONS AND DOSE
Chronic amoebiasis  Acute amoebiasis as adjunct to metronidazole or tinidazole
BY MOUTH
— Child 12–17 years: 500 mg 3 times a day for 10 days
— Adult: 500 mg 3 times a day for 10 days

• SIDE-EFFECTS Flatulence  pruritus  urticaria  vomiting
• PREGNANCY Manufacturer advises avoid—no information available.
• BREAST FEEDING Manufacturer advises avoid.

• MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

Tablet
CAUTIONARY AND ADVISORY LABELS 9
— DILOXANIDE FUROATE (Non-proprietary)
Diloxanide furoate 500 mg  Diloxanide 500mg tablets 30 tablet £93.50

Mepacrine hydrochloride

INDICATIONS AND DOSE
Giardiasis
BY MOUTH
— Adult: 100 mg every 8 hours for 5–7 days

• UNLICENSED USE Not licensed for use in giardiasis.
• CAUTIONS Avoid in psoriasis  elderly  history of psychosis
• INTERACTIONS Appendix 1 (mepacrine).
• SIDE-EFFECTS Aplastic anaemia (on prolonged treatment)  blue/black discoloration of nails  blue/black discoloration of palate  chronic dermatoses (on prolonged treatment)  CNS stimulation (with large doses)  corneal deposits with visual disturbances  dizziness  gastrointestinal disturbances  headache  hepatitis (on prolonged treatment)  nausea (with large doses)  severe exfoliative dermatitis (on prolonged treatment)  transient acute toxic psychosis (with large doses)  vomiting (with large doses)  yellow discoloration of skin (on prolonged treatment)  yellow discoloration of urine (on prolonged treatment)

• HEPATIC IMPAIRMENT Use with caution.
• MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet

2  Bacterial infection

Antibacterials, principles of therapy

Choice of a suitable drug
Before selecting an antibacterial the clinician must first consider two factors—the patient and the known or likely causative organism. Factors related to the patient which must be considered include history of allergy, renal and hepatic function, susceptibility to infection (i.e. whether immunocompromised), ability to tolerate drugs by mouth, severity of illness, ethnic origin, age, whether taking other medication and, if female, whether pregnant, breast-feeding or taking an oral contraceptive.

The known or likely organism and its antibacterial sensitivity, in association with the above factors, will suggest one or more antibacterials, the final choice depending on the microbiological, pharmacological, and toxicological properties.

An example of a rational approach to the selection of an antibacterial is treatment of a urinary-tract infection in a patient complaining of nausea and symptoms of a urinary-tract infection in early pregnancy. The organism is reported as being resistant to ampicillin p. 483 but sensitive to
nitrofurantoin p. 512 (can cause nausea), gentamicin p. 450 (can be given only by injection and best avoided in pregnancy), tetracycline p. 498 (causes dental discoloration) and trimethoprim p. 462 (folic acid antagonist therefore theoretical teratogenic risk), and cefalexin p. 456. The safest antibiotics in pregnancy are the penicillins and cephalosporins; therefore, cefalexin p. 456 would be indicated for this patient.

The principles involved in selection of an antibacterial must allow for a number of variables including changing renal and hepatic function, increasing bacterial resistance, and information on side-effects. Duration of therapy, dosage, and route of administration depend on site, type and severity of infection and response.

**Antibacterial policies**

Local policies often limit the antibacterials that may be used to achieve reasonable economy consistent with adequate cover, and to reduce the development of resistant organisms. A policy may indicate a range of drugs for general use, and permit other drugs only on the advice of the microbiologist or physician responsible for the control of infectious diseases.

**Before starting therapy**

The following precepts should be considered before starting:

- **Viral infections should not be treated with antibacterials.** However, antibacterials may be used to treat secondary bacterial infection (e.g. bacterial pneumonia secondary to influenza);
- **Samples should be taken for culture and sensitivity testing;** ‘blind’ antibacterial prescribing for unexplained pyrexia usually leads to further difficulty in establishing the diagnosis;
- **Knowledge of prevalent organisms** and their current sensitivity is of great help in choosing an antibacterial before bacteriological confirmation is available. Generally, narrow-spectrum antibacterials are preferred to broad-spectrum antibacterials unless there is a clear clinical indication (e.g. life-threatening sepsis);
- **The dose of an antibacterial varies according to a number of factors including age, weight, hepatic function, renal function, and severity of infection.** The prescribing of the so-called ‘standard’ dose in serious infections may result in failure of treatment or even death of the patient; therefore it is important to prescribe a dose appropriate to the condition. An inadequate dose may also increase the likelihood of antibacterial resistance. On the other hand, for an antibacterial with a narrow margin between the toxic and therapeutic dose (e.g. an aminoglycoside) it is also important to avoid an excessive dose and the concentration of the drug in the plasma may need to be monitored;
- **The route of administration of an antibacterial often depends on the severity of the infection.** Life-threatening infections require intravenous therapy. Antibacterials that are well absorbed may be given by mouth even for some serious infections. Parenteral administration is also appropriate when the oral route cannot be used (e.g. because of vomiting) or if absorption is inadequate. Whenever possible, painful intramuscular injections should be avoided in children;
- **Duration of therapy depends on the nature of the infection and the response to treatment.** Courses should not be unduly prolonged because they encourage resistance, they may lead to side-effects and they are costly. However, in certain infections such as tuberculosis or osteomyelitis it may be necessary to treat for prolonged periods. Conversely a single dose of an antibacterial may cure uncomplicated urinary-tract infections. The prescription for an antibacterial should specify the duration of treatment or the date when treatment is to be reviewed.

**Superinfection**

In general, broad-spectrum antibacterial drugs such as the cephalosporins are more likely to be associated with adverse reactions related to the selection of resistant organisms e.g. *fungal infections or antibiotic-associated colitis* (pseudomembranous colitis); other problems associated with superinfection include vaginitis and pruritus ani.

**Therapy**

When the pathogen has been isolated treatment may be changed to a more appropriate antibacterial if necessary. If no bacterium is cultured the antibacterial can be continued or stopped on clinical grounds.

**Notifiable diseases**

Doctors must notify the Proper Officer of the local authority (usually the consultant in communicable disease control) when attending a patient suspected of suffering from any of the diseases listed below; a form is available from the Proper Officer.

<table>
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<tr>
<th>Bacterial infection</th>
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<tr>
<th>Anthrax</th>
<th>Mumps</th>
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<tr>
<td>Botulism</td>
<td>Paratyphoid fever</td>
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<tr>
<td>Brucellosis</td>
<td>Plague</td>
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<tr>
<td>Cholera</td>
<td>Poliomyelitis, acute</td>
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<tr>
<td>Diarrhoea (infectious bloody)</td>
<td>Rabies</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>Rubella</td>
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<tr>
<td>Encephalitis, acute</td>
<td>SARS</td>
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<tr>
<td>Food poisoning</td>
<td>Scarlet fever</td>
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<tr>
<td>Haemolytic uraemic syndrome</td>
<td>Smallpox</td>
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<tr>
<td>Haemorrhagic fever (viral)</td>
<td>Streptococcal disease (Group A, invasive)</td>
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<tr>
<td>Hepatitis, viral</td>
<td>Tetanus</td>
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<tr>
<td>Legionnaires’ disease</td>
<td>Typhus</td>
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<tr>
<td>Leprosy</td>
<td>Tuberculosis</td>
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<tr>
<td>Malaria</td>
<td>Typhoid fever</td>
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<tr>
<td>Measles</td>
<td>Whooping cough</td>
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<tr>
<td>Meningitis</td>
<td>Yellow fever</td>
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<tr>
<td>Meningococcal septicaemia</td>
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<th>Bacterial infection</th>
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It is good practice for doctors to also inform the consultant in communicable disease control of instances of other infections (e.g. psittacosis) where there could be a public health risk.

**Antibacterials, use for prophylaxis**

**Prevention of recurrence of rheumatic fever**

Phenoxyoxymethylpenicillin p. 481 or sulfadiazine p. 495.

**Prevention of secondary case of invasive group A streptococcal infection**

Phenoxyoxymethylpenicillin p. 481.

Patients who are penicillin allergic, *either* erythromycin p. 471 or azithromycin p. 469 [unlicensed indication].

For details of those who should receive chemoprophylaxis contact a consultant in communicable disease control (or a consultant in infectious diseases or the local Public Health England Laboratory).

**Prevention of secondary case of meningococcal meningitis**

Ciprofloxacin p. 490 or rifampicin p. 508 or i/m ceftriaxone p. 459 [unlicensed indication].

For details of those who should receive chemoprophylaxis contact a consultant in communicable disease control (or a consultant in infectious diseases or the local Public Health England Laboratory).
England laboratory). Unless there has been direct exposure of the mouth or nose to infectious droplets from a patient with meningococcal disease who has received less than 24 hours of antibacterial treatment, healthcare workers do not generally require chemoprophylaxis.

**Prevention of secondary case of Haemophilus influenzae type b disease**

Rifampicin p. 508 or (if rifampicin cannot be used) i/m or i/v ceftriaxone p. 459 [unlicensed indication].

For details of those who should receive chemoprophylaxis contact a consultant in communicable disease control (or a consultant in infectious diseases or the local Public Health England laboratory). Unless there has been direct exposure of the mouth or nose to infectious droplets from a patient with meningococcal disease who has received less than 24 hours of antibacterial treatment, healthcare workers do not generally require chemoprophylaxis.

Within 4 weeks of illness onset in an index case with confirmed or suspected invasive *Haemophilus influenzae* type b disease, give antibacterial prophylaxis to all household contacts if there is a vulnerable individual in the household. Also, give antibacterial prophylaxis to the index case if they are in contact with vulnerable household contacts or if they are under 10 years of age. Vulnerable individuals include the immunocompromised, those with underlying medical conditions (including HIV, hepatitis B and C) and give appropriate prophylaxis to prevent viral spread.

**Prevention of secondary case of diphtheria in non-immune patient**

Erythromycin p. 471 (or azithromycin p. 469 or clarithromycin p. 470).

Treat for further 10 days if nasopharyngeal swabs positive after first 7 days’ treatment.

**Prevention of pertussis**

Clarithromycin p. 470 (or azithromycin p. 469 or erythromycin p. 471).

Within 3 weeks of onset of cough in the index case, give antibacterial prophylaxis to all close contacts if amongst them there is at least one unimmunised or partially immunised child under 1 year of age, or if there is at least one individual who has not received a pertussis-containing vaccine more than 1 week and less than 5 years ago (so long as that individual lives or works with children under 4 months of age, is pregnant over 32 weeks gestation, or is a healthcare worker who works with children under 1 year of age or with pregnant women).

**Prevention of pneumococcal infection in asplenia or in patients with sickle-cell disease**

Phenoxymethylpenicillin p. 481.

If penicillin-allergic, erythromycin p. 471.

Antibacterial prophylaxis is not fully reliable. Antibacterial prophylaxis may be discontinued in children over 5 years of age with sickle-cell disease who have received pneumococcal immunisation and who do not have a history of severe pneumococcal infection.

**Prevention of tuberculosis in susceptible close contacts or those who have become tuberculin positive**

Isoniazid p. 506 or isoniazid + rifampicin p. 508 or (if isoniazid-resistant tuberculosis in patients under 35 years) rifampicin.

For details of those who should receive chemoprophylaxis contact the lead clinician for local tuberculosis services (or a consultant in communicable disease control).

**Prevention of infection from animal and human bites**

Co-amoxiclav p. 484 alone (or doxycycline p. 496 + metronidazole p. 475 if penicillin-allergic).

Cleanse wound thoroughly. For tetanus-prone wound, give human tetanus immunoglobulin p. 1065 (with a tetanus-containing vaccine if necessary, according to immunisation history and risk of infection).

Consider rabies prophylaxis for bites from animals in endemic countries. Assess risk of blood-borne viruses (including HIV, hepatitis B and C) and give appropriate prophylaxis to prevent viral spread.

Antibacterial prophylaxis recommended for wounds less than 48–72 hours old when the risk of infection is high (e.g. bites from humans or cats; bites to the hand, foot, face, or genital area; bites involving oedema, crush or puncture injury, or other moderate to severe injury; wounds that cannot be debrided adequately; patients with diabetes mellitus, cirrhosis, asplenia, prosthetic joints or valves, or those who are immunocompromised). Give antibacterial prophylaxis for up to 5 days.

**Prevention of early-onset neonatal infection**

i/v benzylpenicillin sodium p. 480 (or i/v clindamycin p. 467 if history of allergy to penicillins).

Give intrapartum prophylaxis to women with group B streptococcal colonisation, bacteruria, or infection in the current pregnancy, or to women who had a previous baby with an invasive group B streptococcal infection. Consider prophylaxis for women in preterm labour if there is prelabour rupture of membranes or if intrapartum rupture of membranes lasting more than 18 hours is suspected.

**Prevention of infection in gastro-intestinal procedures**

Operations on stomach or oesophagus

Single dose of i/v gentamicin p. 450 or i/v cefuroxime p. 460 or i/v co-amoxiclav p. 484 (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Add i/v teicoplanin p. 464 (or vancomycin p. 465) if high risk of meticillin-resistant *Staphylococcus aureus*.

Open biliary surgery

Single dose of i/v cefuroxime p. 460 + i/v metronidazole p. 475 or i/v gentamicin p. 450 + i/v metronidazole or i/v co-amoxiclav p. 484 alone (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Where i/v metronidazole is suggested, it may alternatively be given by suppository but to allow adequate absorption, it should be given 2 hours before surgery.

Add i/v teicoplanin p. 464 (or vancomycin p. 465) if high risk of meticillin-resistant *Staphylococcus aureus*.

Resections of colon and rectum for carcinoma, and resections in inflammatory bowel disease, and appendicectomy

Single dose of i/v gentamicin p. 450 + i/v metronidazole p. 475 or i/v cefuroxime p. 460 + i/v metronidazole or i/v co-amoxiclav p. 484 alone (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.
Where i/v metronidazole is suggested, it may alternatively be given by suppository but to allow adequate absorption, it should be given 2 hours before surgery.

Add i/v teicoplanin p. 464 (or vancomycin p. 465) if high risk of meticillin-resistant *Staphylococcus aureus*.

**Endoscopic retrograde cholangiopancreatography**

Single dose of i/v gentamicin p. 450 or oral or i/v ciprofloxacin p. 490.

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Prophylaxis recommended if pancreatic pseudocyst, immunocompromised, history of liver transplantation, or risk of incomplete biliary drainage. For biliary complications following liver transplantation, add i/v amoxicillin p. 482 or i/v teicoplanin p. 464 (or vancomycin p. 465).

**Percutaneous endoscopic gastrostomy or jejunostomy**

Single dose of i/v co-amoxiclav p. 484 or i/v cefuroxime p. 460.

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Use single dose of i/v teicoplanin p. 464 (or vancomycin p. 465) if history of allergy to penicillins or cephalosporins, or if high risk of meticillin-resistant *Staphylococcus aureus*.

**Prevention of infection in orthopaedic surgery**

**Joint replacement including hip and knee**

Single dose of i/v cefuroxime p. 460 alone or i/v flucloxacillin p. 486 + i/v gentamicin p. 450 (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

If history of allergy to penicillins or to cephalosporins or if high risk of meticillin-resistant *Staphylococcus aureus*, use single dose of i/v teicoplanin p. 464 (or vancomycin p. 465) + i/v gentamicin (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

**Closed fractures**

Single dose of i/v cefuroxime p. 460 or i/v flucloxacillin p. 486 (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

If history of allergy to penicillins or to cephalosporins or if high risk of meticillin-resistant *Staphylococcus aureus*, use single dose of i/v teicoplanin p. 464 (or vancomycin p. 465) + i/v gentamicin (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

**Open fractures**

Use i/v co-amoxiclav p. 484 alone or i/v cefuroxime p. 460 + i/v metronidazole p. 475 (or i/v clindamycin p. 467 alone if history of allergy to penicillins or to cephalosporins).

Add i/v teicoplanin p. 464 (or vancomycin p. 465) if high risk of meticillin-resistant *Staphylococcus aureus*. Start prophylaxis within 3 hours of injury and continue until soft tissue closure (max. 72 hours).

At first debridement also use a single dose of i/v cefuroxime + i/v metronidazole + i/v gentamicin or i/v co-amoxiclav + i/v gentamicin (or i/v clindamycin + i/v gentamicin if history of allergy to penicillins or to cephalosporins).

At time of skeletal stabilisation and definitive soft tissue closure use a single dose of i/v gentamicin + i/v teicoplanin (or vancomycin) (intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure).

**High lower-limb amputation**

Use i/v co-amoxiclav p. 484 alone or i/v cefuroxime p. 460 + i/v metronidazole p. 475.

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Continue antibacterial prophylaxis for at least 2 doses after procedure (max. duration of prophylaxis 5 days). If history of allergy to penicillin or to cephalosporins, or if high risk of meticillin-resistant *Staphylococcus aureus*, use i/v teicoplanin p. 464 (or vancomycin p. 465) + i/v gentamicin p. 450 + i/v metronidazole.

Where i/v metronidazole is suggested, it may alternatively be given by suppository but to allow adequate absorption, it should be given 2 hours before surgery.

**Prevention of infection in urological procedures**

**Transrectal prostate biopsy**

Single dose of oral ciprofloxacin p. 490 or oral metronidazole p. 475 or i/v gentamicin p. 450 + i/v metronidazole (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Use single dose of i/v gentamicin + i/v metronidazole if high risk of meticillin-resistant *Staphylococcus aureus* (additional intra-operative or postoperative doses of antibacterial may be given for prolonged procedures or if there is major blood loss).

Where i/v metronidazole p. 475 is suggested, it may alternatively be given by suppository but to allow adequate absorption, it should be given 2 hours before surgery.

**Transurethral resection of prostate**

Single dose of oral ciprofloxacin p. 490 or i/v gentamicin p. 450 or i/v cefuroxime p. 460 (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Use single dose of i/v gentamicin p. 450 if high risk of meticillin-resistant *Staphylococcus aureus* (additional intra-operative or postoperative doses of antibacterial may be given for prolonged procedures or if there is major blood loss).

**Prevention of infection in obstetric and gynaecological surgery**

**Caesarean section**

Single dose of i/v cefuroxime p. 460 (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Substitute i/v clindamycin p. 467 if history of allergy to penicillins or cephalosporins. Add i/v teicoplanin p. 464 (or vancomycin p. 465) if high risk of meticillin-resistant *Staphylococcus aureus*.

**Hysterectomy**

Single dose of i/v cefuroxime p. 460 + i/v metronidazole p. 475 or i/v gentamicin p. 450 + i/v metronidazole or i/v co-amoxiclav p. 484 alone (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Use single dose of i/v gentamicin + i/v metronidazole or add i/v teicoplanin p. 464 (or vancomycin p. 465) to other regimens if high risk of meticillin-resistant *Staphylococcus aureus* (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).
Where i/v metronidazole is suggested, it may alternatively be given by suppository but to allow adequate absorption, it should be given 2 hours before surgery.

**Termination of pregnancy**

Single dose of oral metronidazole p. 475 (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

If genitai chlamydial infection cannot be ruled out, give doxycycline p. 496 postoperatively.

**Prevention of infection in cardiology procedures**

**Cardiac pacemaker insertion**

Single dose of i/v cefuroxime p. 460 alone or i/v clavulanic acid p. 480

If anaerobic infection suspected, add metronidazole to broad-spectrum cephalosporin. (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Use single dose of i/v teicoplanin (or vancomycin) + i/v cefuroxime or i/v teicoplanin (or vancomycin) + i/v gentamicin if high risk of meticillin-resistant Staphylococcus aureus (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

**Prevention of infection in vascular surgery**

**Reconstructive arterial surgery of abdomen, pelvis or legs**

Single dose of i/v cefuroxime p. 460 alone or i/v clavulanic acid p. 480 + i/v gentamicin p. 450 (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure.

Add i/v metronidazole p. 475 for patients at risk from anaerobic infections including those with diabetes, gangrene, or undergoing amputation. Use single dose of i/v teicoplanin (or vancomycin) + i/v cefuroxime or i/v teicoplanin (or vancomycin) + i/v gentamicin if history of allergy to penicillins or cephalosporins, or if high risk of meticillin-resistant Staphylococcus aureus (additional intra-operative or postoperative doses may be given for prolonged procedures or if there is major blood loss).

**Prevention of endocarditis**

**NICE guidance: Antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures** (March 2008)

Antibacterial prophylaxis and chlorhexidine mouthwash are not recommended for the prevention of endocarditis in patients undergoing dental procedures.

Antibacterial prophylaxis is not recommended for the prevention of endocarditis in patients undergoing procedures of the:

- upper and lower respiratory tract (including ear, nose, and throat procedures and bronchoscopy);
- genitourinary tract (including urological, gynaecological, and obstetric procedures);
- upper and lower gastro-intestinal tract.

Whilst these procedures can cause bacteraemia, there is no clear association with the development of infective endocarditis. Prophylaxis may expose patients to the adverse effects of antimicrobials when the evidence of benefit has not been proven.

Any infection in patients at risk of endocarditis should be investigated promptly and treated appropriately to reduce the risk of endocarditis.

If patients at risk of endocarditis are undergoing a gastro-intestinal or genitourinary tract procedure at a site where infection is suspected, they should receive appropriate antibacterial therapy that includes cover against organisms that cause endocarditis.

Patients at risk of endocarditis should be:

- advised to maintain good oral hygiene;
- told how to recognise signs of infective endocarditis, and advised when to seek expert advice.

Patients at risk of endocarditis include those with valve replacement, acquired valvular heart disease with stenosis or regurgitation, structural congenital heart disease (including surgically corrected or palliated structural conditions, but excluding isolated atrial septal defect, fully repaired ventricular septal defect, fully repaired patent ductus arteriosus, and closure devices considered to be endothelialised), hypertrophic cardiomyopathy, or a previous episode of infective endocarditis.

**Dermatological procedures**

Advice of a Working Party of the British Society for Antimicrobial Chemotherapy is that patients who undergo dermatological procedures do not require antibacterial prophylaxis against endocarditis.

The British Association of Dermatologists Therapy Guidelines and Audit Subcommittee advise that such dermatological procedures include skin biopsies and excision of moles or of malignant lesions.

**Joint prostheses and dental treatment**

Advice of a Working Party of the British Society for Antimicrobial Chemotherapy is that patients with prosthetic joint implants (including total hip replacements) do not require antibiotic prophylaxis for dental treatment. The Working Party considers that it is unacceptable to expose patients to the adverse effects of antibiotics when there is no evidence that such prophylaxis is of any benefit, but that those who develop any intercurrent infection require prompt treatment with antibiotics to which the infecting organisms are sensitive.

The Working Party has commented that joint infections have rarely been shown to follow dental procedures and are even more rarely caused by oral streptococci.

**Immunosuppression and indwelling intraperitoneal catheters**

Advice of a Working Party of the British Society for Antimicrobial Chemotherapy is that patients who are immunosuppressed (including transplant patients) and patients with indwelling intraperitoneal catheters do not require antibiotic prophylaxis for dental treatment provided there is no other indication for prophylaxis.

The Working Party has commented that there is little evidence that dental treatment is followed by infection in immunosuppressed and immunodeficient patients nor is there evidence that dental treatment is followed by infection in patients with indwelling intraperitoneal catheters.

**Blood infections, bacterial**

**Antibacterial therapy for septicaemia: community-acquired**

- A broad-spectrum antipseudomonal penicillin (e.g. piperacillin with tazobactam p. 479, ticarcillin with clavulanic acid p. 480) or a broad-spectrum cephalosporin (e.g. cefuroxime p. 460)

If meticillin-resistant Staphylococcus aureus suspected, add vancomycin p. 462 (or teicoplanin p. 464).

If anaerobic infection suspected, add metronidazole p. 475 to broad-spectrum cephalosporin.

If other resistant micro-organisms suspected, use a more broad-spectrum beta-lactam antibacterial (e.g. meropenem p. 454).
Antibacterial therapy for septicaemia: hospital-acquired

- A broad-spectrum antipseudomonal beta-lactam antibacterial (e.g. piperacillin with tazobactam p. 479, ticarcillin with clavulanic acid p. 480, cefotaxime p. 458, imipenem with cilastatin p. 454, or meropenem p. 454)
  - If meticillin-resistant *Staphylococcus aureus* suspected, add vancomycin p. 465 (or teicoplanin p. 464).
  - If anaerobic infection suspected, add metronidazole p. 475 to broad-spectrum cephapslorin

**Septicaemia related to vascular catheter**

- Benzylpenicillin sodium p. 465 (or teicoplanin p. 464)
  - If Gram-negative sepsis suspected, especially in the immunocompromised, add a broad-spectrum antipseudomonal beta-lactam.
  - Consider removing vascular catheter, particularly if infection caused by *Staphylococcus aureus*, *pestomonas*, or *Candida* species.

**Meningococcal septicemia**

If meningococcal disease suspected, a single dose of benzylpenicillin sodium p. 480 should be given before urgent transfer to hospital, so long as this does not delay the transfer; cefotaxime p. 457 may be an alternative in meningococcal disease; chloramphenicol p. 452 may be used if history of immediate hypersensitivity reaction to penicillin or to cephalosporins.

- Benzylpenicillin sodium or cefotaxime (or ceftriaxone p. 449)
- *If history of immediate hypersensitivity reaction to penicillin or to cephalosporins, chloramphenicol*
  - To eliminate nasopharyngeal carriage, ciprofloxacin p. 490, or rifampicin p. 508, or ceftriaxone may be used.

**Cardiovascular system infections, bacterial**

**Antibacterial therapy for endocarditis: initial ‘blind’ therapy**

- **Native valve endocarditis**, amoxicillin p. 482 (or ampicillin p. 483)
  - Consider adding low-dose gentamicin p. 450
  - If penicillin-allergic, or if meticillin-resistant *Staphylococcus aureus* suspected, or if severe sepsis, use vancomycin p. 465 + low-dose gentamicin
  - If severe sepsis with risk factors for Gram-negative infection, use vancomycin + meropenem p. 454
- **If prosthetic valve endocarditis**, vancomycin + rifampicin p. 508 + low-dose gentamicin

**Antibacterial therapy for native-valve endocarditis caused by staphylococci**

- Flucloxacinil p. 486
  - *Suggested duration of treatment* 4 weeks (at least 6 weeks if secondary lung abscess or osteomyelitis also present)
- *If penicillin-allergic or if meticillin-resistant Staphylococcus aureus*, vancomycin p. 465 + rifampicin
  - *Suggested duration of treatment* 4 weeks (at least 6 weeks if secondary lung abscess or osteomyelitis also present)

**Antibacterial therapy for prosthetic valve endocarditis caused by staphylococci**

- Flucloxacinil p. 486 + rifampicin p. 508 + low-dose gentamicin
  - *Suggested duration of treatment* at least 6 weeks; review need to continue gentamicin p. 450 at 2 weeks—seek specialist advice if gentamicin considered necessary beyond 2 weeks
- *If penicillin-allergic or if meticillin-resistant Staphylococcus aureus*, vancomycin p. 465 + rifampicin + low-dose gentamicin
  - *Suggested duration of treatment* at least 6 weeks; review need to continue gentamicin at 2 weeks—seek specialist advice if gentamicin considered necessary beyond 2 weeks

**Antibacterial therapy for endocarditis caused by fully-sensitive streptococci**

- Benzylpenicillin sodium p. 480
  - *Suggested duration of treatment* 4–6 weeks (6 weeks for prosthetic valve endocarditis)
- *If penicillin-allergic, vancomycin p. 465 (or teicoplanin p. 464) + low-dose gentamicin
  - *Suggested duration of treatment* 4–6 weeks (stop gentamicin p. 450 after 2 weeks)

**Antibacterial therapy for endocarditis caused by less-sensitive streptococci**

- Benzylpenicillin sodium p. 480 + low-dose gentamicin
  - *Suggested duration of treatment* 4–6 weeks (6 weeks for prosthetic valve endocarditis); review need to continue gentamicin p. 450 at 2 weeks—seek specialist advice if gentamicin considered necessary beyond 2 weeks; stop gentamicin at 2 weeks if micro-organisms moderately sensitive to penicillin
- *If penicillin-allergic or highly penicillin-resistant, vancomycin p. 465 (or teicoplanin p. 464) + low-dose gentamicin
  - *Suggested duration of treatment* 4–6 weeks (6 weeks for prosthetic valve endocarditis); review need to continue gentamicin at 2 weeks—seek specialist advice if gentamicin considered necessary beyond 2 weeks; stop gentamicin at 2 weeks if micro-organisms moderately sensitive to penicillin

**Antibacterial therapy for endocarditis caused by enterococci**

- Amoxicillin p. 482 (or ampicillin p. 483) + low dose gentamicin p. 450 or benzylpenicillin sodium p. 480 + low-dose gentamicin
  - *Suggested duration of treatment* 4–6 weeks (6 weeks for prosthetic valve endocarditis); review need to continue gentamicin at 2 weeks—seek specialist advice if gentamicin considered necessary beyond 2 weeks
- *If penicillin-allergic or penicillin-resistant, vancomycin p. 465 (or teicoplanin p. 464) + low-dose gentamicin
  - *Suggested duration of treatment* 4–6 weeks (6 weeks for prosthetic valve endocarditis); review need to continue gentamicin at 2 weeks—seek specialist advice if gentamicin considered necessary beyond 2 weeks
- *If gentamicin resistant, amoxicillin (or ampicillin)
  - Add streptomycin p. 451 (if susceptible) for 2 weeks
  - *Suggested duration of treatment* at least 6 weeks
Antibacterial therapy for endocarditis caused by Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella species (‘HACEK’ micro-organisms)

- Amoxicillin p. 482 (or ampicillin p. 483) + low-dose gentamicin
  Suggested duration of treatment 4 weeks (6 weeks for prosthetic valve endocarditis); stop gentamicin p. 450 after 2 weeks
- If amoxicillin-resistant, ceftriaxone p. 459 (or cefotaxime p. 457) + low-dose gentamicin
  Suggested duration of treatment 4 weeks (6 weeks for prosthetic valve endocarditis); stop gentamicin after 2 weeks

Central nervous system infections, bacterial

Antibacterial therapy for meningitis: initial empirical therapy

- Transfer patient to hospital urgently.
- If meningococcal disease (meningitis with non-blanching rash or meningococcal septicaemia) suspected, benzylpenicillin sodium p. 480 should be given before transfer to hospital, so long as this does not delay the transfer. If a patient with suspected bacterial meningitis without non-blanching rash cannot be transferred to hospital urgently, benzylpenicillin sodium should be given before the transfer. Cefotaxime p. 457 may be an alternative in penicillin allergy; chloramphenicol p. 452 may be used if history of immediate hypersensitivity reaction to penicillin or to cephalosporins.
- In hospital, consider adjunctive treatment with dexamethasone p. 581 (particularly if pneumococcal meningitis suspected in adults), preferably starting before or with first dose of antibacterial, but no later than 12 hours after starting antibacterial; avoid dexamethasone in septic shock, meningococcal septicaemia, or if immunocompromised, or in meningitis following surgery.
- Adult and child 3 months–50 years, cefotaxime (or ceftriaxone p. 459)
  Consider adding vancomycin p. 465 if prolonged or multiple use of other antibacterials in the last 3 months, or if travelled, in the last 3 months, to areas outside the UK with highly penicillin- and cephalosporin-resistant pneumococci.
  Suggested duration of treatment at least 10 days
- Adult over 50 years cefotaxime (or ceftriaxone) + amoxicillin p. 482 (or ampicillin p. 483)
  Consider adding vancomycin if prolonged or multiple use of other antibacterials in the last 3 months, or if travelled, in the last 3 months, to areas outside the UK with highly penicillin- and cephalosporin-resistant pneumococci.
  Suggested duration of treatment at least 10 days

Antibacterial therapy for meningitis caused by meningococci

- Benzylpenicillin sodium p. 480 or cefotaxime p. 457 (or ceftriaxone p. 459)
  Suggested duration of treatment 7 days.
- If history of immediate hypersensitivity reaction to penicillin or to cephalosporins, chloramphenicol
  Suggested duration of treatment 7 days.

Antibacterial therapy for meningitis caused by pneumococci

- Cefotaxime p. 457 (or ceftriaxone p. 459)
  Consider adjunctive treatment with dexamethasone p. 581, preferably starting before or with first dose of antibacterial, but no later than 12 hours after starting antibacterial. (may reduce penetration of vancomycin p. 465 into cerebrospinal fluid).
  If micro-organism penicillin-sensitive, replace cefotaxime with benzylpenicillin sodium p. 480. If micro-organism highly penicillin- and cephalosporin-resistant, add vancomycin and if necessary rifampicin p. 508.
  Suggested duration of antibacterial treatment 14 days

Central nervous system infections, bacterial

Antibacterial therapy for meningitis caused by Haemophilus influenzae

- Cefotaxime p. 457 (or ceftriaxone p. 459)
  Consider adjunctive treatment with dexamethasone p. 581, preferably starting before or with first dose of antibacterial, but no later than 12 hours after starting antibacterial.
  Suggested duration of antibacterial treatment 10 days. For H. influenzae type b give rifampicin for 4 days before hospital discharge to those under 10 years of age or to those in contact with vulnerable household contacts
- If history of immediate hypersensitivity reaction to penicillin or to cephalosporins, or if micro-organism resistant to cefotaxime, chloramphenicol
  Consider adjunctive treatment with dexamethasone, preferably starting before or with first dose of antibacterial, but no later than 12 hours after starting antibacterial.
  Suggested duration of antibacterial treatment 10 days. For H. influenzae type b give rifampicin p. 508 for 4 days before hospital discharge to those under 10 years of age or to those in contact with vulnerable household contacts

Antibacterial therapy for meningitis caused by Listeria

- Amoxicillin p. 482 (or ampicillin p. 483) + gentamicin
  Suggested duration of treatment 21 days.
- If history of immediate hypersensitivity reaction to penicillin, co-trimoxazole
  Suggested duration of treatment 21 days.

Ear infections, bacterial

Antibacterial therapy for otitis externa

For topical treatments, consider Otitis externa, under Ear p. 976.
Consider systemic antibacterial if spreading cellulitis or patient systemically unwell.
- Fluocinolone
  If penicillin-allergic, clarithromycin p. 470 (or azithromycin p. 469 or erythromycin p. 471)
  If Pseudomonas suspected, ciprofloxacin p. 490 (or an aminoglycoside)

Antibacterial therapy for otitis media

Many infections caused by viruses. Most uncomplicated cases resolve without antibacterial treatment. In children without systemic features, antibacterial treatment may be started after 72 hours if no improvement. Consider earlier treatment if deterioration, if systemically unwell, if at high risk of serious complications (e.g. in immunosuppression,
Eye infections, bacterial

Antibacterial therapy for purulent conjunctivitis
- Chloramphenicol eye drops p. 955.

Gastro-intestinal system infections, bacterial

Antibacterial therapy for gastro-enteritis
Frequently self-limiting and may not be bacterial.
- Antibacterial not usually indicated

Antibacterial therapy for campylobacter enteritis
Frequently self-limiting; treat if immunocompromised or if severe infection.
- Clarithromycin p. 470 (or azithromycin p. 469 or erythromycin p. 471)
- Alternative, ciprofloxacin
  Strains with decreased sensitivity to ciprofloxacin p. 490 isolated frequently

Antibacterial therapy for salmonella (non-typhoid)
 Treat invasive or severe infection. Do not treat less severe infection unless there is a risk of developing invasive infection (e.g. immunocompromised patients, those with haemoglobinopathy, or children under 6 months of age).
- Ciprofloxacin p. 490 or cefotaxime p. 457

Antibacterial therapy for shigellosis
Antibacterial not indicated for mild cases.
- Ciprofloxacin p. 490 or azithromycin p. 469
- Alternatives if micro-organism sensitive, amoxicillin p. 482 or trimethoprim p. 462

Antibacterial therapy for typhoid fever
Infections from Middle–East, South Asia, and South-East Asia may be multiple-antibacterial-resistant and sensitivity should be tested.
- Cefotaxime p. 457 (or ceftriaxone p. 459)
  Azithromycin p. 469 may be an alternative in mild or moderate disease caused by multiple-antibacterial-resistant organisms.
- Alternative if micro-organism sensitive, ciprofloxacin p. 490

Antibacterial therapy for Clostridium difficile infection
- For first episode of mild to moderate infection, oral metronidazole
  Suggested duration of treatment 10–14 days
- For second or subsequent episode of infection, for severe infection, for infection not responding to metronidazole p. 475, or in patients intolerant of metronidazole, oral vancomycin
  For severe infection in patients with multiple comorbidities who are receiving treatment with other antibacterials, or for second or subsequent episode of infection, fidaxomicin p. 468 can replace vancomycin p. 465
  Suggested duration of treatment 10–14 days
- For infection not responding to vancomycin or fidaxomicin, for life-threatening infection, or in patients with ileus, oral vancomycin + i/v metronidazole
  For infection not responding to vancomycin in patients without life-threatening infection or ileus, fidaxomicin can be used instead of vancomycin + metronidazole
  Suggested duration of treatment 10–14 days

Antibacterial therapy for biliary-tract infection
- Ciprofloxacin p. 490 or gentamicin p. 450 or a cephalosporin

Antibacterial therapy for peritonitis
- A cephalosporin + metronidazole p. 1008 or gentamicin p. 450 or metronidazole or gentamicin + clindamycin p. 467 or piperacillin with tazobactam p. 479 alone

Antibacterial therapy for peritonitis: peritoneal dialysis-associated
- Vancomycin p. 465 (or teicoplanin p. 464) + cefazidime p. 458 added to dialysis fluid or vancomycin added to dialysis fluid + ciprofloxacin p. 490 by mouth
  Suggested duration of treatment 14 days or longer

Genital system infections, bacterial

Antibacterial therapy for bacterial vaginosis
- Oral metronidazole
  Suggested duration of treatment 5–7 days (or high-dose metronidazole p. 475 as a single dose)
- Alternatively, topical metronidazole for 5 days or topical clindamycin p. 467 for 7 days

Antibacterial therapy for uncomplicated genital chlamydial infection, non-gonococcal urethritis, and non-specific genital infection
Contact tracing recommended.
- Azithromycin or doxycycline
  Suggested duration of treatment azithromycin p. 469 as a single dose or doxycycline p. 496 for 7 days
- Alternatively, erythromycin p. 471.
  Suggested duration of treatment 14 days

Antibacterial therapy for gonorrhoea: uncomplicated
Contact tracing recommended. Consider chlamydia co-infection. Choice of alternative antibacterial regimen depends on locality where infection acquired.
- Azithromycin p. 469 + i/m ceftriaxone
  Suggested duration of treatment is a single-dose of each antibacterial
- Alternatively, when parenteral administration is not possible, cefixime p. 457 + azithromycin
  Suggested duration of treatment is a single-dose of each antibacterial
- Alternatively, if micro-organism is sensitive to a quinolone, ciprofloxacin p. 490 + azithromycin
  Suggested duration of treatment is a single-dose of each antibacterial
446 Bacterial infection

- Pharyngeal infection, azithromycin p. 469 + i/m ceftriaxone
  
  Suggested duration of treatment is a single-dose of each antibacterial

Antibacterial therapy for pelvic inflammatory disease

Contact tracing recommended.
- Doxycycline p. 496 + metronidazole p. 475 + single-dose of i/m ceftriaxone p. 459 or ofloxacin p. 494 + metronidazole
  
  Suggested duration of treatment 14 days (except i/m ceftriaxone p. 459).
  
  In severely ill patients initial treatment with doxycycline p. 496 + i/v ceftriaxone p. 459 + i/v metronidazole p. 475, then switch to oral treatment with doxycycline + metronidazole to complete 14 days’ treatment

Antibacterial therapy for early syphilis (infection of less than 2 years)

Contact tracing recommended.
- Benzathine benzylpenicillin [unlicensed]
  
  Suggested duration of treatment single-dose (repeat dose after 7 days for women in the third trimester of pregnancy)
  
  Alternatively, doxycycline p. 496 or erythromycin
  
  Suggested duration of treatment 14 days

Antibacterial therapy for late latent syphilis (asymptomatic infection of more than 2 years)

Contact tracing recommended.
- Benzathine benzylpenicillin [unlicensed]
  
  Suggested duration of treatment once weekly for 2 weeks

  Alternatively, doxycycline p. 496
  
  Suggested duration of treatment 28 days

Asymptomatic contacts of patients with infectious syphilis

- Doxycycline p. 496
  
  Suggested duration of treatment 14 days

Musculoskeletal system infections, bacterial

Antibacterial therapy for osteomyelitis

Seek specialist advice if chronic infection or prostheses present.
- Flucloxacillin p. 486
  
  Consider adding fusidic acid p. 463 or rifampicin p. 508 for initial 2 weeks.
  
  Suggested duration of treatment 6 weeks for acute infection

  If penicillin-allergic, clindamycin p. 467
  
  Consider adding fusidic acid or rifampicin for initial 2 weeks.
  
  Suggested duration of treatment 6 weeks for acute infection

  If meticillin-resistant Staphylococcus aureus suspected, vancomycin p. 465 (or teicoplanin p. 464)
  
  Consider adding fusidic acid or rifampicin for initial 2 weeks.
  
  Suggested duration of treatment 6 weeks for acute infection

Antibacterial therapy for septic arthritis

Seek specialist advice if prostheses present.
- Flucloxacillin p. 486
  
  Suggested duration of treatment 4–6 weeks (longer if infection complicated).

  If penicillin-allergic, clindamycin p. 467
  
  Suggested duration of treatment 4–6 weeks (longer if infection complicated).

  If meticillin-resistant Staphylococcus aureus suspected, vancomycin p. 465 (or teicoplanin p. 464)
  
  Suggested duration of treatment 4–6 weeks (longer if infection complicated).

  If gonococcal arthritis or Gram-negative infection suspected, cefotaxime p. 457 (or ceftriaxone p. 459)
  
  Suggested duration of treatment 4–6 weeks (longer if infection complicated; treat gonococcal infection for 2 weeks).

Nose infections, bacterial

Antibacterial therapy for sinusitis

Antibacterial should usually be used only for persistent symptoms and purulent discharge lasting at least 7 days or if severe symptoms. Also, consider antibacterial for those at high risk of serious complications (e.g. in immunosuppression, cystic fibrosis).

- Amoxicillin p. 482 (or amoxicillin p. 483) or doxycycline p. 496 or clarithromycin p. 470 (or azithromycin p. 469 or erythromycin p. 471)
  
  Suggested duration of treatment 7 days.

  Consider oral co-amoxiclav p. 484 if no improvement after 48 hours.

  In severe infection, initial parenteral therapy with co-amoxiclav or cefuroxime p. 460 may be required.

Oral bacterial infections

Antibacterial drugs should only be prescribed for the treatment of oral infections on the basis of defined need. They may be used in conjunction with (but not as an alternative to) other appropriate measures, such as providing drainage or extracting a tooth.

The ‘blind’ prescribing of an antibacterial for unexplained pyrexia, cervical lymphadenopathy, or facial swelling can lead to difficulty in establishing the diagnosis. In severe oral infections, a sample should always be taken for bacteriology.

Oral infections which may require antibacterial treatment include acute periapical or periodontal abscess, cellulitis, acutely created oral-antral communication (and acute sinusitis), severe pericoronitis, localised osteitis, acute necrotising ulcerative gingivitis, and destructive forms of chronic periodontal disease. Most of these infections are readily resolved by the early establishment of drainage and removal of the cause (typically an infected necrotic pulp). Antibacterials may be required if treatment has to be delayed, in immunocompromised patients, or in those with conditions such as diabetes or Paget’s disease. Certain rarer infections including bacterial sialadenitis, osteomyelitis, actinomycosis, and infections involving fascial spaces such as Ludwig’s angina, require antibiotics and specialist hospital care.

Antibacterial drugs may also be useful after dental surgery in some cases of spreading infection. Infection may spread to involve local lymph nodes, to fascial spaces (where it can cause airway obstruction), or into the bloodstream (where it can lead to cavernous sinus thrombosis and other serious complications). Extension of an infection can also lead to...
maxillary sinusitis; osteomyelitis is a complication, which usually arises when host resistance is reduced.

If the oral infection fails to respond to antibacterial treatment within 48 hours the antibacterial should be changed, preferably on the basis of bacteriological investigation. Failure to respond may also suggest an incorrect diagnosis, lack of essential additional measures (such as drainage), poor host resistance, or poor patient compliance.

Combination of a penicillin (or a macrolide) with metronidazole p. 475 may sometimes be helpful for the treatment of severe oral infections or oral infections that have not responded to initial antibacterial treatment.

**Penicillins**

Phenoxymethylpenicillin p. 481 is effective for dentoalveolar abscess.

**Broad-spectrum penicillins**

Amoxicillin p. 482 is as effective as phenoxymethylpenicillin p. 481 but is better absorbed; however, it may encourage emergence of resistant organisms.

Like phenoxymethylpenicillin, amoxicillin is ineffective against bacteria that produce beta-lactamases. Amoxicillin may be useful for short course oral regimens. Co-amoxiclav p. 484 is active against beta-lactamase-producing bacteria that are resistant to amoxicillin. Co-amoxiclav may be used for severe dental infection with spreading cellulitis or dental infection not responding to first-line antibacterial treatment.

**Cephalosporins**

The cephalosporins offer little advantage over the penicillins in dental infections, often being less active against anaerobes. Infections due to oral streptococci (often termed viridans streptococci) which become resistant to penicillin are usually also resistant to cephalosporins. This is of importance in the case of patients who have had rheumatic fever and are on long-term penicillin therapy. Cefalexin p. 456 and cefadroxil p. 458 have been used in the treatment of oral infections.

**Tetracyclines**

In adults, tetracyclines can be effective against oral anaerobes but the development of resistance (especially by oral streptococci) has reduced their usefulness for the treatment of acute oral infections; they may still have a role in the treatment of destructive (refractory) forms of periodontal disease. Doxycycline p. 496 has a longer duration of action than tetracycline p. 498 or oxytetracycline p. 498 and need only be given once daily; it is reported to be more active against anaerobes than some other tetracyclines.

Doxycycline may have a role in the treatment of recurrent aphthous ulceration, or as an adjunct to gingival scaling and root planing for periodontitis.

**Macrolides**

The macrolides are an alternative for oral infections in penicillin-allergic patients or where a beta-lactamase producing organism is involved. However, many organisms are now resistant to macrolides or rapidly develop resistance; their use should therefore be limited to short courses.

**Clindamycin**

Clindamycin p. 467 should not be used routinely for the treatment of oral infections because it may be no more effective than penicillins against anaerobes and there may be cross-resistance with erythromycin-resistant bacteria. Clindamycin can be used for the treatment of dentoalveolar abscess that has not responded to penicillin or to metronidazole p. 475.

**Metronidazole and tinidazole**

Metronidazole p. 475 is an alternative to a penicillin for the treatment of many oral infections where the patient is allergic to penicillin or the infection is due to beta-lactamase-producing anaerobes. It is the drug of first choice for the treatment of acute necrotising ulcerative gingivitis (Vincent’s infection) and pericoronitis; amoxicillin p. 482 is a suitable alternative. For these purposes metronidazole for 3 days is sufficient, but the duration of treatment may need to be longer in pericoronitis. Tinidazole p. 476 is licensed for the treatment of acute ulcerative gingivitis.

**Respiratory system infections, bacterial**

**Antibacterial therapy for haemophilus influenzae epiglottitis**

- Cefotaxime p. 457 (or ceftriaxone p. 459)
- If history of immediate hypersensitivity reaction to penicillin or to cephalosporins, chloramphenicol p. 452

**Antibacterial therapy for chronic bronchitis: acute exacerbations**

Treat if increase in sputum purulence accompanied by an increase in sputum volume or increase in dyspnoea.

- Amoxicillin p. 482 (or ampicillin p. 483) or a tetracycline p. 496
  - Some pneumococci and Haemophilus influenzae strains tetracycline-resistant; approx. 20% H. influenzae strains amoxicillin-resistant
  - **Suggested duration of treatment** 5 days; longer treatment may be necessary in severely ill patients
- **Alternative**, clarithromycin p. 470 (or azithromycin p. 469 or erythromycin p. 471)
  - **Suggested duration of treatment** 5 days; longer treatment may be necessary in severely ill patients

**Antibacterial therapy for pneumonia: low-severity community-acquired**

- Amoxicillin p. 482 (or ampicillin p. 483)
  - Pneumococci with decreased penicillin sensitivity being isolated, but not yet common in UK.
  - If atypical pathogens suspected, add clarithromycin p. 470 (or azithromycin p. 469 or erythromycin p. 471).
  - If staphylococci suspected (e. g. in influenza or measles), add flucloxacinil p. 486.
  - **Suggested duration of treatment** 7 days (14–21 days for infections caused by staphylococci)
- **Alternatives**, doxycycline p. 496 or clarithromycin (or azithromycin or erythromycin)
  - **Suggested duration of treatment** 7 days (14–21 days for infections caused by staphylococci)

**Antibacterial therapy for pneumonia: moderate-severity community-acquired**

- Amoxicillin p. 482 (or ampicillin p. 483) + clarithromycin p. 470 (or azithromycin p. 469 or erythromycin p. 471) or doxycycline p. 496 alone
  - Pneumococci with decreased penicillin sensitivity being isolated, but not yet common in UK.
  - If meticillin-resistant Staphylococcus aureus suspected, add vancomycin p. 465 (or teicoplanin p. 464).
  - **Suggested duration of treatment** 7 days (14–21 days for infections caused by staphylococci)
Antibacterial therapy for pneumonia: high-severity community-acquired

- Benzylpenicillin sodium p. 480 + clarithromycin p. 470 (or azithromycin p. 469 or erythromycin p. 471) or benzylpenicillin sodium + doxycycline
  If meticillin-resistant Staphylococcus aureus suspected, add vancomycin p. 465 (or teicoplanin p. 464).
  **Suggested duration of treatment 7–10 days** (may extend treatment to 14–21 days in some cases e.g. if staphylococci suspected)
- If life-threatening infection, or if Gram-negative infection suspected, or if co-morbidities present, or if living in long-term residential or nursing home, co-amoxiclav p. 484 + clarithromycin (or azithromycin or erythromycin)
  If meticillin-resistant Staphylococcus aureus suspected, add vancomycin (or teicoplanin)
  **Suggested duration of treatment 7–10 days** (may extend treatment to 14–21 days in some cases e.g. if staphylococci or Gram-negative enteric bacilli suspected)
- Alternatives if life-threatening infection, or if Gram-negative infection suspected, or if co-morbidities present, or if living in long-term residential or nursing home, cefuroxime p. 460 + clarithromycin (or azithromycin or erythromycin) or cefotaxime (or ceftriaxone p. 459) + clarithromycin (or azithromycin or erythromycin)
  If meticillin-resistant Staphylococcus aureus suspected, add vancomycin (or teicoplanin).
  **Suggested duration of treatment 7–10 days** (may extend treatment to 14–21 days in some cases e.g. if staphylococci or Gram-negative enteric bacilli suspected)

Antibacterial therapy for pneumonia possibly caused by atypical pathogens

- Clarithromycin p. 470 (or azithromycin p. 469 or erythromycin p. 471)
  If high-severity Legionella infection, add rifampicin p. 508 for the first few days.
  **Suggested duration of treatment 14 days** (usually 7–10 days for Legionella)
- Alternative if Legionella infection suspected, a quinolone
  If high-severity Legionella infection, add clarithromycin (or azithromycin or erythromycin) or rifampicin for the first few days.
  **Suggested duration of treatment usually 7–10 days**
- Alternative for chlamydial or mycoplasma infections, doxycycline p. 496
  **Suggested duration of treatment 14 days**

Antibacterial therapy for pneumonia: hospital-acquired

- Early-onset infection less than 5 days after admission to hospital, co-amoxiclav p. 484 or cefuroxime
  If life-threatening infection, or if history of antibiotic treatment in the last 3 months, or if resistant micro-organisms suspected, treat as for late-onset hospital-acquired pneumonia.
  **Suggested duration of treatment 7 days**
- Late-onset infection (more than 5 days after admission to hospital), an antipseudomonal penicillin (e.g. piperacillin with tazobactam p. 479) or a broad-spectrum cephalosporin (e.g. cefazidime p. 458) or another antipseudomonal beta-lactam or a quinolone (e.g. ciprofloxacin p. 490)
  If meticillin-resistant Staphylococcus aureus suspected, add vancomycin p. 465.
  For severe illness caused by Pseudomonas aeruginosa, consider adding an aminoglycoside.
  **Suggested duration of treatment 7 days** (longer if Pseudomonas aeruginosa confirmed)

Antibacterial therapy for impetigo: small areas of skin infected

Seek local microbiology advice before using topical treatment in hospital.

- Topical fusidic acid p. 1008
  **Suggested duration of treatment 7 days** is usually adequate (max. 10 days).
- Alternatively, if meticillin-resistant Staphylococcus aureus, topical mupirocin p. 1009
  **Suggested duration of treatment 7 days** is usually adequate (max. 10 days).

Impetigo: widespread infection

- Oral flucloxacillin p. 486
  If streptococci suspected in severe infection, add phenoxymethylpenicillin p. 481.
  **Suggested duration of treatment 7 days**.
- If penicillin-allergic, oral clarithromycin p. 470 (or azithromycin p. 469 or erythromycin p. 471)
  **Suggested duration of treatment 7 days**.

Antibacterial therapy for erysipelas

- Phenoxymethylpenicillin p. 481 or benzylpenicillin sodium
  If severe infection, replace phenoxymethylpenicillin or benzylpenicillin sodium with high-dose flucloxacillin p. 486
  **Suggested duration of treatment at least 7 days**.
- If penicillin-allergic, clindamycin p. 467 or clarithromycin p. 470 (or azithromycin p. 469 or erythromycin p. 471)
  **Suggested duration of treatment at least 7 days**.

Antibacterial therapy for cellulitis

- Flucloxacillin p. 486 (high-dose)
  If streptococcal infection confirmed, replace flucloxacillin with phenoxymethylpenicillin p. 481 or benzylpenicillin sodium p. 480
  If Gram-negative bacteria or anaerobes suspected, use broad-spectrum antibiotics.
- If penicillin-allergic, clindamycin p. 467 or clarithromycin p. 470 (or azithromycin p. 469 or erythromycin p. 471) or vancomycin p. 465 (or teicoplanin p. 464)
  If Gram-negative bacteria suspected, use broad-spectrum antibacterials.

Antibacterial therapy for animal and human bites

Cleanse wound thoroughly. For tetanus-prone wound, give human tetanus immunoglobulin p. 1065 (with a tetanus-containing vaccine if necessary, according to immunisation history and risk of infection). Consider rabies prophylaxis for bites from animals in endemic countries. Assess risk of blood-borne viruses (including HIV, hepatitis B and C) and give appropriate prophylaxis to prevent viral spread.

Co-amoxiclav p. 484.
- If penicillin-allergic, doxycycline p. 496 + metronidazole p. 475
Antibacterial therapy for mastitis during breast-feeding

Treat if severe, if systemically unwell, if nipple fissure present, if symptoms do not improve after 12–24 hours of effective milk removal, or if culture indicates infection.

- Flucloxacillin p. 486, if penicillin-allergic, erythromycin

Continue breast-feeding or expressing milk during treatment. Suggested duration of treatment 10–14 days.

AMINOGLYCOSIDES

Aminoglycosides

These include amikacin p. 450, gentamicin p. 450, neomycin sulfate p. 451, streptomycin p. 451, and tobramycin p. 452. All are bactericidal and active against some Gram-positive and many Gram-negative organisms. Amikacin, gentamicin, and tobramycin are also active against Pseudomonas aeruginosa; streptomycin is active against Mycobacterium tuberculosis and is now almost entirely reserved for tuberculosis.

The aminoglycosides are not absorbed from the gut (although there is a risk of absorption in inflammatory bowel disease and liver failure) and must therefore be given by injection for systemic infections.

Gentamicin is the aminoglycoside of choice in the UK and is used widely for the treatment of serious infections. It has a broad spectrum but is inactive against anaerobes and has poor activity against haemolytic streptococci and pneumococci. When used for the ‘blind’ therapy of undiagnosed serious infections it is usually given in conjunction with a penicillin or metronidazole p.

Tobramycin can be administered by nebuliser or by inhalation of powder on a cyclical basis (28 days of tobramycin followed by a 28-day tobramycin-free interval) for the treatment of chronic pulmonary Ps. aeruginosa infection in cystic fibrosis; however, resistance may develop and some patients do not respond to treatment.

Neomycin sulfate is too toxic for parenteral administration and can only be used for infections of the skin or mucous membranes or to reduce the bacterial population of the colon prior to bowel surgery or in hepatic failure. Oral administration may lead to malabsorption. Small amounts of neomycin sulfate may be absorbed from the gut in patients with hepatic failure and, as these patients may also be uraemic, cumulation may occur with resultant ototoxicity.

Once daily dosage

Once daily administration of aminoglycosides is more convenient, provides adequate serum concentrations, and in many cases has largely superseded multiple daily dose regimens (given in 2–3 divided doses during the 24 hours). Local guidelines on dosage and serum concentrations should be consulted. A once-daily, high-dose regimen of an aminoglycoside should be avoided in patients with endocarditis due to Gram-positive bacteria, HACEK endocarditis, burns of more than 20% of the total body surface area, or creatinine clearance less than 20 mL/minute. There is insufficient evidence to recommend a once daily, high-dose regimen of an aminoglycoside in pregnancy.

Serum concentrations

Serum concentration monitoring avoids both excessive and subtherapeutic concentrations thus preventing toxicity and ensuring efficacy. Serum-aminoglycoside concentrations should be measured in patients receiving parenteral aminoglycosides and must be determined in the elderly, in obesity, and in cystic fibrosis, or if high doses are being given, or if there is renal impairment.

Aminoglycosides (by injection)

- CONTRA-INDICATIONS Myasthenia gravis (aminoglycosides may impair neuromuscular transmission)
- CAUTIONS
  - GENERAL CAUTIONS
    - Care must be taken with dosage (the main side-effects of the aminoglycosides are dose-related)- conditions characterised by muscular weakness (aminoglycosides may impair neuromuscular transmission) - if possible, dehydration should be corrected before starting an aminoglycoside
  - SPECIFIC CAUTIONS
    - Whenever possible, parenteral treatment should not exceed 7 days
  - INTERACTIONS → Appendix 1 (aminoglycosides).
    - If possible, aminoglycosides should not be given with potentially ototoxic drugs (e.g. cisplatin). Administration of an aminoglycoside and of an ototoxic diuretic (e.g. furosemide) should be separated by as long a period as practicable.
  - SIDE-EFFECTS
    - Rare Antimicrobial-associated colitis - electrolyte disturbances - hypocalcaemia - hypokalaemia - hypomagnesaemia on prolonged therapy - nausea - peripheral neuropathy - stomatitis - vomiting
    - Very rare Blood disorders - CNS effects - convulsions - encephalopathy - headache
    - Frequency not known Auditory damage - impaired neuromuscular transmission - impaired neuromuscular transmission - irreversible ototoxicity - nephrotoxicity - transient myasthenic syndrome in patients with normal neuromuscular function with large doses given during surgery - vestibular damage
  - SIDE-EFFECTS, FURTHER INFORMATION
    - Nephrotoxicity Occurs most commonly in the elderly; therefore, monitoring is particularly important in these patients, who may require reduced doses.
    - PREGNANCY There is a risk of auditory or vestibular nerve damage in the infant when aminoglycosides are used in the second and third trimesters of pregnancy. The risk is greatest with streptomycin. The risk is probably very small with gentamicin and tobramycin, but their use should be avoided unless essential.
If given during pregnancy, serum-aminoglycoside concentration monitoring is essential.

- **RENAL IMPAIRMENT** If there is impairment of renal function, the interval between doses must be increased; if the renal impairment is severe, the dose itself should be reduced as well. Excretion of aminoglycosides is principally via the kidney and accumulation occurs in renal impairment. Otoxicity and nephrotoxicity occur commonly in patients with renal failure. A once-daily, high-dose regimen of an aminoglycoside should be avoided in patients with a creatinine clearance less than 20 mL/minute.

Serum-aminoglycoside concentrations must be monitored in patients with renal impairment; earlier and more frequent measurement of aminoglycoside concentration may be required.

- **MONITORING REQUIREMENTS**
  - Serum concentration monitoring avoids both excessive and subtherapeutic concentrations thus preventing toxicity and ensuring efficacy.
  - Serum-aminoglycoside concentrations should be measured in all patients receiving parenteral aminoglycosides and must be determined in the elderly, obesity, if high doses are being given and in cystic fibrosis.
  - In patients with normal renal function, aminoglycoside concentrations should be measured after 3 or 4 doses of a multiple daily dose regimen and after a dose change. For multiple daily dose regimens, blood samples should be taken approximately 1 hour after intramuscular or intravenous administration (‘peak’ concentration) and also just before the next dose (‘trough’ concentration). If the pre-dose (‘trough’) concentration is high, the interval between doses must be increased. If the post-dose (‘peak’) concentration is high, the dose must be decreased. For once daily dose regimens, consult local guidelines on serum concentration monitoring.
  - Renal function should be assessed before starting an aminoglycoside and during treatment.
  - Auditory and vestibular function should also be monitored during treatment.

**INDICATIONS AND DOSE**

**Gentamicin**

**AMIKACIN (Non-proprietary)**

- **Indications and dosages**
  - **Serious Gram-negative infections resistant to gentamicin**
    - Multiple daily dose regimen
    - Adult: 15 mg/kg daily in 2 divided doses, increased to 22.5 mg/kg daily in 3 divided doses for up to 10 days, higher dose to be used in severe infections; maximum 1.5 g per day; maximum 15 g per course
  - **Serious Gram-negative infections resistant to gentamicin**
    - Once daily dose regimen: pre-dose (‘trough’) concentration should be less than 5 mg/litre.
  - **Indications for administration**
    - For intravenous infusion (Amikin®); intermittent in Glucose 5% or Sodium chloride 0.9%. To be given over 30 minutes.
  - **Prescribing and dispensing information**
    - Once daily dose regimens not to be used for endocarditis, febrile neutropenia, or meningitis. Consult local guidelines.
  - **Medication forms**
    - There can be variation in the licensing of different medicines containing the same drug.
    - **Solution for injection**
      - Amikacin (as Amikacin sulfate) 250 mg per 1 ml
      - Amikacin 500mg/2ml solution for injection vials | 5 vial (Actavis) £60.00
      - Amikin (Bristol-Myers Squibb Pharmaceuticals Ltd)
      - Amikacin (as Amikacin sulfate) 50 mg per 1 ml
      - Amikin 100mg/2ml solution for injection vials | 5 vial (Potter) £10.33

**Amikacin**

**INDICATIONS AND DOSE**

Gram-positive bacterial endocarditis or HACEK endocarditis (in combination with other antibacterials)

- **By intramuscular injection or by slow intravenous injection or by intravenous infusion**
  - Adult: 1 mg/kg every 12 hours, intravenous injection to be administered over at least 3 minutes, to be given in a multiple daily dose regimen
  - Septicaemia | Meningitis and other CNS infections | Biliary-tract infection | Acute pyelonephritis | Endocarditis | Pneumonia in hospital patients | Adjunct in listerial meningitis | Prostatitis

- **By intravenous infusion**
  - Adult: 3–5 mg/kg daily in 3 divided doses, to be given in a multiple daily dose regimen, divided doses to be given every 8 hours, intravenous injection to be administered over at least 3 minutes
  - Surgical prophylaxis (including joint replacement surgery)
    - By slow intravenous injection
      - Adult: 1.5 mg/kg, intravenous injection to be administered over at least 3 minutes, administer dose up to 30 minutes before the procedure, dose may be repeated every 8 hours for high-risk procedures and joint replacement surgery; up to 3 further doses may be given
  - By intravenous infusion
    - Adult: 5 mg/kg for 1 dose, administer dose up to 30 minutes before the procedure

**Doses at extremes of body-weight**

To avoid excessive dosage in obese patients, use ideal weight for height to calculate dose and monitor serum-gentamicin concentration closely.

**Side-effects**

- Uncommon Rash

**Monitoring requirements**

- Multiple daily dose regimen: one-hour (‘peak’) serum concentration should not exceed 30 mg/litre; pre-dose (‘trough’) concentration should be less than 10 mg/litre.

**Side-effects**

- Uncommon Rash

**Monitoring requirements**

For multiple daily dose regimen, one-hour (‘peak’) serum concentration should be 5–10 mg/litre; pre-dose (‘trough’) concentration should be less than 5 mg/litre.
Neomycin sulfate

**INDICATIONS AND DOSE**

**BY MOUTH**

- **Adult:** 1 g every 1 hour for 4 hours, then 1 g every 4 hours for 2–3 days

**Hepatic coma**

- **Adult:** Up to 4 g daily in divided doses usually for 5–7 days

**CONTRA-INDICATIONS**

Intestinal obstruction - myasthenia gravis (aminoglycosides may impair neuromuscular transmission).

**CAUTIONS**

Avoid prolonged use

**CAUTIONS, FURTHER INFORMATION**

Although neomycin is associated with the same cautions as other aminoglycosides it is generally considered too toxic for systemic use.

**INTERACTIONS**

→ Appendix 1 (aminoglycosides).

**SIDE-EFFECTS**

- **Common or very common** Rash
- **Frequency not known** Impaired intestinal absorption with steatorrhea and diarrhoea - increased salivation

**SIDE-EFFECTS, FURTHER INFORMATION**

Although neomycin is associated with the same side effects as other aminoglycosides it is generally considered toxic for systemic use.

**PRESCRIBING AND DISPENSING INFORMATION**

Local guidelines may vary in the dosing advice provided for once daily administration.

**MEDICATIONS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops, oral suspension, oral solution, cream

**Solution for injection**

- **GENTAMICIN (Non-proprietary)**
  - Gentamicin (as Gentamicin sulfate) 5 mg per 1 ml Gentamicin Intrathecal 5mg/1ml solution for injection ampoules | 5 ampoule £22.50 (Hospital only)
  - Gentamicin (as Gentamicin sulfate) 10 mg per 1 ml Gentamicin Paediatric 20mg/2ml solution for injection vials | 5 vial £11.25
  - Gentamicin (as Gentamicin sulfate) 40 mg per 1 ml Gentamicin 80mg/2ml solution for injection vials | 5 vial £20.00
  - Gentamicin 80mg/2ml solution for injection ampoules | 10 ampoule £30.00
  - **Cidomycin** (Sanofi)
    - Gentamicin (as Gentamicin sulfate) 40 mg per 1 ml Cidomycin Adult Injectable 80mg/2ml solution for injection vials | 5 vial £6.88
    - Cidomycin Adult Injectable 80mg/2ml solution for injection ampoules | 5 ampoule £6.88

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, cream

**Tablet**

- **NEOMYCIN SULFATE (Non-proprietary)**
  - Neomycin sulfate 500 mg Neomycin 500mg tablets | 100 tablet £3.49

**Streptomycin**

**INDICATIONS AND DOSE**

Tuberculosis, resistant to other treatment, in combination with other drugs

**BY DEEP INTRAMUSCULAR INJECTION**

- **Adult:** 15 mg/kg daily (max. per dose 1 g), reduce dose in those under 50 kg and those over 40 years

**Adjunct to doxycycline in brucellosis (administered on expert advice)**

**BY DEEP INTRAMUSCULAR INJECTION**

- **Adult:** (consult local protocol)

**Enterococcal endocarditis**

- **Adult:** (consult local protocol)

**UNLICENSED USE**

Use in tuberculosis is an unlicensed indication.

**Important safety information**

Side-effects increase after a cumulative dose of 100 g, which should only be exceeded in exceptional circumstances.

**SIDE-EFFECTS**

- **Common or very common** Rash
- **Frequency not known** Hypersensitivity reactions - paraesthesia of mouth

**RENAI IMPAIRMENT** Should preferably be avoided. If essential, use with great care and consider dose reduction.

**MONITORING REQUIREMENTS**

- One-hour (‘peak’) concentration should be 15–40 mg/litre; pre-dose (‘trough’) concentration should be less than 5 mg/litre (less than 1 mg/litre in renal impairment or in those over 50 years).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: powder for solution for injection
Tobramycin

INDICATIONS AND DOSE
Septicaemia | Meningitis and other CNS infections | Biliary-tract infection | Acute pyelonephritis or prostatitis | Pneumonia in hospital patients
BY INTRAMUSCULAR INJECTION OR BY SLOW INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION
> Adult: 3 mg/kg daily in 3 divided doses; increased if necessary up to 5 mg/kg daily in 3–4 divided doses, increased dose used in severe infection; dose to be reduced back to 3 mg/kg as soon as clinically indicated

Inhalation
BY INTRAMUSCULAR INJECTION
> Adult: 2–3 mg/kg for 1 dose

Chronic Pseudomonas aeruginosa infection in patients with cystic fibrosis
BY INHALATION OF NEBULISED SOLUTION
> Adult: 300 mg every 12 hours for 28 days, subsequent courses repeated after 28-day interval without tobramycin nebuliser solution

BY INHALATION OF POWDER
> Adult: 112 mg every 12 hours for 28 days, subsequent courses repeated after 28-day interval without tobramycin inhalation powder

Doses at extremes of body-weight
To avoid excessive dosage in obese patients, use ideal weight for height to calculate parental dose and monitor serum-tobramycin concentration closely.

CAUTIONS
> When used by inhalation Severe haemoptysis—risk of further haemorrhage

SIDE-EFFECTS
> Uncommon
> With intramuscular use Rash
> With intravenous use Rash
> Frequency not known
> When used by inhalation Bronchospasm—cough (more frequent by inhalation of powder) — dysphonia — epistaxis — haemoptysis — laryngitis — mouth ulcers — pharyngitis — salivary hypersecretion — taste disturbances

MONITORING REQUIREMENTS
> With intramuscular use or intravenous use One-hour (‘peak’) serum concentration should not exceed 10 mg/litre; pre-dose (‘trough’) concentration should be less than 2 mg/litre.
> When used by inhalation Measure lung function before and after initial dose of tobramycin and monitor for bronchospasm; if bronchospasm occurs in a patient not using a bronchodilator, repeat test using bronchodilator. Monitor renal function before treatment and then annually.

DIRECTIONS FOR ADMINISTRATION
> With intravenous use For intravenous infusion (Nebcin®); intermittent or via drip tubing in Glucose 5% or Sodium chloride 0.9%. For adult intermittent infusion suggested volume 50–100 mL, given over 20–60 minutes.
> When used by inhalation Other inhaled drugs should be administered before tobramycin.

PATIENT AND CARER ADVICE
Patient counselling is advised for Tobramycin dry powder for inhalation (administration).

NATIONAL FUNDING/ACCESS DECISIONS
NICe technology appraisals (TAs)
> Tobramycin dry powder inhalation for pseudomonal lung infection in cystic fibrosis (March 2013) NICE TA276
Tobramycin dry powder for inhalation is recommended for chronic pulmonary infection caused by Pseudomonas aeruginosa in patients with cystic fibrosis only if there is an inadequate response to colistimethate sodium, or if colistimethate sodium cannot be used because of contraindications or intolerance. The manufacturer must provide tobramycin dry powder for inhalation at the discount agreed as part of the patient access scheme to the secondary, tertiary and secondary care in the NHS. Patients currently receiving tobramycin dry powder for inhalation can continue treatment until they and their clinician consider it appropriate to stop. www.nice.org.uk/TA276

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

Solution for injection
> TOBRAMYCIN (Non-proprietary)
Tobramycin (as Tobramycin sulfate) 40 mg per 1 ml Tobramycin 40mg/2ml solution for injection vials | 10 vial | £37.00 | 10 vial (Hospital only) Tobramycin 80mg/2ml solution for injection vials | 5 vial | £20.80 | 10 vial | £37.72 | 10 vial (Hospital only) Tobramycin 240mg/6ml solution for injection vials | 1 vial | £19.20
> Brands may include Nebcin

Inhalation powder
> Tobi Podhaler (Novartis Pharmaceuticals UK Ltd)
Tobramycin 28 mg Tobi Podhaler 28mg inhalation powder capsules with device | 56 capsule | £44.50 | 224 capsule | £1,790.00

Nebuliser liquid
> Bramitol (Chesi Ltd)
Tobramycin 75 mg per 1 ml Bramitol 300mg/4ml nebuliser solution 4ml ampoules | 56 ampoule | £1,177.00
> TOBI (Novartis Pharmaceuticals UK Ltd)
Tobramycin 60 mg per 1 ml Tobi 300mg/5ml nebuliser solution 5ml ampoules | 56 ampoule | £1,187.20 DT price | £1,187.20
> Brands may include Tymbrel

BACTERIAL TRANSEPITIDATION INHIBITORS
Chloramphenicol

DRUG ACTION
Chloramphenicol is a potent broad-spectrum antibiotic.

INDICATIONS AND DOSE
Life threatening infections particularly those caused by Haemophilus influenzae | Typhoid fever
BY MOUTH OR BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION
> Adult: 12.5 mg/kg every 6 hours, in exceptional cases dose can be doubled for severe infections such as septicaemia and meningitis, providing high doses reduced as soon as clinically indicated

CONTRA-INDICATIONS
Acute porphyrias p. 864

CAUTIONS
Avoid repeated courses and prolonged treatment

INTERACTIONS
> Appendix 1 (chloramphenicol).

SIDE-EFFECTS
Blood disorders—depression—diarrhoea—dry mouth—erythema multiforme—glossitis—headache—nausea—nighturnal haemoglobinuria—optic neuritis—peripheral neuritis—reversible and irreversible aplastic anaemia (with reports of resulting leukaemia)—stomatitis—urticaria—vomiting

SIDE-EFFECTS, FURTHER INFORMATION
Associated with serious haematological side-effects when given systemically and should therefore be reserved for the treatment of life-threatening infections.

PREGNANCY
Manufacturer advises avoid; neonatal ‘grey-baby syndrome’ if used in third trimester.

BREAST FEEDING
Manufacturer advises avoid; use another antibiotic; may cause bone-marrow toxicity in infant;
concentration in milk usually insufficient to cause ‘grey syndrome’.

- **HEPATIC IMPAIRMENT**
  Avoid if possible—increased risk of bone-marrow depression.
  Reduce dose and monitor plasma-cloramphenicol concentration in hepatic impairment.

- **RENAL IMPAIRMENT**
  Avoid in severe renal impairment unless no alternative; dose-related depression of haematopoiesis.

- **MONITORING REQUIREMENTS**
  Plasma concentration monitoring preferred in the elderly.
  Recommended peak plasma concentration (approx. 2 hours after administration by mouth; intravenous injection or infusion) 10–25 mg/litre; pre-dose (‘ trough’ ) concentration should not exceed 15 mg/litre.
  Blood counts required before and periodically during treatment.

- **DIRECTIONS FOR ADMINISTRATION**
  For *intra venous infusion* (*Kemicetine*®), give intermittently or via drip tubing in Glucose 5% or Sodium chloride 0.9%.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  **Capsule**
  - **CHLORAMPHENICOL (Non-proprietary)**
  - Chloramphenicol 250 mg Chloramphenicol 250mg capsules | 60 capsule (£377.00)

  **Powder for solution for injection**
  - **ELECTROLYTES:** May contain Sodium
  - Kemicetine (Pfizer Ltd)
  - Chloramphenicol (as Chloramphenicol sodium succinate) 1 gram
  - Kemicetine 1g powder for solution for injection vials | 1 vial (£1.39)

### CARBAPENEMES

**Carbapenems**

The carbapenems are beta-lactam antibacterials with a broad-spectrum of activity which includes many Gram-positive and Gram-negative bacteria, and anaerobes; *imipenem* (imipenem with cilastatin p. 454) and meropenem p. 454 have good activity against *Pseudomonas aeruginosa*. The carbapenems are not active against meticillin-resistant *Staphylococcus aureus* and *Enterococcus faecium*.

Imipenem (imipenem with cilastatin) and meropenem are used for the treatment of severe hospital-acquired infections and polymicrobial infections including septicaemia, hospital-acquired pneumonia, intra-abdominal infections, skin and soft-tissue infections, and complicated urinary-tract infections.

Ertapenem below is licensed for treating abdominal and surgical infections, skin and soft-tissue infections, and complicated infections and polymicrobial infections including those of other beta-lactam antibiotics. Meropenem has less specific enzyme inhibitor, which blocks its renal metabolism. Meropenem and ertapenem are stable to the renal enzyme which inactivates imipenem and therefore can be given without cilastatin.

Side-effects of imipenem with cilastatin are similar to those of other beta-lactam antibiotics. Meropenem has less seizure-inducing potential and can be used to treat central nervous system infection.

### Ertapenem

#### INDICATIONS AND DOSE

**Abdominal infections | Acute gynaecological infections | Community-acquired pneumonia**

**BY INTRAVENOUS INFUSION**
- Adult: 1 g once daily

**Diabetic foot infections of the skin and soft tissue**

**BY INTRAVENOUS INFUSION**
- Adult: 1 g once daily

**Surgical prophylaxis, colorectal surgery**

**BY INTRAVENOUS INFUSION**
- Adult: 1 g for 1 dose, dose to be completed within 1 hour before surgery

- **CAUTIONS**
  - CNS disorders—risk of seizures • elderly

- **INTERACTIONS**
  - Appendix 1 (ertapenem).

- **SIDE-EFFECTS**
  - Common or very common
    - Diarrhoea • headache • injection-site reactions • nausea • pruritus • raised platelet count • rash (also reported with eosinophilia and systemic symptoms) • vomiting
  - Uncommon
    - Abdominal pain • anorexia • antibiotic-associated colitis • asthenia • bradycardia • chest pain • confusion • constipation • dizziness • dry mouth • dyspepsia • dysphoria • hypotension • melaena • oedema • ototoxicity • pharyngeal discomfort • raised glucose • seizures • sleep disturbances • taste disturbances
  - Rare
    - Agitation • anxiety • arrhythmia • blood disorders • cholecytitis • cough • depression • dysphagia • electrolyte disturbances • haemorrhage • hypoglycaemia • increase in blood pressure • jaundice • liver disorder • muscle cramp • nasal congestion • neutropenia • pelvic peritonitis • renal impairment • scleral disorder • syncope • thrombocytopenia • tremor • wheezing
  - Frequency not known
    - Dyskinesia • hallucinations

- **ALLERGY AND CROSS-SENSITIVITY**
  - Avoid if history of immediate hypersensitivity reaction to beta-lactam antibacterials. Use with caution in patients with sensitivity to beta-lactam antibacterials.

- **PREGNANCY**
  - Manufacturer advises avoid unless potential benefit outweighs risk.

- **BREAST FEEDING**
  - Present in milk—manufacturer advises avoid.

- **RENAL IMPAIRMENT**
  - Risk of seizures; max. 500 mg daily if eGFR less than 30 mL/minute/1.73 m².

- **DIRECTIONS FOR ADMINISTRATION**
  - For *intra venous infusion* (*Invanz®*), give intermittently in Sodium chloride 0.9%. Reconstitute 1 g with 10 mL Water for injections or Sodium chloride 0.9%; dilute requisite dose in infusion fluid to a final concentration not exceeding 20 mg/mL; give over 30 minutes; incompatible with glucose solutions.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Powder for solution for infusion**
  - **ELECTROLYTES:** May contain Sodium
  - *Invanz* (Merck Sharp & Dohme Ltd)
  - Ertapenem (as Ertapenem sodium) 1 gram
  - Invanz 1g powder for solution for infusion vials | 1 vial (£31.65)
Imipenem with cilastatin

INDICATIONS AND DOSE
Aerobic and anaerobic Gram-positive and Gram-negative infections (not indicated for CNS infections) | Hospital-acquired sepsicaemia

**BY INTRAVENOUS INFUSION**
- Adult: 500 mg every 6 hours, alternatively 1 g every 8 hours

Infection caused by *Pseudomonas* or other less sensitive organisms
Empirical treatment of infection in febrile patients with neutropenia | Life-threatening infection

**BY INTRAVENOUS INFUSION**
- Adult: 1 g every 6 hours

**CAUTIONS**
- CNS disorders | epilepsy

**INTERACTIONS**
- Appendix 1 (imipenem with cilastatin).

**SIDE-EFFECTS**
- Common or very common | Diarrhoea | eosinophilia | nausea (may reduce rate of infusion) | rash | vomiting
- Uncommon | Confusion | dizziness | drowsiness | hallucinations | hypotension | leucopenia | myoclonic activity | seizures | thrombocytopenia | thrombocytosis
- Rare | Acute renal failure | anaphylactic reactions | antibiotic-associated colitis | encephalopathy | hearing loss | hepatitis | paraesthesia | polyuria | Stevens-Johnson syndrome | taste disturbances | tooth | tongue or urine discoloration | toxic epidermal necrolysis | tremor
- Very rare | Abdominal pain | aggravation of myasthenia gravis | asthenia | ataxia | cyanosis | dyspnoea | flushing | glossitis | haemolytic anaemia | headache | heartburn | hyperhidrosis | hyperkalaemia | hyperventilation | palpitation | polyarthralgia | tachycardia | tinnitus
- Frequency not known | Neurotoxicity (at high dose, renal failure, CNS disease)

**ALLERGY AND CROSS-SENSITIVITY**
Avoid if history of immediate hypersensitivity reaction to beta-lactam antibacterials. Use with caution in patients with sensitivity to beta-lactam antibacterials.

**PREGNANCY**
Manufacturer advises avoid unless potential benefit outweighs risk (toxicity in animal studies).

**BREAST FEEDING**
Present in milk but unlikely to be absorbed.

**RENAL IMPAIRMENT**
Risk of CNS side-effects; reduce dose if eGFR less than 70 mL/minute/1.73 m² — consult product literature.

**EFFECT ON LABORATORY TESTS**
Positive Coombs’ test.

**DIRECTIONS FOR ADMINISTRATION**
For intravenous infusion dilute to a concentration of 5 mg (as imipenem)/mL in Sodium chloride 0.9%; give up to 500 mg (imipenem) over 20–30 minutes, give dose greater than 500 mg (imipenem) over 40–60 minutes.

**PRESCRIBING AND DISPENSING INFORMATION**
Dose expressed in terms of imipenem.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**

| ELECTROLYTES: May contain Sodium |
| IMIPENEM WITH CILASTATIN (Non-proprietary) |
| Cilastatin (as Cilastatin sodium) 500 mg, Imipenem (as Imipenem monohydrate) 500 mg | Primaxin IV 500mg powder for solution for infusion vials | 1 vial £12.00 |
| Cilastatin (as Cilastatin sodium) 500 mg, Imipenem (as Imipenem monohydrate) 500 mg | Primaxin 500mg powder for solution for infusion vials | 1 vial £10.00 |
| 5 vial £60.00 (Hospital only) | 10 vial £55.45–65.45 |
| Primaxin IV (Merk Sharp & Dohme Ltd) |
| Cilastatin (as Cilastatin sodium) 500 mg, Imipenem (as Imipenem monohydrate) 500 mg | Primaxin IV 500mg powder for solution for infusion vials | 1 vial £12.00 |

**Meropenem**

INDICATIONS AND DOSE
Aerobic and anaerobic Gram-positive and Gram-negative infections | Hospital acquired sepsicaemia

**BY INTRAVENOUS INFUSION OR BY INTRAVENOUS INJECTION**
- Adult: 0.5–1 g every 8 hours

Exacerbations of chronic lower respiratory-tract infection in cystic fibrosis

**BY INTRAVENOUS INFUSION OR BY INTRAVENOUS INJECTION**
- Adult: 2 g every 8 hours

Meningitis

**BY INTRAVENOUS INFUSION OR BY INTRAVENOUS INJECTION**
- Adult: 2 g every 8 hours

Endocarditis (in combination with another antibacterial)

**BY INTRAVENOUS INFUSION OR BY INTRAVENOUS INJECTION**
- Adult: 2 g every 8 hours

**UNLICENSED USE**
Not licensed for use in endocarditis.

**INTERACTIONS**
- Appendix 1 (meropenem).

**SIDE-EFFECTS**
- Common or very common | Abdominal pain | diarrhoea | disturbances in liver function tests | headache | nausea | pruritus | rash | thrombocytopenia | vomiting
- Uncommon | Eosinophilia | leucopenia | paraesthesia | thrombocytopenia
- Rare | Convulsions | Frequency not known | Antibiotic-associated colitis | haemolytic anaemia | Stevens-Johnson syndrome | toxic epidermal necrolysis

**ALLERGY AND CROSS-SENSITIVITY**
Avoid if history of immediate hypersensitivity reaction to beta-lactam antibacterials. Use with caution in patients with sensitivity to beta-lactam antibacterials.

**PREGNANCY**
Use only if potential benefit outweighs risk — no information available.

**BREAST FEEDING**
Unlikely to be absorbed (however, manufacturer advises avoid).

**HEPATIC IMPAIRMENT**
Monitor liver function in hepatic impairment.

**RENAL IMPAIRMENT**
Use normal dose every 12 hours if eGFR 26–50 mL/minute/1.73 m². Use half normal dose every 12 hours if eGFR 10–25 mL/minute/1.73 m². Use half normal dose every 24 hours if eGFR less than 10 mL/minute/1.73 m².

**EFFECT ON LABORATORY TESTS**
Positive Coombs’ test.

**DIRECTIONS FOR ADMINISTRATION**
Intravenous injection to be administered over 5 minutes. For intravenous infusion (Meropenem®), give intermittently in Glucose 5% or Sodium chloride 0.9%. Dilute dose in infusion fluid to a final concentration of 1–20 mg/mL; give over 15–30 minutes.

**MEDIcular FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**

| ELECTROLYTES: May contain Sodium |
| MEROPENEM (Non-proprietary) |
| Meropenem (as Meropenem trihydrate) 500 mg | Meropenem 500mg powder for solution for injection vials | 10 vial £92.70–£88.00 |
| Meropenem (as Meropenem trihydrate) 1 gram | Meropenem 1g powder for solution for injection vials | 10 vial £139.20–£171.90 |
| Meropenem (as Meropenem trihydrate) 500 mg | Meropenem 500mg powder for solution for injection vials | 10 vial £103.14 |
| Meropenem (as Meropenem trihydrate) 1 gram | Meropenem 1g powder for solution for injection vials | 10 vial £206.28 |
CEPHALOSPORINS

Cephalosporins

The cephalosporins are broad-spectrum antibiotics which are used for the treatment of septicaemia, pneumonia, meningitis, biliary-tract infections, peritonitis, and urinary-tract infections. The pharmacology of the cephalosporins is similar to that of the penicillins, excretion being principally renal. Cephalosporins penetrate the cerebrospinal fluid poorly unless the meninges are inflamed; cefotaxime p. 457 and ceftriaxone p. 459 are suitable cephalosporins for infections of the CNS (e.g. meningitis).

The principal side-effect of the cephalosporins is hypersensitivity and about 0.5–6.5% of penicillin-sensitive patients will also be allergic to the cephalosporins. If a cephalosporin is essential in patients with a history of alternative antibiotic is not available, then cefixime p. 457, cefotaxime, ceftazidime p. 458, ceftriaxone, or cefuroxime p. 450 can be used with caution; cefaclor below, cefadroxil p. 456, cefalexin p. 456, cefradine p. 458, and cefotetan fosamil p. 458 should be avoided.

The orally active ‘first generation’ cephalosporins, cefalexin, cefadroxil, and cefadroxil and the ‘second generation’ cephalosporin, cefaclor below, have a similar antimicrobial spectrum. They are useful for urinary-tract infections which do not respond to other drugs or which occur in pregnancy, respiratory-tract infections, otitis media, sinusitis, and skin and soft-tissue infections. Cefaclor below has good activity against *H. influenzae*.

**Cefuroxime axetil**, an ester of the ‘second generation’ cephalosporin cefuroxime, has the same antibacterial spectrum as the parent compound; it is poorly absorbed and needs to be given with food to maximise absorption.

Cefixime is an orally active ‘third generation’ cephalosporin. It has a longer duration of action than the other cephalosporins that are active by mouth. It is only licensed for acute infections.

Cefuroxime is a ‘second generation’ cephalosporin that is less susceptible than the earlier cephalosporins to inactivation by beta-lactamases. It is, therefore, active against certain bacteria which are resistant to the other drugs and has greater activity against *Haemophilus influenzae*.

Cefotaxime, ceftazidime and ceftriaxone are ‘third generation’ cephalosporins with greater activity than the ‘second generation’ cephalosporins against certain Gram-negative bacteria. However, they are less active than cefuroxime against Gram-positive bacteria, most notably *Staphylococcus aureus*. Their broad antibacterial spectrum may encourage superinfection with resistant bacteria or fungi.

Ceftazidime has good activity against pseudomonas. It is also active against other Gram-negative bacteria. Ceftriaxone has a longer half-life and therefore needs to be given only once daily. Indications include serious infections such as septicaemia, pneumonia, and meningitis. The calcium salt of ceftriaxone forms a precipitate in the gall bladder which may rarely cause symptoms but these usually resolve when the antibiotic is stopped.

Cefadroxil fosamil is a ‘fifth generation’ cephalosporin with bactericidal activity similar to cefotaxime; however, cefadroxil fosamil has an extended spectrum of activity against Gram-positive bacteria that includes meticillin-resistant *Staphylococcus aureus* and multi-drug resistant *Streptococcus pneumoniae*. Cefadroxil fosamil is licensed for the treatment of community-acquired pneumonia and complicated skin and soft-tissue infections, but there is no experience of its use in pneumonia caused by meticillin-resistant *S. aureus*.

Cephalosporins

**INTERACTIONS** → Appendix 1 (cephalosporins).

**SIDE-EFFECTS**

- Rare Antibiotic-associated colitis
- Frequency not known Abdominal discomfort, agranulocytosis, allergic reactions, anaphylaxis, aplastic anaemia, blood disorders, confusion, diarrhoea, disturbances in liver enzymes, dizziness, eosinophilia, haemolytic anaemia, hallucinations, headache, hyperactivity, hypertension, leucopenia, nausea, nervousness, pruritus, rashes, reversible interstitial nephritis, serum sickness-like reactions with rashes, fever and arthralgia, sleep disturbances, Stevens-Johnson syndrome, thrombocytopenia, toxic epidermal necrolysis, transient cholestatic jaundice, transient hepatitis, urticaria, vomiting

**SIDE-EFFECTS, FURTHER INFORMATION** Antibiotic-associated colitis Antibiotic-associated colitis may occur more commonly with second- and third-generation cephalosporins.

**ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in patients with cephalosporin hypersensitivity. Cross-sensitivity with other beta-lactam antibacterials About 0.5–6.5% of penicillin-sensitive patients will also be allergic to the cephalosporins. Patients with a history of immediate hypersensitivity to penicillin and other beta-lactams should not receive a cephalosporin. Cephalosporins should be used with caution in patients with sensitivity to penicillin and other beta-lactams.

**EFFECT ON LABORATORY TESTS** False positive urinary glucose (if tested for reducing substances). False positive Coombs’ test.

Cefaclor

**INDICATIONS AND DOSE**

Susceptible infections due to sensitive Gram-positive and Gram-negative bacteria

**INITIALLY BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

- Child 1-11 months: 20 mg/kg daily in 3 divided doses, alternatively (by mouth) 62.5 mg 3 times a day
- Child 1-4 years: 20 mg/kg daily in 3 divided doses, alternatively (by mouth) 125 mg 3 times a day
- Child 5-11 years: 20 mg/kg daily in 3 divided doses, usual max. 1 g daily, alternatively (by mouth) 250 mg 3 times a day
- Child 12-17 years: 250 mg 3 times a day; maximum 4 g per day
- Adult: 250 mg 3 times a day; maximum 4 g per day

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

- Child 12-17 years: 375 mg every 12 hours, dose to be taken with food
- Adult: 375 mg every 12 hours, dose to be taken with food

Severe susceptible infections due to sensitive Gram-positive and Gram-negative bacteria

**BY MOUTH**

- Child 1-11 months: 40 mg/kg daily in 3 divided doses, usual max. 1 g daily, alternatively 125 mg 3 times a day
- Child 1-4 years: 40 mg/kg daily in 3 divided doses, usual max. 1 g daily, alternatively 250 mg 3 times a day
**INDICATIONS AND DOSE**

Susceptible infections due to sensitive Gram-positive and Gram-negative bacteria

**BY MOUTH**

- **Child 6–17 years (body-weight up to 40 kg):** 0.5 g twice daily
- **Child 6–17 years (body-weight 40 kg and above):** 0.5–1 g twice daily
- **Adult:** 0.5–1 g twice daily

**Skin infections** | **Soft-tissue infections** | **Uncomplicated urinary-tract infections**

**BY MOUTH**

- **Child 6–17 years (body-weight 40 kg and above):** 1 g once daily
- **Adult:** 1 g daily

**PREGNANCY** Not known to be harmful.

**BREAST FEEDING** Present in milk in low concentration, but appropriate to use.

**RENAL IMPAIRMENT** In adults 1 g initially, then 500 mg every 12 hours if eGFR 26–50 mL/minute/1.73 m². 1 g initially, then 500 mg every 24 hours if eGFR 11–26 mL/minute/1.73 m². 1 g initially, then 500 mg every 36 hours if eGFR less than 11 mL/minute/1.73 m².

**MEDITCINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

CAUTIONARY AND ADVISORY LABELS 9

- **CEFADROXIL (Non-proprietary)**
  - Cefadroxil (as Cefadroxil monohydrate) 500 mg Cefadroxil 500mg capsules | 20 capsule (£0.96) £22.36 DT price = £22.36 | 100 capsule (£0.96) £111.90

**Cefalexin**

(Chephalexin)

**INDICATIONS AND DOSE**

Susceptible infections due to sensitive Gram-positive and Gram-negative bacteria

**BY MOUTH**

- **Child 1–11 months:** 12.5 mg/kg twice daily, alternatively 125 mg twice daily
- **Child 1–4 years:** 12.5 mg/kg twice daily, alternatively 125 mg 3 times a day
- **Child 5–11 years:** 12.5 mg/kg twice daily, alternatively 250 mg 3 times a day
- **Child 12–17 years:** 500 mg 2–3 times a day
- **Adult:** 250 mg every 6 hours, alternatively 500 mg every 6–12 hours; increased to 1–1.5 g every 6–8 hours, increased dose to be used for severe infections

**Serious susceptible infections due to sensitive Gram-positive and Gram-negative bacteria**

**BY MOUTH**

- **Child 1 month–11 years:** 25 mg/kg 2–4 times a day (max. per dose 1 g 4 times a day)
- **Child 12–17 years:** 1–1.5 g 3–4 times a day

**Prophylaxis of recurrent urinary-tract infection**

**BY MOUTH**

- **Child:** 12.5 mg/kg once daily (max. per dose 125 mg), dose to be taken at night
- **Adult:** 125 mg once daily, dose to be taken at night

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**SIDE-EFFECTS**

**SIDE-EFFECTS, FURTHER INFORMATION**

**Skin reactions** Cefaclor is associated with protracted skin reactions, especially in children.

**PREGNANCY** Not known to be harmful.

**BREAST FEEDING** Present in milk in low concentration, but appropriate to use.

**RENAL IMPAIRMENT** No dose adjustment required. Manufacturer advises caution.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Modified-release tablet**

CAUTIONARY AND ADVISORY LABELS 9, 21, 25

- **Distacol MR** (Flynn Pharma Ltd)
  - Cefaclor (as Cefaclor monohydrate) 375 mg Distacol MR 375mg tablets | 14 tablet (£0.70) DT price = £0.70

**Capsule**

CAUTIONARY AND ADVISORY LABELS 9

- **CEFACLOL (Non-proprietary)**
  - Cefaclor (as Cefaclor monohydrate) 250 mg Cefaclor 250mg capsules | 21 capsule (£0.60) no price available DT price = £6.80
  - Cefaclor (as Cefaclor monohydrate) 500 mg Cefaclor 500mg capsules | 50 capsule (£2.80)
  - **Distacol** (Flynn Pharma Ltd)
  - Cefaclor (as Cefaclor monohydrate) 500 mg Distacol 500mg capsules | 21 capsule (£0.75) DT price = £0.75
  - Brands may include Keftid

**Oral suspension**

CAUTIONARY AND ADVISORY LABELS 9

- **CEFACLOL (Non-proprietary)**
  - Cefaclor (as Cefaclor monohydrate) 25 mg per 1 ml Cefaclor 125mg/5ml oral suspension sugar free (sugar-free) | 100 ml (£0.25) £5.16 DT price = £5.16
  - Cefaclor 125mg/5ml oral suspension | 100 ml (£0.25) £6.75
  - Cefaclor (as Cefaclor monohydrate) 50 mg per 1 ml Cefaclor 250mg/5ml oral suspension sugar free (sugar-free) | 100 ml (£0.50) £11.95 DT price = £10.32
  - Cefaclor 250mg/5ml oral suspension | 100 ml (£0.50) no price available
  - **Distacol** (Flynn Pharma Ltd)
  - Cefaclor (as Cefaclor monohydrate) 25 mg per 1 ml Distacol 125mg/5ml oral suspension | 100 ml (£0.25) £4.13
  - Cefaclor (as Cefaclor monohydrate) 50 mg per 1 ml Distacol 250mg/5ml oral suspension | 100 ml (£0.50) £9.26
  - Brands may include Keftid

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**Cefadroxil**

**CEFADROXIL (Non-proprietary)**

Cefadroxil (as Cefadroxil monohydrate) 500 mg Cefadroxil 500mg capsules | 20 capsule (£0.96) £22.36 DT price = £22.36 | 100 capsule (£0.96) £111.90

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**INFECTION**

**MEDICINAL FORMS**

Pregnancy

- Not known to be harmful.

Breastfeeding

- Present in milk in low concentration, but appropriate to use.

Renal impairment

- In adults 1 g initially, then 500 mg every 12 hours if eGFR 26–50 mL/minute/1.73 m². 1 g initially, then 500 mg every 24 hours if eGFR 11–26 mL/minute/1.73 m². 1 g initially, then 500 mg every 36 hours if eGFR less than 11 mL/minute/1.73 m².

- In children Reduce dose if estimated glomerular filtration rate less than 50 mL/minute/1.73 m².

**SIDE-EFFECTS**

Skin reactions Cefaclor is associated with protracted skin reactions, especially in children.

**PREGNANCY** Not known to be harmful.

**BREAST FEEDING** Present in milk in low concentration, but appropriate to use.

**RENAL IMPAIRMENT** No dose adjustment required. Manufacturer advises caution.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Modified-release tablet**

CAUTIONARY AND ADVISORY LABELS 9, 21, 25

- **Distacol MR** (Flynn Pharma Ltd)
  - Cefaclor (as Cefaclor monohydrate) 375 mg Distacol MR 375mg tablets | 14 tablet (£0.70) DT price = £0.70

**Capsule**

CAUTIONARY AND ADVISORY LABELS 9

- **CEFACLOL (Non-proprietary)**
  - Cefaclor (as Cefaclor monohydrate) 250 mg Cefaclor 250mg capsules | 21 capsule (£0.60) no price available DT price = £6.80
  - Cefaclor (as Cefaclor monohydrate) 500 mg Cefaclor 500mg capsules | 50 capsule (£2.80)
  - **Distacol** (Flynn Pharma Ltd)
  - Cefaclor (as Cefaclor monohydrate) 500 mg Distacol 500mg capsules | 21 capsule (£0.75) DT price = £0.75
  - Brands may include Keftid

**Oral suspension**

CAUTIONARY AND ADVISORY LABELS 9

- **CEFACLOL (Non-proprietary)**
  - Cefaclor (as Cefaclor monohydrate) 25 mg per 1 ml Cefaclor 125mg/5ml oral suspension sugar free (sugar-free) | 100 ml (£0.25) £5.16 DT price = £5.16
  - Cefaclor 125mg/5ml oral suspension | 100 ml (£0.25) £6.75
  - Cefaclor (as Cefaclor monohydrate) 50 mg per 1 ml Cefaclor 250mg/5ml oral suspension sugar free (sugar-free) | 100 ml (£0.50) £11.95 DT price = £10.32
  - Cefaclor 250mg/5ml oral suspension | 100 ml (£0.50) no price available
  - **Distacol** (Flynn Pharma Ltd)
  - Cefaclor (as Cefaclor monohydrate) 25 mg per 1 ml Distacol 125mg/5ml oral suspension | 100 ml (£0.25) £4.13
  - Cefaclor (as Cefaclor monohydrate) 50 mg per 1 ml Distacol 250mg/5ml oral suspension | 100 ml (£0.50) £9.26
  - Brands may include Keftid

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**Cefadroxil**

**CEFADROXIL (Non-proprietary)**

Cefadroxil (as Cefadroxil monohydrate) 500 mg Cefadroxil 500mg capsules | 20 capsule (£0.96) £22.36 DT price = £22.36 | 100 capsule (£0.96) £111.90
PATIENT AND CARER ADVICE

▶ In adults

PREGNANCY

CAUTIONARY AND ADVISORY LABELS

Oral suspension

Ceporex

▶ CEFAXLINE (Non-proprietary)

▶ ORAL SUSPENSION

BNF 70

Bacterial infection 457

Cefixime

INDICATIONS AND DOSE

Acute infections due to sensitive Gram-positive and Gram-negative bacteria

BY MOUTH

▶ Child 6-11 months: 75 mg daily

▶ Child 1-4 years: 100 mg daily

▶ Child 5-9 years: 200 mg daily

▶ Child 10-17 years: 200-400 mg daily, alternatively 100–200 mg twice daily

▶ Adult: 200–400 mg daily in 1–2 divided doses

Uncomplicated gonorrhoea

BY MOUTH

▶ Adult: 400 mg for 1 dose

Cefotaxime

INDICATIONS AND DOSE

Uncomplicated gonorrhoea

BY INTRAMUSCULAR INJECTION

▶ Adult: 500 mg for 1 dose

Infections due to sensitive Gram-positive and Gram-negative bacteria

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<tr>
<td>Adult: 1 g every 12 hours</td>
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</table>

Severe susceptible infections due to sensitive Gram-positive and Gram-negative bacteria

Meningitis

| BY INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION |
| Adult: 8 g daily in 4 divided doses, increased if necessary to 12 g daily in 3–4 divided doses, intramuscular doses over 1 g should be divided between more than one site |

Emergency treatment of suspected bacterial meningitis or meningococcal disease, before urgent transfer to hospital, in patients who cannot be given benzylpenicillin (e.g. because of an allergy)

| BY INTRAVENOUS INJECTION OR BY INTRAMUSCULAR INJECTION |
| Child 1 month-11 years: 50 mg/kg for 1 dose |
| Child 12-17 years: 1 g for 1 dose |
| Adult: 1 g for 1 dose |
Cefradine (Cephradine)

INDICATIONS AND DOSE
Susceptible infections due to sensitive Gram-positive and Gram-negative bacteria | Surgical prophylaxis

BY MOUTH
- Child 7-11 years: 25–50 mg/kg daily in 2–4 divided doses
- Child 12-17 years: 250–500 mg 4 times a day, alternatively 0.5–1 g twice daily; increased if necessary up to 1 g 4 times a day, increased dose may be used in severe infections
- Adult: 250–500 mg 4 times a day, alternatively 0.5–1 g twice daily; increased if necessary up to 1 g 4 times a day, increased dose may be used in severe infections

UNLICENSED USE
Not licensed for use in children for prevention of Staphylococcus aureus lung infection in cystic fibrosis.

PREGNANCY
Not known to be harmful.

BREAST FEEDING
Present in milk in low concentration, but appropriate to use.

RENAL IMPAIRMENT
- In adults Use half normal dose if eGFR 5–20 mL/minute/1.73 m². Use one-quarter normal dose if eGFR less than 5 mL/minute/1.73 m².
- In children Reduce dose if estimated glomerular filtration rate less than 20 mL/minute/1.73 m².

PROFESSION SPECIFIC INFORMATION
Dental practitioners’ formulary Cefradine Capsules may be prescribed.

Ceftaroline fosamil

INDICATIONS AND DOSE
Community-acquired pneumonia

BY INTRAVENOUS INFUSION
- Adult: 600 mg every 12 hours for 5–7 days

Complicated skin and soft-tissue infections

BY INTRAVENOUS INFUSION
- Adult: 600 mg every 12 hours for 5–14 days

CAUTIONS
Seizure disorders

PREGNANCY
Manufacturer advises avoid unless essential—no information available.

BREAST FEEDING
Manufacturer advises avoid—no information available.

RENAL IMPAIRMENT
400 mg every 12 hours if eGFR 30–50 mL/minute/1.73 m². Manufacturer advises avoid if eGFR less than 30 mL/minute/1.73 m².

DIRECTIONS FOR ADMINISTRATION
For intravenous infusion, give intermittently in Glucose 5% or Sodium chloride 0.9%. Suggested volume 40–100 mL, given over 20–60 minutes; incompatible with alkaline solutions.

Ceftaroline fosamil (as Ceftaroline fosamil acetic acid solvate monohydrate) 600 mg. Zinforo 600mg powder for concentrate for solution for infusion vials | 10 vial (£375.00)

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium, has advised (Dec 2012) that ceftaroline fosamil (Zinforo)® is accepted for restricted use within NHS Scotland when meticillin–resistant S. aureus is suspected in complicated skin and soft-tissue infection and vancomycin cannot be used.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS
- CEFRADINE (Non-proprietary)
  - Cefradine 250 mg Cefradine 250mg capsules | 20 capsule (£4.79)
  - £6.00 DT price = £2.25 | 100 capsule (£23.73) no price available
  - Cefradine 500 mg Cefradine 500mg capsules | 20 capsule (£9.00) no price available
  - Brands may include Nicef

Ceftazidime

INDICATIONS AND DOSE
Prophylaxis for transurethral resection of prostate

BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION OR BY DEEP INTRAMUSCULAR INJECTION
- Adult: 1 g, single dose to be administered up to 30 minutes before procedure and may be repeated if necessary when catheter removed

Complicated urinary-tract infection

BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION OR BY DEEP INTRAMUSCULAR INJECTION
- Adult 18–79 years: 1–2 g every 8–12 hours
- Adult 80 years and over: 1–2 g every 8–12 hours; usual maximum 3 g per day
Pseudomonal lung infection in cystic fibrosis
BY INTRAVENOUS INFUSION OR BY INTRAMUSCULAR INJECTION
Adult: 100–150 mg/kg daily in 3 divided doses; maximum 9 g per day

Septicemia | Hospital-acquired pneumonia
BY INTRAVENOUS INFUSION OR BY INTRAMUSCULAR INJECTION
Adult 18–79 years: 2 g every 8 hours
Adult 80 years and over: 2 g every 8 hours; usual maximum 3 g per day

Fever during neutropenia
BY INTRAVENOUS INFUSION OR BY INTRAMUSCULAR INJECTION
Adult 18–79 years: 2 g every 8 hours
Adult 80 years and over: 2 g every 8 hours; usual maximum 3 g per day

Meningitis
BY INTRAVENOUS INFUSION OR BY INTRAMUSCULAR INJECTION
Adult 18–79 years: 2 g every 8 hours
Adult 80 years and over: 2 g every 8 hours; usual maximum 3 g per day

Susceptible infections due to sensitive Gram-positive and
Gram-negative bacteria
BY INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INFUSION
Adult 18–79 years: 1–2 g every 8 hours
Adult 80 years and over: 1–2 g every 8 hours; usual maximum 3 g per day

SIDE-EFFECTS
Paraesthesia - taste disturbances
PREGNANCY
Not known to be harmful.
BREAST FEEDING
Present in milk in low concentration, but appropriate to use.
HEPATIC IMPAIRMENT
Manufacturer advises caution in severe impairment.
RENAL IMPAIRMENT
Reduce dose if eGFR less than 50 mL/minute/1.73 m²—consult product literature.

DIRECTIONS FOR ADMINISTRATION
Intramuscular administration used when intravenous administration not possible; single doses over 1 g by intravenous route only. For intravenous infusion give intermittently or via drip tubing in Glucose 5% or 10% or Sodium chloride 0.9%. Dissolve 2 g initially in 10 mL (3 g in 15 mL) infusion fluid. For Fortum® dilute further to a concentration of 40 mg/mL. For Kefadin® dilute further to a concentration of 20 mg/mL. Give over up to 30 minutes.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion, solution for infusion, eye drops

Powder for solution for injection
ELECTROLYTES: May contain Sodium

Ceftazidime (Non-proprietary)
Ceftazidime (as Ceftazidime pentahydrate) 500 mg Ceftazidime 500 mg powder for solution for injection vials | 1 vial (Fortum) £4.33-£4.73
Ceftazidime (as Ceftazidime pentahydrate) 1 g gram Ceftazidime 1 g powder for solution for injection vials | 1 vial (Fortum) £7.90-£11.82 | 5 vial (PZN) £39.55 | 10 vial (PZN) £13.90
Ceftazidime (as Ceftazidime pentahydrate) 2 gram Ceftazidime 2 g powder for solution for injection vials | 1 vial (Fortum) £17.75-£22.10 | 5 vial (PZN) £79.15 | 10 vial (PZN) £21.30
Fortum (GlaxoSmithKline UK Ltd)
Ceftazidime (as Ceftazidime pentahydrate) 500 mg Fortum 500 mg powder for solution for injection vials | 1 vial (PZN) £4.40 (Hospital only)
Ceftazidime (as Ceftazidime pentahydrate) 1 gram Fortum 1 g powder for solution for injection vials | 1 vial (PZN) £8.79 (Hospital only)

Ceftazidime (as Ceftazidime pentahydrate) 2 gram Fortum 2 g powder for solution for injection vials | 1 vial (PZN) £17.59 (Hospital only)
Ceftazidime (as Ceftazidime pentahydrate) 3 gram Fortum 3 g powder for solution for injection vials | 1 vial (PZN) £25.76 (Hospital only)

Ceftazidime

INDICATIONS AND DOSE
Surgical prophylaxis
BY DEEP INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INFUSION
Adult: 1 g for 1 dose, to be administered up to 30 minutes before procedure

Prophylaxis before colorectal surgery
BY DEEP INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INFUSION
Adult: 2 g for 1 dose, to be administered up to 30 minutes before procedure, intramuscular doses over 1 g divided between more than one site

Uncomplicated gonorrhoea | Pelvic inflammatory disease
BY DEEP INTRAMUSCULAR INFUSION
Adult: 500 mg for 1 dose

Early syphilis
BY DEEP INTRAMUSCULAR INJECTION
Adult: 500 mg daily for 10 days

Endocarditis caused by haemophilus, actinobacillus, cardiobacterium, eikenella, and kingella species (‘HACEK organisms’) (in combination with another antibacterial)
BY INTRAVENOUS INFUSION
Adult: 2–4 g daily

Susceptible infections due to sensitive Gram-positive and
Gram-negative bacteria
BY DEEP INTRAMUSCULAR INFUSION OR BY INTRAVENOUS INFUSION
Adult: 1 g daily; increased to 2–4 g daily, increased dose to be used for severe infections, intramuscular doses over 1 g divided between more than one site, single intravenous doses above 1 g to be administered by intravenous infusion only

Meningitis
BY INTRAVENOUS INFUSION
Child 1 month–11 years (body-weight up to 50 kg): 50–80 mg/kg daily, doses of 50 mg/kg and over to be administered by intravenous infusion only

BY DEEP INTRAMUSCULAR INFUSION OR BY INTRAVENOUS INFUSION
Child 1 month–11 years (body-weight 50 kg and above): 2–4 g daily, intramuscular doses over 1 g divided between more than one site, single intravenous doses above 1 g to be administered by intravenous infusion only

Prevention of secondary case of meningococcal meningitis
BY INTRAMUSCULAR INJECTION
Adult: 250 mg for 1 dose

Prevention of secondary case of Haemophilus influenzae type b disease
BY INTRAMUSCULAR INFUSION OR BY INTRAVENOUS INFUSION
Adult: 1 g daily for 2 days

UNLICENSED USE
Not licensed for prophylaxis of meningococcal meningitis or Haemophilus influenzae type b disease.
In adults Not licensed for early syphilis. Not licensed for endocarditis caused by haemophilus, actinobacillus, cardio bacterium, eikenella, and kingella species (HACEK organisms) (in combination with another antibacterial). Dose not licensed for treatment of uncomplicated gonorrhoea or pelvic inflammatory disease.

- **CONTRA-INDICATIONS** Concomitant treatment with intravenous calcium (including total parenteral nutrition containing calcium) in neonates over 41 weeks corrected gestational age—risk of precipitation in urine and lungs - neonates less than 41 weeks corrected gestational age - neonates over 41 weeks corrected gestational age with jaundice, hypoa lbuminaemia, acidosis, unconjugated hyperbilirubinaemia, or impaired bilirubin binding

- **CAUTIONS** Dehydration (risk of ceftriaxone precipitation in gall bladder) - may displace bilirubin from serum albumin, administer over 60 minutes in neonates - treatment longer than 14 days - use with caution in neonates

- **SIDE-EFFECTS**
  - Common or very common Calcium ceftriaxone precipitates in gall bladder—consider discontinuation if symptomatic - calcium ceftriaxone precipitates in urine (particularly in very young, dehydrated or those who are immobilised)—consider discontinuation if symptomatic
  - Rare  Pancreatitis, prolongation of prothrombin time

- **PREGNANCY** Not known to be harmful.

- **BREAST FEEDING** Present in milk in low concentration, but appropriate to use.

- **HEPATIC IMPAIRMENT** Reduce dose if both hepatic and severe renal impairment. Monitor plasma concentration if both hepatic and severe renal impairment.

- **RENAL IMPAIRMENT** Use with caution in renal failure. Monitor plasma concentration if both hepatic and severe renal impairment.

  - In adults Reduce dose if eGFR less than 10 mL/minute/1.73 m² (max. 2 g daily).
  - In children Max. 50 mg/kg daily (max. 2 g daily) in severe renal impairment.

- **DIRECTIONS FOR ADMINISTRATION** For intravenous injection, give over at least 2–4 minutes.

  - With intravenous use in children For intravenous infusion, dilute reconstituted solution with Glucose 5% or 10% or Sodium Chloride 0.9%; give over at least 30 minutes (60 minutes in neonates). Not to be given simultaneously with parenteral nutrition or infusion fluids containing calcium, even by different infusion lines; may be infused sequentially with infusion fluids containing calcium if flush with sodium chloride 0.9% between infusions or give infusions by different infusion lines at different sites. Displacement value may be significant, consult local guidelines.

  - With intramuscular use in children For intramuscular injection ceftriaxone may be mixed with 1% Lidocaine Hydrochloride Injection to reduce pain at intramuscular injection site; final concentration 250–350 mg/mL. Displacement value may be significant, consult local guidelines.

  - With intravenous use in adults For intravenous infusion (Rocephin®; Ceftriaxone Injection, Genus), give intermittently or via drip tubing in Glucose 5% or 10% or Sodium chloride 0.9%. Reconstitute 2-g vial with 40 mL infusion fluid. Give by intermittent infusion over at least 30 minutes (60 minutes in neonates). Not to be given simultaneously with total parenteral nutrition or infusion fluids containing calcium, even by different infusion lines. May be infused sequentially with infusion fluids containing calcium if flush with sodium chloride 0.9% between infusions or give infusions by different infusion lines at different sites.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion

- **Powder for solution for injection**
  - **Ceftriaxone (Non-proprietary)**
    - Ceftriaxone (as Ceftriaxone sodium) 250 mg Ceftriaxone 250mg powder for solution for injection vials | 1 vial (PO) £1.80–£2.30 DT price = £2.40
    - Ceftriaxone (as Ceftriaxone sodium) 1 gram Ceftriaxone 1g powder for solution for injection vials | 1 vial (PO) £9.58 DT price = £9.58 | 5 vial (PO) £45.75 | 10 vial (PO) £11.00
    - Ceftriaxone (as Ceftriaxone sodium) 2 gram Ceftriaxone 2g powder for solution for injection vials | 1 vial (PO) £18.39 DT price = £15.18 | 10 vial (PO) £13.00
    - Ceftriaxone 2g powder for solution for infusion vials | 1 vial (PO) £19.10 DT price = £19.18
  - Rocephin (Roche Products Ltd)
    - Ceftriaxone (as Ceftriaxone sodium) 250 mg Rocephin 250mg powder for solution for injection vials | 1 vial (PO) £2.40 DT price = £2.40
    - Ceftriaxone (as Ceftriaxone sodium) 1 gram Rocephin 1g powder for solution for injection vials | 1 vial (PO) £9.58 DT price = £9.58
    - Ceftriaxone (as Ceftriaxone sodium) 2 gram Rocephin 2g powder for solution for injection vials | 1 vial (PO) £13.18 DT price = £19.18

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**Cefuroxime**

**INDICATIONS AND DOSE**

Susceptible infections due to Gram-positive and Gram-negative bacteria

**BY MOUTH**

- Child 3 months-1 year: 10 mg/kg twice daily (max. per dose 125 mg)
- Child 2-11 years: 15 mg/kg twice daily (max. per dose 250 mg)
- Child 12-17 years: 250 mg twice daily, dose may be doubled in severe lower respiratory-tract infections or if pneumonia is suspected
- Adult: 250 mg twice daily, dose may be doubled in severe lower respiratory-tract infections or if pneumonia is suspected

**BY INTRAVENOUS INFUSION OR BY INTRAVENOUS INJECTION OR BY INTRAMUSCULAR INJECTION**

- Child: 20 mg/kg every 8 hours (max. per dose 750 mg); increased to 50–60 mg/kg every 6–8 hours (max. per dose 1.5 g), increased dose used for severe infection and cystic fibrosis
- Adult: 750 mg every 6–8 hours; increased if necessary up to 1.5 g every 6–8 hours, increased dose used for severe infections

**Lyme disease**

**BY MOUTH**

- Adult: 500 mg twice daily for 14–21 days (for 28 days in Lyme arthritis)

**Lower urinary-tract infection**

**BY MOUTH**

- Child 12-17 years: 125 mg twice daily
- Adult: 125 mg twice daily

**Pyelonephritis**

**BY MOUTH**

- Adult: 250 mg twice daily

**Surgical prophylaxis**

**INITIALLY BY INTRAVENOUS INJECTION**

- Adult: 1.5 g, to be administered up to 30 minutes before the procedure, then (by intravenous injection or by intramuscular injection) 750 mg every 8 hours if required for up to 3 doses (in high risk procedures)
**DIAMINOPYRIMIDINES**

**Co-trimoxazole**

- **DRUG ACTION** Sulfamethoxazole and trimethoprim are used in combination (as co-trimoxazole) because of their synergistic activity (the importance of the sulfonamides has decreased as a result of increasing bacterial resistance and their replacement by antibacterials which are generally more active and less toxic).

### INDICATIONS AND DOSE

**Treatment of susceptible infections**

**BY MOUTH**

- **Child**: 120 mg/kg daily in 2–4 divided doses for 14–21 days, oral route preferred for children
- **Adult**: 120 mg/kg daily in 2–4 divided doses for 14–21 days, oral route preferred for children

**Prophylaxis of Pneumocystis jirovecii (Pneumocystis carinii) infections**

**BY MOUTH**

- **Child**: 450 mg/m² twice daily (max. per dose 960 mg twice daily) for 3 days of the week (either consecutively or on alternate days), dose regimens may vary, consult local guidelines
- **Adult**: 960 mg once daily, reduced if not tolerated to 480 mg once daily, alternatively 960 mg once daily on alternate days, alternate day dose to be given 3 times weekly, alternatively 960 mg twice a day on alternate days, alternate day dose to be given 3 times weekly

**Dose equivalence and conversion**

480 mg of co-trimoxazole consists of sulfamethoxazole 400 mg and trimethoprim 80 mg.

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**Open fractures, prophylaxis**

**By intravenous infusion or by intravenous injection**

- **Adult**: 1.5 g every 8 hours until soft tissue closure (maximum duration 72 hours)

**UNLICENSED USE** Duration of treatment in Lyme disease is unlicensed.

**PREGNANCY** Not known to be harmful.

**BREAST FEEDING** Present in milk in low concentration, but appropriate to use.

**RENAL IMPAIRMENT**

- In adults Use parenteral dose of 750 mg twice daily if eGFR 10–20 mL/minute/1.73 m². Use parenteral dose of 750 mg once daily if eGFR less than 10 mL/minute/1.73 m².
- In children Reduce parenteral dose if estimated glomerular filtration rate less than 20 mL/minute/1.73 m².

**DIRECTIONS FOR ADMINISTRATION** Single doses over 750 mg should be administered by the intravenous route only.

- With intravenous use in children Displacement value may be significant when reconstituting injection, consult local guidelines. For intermittent intravenous infusion, dilute reconstituted solution further in glucose 5% or sodium chloride 0.9%, give over 30 minutes.
- With intravenous use in adults For intravenous infusion (Zinacef®), give intermittently or via drip tubing in Glucose 5% or Sodium chloride 0.9%. Dissolve initially in water for injections (at least 2 mL for each 250 mg, 15 mL for 1.5 g); suggested volume 50–100 mL given over 30 minutes.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, infusion

**Tablet**

| CAUTIONARY AND ADVISORY LABELS | 9, 21, 25 |
| **CEFUXORIME (Non-proprietary)** |  |
| Cefuroxime (as Cefuroxime axetil) 250 mg | 14 tablet (Pack) £17.72 DT price = £17.72 |
| Cefuroxime (as Cefuroxime axetil) 125 mg | 14 tablet (Pack) £4.56 DT price = £4.56 |
| Zinact (GlaxoSmithKline UK Ltd) |  |
| Cefuroxime (as Cefuroxime axetil) 250 mg | 14 tablet (Pack) £9.11 DT price = £9.72 |

**Oral suspension**

| CAUTIONARY AND ADVISORY LABELS | 9, 21 |
| **EXCIPIENTS**: May contain Aspartame, sucrose |  |
| **Zinact (GlaxoSmithKline UK Ltd)** |  |
| Cefuroxime (as Cefuroxime axetil) 25 mg per 1 ml | Zinact 125mg/5ml oral suspension | 70 ml (Pack) £5.20 |

**Powder for injection**

| ELECTROLYTES: May contain Sodium |  |
| **CEFUXORIME (Non-proprietary)** |  |
| Cefuroxime (as Cefuroxime sodium) 250 mg | Cefuroxime 250mg powder for injection vials | 10 vial (Pack) £2.25 |
| Cefuroxime (as Cefuroxime sodium) 750 mg | Cefuroxime 750mg powder for injection vials | 1 vial (Pack) £2.52 | 10 vial (Pack) £25.20 |
| Cefuroxime (as Cefuroxime sodium) 1.5 gram | Cefuroxime 1.5g powder for injection vials | 1 vial (Pack) £5.05 | 10 vial (Pack) £50.50 |
| **Zinacef (GlaxoSmithKline UK Ltd)** |  |
| Cefuroxime (as Cefuroxime sodium) 250 mg | Zinacef 250mg powder for injection vials | 5 vial (Pack) £11.72 (Hospital only) |
| Cefuroxime (as Cefuroxime sodium) 750 mg | Zinacef 750mg powder for injection vials | 5 vial (Pack) £4.70 |

### Important safety information

**RESTRICTIONS ON THE USE OF CO-TRIMOXAZOLE**

Co-trimoxazole is the drug of choice in the prophylaxis and treatment of Pneumocystis jirovecii (Pneumocystis carinii) pneumonia; it is also indicated for nocardiosis, Stenotrophomonas maltophilia infection [unlicensed indication], and toxoplasmosis. It should only be considered for use in acute exacerbations of chronic bronchitis and infections of the urinary tract when there is bacteriological evidence of sensitivity to co-trimoxazole and good reason to prefer this combination to a single antibacterial; similarly it should only be used in acute otitis media in children when there is good reason to prefer it. Co-trimoxazole is also used for the treatment of infections caused by Burkholderia cepacia in cystic fibrosis [unlicensed indication].

**CONTRA-INDICATIONS**

Acute porphyrias p. 864

**CAUTIONS**

Asthma - avoid in blood disorders (unless under specialist supervision) - avoid in infants under 6 weeks (except for treatment or prophylaxis of pneumocystis pneumonia) because of the risk of kernicterus - elderly (increased risk of serious side-effects) (in adults) - G6PD deficiency (risk of haemolytic anaemia) - maintain adequate fluid intake - predisposition to folate deficiency - predisposition to hyperkalaemia (in adults)

**INTERACTIONS**

Appendix 1 (trimethoprim, sulfamethoxazole).
In children
Monitor blood counts on prolonged treatment.

HEPATIC IMPAIRMENT

BREAST FEEDING
Small risk of kernicterus in jaundiced infants and of haemolysis in G6PD-deficient infants (due to sulfamethoxazole).

HEPATIC IMPAIRMENT
Manufacturer advises avoid in severe liver disease.

RENAL IMPAIRMENT
Use half normal dose if eGFR 15–30 mL/minute/1.73 m². Avoid if eGFR less than 15 mL/minute/1.73 m² and if plasma-sulfamethoxazole concentration cannot be monitored.

MONITORING REQUIREMENTS
Monitor blood counts on prolonged treatment.

In children Plasma concentration monitoring may be required with high doses; seek expert advice.

DIRECTIONS FOR ADMINISTRATION

With intravenous use in children For intermittent intravenous infusion, may be further diluted in glucose 5% or 10% or sodium chloride 0.9%. Dilute contents of 1 ampoule (5 mL) to 125 mL, 2 ampoules (10 mL) to 250 mL or 3 ampoules (15 mL) to 500 mL; suggested duration of infusion 60–90 minutes (but may be adjusted according to fluid requirements); if fluid restriction necessary, 1 ampoule (5 mL) may be diluted with 75 mL glucose 5% and the required dose infused over max. 60 minutes; check container for haze or precipitant during administration. In severe fluid restriction may be given undiluted via a central venous line.

With intravenous use in adults For intravenous infusion (Septrin® for infusion), give intermittently in Glucose 5% or 10% or Sodium chloride 0.9%. Dilute contents of 1 ampoule (5 mL) to 125 mL, 2 ampoules (10 mL) to 250 mL or 3 ampoules (15 mL) to 500 mL; suggested duration of infusion 60–90 minutes (but may be adjusted according to fluid requirements); if fluid restriction necessary, 1 ampoule (5 mL) may be diluted with 75 mL glucose 5% and infused over max. 60 minutes.

PRESCRIBING AND DISPENSING INFORMATION
Co-trimoxazole is a mixture of trimethoprim and sulfamethoxazole (sulfamethoxazole) in the proportions of 1 part to 5 parts.

SIDE-EFFECTS, FURTHER INFORMATION

Blood disorders or rash
Co-trimoxazole is associated with rare but serious side effects. Discontinue immediately if blood disorders (including leucopenia, thrombocytopenia, neutropenia, photosensitivity) develop.

PREGNANCY
Teratogenic risk in first trimester (trimethoprim a folate antagonist). Neonatal haemolysis and methaemoglobinemia in third trimester; fear of increased risk of kernicterus in neonates appears to be unfounded.

BREAST FEEDING
Small risk of kernicterus in jaundiced infants and of haemolysis in G6PD-deficient infants (due to sulfamethoxazole).

Sulfamethoxazole 40 mg per 1 mL, Trimethoprim 8 mg per 1 mL Septrin Paediatric 40mg/200mg/5ml oral suspension (sugar-free) | 100 mL £2.45
Sulfamethoxazole 80 mg per 1 mL, Trimethoprim 16 mg per 1 mL Septrin Adult 80mg/400mg/5ml oral suspension | 100 mL £0.94.41
Solution for infusion
EXCIPIENTS: May contain Alcohol, propylene glycol, sulfites
ELECTROLYTES: May contain Sodium

Septrin (Aspen Pharma Trading Ltd)

Sulfamethoxazole 80 mg per 1 mL, Trimethoprim 16 mg per 1 mL Septrin Forte 160mg/800mg tablets | 100 tablet £3.46 DT price = £3.46

Septrin tablets | 100 tablet £15.52

Septrin for Infusion

Flavours of oral liquid formulations may include banana, or vanilla.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet

CO-TRIMOXAZOLE (Non-proprietary)

Sulfamethoxazole 400 mg, Trimethoprim 80 mg Co-trimoxazole 80mg/400mg tablets | 28 tablet £3.00 DT price = £3.34
Sulfamethoxazole 800 mg, Trimethoprin 160 mg Co-trimoxazole 160mg/800mg tablets | 100 tablet £3.40 DT price = £3.46

Septrin (Aspen Pharma Trading Ltd)

Sulfamethoxazole 400 mg, Trimethoprim 80 mg Septrin tablets | 100 tablet £15.52
Sulfamethoxazole 800 mg, Trimethoprin 160 mg Septrin Forte 160mg/800mg tablets | 100 tablet £3.46 DT price = £3.46

Oral suspension

CAUTIONARY AND ADVISORY LABELS 9

INDICATIONS AND DOSE

Urinary-tract infections | Respiratory tract infections

BY MOUTH

Child 4-5 weeks: 4 mg/kg twice daily (max. per dose 200 mg)

Child 6 weeks-5 months: 4 mg/kg twice daily (max. per dose 200 mg), alternatively 25 mg twice daily

Child 6 months-5 years: 4 mg/kg twice daily (max. per dose 200 mg), alternatively 50 mg twice daily

Child 6-11 years: 4 mg/kg twice daily (max. per dose 200 mg), alternatively 100 mg twice daily

Child 12-17 years: 200 mg twice daily

Adult: 200 mg twice daily

Prophylaxis of urinary-tract infection (considered for recurrent infection, significant urinary-tract anomalies, or significant kidney damage)

BY MOUTH

Child 4-5 weeks: 2 mg/kg once daily (max. per dose 100 mg), dose to be taken at night

Child 6 weeks-5 months: 2 mg/kg once daily (max. per dose 100 mg), dose to be taken at night, alternatively 12.5 mg once daily, dose to be taken at night

Child 6 months-5 years: 2 mg/kg once daily (max. per dose 100 mg), dose to be taken at night, alternatively 25 mg once daily, dose to be taken at night

Child 6-11 years: 2 mg/kg once daily (max. per dose 100 mg), dose to be taken at night, alternatively 50 mg once daily, dose to be taken at night

Child 12-17 years: 100 mg once daily, dose to be taken at night

Adult: 100 mg once daily, dose to be taken at night

Trimethoprim
Treatment of mild to moderate Pneumocystis jirovecii (Pneumocystis carinii) pneumonia in patients who cannot tolerate co-trimoxazole (in combination with dapsone)

**BY MOUTH**
- Child: 5 mg/kg every 6–8 hours
- Adult: 5 mg/kg every 6–8 hours

**Acne resistant to other antibacterials**

**BY MOUTH**
- Adult: 300 mg twice daily

**Prostatitis**
- Adult: (consult product literature)

**Shigellosis | Invasive salmonella infection**
- BY MOUTH
  - Adult: (consult product literature)

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**FUSIDATES**

**Fusidic acid**

- **DRUG ACTION** Fusidic acid and its salts are narrow-spectrum antibiotics used for staphylococcal infections.

**INDICATIONS AND DOSE**

**Staphylococcal skin infection**

**BY MOUTH USING TABLETS**
- Child 12-17 years: 250 mg every 12 hours for 5-10 days
- Adult: 250 mg every 12 hours for 5-10 days

**Penicillin-resistant staphylococcal infection including osteomyelitis | Staphylococcal endocarditis in combination with other antibacterials**

**BY MOUTH USING ORAL SUSPENSION**
- Child 12-17 years: 500 mg every 8 hours, increased to 1 g every 8 hours, increased dose can be used for severe infections
- Adult: 500 mg every 8 hours, increased to 1 g every 8 hours, increased dose can be used for severe infections

**Dose equivalence and conversion**

Fusidic acid is incompletely absorbed and doses recommended for suspension are proportionately higher than those for sodium fusidate tablets.

- **INTERACTIONS** → Appendix 1 (fusidic acid).

**SIDE-EFFECTS**
- **Common or very common** Abdominal pain - diarrhoea - dizziness - drowsiness - dyspepsia - nausea - vomiting
- **Uncommon** Anorexia - headache - malaise - pruritus - rash
- **Frequency not known** Acute renal failure (usually with jaundice) - blood disorders - reversible jaundice especially after high dosage (withdraw therapy if persistent)

**PREGNANCY** Not known to be harmful; manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING** Present in milk—manufacturer advises caution.

**HEPATIC IMPAIRMENT** Impaired biliary excretion; possibly increased risk of hepatotoxicity; avoid or reduce dose; monitor liver function in hepatic impairment.

**MONITORING REQUIREMENTS** Monitor liver function with high doses or on prolonged therapy.

**PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid formulations may include banana and orange.

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**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.
GLYCOPEPTIDE ANTIBACTERIALS

Teicoplanin

**DRUG ACTION** The glycopeptide antibiotic teicoplanin has bactericidal activity against aerobic and anaerobic Gram-positive bacteria including multi-resistant staphylococci. However, there are reports of *Staphylococcus aureus* with reduced susceptibility to glycopeptides and increasing reports of glycopeptide-resistant enterococci. Teicoplanin reduced susceptibility to glycopeptides and increasing its bactericidal activity against aerobic and anaerobic Gram-positive bacteria including multi-resistant *Staphylococcus aureus*. However, there are reports of *Staphylococcus aureus* with reduced susceptibility to glycopeptides.

**INDICATIONS AND DOSE**

- **Clostridium difficile infection**
  - **BY MOUTH**
    - Adult: 100–200 mg twice daily for 10–14 days
  - **Serious infections caused by Gram-positive bacteria (e.g. complicated skin and soft tissue infections, pneumonia)**
    - **BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION OR BY INTRAMUSCULAR INJECTION**
      - Adult (body-weight up to 70 kg): Initially 400 mg every 12 hours for 3 doses, followed by 400 mg once daily
      - Adult (body-weight 70 kg and above): Initially 6 mg/kg every 12 hours for 3 doses, then 6 mg/kg once daily
  - **Streptococcal or enterococcal endocarditis (in combination with another antibacterial)**
    - Adult: Initially 10 mg/kg every 12 hours for 3–5 doses, then 10 mg/kg once daily, subsequent doses can be given by intramuscular injection
  - **Bone and joint infections**
    - Adult: Initially 12 mg/kg every 12 hours for 3–5 doses, then 12 mg/kg once daily, subsequent doses can be given by intramuscular injection, increased risk of fever and rash with doses of 12 mg/kg
  - **Surgical prophylaxis**
    - Adult: 400 mg, to be administered up to 30 minutes before the procedure
  - **Surgical prophylaxis in open fractures**
    - Adult: 800 mg, to be administered up to 30 minutes before skeletal stabilisation and definitive soft-tissue closure
  - **Peritonitis associated with peritoneal dialysis (added to dialysis fluid)**
    - **BY INTRAPERITONEAL INFUSION**
      - Adult: (consult local protocol)
  - **PHARMACOKINETICS**
    - Teicoplanin should not be given by mouth for systemic infections because it is not absorbed significantly.

**SIDE-EFFECTS**
- **Common or very common**
  - Pruritus
  - Rash
- **Uncommon**
  - Bronchospasm
  - Dizziness
  - Eosinophilia
  - Fever
  - Headache
  - Leucopenia
  - Mild hearing loss
  - Nausea
  - Thrombocytopenia
  - Thrombophlebitis
  - Tinnitus
  - Vestibular disorders
  - Vomiting
- **Frequency not known**
  - Exfoliative dermatitis
  - Nephrotoxicity
  - Renal failure
  - Stevens-Johnson syndrome
  - Toxic epidermal necrolysis

**ALLERGIC AND CROSS-SENSITIVITY**
- **Caution if history of vancomycin sensitivity.**
- **PREGNANCY**
  - Manufacturer advises use only if potential benefit outweighs risk.
- **BREAST FEEDING**
  - No information available.
- **RENAL IMPAIRMENT**
  - Use normal dose regimen on days 1–4, then use normal maintenance dose every 48 hours if eGFR 30–80 ml/min/1.73 m² and use normal maintenance dose every 72 hours if eGFR less than 30 ml/min/1.73 m². Plasma-teicoplanin concentration should be monitored during parenteral maintenance treatment. Also monitor renal and auditory function during prolonged treatment in renal impairment.
- **MONITORING REQUIREMENTS**
  - Blood counts and liver and kidney function tests required.
  - With intramuscular use or intravenous use Plasma-teicoplanin concentration is not measured routinely because a relationship between plasma concentration and toxicity has not been established. However, the plasma-teicoplanin concentration can be used to optimise parenteral treatment in severe sepsis or burns, deep-seated staphylococcal infection (including bone and joint infection), endocarditis and in intravenous drug abusers. Pre-dose (‘trough’) concentrations should be greater than 15 mg/litre (greater than 20 mg/litre in endocarditis or deep-seated infection such as bone and joint infection), but less than 60 mg/litre. Plasma-teicoplanin concentration should be measured in elderly patients.
- **DIRECTIONS FOR ADMINISTRATION**
  - With intravenous use For intravenous infusion (Targocid®), give intermittently in Glucose 5% or Sodium chloride 0.9%; reconstitute initially with water for injections provided; infuse over 30 minutes. Continuous infusion not usually recommended.
  - With oral use Injection can be used to prepare solution for oral administration.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

**Powder and solvent for solution for injection**
- **ELECTROLYTES**: May contain Sodium
- **Targocid (Sanofi)**
  - **Teicoplanin 200 mg**
    - Targocid 200mg powder and solvent for solution for injection vials 1 vial £3.93
  - **Teicoplanin 400 mg**
    - Targocid 400mg powder and solvent for solution for injection vials 1 vial £7.32

**Telavancin**

**DRUG ACTION** Telavancin is a glycopeptide antibacterial; it has bactericidal activity against aerobic and anaerobic Gram-positive bacteria including multi-resistant *Staphylococcus aureus*. However, there are reports of *Staphylococcus aureus* with reduced susceptibility to
glycopeptides. There are increasing reports of glycopeptide-resistant enterococci.

**INDICATIONS AND DOSE**

Hospital-acquired pneumonia, known or suspected to be caused by meticillin-resistant Staphylococcus aureus when other antibacterials cannot be used

**BY INTRAVENOUS INFUSION**

- Adult: 10 mg/kg daily for 7–21 days

**CAUTIONS**

Conditions that predispose to renal impairment - predisposition to QT interval prolongation (including electrolyte disturbances, congenital long QT syndrome, uncompensated heart failure, severe left ventricular hypertrophy)

**INTERACTIONS**

Use with caution if concomitant use with nephrotoxic drugs.

**SIDE-EFFECTS**

- **Common or very common** Acute renal failure, chills, constipation, diarrhoea, dizziness, fungal infection, headache, insomnia, malaise, nausea, pruritus, rash, taste disturbances, vomiting

- **Uncommon** Abdominal pain, agranulocytosis, alopecia, anaphylaxis, anorexia, arthralgia, atrial fibrillation, back pain, blood disorders, blurred vision, bradycardia, confusion, congestive cardiac failure, decreased appetite, depression, dry mouth, dyspepsia, dysphonia, dysuria, electrolyte disturbances, erythema, eye irritation, flatulence, flushing, haematuria, haemorrhage, hepatic failure, hepatitis, hiccups, hyperhidrosis, hypertension, hypotension, increased INR, microalbuminuria, myalgia, nasal congestion, oedema, oliguria, oral hypoesthesia, palpitation, paraesthesia, pharyngolaryngeal pain, phlebitis, pollakiuria, pyrexia, QT interval prolongation, sinus tachycardia, somnolence, supraventricular extrasystoles, tinnitus, tremor, urinary tract infection, urticaria, ventricular extrasystoles

- **Rare** Deafness

- **Frequency not known** Flushing of the upper body (‘red man’ syndrome), non-cardiac chest pain

**ALLERGY AND CROSS-SENSITIVITY**

Use with caution in patients with vancomycin or teicoplanin sensitivity.

**CONCEPTION AND CONTRACEPTION**

Effective contraception required during treatment.

**PREGNANCY**

Avoid (teratogenic in animal studies).

**BREAST FEEDING**

Manufacturer advises avoid unless potential benefit outweighs risk - no information available.

**HEPATIC IMPAIRMENT**

Manufacturer advises caution in severe impairment - no information available.

**RENAL IMPAIRMENT**

In chronic renal failure, use 7.5 mg/kg once daily if eGFR 30–50 mL/minute/1.73 m². Avoid in acute renal failure - risk of mortality increased. In chronic renal failure, avoid if eGFR less than 30 mL/minute/1.73 m².

**MONITORING REQUIREMENTS**

Monitor renal function daily for at least the first 3–5 days, then every 2–3 days thereafter.

**DIRECTIONS FOR ADMINISTRATION**

For intravenous infusion (Vibativ®). Avoid rapid infusion (can cause ‘red man’ syndrome). Give intermittently in Glucose 5% or Sodium chloride 0.9%; reconstitute each 750 mg with 45 mL glucose 5%, sodium chloride 0.9%, or water for injections to produce a 15 mg/mL solution; for doses of 150–800 mg, dilute requisite dose in 100 to 250 mL infusion fluid; for doses outside this range, dilute to a final concentration of 0.6–8 mg/mL, give over at least 60 minutes.

**INDICATIONS AND DOSE**

Clostridium difficile infection

**BY MOUTH**

- Adult: 125 mg 4 times a day for 10–14 days, dose may be increased if infection fails to respond or is life-threatening, increased if necessary up to 500 mg 4 times a day

Infections due to Gram-positive bacteria including endocarditis, osteomyelitis, sepsicaemia and soft-tissue infections

**BY INTRAVENOUS INFUSION**

- Adult: 1–1.5 g every 12 hours
- Elderly: 500 mg every 12 hours, alternatively 1 g once daily

**SUPRATHEMICAL PROPHYLAXIS**

(when high risk of MRSA)

**BY INTRAVENOUS INFUSION**

- Adult: 1 g

Peritonitis associated with peritoneal dialysis

**BY INTRAPERITONEAL ADMINISTRATION**

Adult: (consult local protocol)

**PHARMACOKINETICS**

Vancomycin should not be given by mouth for systemic infections because it is not absorbed significantly.

**UNLICENSED USE**

Vancomycin doses in BNF publications may differ from those in product literature. Use of vancomycin (added to dialysis fluid) for the treatment of peritonitis associated with peritoneal dialysis is an unlicensed route.

**CAUTIONS**

**GENERAL CAUTIONS**

Avoid if history of deafness, elderly

**SPECIFIC CAUTIONS**

- With oral use - Systemic absorption may follow oral administration especially in inflammatory bowel disorders or following multiple doses

**INTERACTIONS**

Appendix 1 (vancomycin).

**SIDE-EFFECTS**

- **Common or very common**

- **Rare**

- **Frequency not known**

- **With intravenous use** Anaphylaxis, cardiac arrest on rapid infusion, chills, dysphoria, eosinophilia, exfoliative
Bacterial infection

**DERMATITIS** - fever, flushing of the upper body (‘red man’ syndrome) - nausea - pain and muscle spasm of back and chest - phlebitis (irritant to tissue) - pruritus - rashes - severe hypotension on rapid infusion - shock on rapid infusion - Stevens-Johnson syndrome - toxic epidermal necrolysis - urticaria - vasculitis - wheezing

**SIDE-EFFECTS, FURTHER INFORMATION**

**Nephrotoxicity** - Vancomycin is associated with a higher incidence of nephrotoxicity than teicoplanin.

- **ALLERGY AND CROSS-SENSITIVITY**
  - **Caution** if teicoplanin sensitivity.

- **PREGNANCY**
  - Manufacturer advises use only if potential benefit outweighs risk. Plasma-vancomycin concentration monitoring essential to reduce risk of fetal toxicity.

- **BREAST FEEDING**
  - Present in milk—significant absorption following oral administration unlikely.

- **RENAI IMPAIRMENT**
  - Reduce dose. In renal impairment monitor plasma-vancomycin concentration and renal function regularly. Also monitor auditory function.

- **MONITORING REQUIREMENTS**
  - All patients require plasma-vancomycin measurement (after 3 or 4 doses if renal function normal, earlier if renal impairment).
  - Pro-dose (‘ trough’) concentration should be 10–15 mg/litre (15–20 mg/litre for endocarditis or less sensitive strains of meticillin-resistant *Staphylococcus aureus* or for complicated infections caused by *S. aureus*). An initial loading dose, by intravenous infusion, may be considered—consult local guidelines.
  - All patients require blood counts, urinalysis, and renal function tests.
  - Monitor auditory function in elderly.

- **DIRECTIONS FOR ADMINISTRATION**
  - With intravenous use Avoid rapid infusion (risk of anaphylactoid reactions and rotate infusion sites.
  - For intravenous infusion (Vancocin®), give intermittently in Glucose 5% or Sodium chloride 0.9%; reconstitute each 500 mg with 10 mL water for injections and dilute with infusion fluid to a concentration of up to 5 mg/mL (10 mg/mL in fluid restriction but increased risk of infusion-related effects); give over at least 60 minutes (rate not to exceed 10 mg/minute for doses over 500 mg); use continuous infusion only if intermittent not feasible.
  - With oral use Injection can be used to prepare solution for oral administration; flavouring syrups may be added to the solution at the time of administration.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops, solution for injection, oral suspension, oral solution, pastille, infusion

  **Capsule**
  - **CAUTIONARY AND ADVISORY LABELS 9**
  - **VANCYMYOCIN (Non-proprietary)**
    - Vancomycin (as Vancomycin hydrochloride) 125 mg
    - Vancomycin 125 mg capsules | 28 capsule PDr | £13.47
    - Vancomycin (as Vancomycin hydrochloride) 250 mg
    - Vancomycin 250 mg capsules | 28 capsule PDr | £14.08
  - **Brands may include Vancocin Matrigel**

  **Powder for solution for infusion**
  - **VANCYMYOCIN (Non-proprietary)**
    - Vancomycin (as Vancomycin hydrochloride) 500 mg
    - Vancomycin 500 mg powder for solution for infusion vials | 1 vial PDr | £6.25–£7.25
    - Vancomycin 500 mg powder for concentrate for solution for infusion vials | 1 vial PDr | £7.50–£8.50
    - Vancomycin (as Vancomycin hydrochloride) 1 gram
    - Vancomycin 1 g powder for solution for infusion vials | 1 vial PDr | £12.50–£14.50
    - (Hospital only) | 1 vial PDr | £17.25

  - **Vancocin (Flynn Pharma Ltd)**
    - Vancomycin (as Vancomycin hydrochloride) 500 mg
    - Vancomycin 500 mg powder for solution for infusion vials | 1 vial PDr | £6.25
    - Vancomycin (as Vancomycin hydrochloride) 1 gram
    - Vancomycin 1 g powder for solution for infusion vials | 1 vial PDr | £12.50

  **GLYCYLCYCLINE ANTIBACTERIALS**

  **Tigecycline**
  - **DRUG ACTION** Tigecycline is a glycylcycline antibacterial structurally related to the tetracyclines. Tigecycline is active against Gram-positive and Gram-negative bacteria, including tetracycline-resistant organisms, and some anaerobes. It is also active against meticillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci, but *Pseudomonas aeruginosa* and many strains of *Proteus spp* are resistant to tigecycline.

  **INDICATIONS AND DOSE**
  - Treatment of complicated skin and soft-tissue infections and complicated abdominal infections caused by multiple-antibacterial resistant organisms when other antibacterials cannot be used
  - **BY INTRAVENOUS INFUSION**
    - Adult: Initially 100 mg, then 50 mg every 12 hours for 5–14 days, not recommended for the treatment of foot infections in patients with diabetes

  **CAUTIONS**
  - Cholestasis

  **INTERACTIONS** → Appendix 1 (tigecycline).

  **SIDE-EFFECTS**
  - **Common or very common** Abdominal pain - anorexia - bilirubinaemia - diarrhoea - dizziness - dyspepsia - headache - hypoglycaemia - injection-site reactions - nausea - prolonged activated partial thromboplastin time - prolonged prothrombin time - pruritus - rash - vomiting
  - **Uncommon** Cholestatic jaundice - hypoproteinaemia - pancreatitis
  - **Frequency not known** Antibiotic-associated colitis - hepatic failure - Stevens-Johnson syndrome - thrombocytopenia

  **SIDE-EFFECTS, FURTHER INFORMATION**
  - Side-effects similar to those of the tetracyclines can potentially occur.

  **ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in patients hypersensitive to tetracyclines.

  **PREGNANCY** Tetracyclines should not be given to pregnant women; effects on skeletal development have been documented in the first trimester in animal studies. Administration during the second or third trimester may cause discoloration of the child’s teeth, and maternal hepatotoxicity has been reported with large parental doses.

  **BREAST FEEDING** Manufacturer advises caution—present in milk in animal studies.

  **HEPATIC IMPAIRMENT** Initially 100 mg then 25 mg every 12 hours in severe hepatic impairment.

  **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Tygacil®), give intermittently in Glucose 5% or Sodium Chloride 0.9%. Reconstitute each vial with 5.3 mL infusion fluid to produce a 10 mg/mL solution; dilute requisite dose in 100 mL infusion fluid; give over 30–60 minutes.

  **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Powder for solution for infusion**
  - **Tygacil (Pfizer Ltd)**
    - Tigecycline 50 mg
    - Tigecycline 50 mg powder for solution for infusion vials | 10 vial PDr | £323.10
LINCOSAMIDE ANTIBACTERIALS

Clindamycin

- **DRUG ACTION** Clindamycin is active against Gram-positive cocci, including streptococci and penicillin-resistant staphylococci, and also against many anaerobes, especially *Bacteroides fragilis*. It is well concentrated in bone and excreted in bile and urine.

**INDICATIONS AND DOSE**

Staphylococcal bone and joint infections such as osteomyelitis | Peritonitis | Intra-abdominal sepsis | Metacillin-resistant Staphylococcus aureus (MRSA) in bronchiectasis, bone and joint infections, and skin and soft-tissue infections.

- **ERYSIPHELS or CELLULITIS in penicillin-allergic patients**
  - **BY MOUTH**
    - **Child:** 3–6 mg/kg 4 times a day (max. per dose 450 mg)
    - **Adult:** 150–300 mg every 6 hours; increased if necessary up to 450 g every 6 hours if required, increased dose used in severe infection
  - **BY DEEP INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INFUSION**
    - **Adult:** 0.6–2.7 g daily in 2–4 divided doses; increased if necessary up to 4.8 g daily, increased dose used if life-threatening infection, single doses above 600 mg to be administered by intravenous infusion only, single doses by intravenous infusion not to exceed 1.2 g.

- **TREATMENT OF MILD TO MODERATE PNEUMOCYSTIS PNEUMONIA (IN COMBINATION WITH PRIMAQUINE)**
  - **BY MOUTH**
    - **Child:** 7–13 mg/kg every 8 hours (max. per dose 450 mg) for 7 days
    - **Adult:** 450 mg every 8 hours for 7 days

**DACLACIN T® PREPARATIONS**

- **ACNE VULGARIS**
  - **TO THE SKIN**
    - **Adult:** Apply twice daily, to be applied thinly
  - **ZINDACLIN® GEL**
    - **TO THE SKIN**
      - **Adult:** Apply once daily, to be applied thinly

- **UNLICENSED USE** Not licensed for treatment of falciparum malaria. Not licensed for treatment of mild to moderate pneumocystis infection.

- **CONTRA-INDICATIONS** Diarrhoeal states • Avoid injections containing benzyl alcohol in neonates

- **CAUTIONS** Avoid in Acute porphyrias p. 864 • middle-aged and elderly women, especially after an operation (antibiotics-associated colitis more common)

- **INTERACTIONS** Appendix 1 (clindamycin).

- **SIDE-EFFECTS**
  - **GENERAL SIDE-EFFECTS** Abdominal discomfort • anaphylactoid reactions • antibiotic-associated colitis • diarrhoea (discontinue treatment) • eosinophilia • exfoliative dermatitis • jaundice • leukopenia • nausea • oesophageal ulcers • oesophagitis • polyarthralgia • pruritus • rash • Stevens-Johnson syndrome • taste disturbances • thrombocytopenia • toxic epidermal necrolysis • urticaria • vesiculobullous dermatitis • vomiting
  - **SPECIFIC SIDE-EFFECTS**
    - **With intramuscular use** Induration (after intramuscular injection) • abscess (after intramuscular injection) • pain (after intramuscular injection)
    - **With intravenous use** Thrombophlebitis (after intravenous injection)

**SIDE-EFFECTS, FURTHER INFORMATION**

**Antibiotic-associated colitis** Clindamycin has been associated with antibiotic-associated colitis, which may be fatal. Although antibiotic-associated colitis can occur with most antibacterials, it occurs more frequently with clindamycin. Patients should therefore discontinue treatment immediately if diarrhoea develops.

- **PREGNANCY** Not known to be harmful.

- **BREAST FEEDING** Amount probably too small to be harmful but bloody diarrhoea reported in 1 infant.

- **MONITORING REQUIREMENTS**
  - **Monitor liver and renal function if treatment exceeds 10 days.**
  - **In children** Monitor liver and renal function in infants.

- **DIRECTIONS FOR ADMINISTRATION** Avoid rapid intravenous administration.

  - With intravenous use in children For **intravenous infusion**, dilute to a concentration of not more than 18 mg/mL with Glucose 5% or Sodium Chloride 0.9%; give over 10–60 minutes at a max. rate of 20 mg/kg/hour.

  - With intravenous use in adults For **intravenous infusion** *(Dalacin® C Phosphate)*, give continuously or intermittently in Glucose 5% or Sodium Chloride 0.9%; dilute to not more than 18 mg/mL and give over 10–60 minutes at a rate not exceeding 30 mg/minute (1.2 g over at least 60 minutes; higher doses by continuous infusion).

- **PATIENT AND CARER ADVICE** Patients and their carers should be advised to discontinue immediately and contact doctor if diarrhoea develops. Capsules should be swallowed with a glass of water.

- **PROFESSION SPECIFIC INFORMATION**
  - Dental practitioners’ formulary Clindamycin Capsules may be prescribed.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution.

**Capsule**

| CAUTIONARY AND ADVISORY LABELS | 9, 27 |

- **CLINDAMYCN (NON-PROPRIETARY)**
  - Clindamycin (as Clindamycin hydrochloride) 150 mg Clindamycin 150mg capsules | 24 capsule (£) £7.80 DT price = £3.38 | 100 capsule (£) £66.18
  - Clindamycin (as Clindamycin hydrochloride) 300 mg Clindamycin 300mg capsules | 30 capsule (£) £10.20 DT price = £3.19
  - Dalacin C (Pfizer Ltd)
  - Clindamycin (as Clindamycin hydrochloride) 75 mg Dalacin C 75mg capsules | 24 capsule (£) £7.45 DT price = £7.45
  - Clindamycin (as Clindamycin hydrochloride) 150 mg Dalacin C 150mg capsules | 24 capsule (£) £11.72 DT price = £3.38 |
  - 100 capsule (£) £66.18

**Solution for injection**

| EXCIPIENTS: May contain Benzyl alcohol |

- **CLINDAMYCN (NON-PROPRIETARY)**
  - Clindamycin (as Clindamycin phosphate) 150 mg per 1 ml Clindamycin 600mg/4ml solution for injection ampoules | 5 ampoule (£) £61.75
  - Clindamycin 300mg/2ml solution for injection ampoules | 5 ampoule (£) £28.50–£31.01
  - Dalacin C (Pfizer Ltd)
  - Clindamycin (as Clindamycin phosphate) 150 mg per 1 ml Dalacin C Phosphate 300mg/2ml solution for injection ampoules | 5 ampoule (£) £31.01
  - Dalacin C Phosphate 600mg/4ml solution for injection ampoules | 5 ampoule (£) £61.75

**Liquid**

| EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), hydroxybenzoates (parabens), propylene glycol |
Daptomycin

**DRUG ACTION** Daptomycin is a lipopeptide antibiotic with a spectrum of activity similar to vancomycin but its efficacy against enterococci has not been established. It needs to be given with other antibacterials for mixed infections involving Gram-negative bacteria and some anaerobes.

**INDICATIONS AND DOSE**

**Complicated skin and soft-tissue infections caused by Gram-positive bacteria, including meticillin-resistant Staphylococcus aureus (MRSA)**

**BY SLOW INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION**

- Adult: 4 mg/kg once daily; increased to 6 mg/kg once daily, increase dose only if associated with *Staphylococcus aureus* bacteraemia

Staphylococcal endocarditis caused by organisms resistant to vancomycin or in patients intolerant of vancomycin (in combination with other antibacterials)

**BY SLOW INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION**

- Adult: 6 mg/kg once daily

**UNLICENSED USE** Not licensed for use in left-sided endocarditis.

**INTERACTIONS** → Appendix 1 (daptomycin).

Monitor creatine kinase more frequently than weekly during treatment if receiving another drug known to cause myopathy (preferably avoid concomitant use).

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain - anaemia - anxiety - arthralgia - asthenia - constipation - diarrhoea - dizziness - flatulence - headache - hypertension - hypotension - injection-site reactions - isoniazid - nausea - pruritis - rash - vomiting


- **Rare** Jaundice - rhabdomyolysis

- **Frequency not known** Antibiotic-associated colitis - elevated creatine kinase - eosinophilic pneumonia - peripheral neuropathy - syncope - wheezing

**SIDE-EFFECTS, FURTHER INFORMATION**

**Muscle effects** If unexplained muscle pain, tenderness, weakness, or cramps develop during treatment, measure creatine kinase every 2 days; discontinue if unexplained muscular symptoms and creatine elevated markedly.

**PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk—no information available.

**BREAST FEEDING** Present in milk in small amounts, but absorption from gastrointestinal tract negligible.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in severe hepatic impairment—no information available.

**RENAL IMPAIRMENT** Use normal dose every 48 hours if eGFR less than 30 mL/minute/1.73 m². If eGFR less than 80 mL/minute/1.73 m², monitor renal function, and monitor creatine kinase before treatment and then at least weekly during treatment.

**MONITORING REQUIREMENTS** Monitor creatine kinase before treatment and then weekly during treatment (more frequently if creatine kinase elevated more than 5 times upper limit of normal before treatment).

**EFFECT ON LABORATORY TESTS** Interference with assay for prothrombin time and INR—take blood sample immediately before daptomycin dose.

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Cubicin®), give intermittently in Sodium chloride 0.9%; reconstitute with sodium chloride 0.9% (350 mg in 7 mL, 500 mg in 10 mL); gently rotate vial without shaking; allow to stand for at least 10 minutes then rotate gently to dissolve; dilute requisite dose in 50 mL infusion fluid and give over 30 minutes. For intravenous injection, give over 2 minutes.

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (February 2008) that daptomycin (Cubicin®) is accepted for restricted use within NHS Scotland for the treatment of MRSA bacteraemia associated with right-sided endocarditis or with complicated skin and soft-tissue infections.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**

- Cubicin (Novartis Pharmaceuticals UK Ltd)
  - Daptomycin 350 mg (Cubicin 350mg powder for concentrate for solution for infusion vials) 1 vial (PMD) £62.00
  - Daptomycin 500 mg (Cubicin 500mg powder for concentrate for solution for infusion vials) 1 vial (PMD) £88.57 (Hospital only)

**MACROCYCLIC ANTIBACTERIALS**

Fidaxomicin

**DRUG ACTION** Fidaxomicin is a macrocyclic antibacterial that is poorly absorbed from the gastro-intestinal tract, and, therefore, it should not be used to treat systemic infections.

**INDICATIONS AND DOSE**

**Clostridium difficile infection**

**BY MOUTH**

- Adult: 200 mg every 12 hours for 10 days, limited clinical data is available on the use of fidaxomicin in severe or life-threatening *Clostridium difficile* infection

**CAUTIONS** Inflammatory bowel disease - severe or life-threatening *C. difficile* infection

**INTERACTIONS** → Appendix 1 (fidaxomicin).

**SIDE-EFFECTS**

- **Common or very common** Constipation - nausea - vomiting

- **Uncommon** Abdominal distension - decreased appetite - dizziness - dry mouth - flatulence - headache - taste disturbance

**ALLERGY AND CROSS-SENSITIVITY** Use with caution in macrolide hypersensitivity.

**PREGNANCY** Manufacturer advises avoid—no information available.

**BREAST FEEDING** Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in moderate to severe impairment—no information available.

**RENAL IMPAIRMENT** Manufacturer advises caution in severe impairment—no information available.
MACROLIDES AND RELATED DRUGS

Macrolides

The macrolides have an antibacterial spectrum that is similar but not identical to that of penicillin; they are thus an alternative in penicillin-allergic patients. They are active against Haemophilus influenzae, non-gonococcal urethritis. Erythromycin has poor activity against Streptococcus pneumoniae, is suspected higher doses are needed.

Erythromycin p. 471 is also used in the treatment of early syphilis, uncomplicated genital chlamydial infection, and uncomplicated gonococcal urethritis. Erythromycin has poor activity against Haemophilus influenzae. Erythromycin causes nausea, vomiting, and diarrhoea in some patients; in mild to moderate infections this can be avoided by giving a lower dose, but if a more serious infection, such as Legionella pneumonia, is suspected higher doses are needed.

Azithromycin below is a macrolide with slightly less activity than erythromycin against Gram-positive bacteria, but enhanced activity against some Gram-negative organisms including H. influenzae. Plasma concentrations are very low, but tissue concentrations are much higher. It has a long tissue half-life and once daily dosage is recommended. Azithromycin is also used in the treatment of uncomplicated genital chlamydial infection, non-gonococcal urethritis, uncomplicated gonorrhoea, typhoid [unlicensed indication], and trachoma [unlicensed indication].

Clarithromycin p. 470 is an erythromycin derivative with slightly greater activity than the parent compound. Tissue concentrations are higher than with erythromycin. It is given twice daily. Clarithromycin is also used in regimens for Helicobacter pylori eradication.

Telithromycin p. 473 is a ketolide derivative of erythromycin with an antibacterial spectrum similar to that of other macrolides and it is also active against penicillin- and erythromycin-resistant Streptococcus pneumoniae.

Erythromycin, azithromycin, and clarithromycin have a role in the treatment of Lyme disease p. 500.

Macrolides

- **Cautions** Electrolyte disturbances (predisposition to QT interval prolongation) - may aggravate myasthenia gravis - predisposition to QT interval prolongation

- **Side-effects**

  **General side-effects**

  - Common or very common Abdominal discomfort - diarrhoea - nausea - vomiting
  - Uncommon Cholestatic jaundice - hepatotoxicity - rash
  - Rare Antibiotic-associated colitis - arrhythmias - pancreatitis - QT interval prolongation - Stevens-Johnson syndrome - toxic epidermal necrolysis
  - Frequency not known Reversible hearing loss (sometimes with tinnitus) can occur after large doses

**Specific side-effects**

- With intravenous use Local tenderness - phlebitis

- **Side-effects, further information**

Gastro-intestinal side-effects are mild and less frequent with azithromycin and clarithromycin than with erythromycin.

Azithromycin

**Indications and dose**

Prevention of secondary case of invasive group A streptococcal infection in patients who are allergic to penicillin

**By mouth**

- Child 6 months-11 years: 12 mg/kg once daily (max. per dose 500 mg) for 5 days
- Child 12-17 years: 500 mg once daily for 5 days
- Adult: 500 mg once daily for 5 days

Respiratory-tract infections, otitis media, skin and soft-tissue infections

**By mouth**

- Child 6 months-17 years: 10 mg/kg once daily (max. per dose 500 mg) for 3 days
- Child 6 months-17 years (body-weight 15-25 kg): 200 mg once daily for 3 days
- Child 6 months-17 years (body-weight 26-35 kg): 300 mg once daily for 3 days
- Child 6 months-17 years (body-weight 36-45 kg): 400 mg once daily for 3 days
- Child 6 months-17 years (body-weight 46 kg and above): 500 mg once daily for 3 days
- Adult: 500 mg once daily for 3 days, alternatively initially 500 mg once daily for 1 day, then 250 mg once daily for 4 days

Uncomplicated genital chlamydial infections | Non-gonococcal urethritis

**By mouth**

- Child 12-17 years: 1 g for 1 dose
- Adult: 1 g for 1 dose

Uncomplicated gonorrhoea

**By mouth**

- Adult: 1 g for 1 dose

Lyme disease

**By mouth**

- Adult: 500 mg daily for 7–10 days

Mild to moderate typhoid due to multiple-antibacterial resistant organisms

**By mouth**

- Adult: 500 mg daily for 7 days

Community-acquired pneumonia, low to moderate severity

**By mouth**

- Adult: 500 mg once daily for 3 days, alternatively initially 500 mg once daily for 1 day, then 250 mg once daily for 4 days

continued
Community-acquired pneumonia, high severity
INITIALLY BY INTRavenous INFUSION
- Adult: Initially 500 mg once daily for at least 2 days, then (by mouth) 500 mg once daily for a total duration of 7–10 days

Antibacterial prophylaxis for insertion of intra-uterine device
BY MOUTH
- Adult: 1 g for 1 dose

UNLICENSED USE Not licensed for uncomplicated gonorrhoea, mild or moderate typhoid due to multiple-antibacterial-resistant organisms, Lyme disease, or prophylaxis of group A streptococcal infection. Not licensed for community-acquired pneumonia (high severity) when oral treatment continues for more than 3 days.

INTERACTIONS Appendix 1 (macrolides). Caution with concomitant use of drugs that prolong the QT interval.

SIDE-EFFECTS
- Common or very common Anorexia · arthralgia · arthralgia · disturbances in taste · disturbances in vision · dizziness · dyspepsia · flatulence · headache · malaise · paraesthesia · reversible hearing loss (sometimes with tinnitus) after long-term therapy.
- Uncommon Anxiety · chest pain · constipation · gastritis · hyperaesthesia · leucopenia · oedema · photosensitivity · sleep disturbances
- Rare Agitation
- Frequency not known Acute renal failure · convulsions · haemolytic anaemia · interstitial nephritis · smell disturbances · syncope · thrombocytopenia · tongue discoloration

PREGNANCY Manufacturers advise use only if adequate alternatives not available.

BREAST FEEDING Present in milk; use only if no suitable alternatives.

HEPATIC IMPAIRMENT Manufacturers advise avoid in severe liver disease–no information available.

RENAL IMPAIRMENT
- In adults Use with caution if eGFR less than 10 mL/minute/1.73 m².
- In children Use with caution if estimated glomerular filtration rate less than 10 mL/minute/1.73 m².

DIRECTIONS FOR ADMINISTRATION For intravenous infusion (Zedbac®), give intermittently in Glucose 5% or Sodium Chloride 0.9%. Reconstitute 500 mg with 4.8 mL water for injections to produce a 100 mg/mL solution, then dilute 5 mL of solution with infusion fluid to a final concentration of 1 or 2 mg/mL; give the 1 mg/mL solution over 3 hours or give the 2 mg/mL solution over 1 hour.

PRESCRIBING AND DISPENSING INFORMATION Flavours of oral liquid formulations may include cherry or banana.

PATIENT AND CARER ADVICE Medicines for Children leaflet: Azithromycin for bacterial infections www.medicinesforchildren.org.uk/ azithromycin-bacterial-infections-0

PROFESSION SPECIFIC INFORMATION
Dental practitioners’ formulary Azithromycin Capsules may be prescribed. Azithromycin Tablets may be prescribed. Azithromycin Oral Suspension 200 mg/5 mL may be prescribed.

EXCEPTIONS TO LEGAL CATEGORY Azithromycin tablets can be sold to the public for the treatment of confirmed, asymptomatic Chlamydia trachomatis genital infection in those over 16 years of age, and for the epidemiological treatment of their sexual partners, subject to maximum single dose of 1 g, maximum daily dose 1 g, and a pack size of 1 g.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Tablet
CAUTIONARY AND ADVISORY LABELS 5, 9
- AZITHROMYCIN (Non-proprietary)
  - Azithromycin 250 mg Azithromycin 250mg tablets | 4 tablet | £10.11 DT price = £15.11
  - Azithromycin 500 mg Azithromycin 500mg tablets | 3 tablet | £15.11

- Zithromax (Pfizer Ltd)
  - Azithromycin (as Azithromycin dihydrate) 250 mg Zithromax 250mg capsules | 4 capsule | £0.10 | 6 capsule | £0.15 DT price = £0.15

- Zithromax (as Azithromycin dihydrate) 250 mg Zithromax 250mg capsules | 6 capsule | £0.10 DT price = £0.15

Oral suspension
CAUTIONARY AND ADVISORY LABELS 5, 9
- AZITHROMYCIN (Non-proprietary)
  - Azithromycin 40 mg per 1 ml Azithromycin 200mg/5ml oral suspension | 15 ml | £0.18 DT price = £0.20 | 30 ml | £0.20 DT price = £0.40
  - Azithromycin (as Azithromycin dihydrate) 250 mg Zithromax 250mg/5ml oral suspension | 15 ml | £0.06 DT price = £0.10 | 30 ml | £0.10 DT price = £0.20

Powder for solution for infusion
ELECTROLYTES: May contain Sodium
- Zedbac (Aspire Pharma Ltd)
  - Azithromycin (as Azithromycin dihydrate) 500 mg Zedbac 500mg powder for solution for infusion vials | 1 vial | £0.30

Clarithromycin

INDICATIONS AND DOSE
Respiratory-tract infections | Mild to moderate skin and soft-tissue infections | Otitis media
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
- Child 1 month–11 years (body-weight up to 8 kg): 7.5 mg/kg twice daily
- Child 1 month–11 years (body-weight 8–11 kg): 62.5 mg twice daily
- Child 1 month–11 years (body-weight 12–19 kg): 125 mg twice daily
- Child 1 month–11 years (body-weight 20–29 kg): 187.5 mg twice daily
- Child 1 month–11 years (body-weight 30–40 kg): 250 mg twice daily
- Child 12–17 years: 250 mg twice daily usually for 7–14 days, increased to 500 mg twice daily, if required in severe infections (e.g. pneumonia)
- Adult: 250 mg twice daily usually for 7–14 days, increased to 500 mg twice daily, if required in severe infections (e.g. pneumonia)

BY MOUTH USING MODIFIED-RELEASE MEDICINES
- Child 12–17 years: 500 mg once daily usually for 7–14 days, increased to 1 g once daily, if required in severe infections (e.g. pneumonia)
- Adult: 500 mg once daily usually for 7–14 days, increased to 1 g once daily, if required in severe infections (e.g. pneumonia)

BY INTRAVENOUS INFUSION
- Adult: 500 mg every 12 hours maximum duration 5 days, switch to oral route when appropriate, to be administered into a large proximal vein
**Bacterial infection** 471

**Lyme disease**

**BY MOUTH**
- Child 12–17 years: 500 mg twice daily for 14–21 days
- Adult: 500 mg twice daily for 14–21 days

**Prevention of pertussis**

**BY MOUTH**
- Child 1 month–11 years (body-weight up to 8 kg): 7.5 mg/kg twice daily for 7 days
- Child 1 month–11 years (body-weight 8–11 kg): 62.5 mg twice daily for 7 days
- Child 1 month–11 years (body-weight 12–19 kg): 125 mg twice daily for 7 days
- Child 1 month–11 years (body-weight 20–29 kg): 187.5 mg twice daily for 7 days
- Child 1 month–11 years (body-weight 30–40 kg): 250 mg twice daily for 7 days
- Child 12–17 years: 500 mg twice daily for 7 days
- Adult: 500 mg twice daily for 7 days

**Helicobacter pylori eradication in combination with a proton pump inhibitor and amoxicillin**

**BY MOUTH**
- Adult: 500 mg twice daily

**Helicobacter pylori eradication in combination with a proton pump inhibitor and metronidazole**

**UNLICENSED USE** Tablets not licensed for use in children under 12 years; oral suspension not licensed for use in infants under 6 months. Intravenous infusion not licensed for use in children under 12 years.

**INTERACTIONS** → Appendix 1 (macrolides). Caution with concomitant use of drugs that prolong the QT interval.

**SIDE-EFFECTS**
- **Common or very common** Dyspepsia; headache; hyperhidrosis; insomnia; taste disturbances
- **Uncommon** Anorexia; anxiety; blood disorders; chest pain; constipation; dizziness; dry mouth; flattulence; gastritis; glossitis; hepatic dysfunction including jaundice; leucopenia; malaise; myalgia; stomatitis; tinnitus; tremor
- **Frequency not known** Abnormal dreams; confusion; convulsions; depression; hypoglycaemia; interstitial nephritis; myopathy; paraesthesia; psychotic disorders; renal failure; smell disturbances; tongue discoloration; tooth discoloration

**PREGNANCY** Manufacturer advises avoid, particularly in the first trimester, unless potential benefit outweighs risk.

**BREAST FEEDING** Manufacturer advises avoid unless potential benefit outweighs risk—present in milk.

**HEPATIC IMPAIRMENT** Avoid in severe impairment if renal impairment also present.

**RENAL IMPAIRMENT** Avoid if severe hepatic impairment also present.
- In adults Use half normal dose if eGFR less than 30 mL/minute/1.73 m², max. duration 14 days. Avoid **Klaricid XL®** or clarithromycin m/t preparations if eGFR less than 30 mL/minute/1.73 m²
- In children Use half normal dose if estimated glomerular filtration rate less than 30 mL/minute/1.73 m², max. duration 14 days. Avoid **Klaricid XL®** or clarithromycin m/t preparations if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use in children: For intermittent intravenous infusion dilute reconstituted solution further in Glucose 5% or Sodium chloride 0.9% to a concentration of 2 mg/mL; give into large proximal vein over 60 minutes.

- With intravenous use in adults: For intravenous infusion (Klaricid® I.V.), give intermittently in Glucose 5% or Sodium Chloride 0.9%; dissolve initially in water for injections (500 mg in 10 mL) then dilute to a concentration of 2 mg/mL; give over 60 minutes.

**PATIENT AND CARER ADVICE**


**PROFESSION SPECIFIC INFORMATION**

**Dental practitioners’ formulary** Clarithromycin Tablets may be prescribed. Clarithromycin Oral Suspension may be prescribed.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion

**Tablet**

**CAUTIONARY AND ADVISORY LABELS**
- **CLARITHROMYCIN (Non-proprietary)**
  - Clarithromycin 250 mg Clarithromycin 250mg tablets | 14 tablet (£6.72 DT price = £6.72)
  - Clarithromycin 500 mg Clarithromycin 500mg tablets | 14 tablet (£12.15 DT price = £12.15)

**Modified-release tablet**

**CAUTIONARY AND ADVISORY LABELS**
- **CLARITHROMYCIN (Non-proprietary)**
  - Clarithromycin 25 mg per 1 ml Clarithromycin 25mg/5ml oral suspension | 70 ml (£6.72 DT price = £6.72)
  - Clarithromycin 50 mg per 1 ml Clarithromycin 250mg/5ml oral suspension | 70 ml (£21.75 DT price = £21.75)

**Granules**

**CAUTIONARY AND ADVISORY LABELS**
- **Klaricid** (BGP Products Ltd)
  - Clarithromycin 500 mg Klaricid Adult 250mg granules sachets | 14 sachet (£6.68)

**Oral suspension**

**CAUTIONARY AND ADVISORY LABELS**
- **CLARITHROMYCIN (Non-proprietary)**
  - Clarithromycin 25 mg per 1 ml Clarithromycin 125mg/5ml oral suspension | 70 ml (£4.22 DT price = £4.22)
  - Clarithromycin 50 mg per 1 ml Clarithromycin 250mg/5ml oral suspension | 70 ml (£6.17 DT price = £6.17)

**Powder for solution for infusion**

**ELECTROLYTES** May contain Sodium

**CLARITHROMYCIN (Non-proprietary)**
- Clarithromycin 500 mg Clarithromycin 500mg powder for solution for infusion vials | 1 vial (£9.45 DT price = £9.45)

**Klaricid** (BGP Products Ltd)
- Clarithromycin 500 mg Clarithromycin 125mg/5ml oral suspension | 70 ml (£3.15 DT price = £3.15)

**Klaricid IV** (BGP Products Ltd)
- Clarithromycin 500 mg Clarithromycin 500mg powder for solution for infusion vials | 1 vial (£9.45 DT price = £9.45)

**ERYTHROMYCIN**

**INDICATIONS AND DOSE**

Susceptible infections in patients with penicillin hypersensitivity (e.g. respiratory-tract infections (including Legionella infection), skin and oral infections, and campylobacter enteritis)

**BY MOUTH**
- Child 1 month–1 year: 125 mg 4 times a day, total daily dose may alternatively be given in two divided doses. Increased to 250 mg 4 times a day in severe infections
- Child 2–7 years: 250 mg 4 times a day, total daily dose may alternatively be given in two divided doses. Increased to 500 mg 4 times a day in severe infections
472 Bacterial infection

- Child 8-17 years: 250–500 mg 4 times a day, total daily dose may alternatively be given in two divided doses. Increased to 500–1000 mg 4 times a day in severe infections
- Adult: 250–500 mg 4 times a day, total daily dose may alternatively be given in two divided doses. Increased to 500–1000 mg 4 times a day in severe infections

**BY INTRAVENOUS INFUSION**
- Child: 1.25 mg/kg every 6 hours (max. per dose 1 g)
- Adult: 6.25 mg/kg every 6 hours, for mild infections when oral treatment not possible; increased to 12.5 mg/kg every 6 hours in severe infections

### Lyme disease
**BY MOUTH**
- Adult: 500 mg 4 times a day for 14–21 days

### Early syphilis
**BY MOUTH**
- Adult: 500 mg 4 times a day for 14 days

### Uncomplicated genital chlamydia | Non-gonococcal urethritis
**BY MOUTH**
- Adult: 500 mg twice daily for 14 days

### Chronic prostatitis
**BY MOUTH**
- Adult: 250–500 mg 4 times a day, total daily dose may alternatively be given in two divided doses. Increased to 4 g daily in divided doses in severe infections

**BY INTRAVENOUS INFUSION**
- Adult: 6.25 mg/kg every 6 hours, for mild infections when oral treatment is not possible. Increased to 12.5 mg/kg every 6 hours in severe infections

### Prevention and treatment of pertussis
**BY MOUTH**
- Child 1 month-1 year: 125 mg 4 times a day, total daily dose may alternatively be given in two divided doses. Increased to 250 mg 4 times a day in severe infections
- Child 2-7 years: 250 mg 4 times a day, total daily dose may alternatively be given in two divided doses. Increased to 500 mg 4 times a day in severe infections
- Child 8-17 years: 250–500 mg 4 times a day, total daily dose may alternatively be given in two divided doses. Increased to 500–1000 mg 4 times a day in severe infections
- Adult: (consult local protocol)

### Prevention of secondary case of diphtheria in non-immune patient
**BY MOUTH**
- Child 1 month-1 year: 125 mg every 6 hours for 7 days, treat for further 10 days if nasopharyngeal swabs positive after first 7 days' treatment
- Child 2-7 years: 250 mg every 6 hours for 7 days, treat for further 10 days if nasopharyngeal swabs positive after first 7 days' treatment
- Child 8-17 years: 500 mg every 6 hours for 7 days, treat for further 10 days if nasopharyngeal swabs positive after first 7 days' treatment

### Prevention of secondary case of invasive group A streptococcal infection in penicillin allergic patients
**BY MOUTH**
- Child 1 month-1 year: 125 mg every 6 hours for 10 days
- Child 2-7 years: 250 mg every 6 hours for 10 days
- Child 8-17 years: 250–500 mg every 6 hours for 10 days
- Adult: 250–500 mg every 6 hours for 10 days

### Prevention of pneumococcal infection in asplenia or in patients with sickle-cell disease, and who are penicillin allergic
**BY MOUTH**
- Child 1 month-1 year: 125 mg twice daily, antibiotic prophylaxis is not fully reliable
- Child 2-7 years: 125 mg twice daily, antibiotic prophylaxis is not fully reliable. It may be discontinued in those over 5 years of age with sickle-cell disease who have received pneumococcal immunisation and who do not have a history of severe pneumococcal infection
- Child 8-17 years: 500 mg twice daily, antibiotic prophylaxis is not fully reliable. It may be discontinued in those over 5 years of age with sickle-cell disease who have received pneumococcal immunisation and who do not have a history of severe pneumococcal infection
- Adult: 500 mg twice daily, antibiotic prophylaxis is not fully reliable. It may be discontinued in those over 5 years of age with sickle-cell disease who have received pneumococcal immunisation and who do not have a history of severe pneumococcal infection

### Prevention of recurrence of rheumatic fever
**BY MOUTH**
- Child 1 month-1 year: 125 mg twice daily
- Child 2-17 years: 250 mg twice daily

### Rosacea
**BY MOUTH**
- Adult: 500 mg twice daily courses usually last 6–12 weeks and are repeated intermittently

### Acne
**BY MOUTH**
- Adult: 500 mg twice daily

### UNLICENSED USE
- With intravenous use or oral use in children Not licensed for use in gastro-intestinal stasis.
- **CAUTIONS** Avoid in Acute porphyrias p. 864 .- neonate under 2 weeks (risk of hypertrophic pyloric stenosis) (in neonates)

### STIEMYCIN®
Some manufacturers advise preparations containing alcohol are not suitable for use with benzyl peroxide

**INTERACTIONS** → See Appendix 1 (macrolides). Caution with concomitant use of drugs that prolong the QT interval.

### PREGNANCY
- Not known to be harmful.

### BREAST FEEDING
- Only small amounts in milk—not known to be harmful.

### HEPATIC IMPAIRMENT
- May cause idiosyncratic hepatotoxicity.

### RENAL IMPAIRMENT
- In adults Max. 1.5 g daily in severe renal impairment (ototoxicity).
- In children Reduce dose in severe renal impairment (ototoxicity).

### DIRECTIONS FOR ADMINISTRATION
- With intravenous use in children Dilute reconstituted solution further in glucose 5% (neutralised with sodium bicarbonate) or sodium chloride 0.9% to a concentration of 1–5 mg/mL; give over 20–60 minutes. Concentration of up to 10 mg/mL may be used in fluid-restriction if administered via a central venous catheter.
- With intravenous use in adults For intravenous infusion (as lactobionate), give intermittently in Glucose 5% (neutralised with sodium bicarbonate) or Sodium chloride 0.9%; dissolve initially in water for injections (1 g in 20 mL) then dilute to a concentration of 1–5 mg/mL; give over 20–60 minutes.
**Prescribing and dispensing information** Flavours of oral liquid formulations may include banana.

**Patient and carer advice**


**Profession specific information**

Dental practitioners’ formulation Erythromycin tablets e/c may be prescribed. Erythromycin ethyl succinate oral suspension may be prescribed. Erythromycin stearate tablets may be prescribed. Erythromycin ethyl succinate tablets may be prescribed.

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**Cautionary and advisory labels**

- Erythromycin (A/Mo)
  - Erythromycin (as Erythromycin stearate) 250 mg Erythromycin 250 tablets | 100 tablet (PBS) £18.20 DT price = £18.20
  - Erythromycin (as Erythromycin stearate) 500 mg Erythromycin 500 tablets | 100 tablet (PBS) £36.40 DT price = £36.40
- Erythroped A (A/Mo)
  - Erythromycin (as Erythromycin ethyl succinate) 500 mg Erythroped A 500mg tablets | 28 tablet (PBS) £10.78 DT price = £10.78
  - Brains may include Erythromycin Gastro-resistant tablet

**Oral suspension**

**Cautionary and advisory labels**

- Erythromycin (Non-commercial)
  - Erythromycin 250 mg Erythromycin 250mg gastro-resistant tablets | 28 tablet (PBS) £3.33 DT price = £3.33
  - Erythromycin (as Erythromycin ethyl succinate) 25 mg per 1 ml Erythromycin ethyl succinate 125mg/5ml oral suspension | 100 ml (PBS) £3.53 DT price = £3.53
  - Erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (sugar-free) | 100 ml (PBS) £4.00 DT price = £4.00
- Erythromycin (as Erythromycin ethyl succinate) 50 mg per 1 ml Erythromycin ethyl succinate 250mg/5ml oral suspension | 100 ml (PBS) £5.54 DT price = £5.54
  - Erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (sugar-free) | 100 ml (PBS) £7.99 DT price = £7.99
  - Erythromycin (as Erythromycin ethyl succinate) 100 mg per 1 ml Erythromycin ethyl succinate 500mg/5ml oral suspension | 100 ml (PBS) £10.43 DT price = £10.43
  - Erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (sugar-free) | 100 ml (PBS) £12.99 DT price = £12.99
- Erythroped (A/Mo)
  - Erythromycin (as Erythromycin ethyl succinate) 25 mg per 1 ml Erythroped Pi SF 125mg/5ml oral suspension (sugar-free) | 140 ml (PBS) £3.06
  - Erythromycin (as Erythromycin ethyl succinate) 50 mg per 1 ml Erythroped SF 250mg/5ml oral suspension (sugar-free) | 140 ml (PBS) £5.95
  - Erythromycin (as Erythromycin ethyl succinate) 100 mg per 1 ml Erythroped Forte SF 500mg/5ml oral suspension (sugar-free) | 140 ml (PBS) £10.56
- Powder for solution for infusion
  - Erythromycin (A/Mo)
  - Erythromycin (as Erythromycin-lactobionate) 1 gram Erythromycin IV lactobionate 1g powder for solution for infusion vials | 1 vial (PBS) £0.80

**Renal impairment**

Manufacturer advises avoiding if eGFR less than 30 mL/minute/1.73 m²—if no other options are available.

**Contra-indications**

Congenital history of QT interval prolongation (if not excluded by ECG) • family history of QT interval prolongation (if not excluded by ECG) • history of telithromycin-associated hepatitis • history of telithromycin-associated jaundice • myasthenia gravis • prolongation of QT interval

**Caution** Avoid in Acute porphyrias p. 864 • bradycardia—risk of QT interval prolongation • coronary heart disease—risk of QT interval prolongation • hypokalaemia—risk of QT interval prolongation • hypomagnesaemia—risk of QT interval prolongation • ventricular arrhythmias—risk of QT interval prolongation

**Interactions**

Appendix 1 (telithromycin). Caution with concomitant use of drugs that prolong the QT interval.

**Side-effects**

- Common or very common Abdominal pain • diarrhoea • dizziness • flatulence • headache • nausea • taste disturbances • vomiting
- Uncommon Anorexia • blurred vision • constipation • drowsiness • eosinophilia • flushing • hepatitis • insomnia • nervousness • palpitations • pruritus • rash • stomatitis • urticaria
- Rare Arrhythmias • cholestatic jaundice • diplopia • hypotension • paraesthesia • transient loss of consciousness
- Very rare Altered sense of smell • antibiotic-associated colitis • erythema multiforme • muscle cramp
- Frequency not known Arthralgia • confusion • hallucinations • pancreatitis

**Pregnancy**

Toxicity in animal studies—manufacturer advises use only if potential benefit outweighs risk.

**Breast feeding**

Manufacturer advises avoid—present in milk in animal studies

**Hepatic impairment**

Manufacturer advises caution.

**Renal impairment**

Manufacturer advises avoid if possible if eGFR less than 30 mL/minute/1.73 m²—if no other options are available.

**Telithromycin**

**Drug action**

The ketolide telithromycin is a derivative of erythromycin. The antibacterial spectrum of telithromycin is similar to that of macrolides and it is also active against penicillin- and erythromycin-resistant Streptococcus pneumoniae.

**Indications and dose**

Treatment of sinusitis or exacerbations of chronic bronchitis if caused by organisms resistant to beta-lactam antibacterials and other macrolides, or if conventional treatment is contra-indicated

**By mouth**

- Adult: 800 mg once daily for 5 days

Treatment of community-acquired pneumonia if caused by organisms resistant to beta-lactam antibacterials and other macrolides, or if conventional treatment is contra-indicated

**By mouth**

- Adult: 800 mg once daily for 7–10 days

Treatment of beta-haemolytic streptococcal pharyngitis if caused by organisms resistant to beta-lactam antibacterials and other macrolides, or if conventional treatment is contra-indicated

**By mouth**

- Child 12-17 years: 800 mg once daily for 5 days

- Adult: 800 mg once daily for 5 days

**Contra-indications**

Congenital history of QT interval prolongation (if not excluded by ECG) • family history of QT interval prolongation (if not excluded by ECG) • history of telithromycin-associated hepatitis • history of telithromycin-associated jaundice • myasthenia gravis • prolongation of QT interval

**Caution** Avoid in Acute porphyrias p. 864 • bradycardia—risk of QT interval prolongation • coronary heart disease—risk of QT interval prolongation • hypokalaemia—risk of QT interval prolongation • hypomagnesaemia—risk of QT interval prolongation • ventricular arrhythmias—risk of QT interval prolongation

**Interactions**

Appendix 1 (telithromycin). Caution with concomitant use of drugs that prolong the QT interval.

**Side-effects**

- Common or very common Abdominal pain • diarrhoea • dizziness • flatulence • headache • nausea • taste disturbances • vomiting
- Uncommon Anorexia • blurred vision • constipation • drowsiness • eosinophilia • flushing • hepatitis • insomnia • nervousness • palpitations • pruritus • rash • stomatitis • urticaria
- Rare Arrhythmias • cholestatic jaundice • diplopia • hypotension • paraesthesia • transient loss of consciousness
- Very rare Altered sense of smell • antibiotic-associated colitis • erythema multiforme • muscle cramp
- Frequency not known Arthralgia • confusion • hallucinations • pancreatitis

**Pregnancy**

Toxicity in animal studies—manufacturer advises use only if potential benefit outweighs risk.

**Breast feeding**

Manufacturer advises avoid—present in milk in animal studies

**Hepatic impairment**

Manufacturer advises caution.

**Renal impairment**

Manufacturer advises avoid if possible if eGFR less than 30 mL/minute/1.73 m²—if no other options are available.
alternative, use alternating daily doses of 800 mg and 400 mg, starting with 800 mg dose.

**PATIENT AND CARER ADVICE** Visual disturbances or transient loss of consciousness may affect performance of skilled tasks (e.g. driving); effects may occur after the first dose. Administration at bedtime may reduce these side-effects. Patients should be advised not to drive or operate machinery if affected. Hepatic disorders Counselling on hepatic disorders is advised. Patients should be told how to recognise signs of liver disorder, and advised to discontinue treatment and seek prompt medical attention if symptoms such as anorexia, nausea, vomiting, abdominal pain, jaundice, or dark urine develop.

**MEDICINAL FORMS**
Medicines not identified.

**MONOCYCLIC BETA-LACTAM ANTIBACTERIALS**

**Aztreonam**

**DRUG ACTION** Aztreonam is a monocylic beta-lactam (‘monobactam’) antibiotic with an antibacterial spectrum limited to Gram-negative aerobic bacteria including *Pseudomonas aeruginosa*, *Neisseria meningitidis*, and *Haemophilus influenzae*; it should not be used alone for ‘blind’ treatment since it is not active against Gram-positive organisms. Aztreonam is also effective against *Neisseria gonorrhoeae* (but not against concurrent chlamydial infection).

**INDICATIONS AND DOSE**
Gram-negative infections including *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Neisseria meningitidis*

**BY DEEP INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INFUSION OR BY INTRAVENOUS INJECTION**
- Adult: 1 g every 9 hours, alternatively 2 g every 12 hours, single doses over 1 g by intravenous route only
- Severe gram-negative infections including *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Neisseria meningitidis*, and lung infections in cystic fibrosis
  - By intravenous infusion or by intravenous injection
    - Adult: 2 g every 6–8 hours
  - Gonorrhoea / Cystitis
    - By intramuscular injection
      - Adult: 1 g for 1 single dose
  - Urinary-tract infections
    - By deep intramuscular injection or by intravenous infusion or by intravenous injection
      - Adult: 0.5–1 g every 8–12 hours
  - Chronic pulmonary *Pseudomonas aeruginosa* infection in patients with cystic fibrosis
    - By inhalation of nebulised solution
      - Adult: 75 mg 3 times a day for 28 days, doses to be administered at least 4 hours apart, subsequent courses repeated after 28-day interval without aztreonam nebuliser solution

**CAUTIONS**
- When used by inhalation Haemoptysis—risk of further haemorrhage

**INTERACTIONS** → Appendix 1 (aztreonam).

**SIDE-EFFECTS**

**SPECIFIC SIDE-EFFECTS**
- Rare
  - Frequency not known Bronchospasm - rash
  - When used by inhalation Arthralgia - cough - haemoptysis - pharyngolaryngeal pain - pyrexia - rhinorrhea - wheezing
  - With systemic use Abdominal pain - diarrhea - erythema multiforme - flushing - mouth ulcers - nausea - taste disturbances - toxic epidermal necrolysis - vomiting

**ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in aztreonam hypersensitivity. Use with caution in patients with hypersensitivity to other beta-lactam antibiotics (although aztreonam may be less likely than other beta-lactams to cause hypersensitivity in penicillin-sensitive patients).

**PREGNANCY**
- With systemic use No information available; manufacturer of injection advises avoid.
- When used by inhalation No information available; manufacturer of powder for nebuliser solution advises avoid unless essential.

**BREAST FEEDING** Amount in milk probably too small to be harmful.

**HEPATIC IMPAIRMENT**
- With systemic use Use injection with caution. Monitor liver function.

**RENAI IMPAIRMENT**
- With systemic use If eGFR 10–30 mL/minute/1.73 m², usual initial dose of injection, then half normal dose. If eGFR less than 10 mL/minute/1.73 m², usual initial dose of injection, then one-quarter normal dose.

**MONITORING REQUIREMENTS**
- When used by inhalation Measure lung function before and after initial dose of aztreonam and monitor for bronchospasm.

**DIRECTIONS FOR ADMINISTRATION**
- With intravenous use For intravenous injection, give over 3–5 minutes. For intravenous infusion (Azactam®), give intermittently in glucose 5% or sodium chloride 0.9%. Dissolve initially in water for injections (1 g per 3 mL) then dilute to a concentration of less than 20 mg/mL; to be given over 20–60 minutes.
- When used by inhalation Other inhaled drugs should be administered before aztreonam; a bronchodilator should be administered before each dose.

**NATIONAL FUNDING/ACCESS DECISIONS**

**Scottish Medicines Consortium (SMC) Decisions**
The *Scottish Medicines Consortium* has advised (December 2014) that aztreonam powder for nebuliser solution (Cayston®) is accepted for restricted use within NHS Scotland when inhaled colistimethate sodium and inhaled tobramycin are not tolerated or are not providing satisfactory therapeutic benefit (measured as ≥ 2% decline in forced expiratory volume in 1 second).

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**
- Azactam (Bristol-Myers Squibb Pharmaceuticals Ltd)
- Aztreonam 1 gram Azactam 1g powder for solution for injection vials | 1 vial (PO) £9.40 (Hospital only)
- Aztreonam 2 gram Azactam 2g powder for solution for injection vials | 1 vial (PO) £18.82 (Hospital only)

**Powder and solvent for nebuliser solution**
- Cayston (Gilead Sciences International Ltd)
- Aztreonam (as Aztreonam lysine) 75 mg Cayston 75mg powder and solvent for nebuliser solution vials with Altera Nebuliser Handset | 84 vial (PO) £2,181.53
**5-NITROIMIDAZOLE DERIVATIVES**

**Metronidazole**

**DRUG ACTION** Metronidazole is an antimicrobial drug with high activity against anaerobic bacteria and protozoa.

**INDICATIONS AND DOSE**

**Anaerobic infections**

- **BY MOUTH**
  - Child 1 month: 7.5 mg/kg every 12 hours usually treated for 7 days (for 10–14 days in *Clostridium difficile* infection)
  - Child 2 months–11 years: 7.5 mg/kg every 8 hours (max. per dose 400 mg) usually treated for 7 days (for 10–14 days in *Clostridium difficile* infection)
  - Child 12–17 years: 400 mg every 8 hours
  - Adult: 400 mg every 8 hours, alternatively 500 mg every 8 hours usually treated for 7 days (for 10–14 days in *Clostridium difficile* infection)

- **BY RECTUM**
  - Child 1–11 months: 125 mg 3 times a day for 3 days, then 125 mg twice daily, for usual total treatment duration of 7 days
  - Child 1–4 years: 250 mg 3 times a day for 3 days, then 250 mg twice daily, for usual total treatment duration of 7 days
  - Child 5–9 years: 500 mg 3 times a day for 3 days, then 500 mg twice daily, for usual total treatment duration of 7 days
  - Child 10–17 years: 1 g 3 times a day for 3 days, then 1 g twice daily, for usual total treatment duration of 7 days
  - Adult: 1 g 3 times a day for 3 days, then 1 g twice daily, for usual total treatment duration of 7 days

- **BY INTRAVENOUS INFUSION**
  - Adult: 500 mg every 8 hours usually treated for 7 days (for 10–14 days in *Clostridium difficile* infection), to be given over 20 minutes

**Helicobacter pylori eradication; in combination with clarithromycin and esomeprazole; or in combination with amoxicillin and lansoprazole; or in combination with clarithromycin and omeprazole; or in combination with clarithromycin and pantoprazole; or in combination with clarithromycin and rabeprazole**

- **BY MOUTH**
  - Adult: 400 mg twice daily

**Helicobacter pylori eradication; combination with amoxicillin and omeprazole**

- **BY MOUTH**
  - Adult: 400 mg 3 times a day

**Helicobacter pylori eradication failure (two-week regimen comprising a proton pump inhibitor plus tripotassium dicitratabismuthate plus tetracycline)**

- **BY MOUTH**
  - Adult: 400–500 mg 3 times a day for 2 weeks

**Fistulating Crohn’s disease**

- **BY MOUTH**
  - Adult: 10–20 mg/kg daily in divided doses, usual dose 400–500 mg 3 times a day usually given for 1 month but no longer than 3 months because of concerns about peripheral neuropathy

**Leg ulcers and pressure sores**

- **BY MOUTH**
  - Adult: 400 mg every 8 hours for 7 days

**Bacterial vaginosis (notably *Gardnerella vaginalis* infection)**

- **BY MOUTH**
  - Adult: 400–500 mg twice daily for 5–7 days, alternatively 2 g for 1 dose

**Bacterial vaginosis**

- **BY VAGINA USING VAGINAL GEL**
  - Adult: 1 applicatorful daily for 5 days, dose to be administered at night

**Pelvic inflammatory disease**

- **BY MOUTH**
  - Adult: 400 mg twice daily for 14 days

**Acute ulcerative gingivitis**

- **BY MOUTH**
  - Child 1–2 years: 50 mg every 8 hours for 3–7 days
  - Child 3–6 years: 100 mg every 12 hours for 3–7 days
  - Child 7–9 years: 100 mg every 8 hours for 3–7 days
  - Child 10–17 years: 200–250 mg every 8 hours for 3 days
  - Adult: 200–250 mg every 8 hours for 3 days

**Acute oral infections**

- **BY MOUTH**
  - Child 1–2 years: 50 mg every 8 hours for 3–7 days
  - Child 3–6 years: 100 mg every 12 hours for 3–7 days
  - Child 7–9 years: 100 mg every 8 hours for 3–7 days
  - Adult: 200 mg every 8 hours for 3–7 days

**Surgical prophylaxis**

- **BY MOUTH**
  - Adult: 400–500 mg, to be administered 2 hours before surgery, then 400–500 mg every 8 hours if required for up to 3 doses (in high-risk procedures)

- **BY RECTUM**
  - Adult: 1 g, to be administered 2 hours before surgery, then 1 g every 8 hours if required for up to 3 doses (in high-risk procedures)

- **BY INTRAVENOUS INFUSION**
  - Adult: 500 mg, to be administered up to 30 minutes before the procedure (if rectal administration inappropriate), then 500 mg every 8 hours if required for up to 3 doses (in high-risk procedures)

**Invasive intestinal amoebiasis / Extra-intestinal amoebiasis (including liver abscess)**

- **BY MOUTH**
  - Child 1–2 years: 200 mg 3 times a day for 5 days in intestinal infection (for 5–10 days in extra-intestinal infection)
  - Child 3–6 years: 200 mg 4 times a day for 5 days in intestinal infection (for 5–10 days in extra-intestinal infection)
  - Child 7–9 years: 400 mg 3 times a day for 5 days in intestinal infection (for 5–10 days in extra-intestinal infection)
  - Child 10–17 years: 800 mg 3 times a day for 5 days in intestinal infection (for 5–10 days in extra-intestinal infection)
  - Adult: 800 mg 3 times a day for 5 days in intestinal infection (for 5–10 days in extra-intestinal infection)

**Urogenital trichomoniasis**

- **BY MOUTH**
  - Child 1–2 years: 50 mg 3 times a day for 7 days
  - Child 3–6 years: 100 mg twice daily for 7 days
  - Child 7–9 years: 100 mg 3 times a day for 7 days
  - Child 10–17 years: 200 mg 3 times a day for 7 days, alternatively 400–500 mg twice daily for 5–7 days, alternatively 2 g for 1 dose
  - Adult: 200 mg 3 times a day for 7 days, alternatively 400–500 mg twice daily for 5–7 days, alternatively 2 g for 1 dose

**Giardiasis**

- **BY MOUTH**
  - Child 1–2 years: 500 mg once daily for 3 days

continued
- **Child 3–6 years:** 600–800 mg once daily for 3 days
- **Child 7–9 years:** 1 g once daily for 3 days
- **Child 10–17 years:** 2 g once daily for 3 days, alternatively 400 mg 3 times a day for 5 days, alternatively 500 mg twice daily for 7–10 days
- **Adult:** 2 g once daily for 3 days, alternatively 400 mg 3 times a day for 5 days, alternatively 500 mg twice daily for 7–10 days

**Established case of tetanus**

**BY INTRAVENOUS INFUSION**

- **Child 10 g once daily for 3 days**
- **Child 12 g once daily for 3 days**
- **Child 17 g once daily for 3 days**

**INDICATIONS AND DOSE**

**Anoanal infections**

- **Adult:** 2 g once daily for 3 days

**Bacterial vaginosis | Acute ulcerative gingivitis**

- **Adult:** 2 g once daily for 3 days

**Intestinal amoebiasis**

- **Child 1 month to 11 years:** 50–60 mg/kg once daily (max. per dose 2 g) for 3 days
- **Child 12–17 years:** 2 g once daily for 2–3 days
- **Adult:** 2 g once daily for 2–3 days

**DRUG ACTION**

**Tinidazole** is an antimicrobial drug with high activity against anaerobic bacteria and protozoa; it has a longer duration of action than metronidazole.

**INDICATIONS AND DOSE**

**Anaerobic infections**

- **BY MOUTH**
  - **Adult:** Initially 2 g, followed by 1 g daily usually for 5–6 days, alternatively 500 mg twice daily usually for 5–6 days

**Bacterial vaginosis | Acute ulcerative gingivitis**

- **BY MOUTH**
  - **Adult:** 2 g for 1 single dose

**Intestinal amoebiasis**

- **BY MOUTH**
  - **Child 1 month to 11 years:** 50–60 mg/kg once daily (max. per dose 2 g) for 3 days
  - **Child 12–17 years:** 2 g once daily for 2–3 days
  - **Adult:** 2 g once daily for 2–3 days
**Amoebic involvement of liver**

**BY MOUTH**
- Child 1 month-11 years: 50–60 mg/kg once daily (max. per dose 2 g) for 5 days
- Child 12-17 years: 1.5–2 g once daily for 3–6 days
- Adult: 1.5–2 g once daily for 3–6 days

**Urogenital trichomoniasis | Giardiasis**

**BY MOUTH**
- Child 1 month-11 years: 50–75 mg/kg (max. per dose 2 g) for 1 single dose, dose may be repeated once if necessary
- Child 12-17 years: 2 g for 1 single dose, dose may be repeated once if necessary
- Adult: 2 g for 1 single dose

**Helicobacter pylori eradication**

**BY MOUTH**
- Adult: consult local protocol

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**INDICATIONS AND DOSE**

**Bacterial infection**

Pneumonia (when other antibacterials e.g. a glycopetide, such as vancomycin, cannot be used) (initiated under specialist supervision)

**Complicated skin and soft-tissue infections caused by Gram-positive bacteria, when other antibacterials cannot be used (initiated under specialist supervision)**

**BY MOUTH**
- Adult: 600 mg every 12 hours usually for 10–14 days (maximum duration of treatment 28 days)

**BY INTRAVENOUS INFUSION**
- Adult: 600 mg every 12 hours

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**Important safety information**

**CHM ADVICE (OPTIC NEUROPATHY)**

Severe optic neuropathy may occur rarely, particularly if linezolid is used for longer than 28 days. The CHM recommends that:
- patients should be warned to report symptoms of visual impairment (including blurred vision, visual field defect, changes in visual acuity and colour vision) immediately;
- patients experiencing new visual symptoms (regardless of treatment duration) should be evaluated promptly, and referred to an ophthalmologist if necessary;
- visual function should be monitored regularly if treatment is required for longer than 28 days.

**BLOOD DISORDERS**

Haematopoietic disorders (including thrombocytopenia, anaemia, leucopenia, and pancytopenia) have been reported in patients receiving linezolid. It is recommended that full blood counts are monitored weekly. Close monitoring is recommended in patients who:
- receive treatment for more than 10–14 days;
- have pre-existing myelosuppression;
- are receiving drugs that may have adverse effects on haemoglobin, blood counts, or platelet function;
- have severe renal impairment.

If significant myelosuppression occurs, treatment should be stopped unless it is considered essential, in which case intensive monitoring of blood counts and appropriate management should be implemented.

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**CAUTIONS**

- Acute confusional states
- Bipolar depression
- Carcinoid tumour
- Elderly (increased risk of blood disorders)
- History of seizures
- Phaeochromocytoma
- Schizophrenia
- Thyrotoxicosis
- Uncontrolled hypertension

**CAUTIONS, FURTHER INFORMATION**

**Close observation**

Unless close observation and blood pressure monitoring is possible, linezolid should be avoided in uncontrolled hypertension, phaeochromocytoma, carcinoid tumour, thyrotoxicosis, bipolar depression, schizophrenia, or acute confusional states.

**INTERACTIONS**

- Appendix 1 (linezolid, MAOIs).
- Monoamine oxidase inhibition Linezolid is a reversible, non-selective monoamine oxidase inhibitor (MAOI).

Patients should avoid consuming large amounts of tyramine-rich foods (such as mature cheese, yeast extracts, undistilled alcoholic beverages, and fermented soya bean products). In addition, linezolid should not be given with another MAOI or within 2 weeks of stopping another MAOI. Unless close observation and blood-pressure monitoring is possible, avoid in those receiving SSRIs, 5HT, agonists (‘triptans’), tricyclic antidepressants, sympathomimetics, dopaminergics, buspirone, pethidine and possibly other opioid analgesics.

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**OXAZOLIDINONE ANTIBACTERIALS**

**Linezolid**

**DRUG ACTION**

Linezolid, an oxazolidinone antibacterial, is active against Gram-positive bacteria including meticillin-resistant *Staphylococcus aureus* (MRSA), and glycopeptide-resistant enterococci. Resistance to linezolid can develop with prolonged treatment or if the dose is less than that recommended. Linezolid is not active against common Gram-negative organisms; it must be given in combination with other antibacterials for mixed infections that also involve Gram-negative organisms.
**5**

### Infection

#### Bacterial infection

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- **Common or very common** Diarrhoea - eosinophilia - headache - nausea - taste disturbances - vomiting
- **Rare** Renal failure - tachycardia - transient ischaemic attacks
- **Frequency not known** Anaemia - antibiotic-associated colitis - convulsions - hyponatraemia - lactic acidosis - optic neuropathy reported on prolonged therapy - pancytopenia - peripheral neuropathy reported on prolonged therapy - Stevens-Johnson syndrome - tooth discoloration - toxic epidermal necrolysis

**SPECIFIC SIDE-EFFECTS**

- **Uncommon**
- **With intravenous use** injection-site reactions
- **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk — no information available.
- **BREAST FEEDING** Manufacturer advises avoid — present in milk in animal studies.
- **HEPATIC IMPAIRMENT** In severe hepatic impairment manufacturer advises use only if potential benefit outweighs risk.
- **RENAL IMPAIRMENT** Manufacturer advises metabolites may accumulate if eGFR less than 30 mL/minute/1.73 m².
- **MONITORING REQUIREMENTS** Monitor full blood count (including platelet count) weekly.
- **DIRECTIONS FOR ADMINISTRATION** Infusion to be administered over 30–120 minutes.
- **PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid formulations may include orange.
- **PATIENT AND CARER ADVICE** Patients should be advised to read the patient information leaflet given with linezolid.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Tablet**
  - **CAUTIONARY AND ADVISORY LABELS 9, 10**
  - **Zyvox** (Pfizer Ltd)
  - Linezolid 600 mg: Zyvox 600mg tablets | 10 tablet (Pf) £445.00
  - **Oral suspension**
    - **CAUTIONARY AND ADVISORY LABELS 9, 10**
    - **EXCIPIENTS:** May contain Aspartame
    - **Zyvox** (Pfizer Ltd)
    - Linezolid 20 mg per 1 ml: Zyvox 100mg/5ml granules for oral suspension | 150 ml (Pf) £222.50
  - **Infusion**
    - **EXCIPIENTS:** May contain Glucose
    - **ELECTROLYTES:** May contain Sodium
    - **Zyvox** (Pfizer Ltd)
    - Linezolid 2 mg per 1 ml: Zyvox 600mg/300ml infusion bags | 10 bag (Pf) £445.00

**Penicillins**

**Benzylpenicillin and phenoxymethylpenicillin**

Benzylpenicillin sodium p. 480 (Penicillin G) remains an important and useful antibiotic but is inactivated by bacterial beta-lactamases. It is effective for many streptococcal (including pneumococcal), gonococcal, and meningococcal infections and also for anthrax, diphtheria, gas-gangrene, lephtospirosis, and treatment of Lyme disease.

Pneumococci, meningococci, and gonococci which have decreased sensitivity to penicillin have been isolated; benzylpenicillin sodium is no longer the drug of first choice for pneumococcal meningitis. Although benzylpenicillin sodium is effective in the treatment of tetanus, metronidazole p. 1008 is preferred. Benzylpenicillin is inactivated by gastric acid and absorption from the gastrointestinal tract is low; therefore it must be given by injection.

**Benzathine benzylpenicillin** is used for the treatment of early syphilis and late latent syphilis; it is given by intramuscular injection.

Phenoxymethylpenicillin p. 481 (Penicillin V) has a similar antibacterial spectrum to benzylpenicillin sodium, but is less active. It is gastric acid-stable, so is suitable for oral administration. It should not be used for serious infections because absorption can be unpredictable and plasma concentrations variable. It is indicated principally for respiratory-tract infections in children, for streptococcal tonsillitis, and for continuing treatment after one or more injections of benzylpenicillin sodium when clinical response has begun. It should not be used for meningococcal or gonococcal infections. Phenoxymethylpenicillin is used for prophylaxis against streptococcal infections following rheumatic fever and against pneumococcal infections following splenectomy or in sickle-cell disease.

**Penicillinase-resistant penicillins**

Most staphylococci are now resistant to benzylpenicillin because they produce penicillinases. Flucloxacillin p. 486, however, is not inactivated by these enzymes and is thus effective in infections caused by penicillin-resistant staphylococci, which is the sole indication for its use. Flucloxacillin is acid-stable and can, therefore, be given by mouth as well as by injection. Flucloxacillin is well absorbed from the gut.

Temocillin p. 487 is active against Gram-negative bacteria and is stable against a wide range of beta-lactamases. It should be reserved for the treatment of infections caused by beta-lactamase-producing strains of Gram-negative bacteria, including those resistant to third-generation cephalosporins. Temocillin is not active against *Pseudomonas aeruginosa* or *Acinetobacter spp.*

**Broad-spectrum penicillins**

Ampicillin p. 483 is active against certain Gram-positive and Gram-negative organisms but is inactivated by penicillinases including those produced by *Staphylococcus aureus* and by common Gram-negative bacilli such as *Escherichia coli*. Almost all staphylococci, approx. 60% of *E. coli* strains and approx. 20% of *Haemophilus influenzae* strains are now resistant. The likelihood of resistance should therefore be considered before using ampicillin for the ‘blind’ treatment of infections; in particular, it should not be used for hospital patients without checking sensitivity.

Ampicillin is well excreted in the bile and urine. It is principally indicated for the treatment of exacerbations of chronic bronchitis and middle ear infections, both of which may be due to *Streptococcus pneumoniae* and *H. influenzae*, and for urinary-tract infections.

Ampicillin can be given by mouth but less than half the dose is absorbed, and absorption is further decreased by the presence of food in the gut.

Maculopapular rashes commonly occur with ampicillin (and amoxicillin p. 482) but are not usually related to true penicillin allergy. They almost always occur in patients with glandular fever; broad-spectrum penicillins should not therefore be used for ‘blind’ treatment of a sore throat. The risk of rash is also increased in patients with acute or chronic lymphocytic leukaemia or in cytomegalovirus infection.
Amoxicillin is a derivative of ampicillin and has a similar antibacterial spectrum. It is better absorbed than ampicillin when given by mouth, producing higher plasma and tissue concentrations; unlike ampicillin, absorption is not affected by the presence of food in the stomach. Amoxicillin may also be used for the treatment of Lyme disease [not licensed].

Co-amoxiclav p. 484 consists of amoxicillin with the betalactamase inhibitor clavulanic acid. Clavulanic acid itself has no significant antibacterial activity but, by inactivating beta-lactamases, it makes the combination active against beta-lactamase-producing bacteria that are resistant to amoxicillin. These include resistant strains of Staphylococci aureus, E. coli, and H. influenzae, as well as many Bacteroides and Klebsiella spp. Co-amoxiclav should be reserved for infections likely, or known, to be caused by amoxicillin-resistant beta-lactamase-producing strains.

A combination of ampicillin with flucloxacillin p. 486 (as co-fluampicil) p. 485 is available to treat infections involving either streptococci or staphylococci (e.g. cellulitis).

**Antipseudomonal penicillins**

**Piperacillin**, a ureidopenicillin, is only available in combination with the beta-lactamase inhibitor tazobactam.

**Ticarcillin**, a carboxypenicillin, is only available in combination with the beta-lactamase inhibitor clavulanic acid. Both preparations have a broad spectrum of activity against a range of Gram-positive and Gram-negative bacteria, and anaerobes. Piperacillin with tazobactam below against a range of Gram-positive and Gram-negative bacteria, and anaerobes. Both preparations have a broad spectrum of activity against Gram-negative bacteria, and anaerobes. Piperacillin with tazobactam below against a range of Gram-positive and Gram-negative bacteria, and anaerobes. Both preparations have a broad spectrum of activity against Gram-negative bacteria, and anaerobes.

**Mecillinams**
Pivmecillinam hydrochloride p. 486 has significant activity against many Gram-negative bacteria including Escherichia coli, klebsiella, enterobacter, and salmonellae. It is not active against Pseudomonas aeruginosa or enterococci. Pivmecillinam hydrochloride p. 486 is hydrolysed to mecillinam, which is the active drug.

**Penicillins (antipseudomonal)**

**Piperacillin with tazobactam**

**INDICATIONS AND DOSE**

**Hospital-acquired pneumonia** | **Septicaemia** | **Complicated infections involving the urinary-tract or skin and soft tissues**
---|---|---
BY INTRAVENOUS INFUSION
- Adult: 4.5 g every 8 hours; increased if necessary to 4.5 g every 6 hours, increased frequency may be used for severe infections
- Complicated intra-abdominal infections
  - Adult 18 years: 4.5 g every 8 hours; increased if necessary to 4.5 g every 6 hours, increased frequency may be used for severe infections
- Infections in neutropenic patients
  - BY INTRAVENOUS INFUSION
    - Adult: 4.5 g every 6 hours

**SIDE-EFFECTS**

- **Common or very common** Anaphylaxis | Angioedema | Diarrhoea | Fever | Hypersensitivity reactions | Joint pains | Rash | Serum sickness-like reaction | Urticaria
- **Rare** Cerebral irritation | CNS toxicity (including convulsions) | Coagulation disorders | Encephalopathy | Haemolytic anaemia | Interstitial nephritis | Leucopenia | Thrombocytopenia
- **Frequency not known** Antibiotic-associated colitis

**SIDE-EFFECTS, FURTHER INFORMATION**

**CNS toxicity** A rare but serious toxic effect of the penicillins is encephalopathy due to cerebral irritation.

This may result from excessively high doses or in patients with severe renal failure. The penicillins should **not** be given by intrathecal injection because they can cause encephalopathy which may be fatal.

**Diarrhoea** Diarrhoea frequently occurs during oral penicillin therapy. It is most common with broad-spectrum penicillins, which can also cause antibiotic-associated colitis.

**ALLERGY AND CROSS-SENSITIVITY** The most important side-effect of the penicillins is hypersensitivity which causes rashes and anaphylaxis and can be fatal. Allergic reactions to penicillins occur in 1–10% of exposed individuals; anaphylactic reactions occur in fewer than 0.05% of treated patients. Patients with a history of atopic allergy (e.g. asthma, eczema, hay fever) are at a higher risk of anaphylactic reactions to penicillins. Individuals with a history of anaphylaxis, urticaria, or rash immediately after penicillin administration are at risk of immediate hypersensitivity to a penicillin; these individuals should not receive a penicillin. Individuals with a history of a minor rash (i.e. non-confluent, non-pruritic rash restricted to a small area of the body) or a rash that occurs more than 72 hours after penicillin administration are probably not allergic to penicillin and in these individuals a penicillin should not be withheld unnecessarily for serious infections; the possibility of an allergic reaction should, however, be borne in mind.

Other beta-lactam antibiotics (including cephalosporins) can be used in these patients. Patients who are allergic to one penicillin will be allergic to all because the hypersensitivity is related to the basic penicillin structure. Patients with a history of immediate hypersensitivity to penicillins may also react to the cephalosporins and other beta-lactam antibiotics, they should not receive these antibiotics. If a penicillin (or another beta-lactam antibiotic) is essential in an individual with immediate hypersensitivity to penicillin then specialist advice should be sought on hypersensitivity testing or using a beta-lactam antibiotic with a different structure to the penicillin that caused the hypersensitivity.

**BNF 70**

**Bacterial infection** 479
Ticarcillin with clavulanic acid

**INDICATIONS AND DOSE**

Infections due to *Pseudomonas* and *Proteus* spp

- **BY INTRAVENOUS INFUSION**
  - Adult: 3.2 g every 6–8 hours; increased if necessary to 3.2 g every 4 hours, increased frequency used for more severe infections

**CAUTIONS**

High doses may lead to hypernatraemia (owing to sodium content of preparations)

**CAUTIONS, FURTHER INFORMATION**

- **Cholestatic jaundice**
  - Cholestatic jaundice is possibly associated with clavulanic acid. An epidemiological study has shown that the risk of acute liver toxicity was about 6 times greater with co-amoxiclav (amoxicillin, clavulanic acid) than with amoxicillin. Cholestatic jaundice is more common in patients above the age of 65 years and in men; these reactions have only rarely been reported in children. Jaundice is usually self-limiting and very rarely fatal. The duration of treatment should be appropriate to the indication and should not usually exceed 14 days.

- **SIDE-EFFECTS**
  - Eosinophilia. haemorrhagic cystitis (more frequent in children); hypokalaemia; injection-site reactions; nausea. Stevens-Johnson syndrome. toxic epidermal necrolysis; vomiting

- **PREGNANCY**
  - Not known to be harmful.

- **BREAST FEEDING**
  - Trace amounts in milk, but appropriate to use.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution in severe impairment.

- **RENAL IMPAIRMENT**
  - Reduce dose to 3.2 g every eight hours if eGFR 30–60 mL/minute/1.73 m²; 1.6 g every eight hours if eGFR 10–30 mL/minute/1.73 m²; 1.6 g every twelve hours if eGFR less than 10 mL/minute/1.73 m². Accumulation of electrolytes contained in preparation can occur in patients with renal failure.

- **EFFECT ON LABORATORY TESTS**
  - False-positive urinary glucose (if tested for reducing substances).

### BENZYLPCILLIN SODIUM (Penicillin G)

#### PENICILLINS (BETA-LACTAMASE SENSITIVE)

**INDICATIONS AND DOSE**

Mild to moderate susceptible infections | Throat infections | Otitis media | Cellulitis | Pneumonia

**BY INTRAMUSCULAR INJECTION OR BY SLOW INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION**

- Adult: 0.6–1.2 g every 6 hours, dose may be increased if necessary in more serious infections (consult product literature), single doses over 1.2 g to be given by intravenous route only

Endocarditis (in combination with other antibacterial if necessary)

**BY SLOW INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION**

- Adult: 1.2 g every 4 hours, increased if necessary to 2.4 g every 4 hours, dose may be increased in infections such as enterococcal endocarditis

Anthrax (in combination with other antibacterials)

**BY SLOW INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION**

- Adult: 2.4 g every 4 hours

Intrapartum prophylaxis against group B streptococcal infection

**BY SLOW INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION**

- Adult: Initially 3 g for 1 dose, then 1.5 g every 4 hours until delivery

Meningitis | Meningococcal disease

**BY SLOW INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION**

- Adult: 2.4 g every 4 hours

**BY INTRAVENOUS INFUSION**

- Neonate up to 6 days: 50 mg/kg every 12 hours.
- Neonate 7-28 days: 50 mg/kg every 8 hours.
**Phenoxyethylpenicillin (Penicillin V)**

**INDICATIONS AND DOSE**

<table>
<thead>
<tr>
<th>Oral infections</th>
<th>Tonsillitis</th>
<th>Otitis media</th>
<th>Erysipelas</th>
<th>Cellulitis</th>
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<tbody>
<tr>
<td><strong>BY MOUTH</strong></td>
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<tr>
<td>Adult: 1-11 months: 62.5 mg 4 times a day; increased if necessary up to 12.5 mg/kg 4 times a day</td>
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<tr>
<td>Child 1-5 years: 125 mg 4 times a day; increased if necessary up to 12.5 mg/kg 4 times a day</td>
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<tr>
<td>Child 6-11 years: 250 mg 4 times a day; increased if necessary up to 12.5 mg/kg 4 times a day</td>
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<tr>
<td>Child 12-17 years: 500 mg 4 times a day; increased if necessary up to 1 g 4 times a day</td>
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<tr>
<td>Adult: 500 mg every 6 hours, increased if necessary up to 1 g every 6 hours</td>
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**Prevention of recurrence of rheumatic fever BY MOUTH**

| Child 1 month-5 years: 125 mg twice daily | Child 6-17 years: 250 mg twice daily | Adult: 250 mg twice daily |

**Prevention of secondary case of invasive group A streptococcal infection BY MOUTH**

| Child 1-11 months: 62.5 mg every 6 hours for 10 days | Child 1-5 years: 125 mg every 6 hours for 10 days | Child 6-11 years: 250 mg every 6 hours for 10 days |
| Child 12-17 years: 500 mg every 6 hours for 10 days | Adult: 250–500 mg every 6 hours for 10 days |

**Prevention of pneumococcal infection in asplenia or in patients with sickle-cell disease BY MOUTH**

| Child 1-11 months: 62.5 mg twice daily | Child 1-5 years: 125 mg twice daily | Child 6-11 years: 250 mg twice daily |
| Child 12-17 years: 500 mg twice daily | Adult: 250 mg twice daily |

**UNLICENSED USE** Phenoxyethylpenicillin doses in the BNF may differ from product literature.

**PREGNANCY** Not known to be harmful.

**BREAST FEEDING** Trace amounts in milk, but appropriate to use.

**CAUTIONS** Accumulation of sodium from injection can occur with high doses.

**RENAI IMPAIRMENT** Accumulation of sodium from injection can occur in renal failure. High doses may cause neurotoxicity, including cerebral irritation, convulsions, or coma.

| In adults | Reduce dose—consult product literature. |
| In children | Estimated glomerular filtration rate 10–50 mL/minute/1.73 m²; use normal dose every 8–12 hours. Estimated glomerular filtration rate less than 10 mL/minute/1.73 m² use normal dose every 12 hours. |

**EFFECT ON LABORATORY TESTS** False-positive urinary glucose (if tested for reducing substances).

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use in children: Intravenous route recommended in neonates and infants. *For intravenous infusion*, dilute with Glucose 5% or Sodium Chloride 0.9%; give over 15–30 minutes. Longer administration time is particularly important when using doses of 50 mg/kg (or greater) to avoid CNS toxicity.
- With intravenous use in adults: *For intravenous infusion* (Cryspan™), give intermittently in Glucose 5% or Sodium chloride 0.9%; suggested volume 100 mL given over 30–60 minutes. Continuous infusion not usually recommended.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion, eye drops.

**Powder for solution for injection**

**ELECTROLYTES:** May contain Sodium

- BENZYLPPENICILLIN SODIUM (Non-proprietary)
  - Benzylpenicillin sodium 600 mg: Benzylpenicillin 600 mg powder for solution for injection vials | 2 vial (DT price £4.67 DT price + £4.67) | 25 vial (DT price £58.37–£58.38) | Benzylpenicillin sodium 1.2 gram: Benzylpenicillin 1.2 g powder for solution for injection vials | 25 vial (DT price £78.64 DT price + £78.64)
**Penicillins (Broad-Spectrum)**

**Amoxicillin** *(Amoxycillin)*

### INDICATIONS AND DOSE

Susceptible infections (including urinary-tract infections, otitis media, sinusitis, uncomplicated community acquired pneumonia, salmonellosis, oral infections)

- **BY MOUTH**
  - Child 1-11 months: 125 mg 3 times a day; increased if necessary up to 30 mg/kg 3 times a day
  - Child 1-4 years: 250 mg 3 times a day; increased if necessary up to 30 mg/kg 3 times a day
  - Child 5-11 years: 500 mg 3 times a day; increased if necessary up to 30 mg/kg 3 times a day (max. per dose 1 g)
  - Child 12-17 years: 500 mg 3 times a day; increased if necessary up to 1 g 3 times a day, use increased dose in severe infections
  - Adult: 500 mg every 8 hours, increased if necessary to 1 g every 8 hours, increased dose used in severe infections

- **BY INTRAMUSCULAR INJECTION**
  - Adult: 500 mg every 8 hours

- **BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION**
  - Adult: 500 mg every 8 hours, increased to 1 g every 6 hours, use increased dose in severe infections

**Lyme disease (under expert supervision)**

- **BY MOUTH**
  - Child 5-17 years: 500 mg 3 times a day for 14–21 days (for 28 days in Lyme arthritis)
  - Adult: 500 mg 3 times a day for 14–21 days (for 28 days in Lyme arthritis)

**Anthrax (treatment and post-exposure prophylaxis)**

- **BY MOUTH**
  - Child (body-weight up to 20 kg): 80 mg/kg daily in 3 divided doses
  - Child (body-weight 20 kg and above): 500 mg 3 times a day
  - Adult: 500 mg 3 times a day

**Dental abscess (short course)**

- **BY MOUTH**
  - Adult: 3 g, then 3 g after 8 hours

**Urinary-tract infections (short course)**

- **BY MOUTH**
  - Adult: 3 g, then 3 g after 10–12 hours

**Listerial meningitis (in combination with another antibiotic)**

- **BY INTRAVENOUS INFUSION**
  - Adult: 2 g every 4 hours

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**Penicillins (Broad-Spectrum)**

**Amoxicillin** *(Amoxycillin)*

### INDICATIONS AND DOSE

Susceptible infections (including urinary-tract infections, otitis media, sinusitis, uncomplicated community acquired pneumonia, salmonellosis, oral infections)

- **BY MOUTH**
  - Adult: 125 mg twice daily
  - Adult 5-11 years: 250 mg twice daily
  - Adult 12-17 years: 500 mg twice daily

**Endocarditis (in combination with another antibiotic if necessary)**

- **BY INTRAVENOUS INFUSION**
  - Adult: 2 g every 4 hours

Prevention of pneumococcal infection in asplenia or in patients with sickle-cell disease—if cover also needed for Haemophilus influenzae

- **BY MOUTH**
  - Child 1 month–4 years: 125 mg twice daily
  - Child 5–11 years: 250 mg twice daily
  - Child 12–17 years: 500 mg twice daily

**Helicobacter pylori eradication in combination with metronidazole and omeprazole**

- **BY MOUTH**
  - Adult: 500 mg 3 times a day

**Helicobacter pylori eradication; in combination with clarithromycin and esomeprazole; or in combination with clarithromycin and lansoprazole; or in combination with metronidazole and lansoprazole; or in combination with clarithromycin and omeprazole; or in combination with clarithromycin and pantoprazole; or in combination with clarithromycin and rabeprazole**

- **BY MOUTH**
  - Adult: 1 g twice daily

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**Amoxicillin doses in BNF Publications may differ from those in product literature. Amoxicillin is not licensed for use for treatment of Lyme disease.**

**CAUTIONS**

- **GENERAL CAUTIONS**
  - Acute lymphocytic leukaemia (increased risk of erythematous rashes) - chronic lymphocytic leukaemia (increased risk of erythematous rashes) - cytomegalovirus infection (increased risk of erythematous rashes) - glandular fever (erythematous rashes common) - maintain adequate hydration with high doses (particularly during parenteral therapy)

**SPECIFIC CAUTIONS**

- With intravenous use. Accumulation of sodium can occur with high parenteral doses

**SIDE-EFFECTS**

- **Common or very common** Nausea · Vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

If rash occurs, discontinue treatment.

**PREGNANCY** Not known to be harmful.

**BREAST FEEDING** Trace amount in milk, but appropriate to use.

**RENAL IMPAIRMENT** Reduce dose in severe impairment; rashes more common. Risk of crystalluria with high doses (particularly during parenteral therapy). Accumulation of sodium from injection can occur in patients with renal failure.

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use in children. Displacement value may be significant when reconstituting injection, consult local guidelines. Dilute intravenous injection to a concentration of 50 mg/mL (100 mg/mL for neonates). May be further diluted with Glucose 5% or Glucose 10% or Sodium chloride 0.9% or 0.45% for intravenous infusion. Give intravenous infusion over 30 minutes when using doses over 30 mg/kg.

- With intravenous use in adults. For intravenous infusion *(Amoxicil®)*, give intermittently in Glucose 5% or Sodium chloride 0.9%. Reconstituted solutions diluted and given without delay; suggested volume 100 mL given over 30–60 minutes or give via drip tubing in Glucose 5% or Sodium chloride 0.9%; continuous infusion not usually recommended.
Ampicillin

INDICATIONS AND DOSE
Susceptible infections (including urinary-tract infections, otitis media, sinusitis, uncomplicated community-acquired pneumonia, salmonellosis)

BY MOUTH

- Child 1–11 months: 125 mg 4 times a day; increased if necessary up to 30 mg/kg 4 times a day.
- Child 1–4 years: 250 mg 4 times a day; increased if necessary up to 30 mg/kg 4 times a day.
- Child 5–11 years: 500 mg 4 times a day; increased if necessary up to 30 mg/kg 4 times a day (max. per dose 1 g).
- Child 12–17 years: 500 mg 4 times a day; increased if necessary up to 1 g 4 times a day, use increased dose in severe infection.

- Adult: 0.5–1 g every 6 hours

BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION

- Adult: 500 mg every 4–6 hours

BY INTRAMUSCULAR INJECTION

- Adult: 500 mg every 4–6 hours

Endocarditis (in combination with another antibiotic if necessary) | Listerial meningitis (in combination with another antibiotic) 

BY INTRAVENOUS INFUSION

- Adult: 2 g every 4 hours

UNLICENSED USE

Ampicillin doses in BNF may differ from those in product literature.

CAUTIONS

GENERAL CAUTIONS
Acute lymphocytic leukaemia (increased risk of erythematous rashes) | Chronic lymphocytic leukaemia (increased risk of erythematous rashes) | Cytomegalovirus infection (increased risk of erythematous rashes) | Glandular fever (erythematous rashes common)

SPECIFIC CAUTIONS

- With intravenous use: Accumulation of electrolytes contained in parenteral preparations can occur with high doses.

SIDE-EFFECTS

- Common or very common: Nausea, vomiting

SIDE-EFFECTS, FURTHER INFORMATION

If rash occurs, discontinue treatment.

PREGNANCY

Not known to be harmful.

BREAST FEEDING

Trace amounts in milk, but inappropriate to use.

RENAI IMPAIRMENT

Accumulation of electrolytes contained in parenteral preparations can occur in patients with renal failure.

- In adults: Reduce dose if eGFR less than 10 mL/minute/1.73 m²; rashes more common.
- In children: If estimated glomerular filtration rate less than 10 mL/minute/1.73 m²: reduce dose or frequency; rashes more common.

DIRECTIONS FOR ADMINISTRATION

- With oral use: Administer at least 30 minutes before food.
- With intravenous use in children: Displacement value may be significant when reconstituting injection, consult local guidelines. Dilute intravenous injection to a concentration of 50–100 mg/mL. May be further diluted with glucose 5% or sodium chloride 0.9% or 0.45% for infusion. Give over 30 minutes when using doses of greater than 50 mg/kg to avoid CNS toxicity including convulsions.
- With intravenous use in adults: For intravenous infusion (Penbritin®), give intermittently in Glucose 5% or Sodium chloride 0.9%. Reconstituted solutions diluted and given without delay; suggested volume 100 mL given over 30–60 minutes via drip tubing in Glucose 5% or Sodium chloride 0.9%.
**CONTRA-INDICATIONS**

- **associated jaundice or hepatic dysfunction** recommended.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Capsule**
  - **AMPICILLIN (Non-proprietary)**
    - Ampicillin 250 mg
      - Ampicillin 250/500 mg capsules | 28 capsule
      - £25.00 DT price = £4.75
      - £35.00 DT price = £21.37
    - Penbritin (Chemidex Pharma Ltd)
      - Ampicillin 250 mg
        - £2.10 DT price = £4.75
      - Ampicillin 500 mg
        - £5.28 DT price = £21.37

- **Oral suspension**
  - **AMPICILLIN (Non-proprietary)**
    - Ampicillin 25 mg per 1 ml
      - Ampicillin 125mg/5ml oral suspension | 100 ml
        - £29.86 DT price = £29.86
    - Ampicillin 50 mg per 1 ml
      - Ampicillin 250mg/5ml oral suspension | 100 ml
        - £38.86 DT price = £38.86

- **Powder for solution for injection**
  - **AMPICILLIN (Non-proprietary)**
    - Ampicillin (as Ampicillin sodium) 500 mg
      - Ampicillin 500mg powder for solution for injection vials | 10 vial
        - £76.30

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**Co-amoxiclav**

**INDICATIONS AND DOSE**

Infections due to beta-lactamase-producing strains (where amoxicillin alone not appropriate), including respiratory, skin and urinary tract infections, wound infections, and cellulitis and animal bites.

**INITIALLY BY MOUTH USING TABLETS**

- **Child 12-17 years**: 250/125 mg every 8 hours; (by mouth) increased to 500/125 mg every 8 hours, increased dose used for severe infection.
- **Adult**: 250/125 mg every 8 hours; (by mouth) increased to 500/125 mg every 8 hours, increased dose used for severe infection.

**BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION**

- **Adult**: 1.2 g every 8 hours, intravenous injection to be administered over 3–4 minutes.

**Severe dental infection with spreading cellulitis**

**BY MOUTH USING TABLETS**

- **Child 12-17 years**: 250/125 mg every 8 hours for 5 days.
- **Adult**: 250/125 mg every 8 hours for 5 days.

**Surgical prophylaxis**

**BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION**

- **Adult**: 1.2 g, to be administered up to 30 minutes before the procedure, then 1.2 g every 8 hours for up to 2–3 further doses in high risk procedures.

**Dose equivalence and conversion**

Doses are expressed as co-amoxiclav.

A mixture of amoxicillin (as the trihydrate or as the sodium salt) and clavulanic acid (as potassium clavulanate); the proportions are expressed in the form x/y where x and y are the strengths in milligrams of amoxicillin and clavulanic acid respectively.

**CONTRA-INDICATIONS**

History of co-amoxiclav-associated jaundice or hepatic dysfunction. History of penicillin-associated jaundice or hepatic dysfunction.

**CAUTIONS**

**GENERAL CAUTIONS**

- Acute lymphocytic leukaemia (increased risk of erythematous rashes) • chronic lymphocytic leukaemia (increased risk of erythematous rashes) • cytomegalovirus infection (increased risk of erythematous rashes) • glandular fever (erythematous rashes common) – maintain adequate hydration with high doses (particularly during parenteral therapy).

**SPECIFIC CAUTIONS**

- With intravenous use Accumulation of electrolytes contained in parenteral preparations can occur with high doses.

**CAUTIONS, FURTHER INFORMATION**

Cholestatic jaundice Cholestatic jaundice can occur either during or shortly after the use of co-amoxiclav. An epidemiological study has shown that the risk of acute liver toxicity was about 6 times greater with co-amoxiclav than with amoxicillin. Cholestatic jaundice is more common in patients above the age of 65 years and in men; these reactions have only rarely been reported in children. Jaundice is usually self-limiting and very rarely fatal. The duration of treatment should be appropriate to the indication and should not usually exceed 14 days.

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- **Common or very common** Cholestatic jaundice • hepatitis • nausea • vomiting
- **Rare** Dizziness • headache • prolongation of bleeding time
- **Frequency not known** Exfoliative dermatitis • Steven-Johnson syndrome • toxic epidermal necrolysis • vasculitis

**SPECIFIC SIDE-EFFECTS**

- **Rare**
- **With intravenous use** phlebitis at injection site
- **With oral use** superficial staining of teeth with suspension

**SIDE-EFFETS, FURTHER INFORMATION**

Rash If rash occurs, discontinue treatment.

**PREGNANCY** Not known to be harmful.

**BREAST FEEDING** Trace amount in milk, but appropriate to use.

**HEPATIC IMPAIRMENT** Monitor liver function in liver disease.

**RENAL IMPAIRMENT** Risk of crystalluria with high doses (particularly during parenteral therapy).

- **With oral use in adults** Co-amoxiclav 250/125 tablets or 500/250 tablets: If eGFR 10–30 mL/minute/1.73 m², one 250/125 strength tablet every 12 hours or one 500/250 strength tablet every 12 hours; if eGFR less than 10 mL/minute/1.73 m², one 250/125 strength tablet every 24 hours or one 500/125 strength tablet every 24 hours. Co-amoxiclav 400/57 suspension: avoid if eGFR less than 30 mL/minute/1.73 m².

- **With intravenous use in adults** Co-amoxiclav injection (expressed as co-amoxiclav): if eGFR 10–30 mL/minute/1.73 m², 1.2 g initially, then 600 mg every 12 hours; if eGFR less than 10 mL/minute/1.73 m², 1.2 g initially, then 600 mg every 24 hours. Accumulation of electrolytes contained in parenteral preparations can occur in patients with renal failure.

- **With oral use in children** Co-amoxiclav 125/31 suspension, 250/62 suspension, 250/125 suspension, 500/125 tablets: use normal dose every 12 hours if estimated glomerular filtration rate 10–30 mL/minute/1.73 m². Use the normal dose recommended for mild or moderate infections every 12 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m². Co-amoxiclav 400/57 suspension: avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m².

**BNF 70**

chloride 0.9%. Continuous infusion not usually recommended.

**MEDICATIONS FOR CHILDREN**

- **Amoxicillin**
  - **Capsule**
    - **AMPICILLIN (Non-proprietary)**
      - Ampicillin 250 mg
        - Ampicillin 250/500 mg capsules | 28 capsule
          - £25.00 DT price = £4.75
      - **Penbritin** (Chemidex Pharma Ltd)
        - Ampicillin 250 mg
          - £2.10 DT price = £4.75
      - Ampicillin 500 mg
        - £5.28 DT price = £21.37

- **Oral suspension**
  - **AMPICILLIN (Non-proprietary)**
    - Ampicillin 25 mg per 1 ml
      - Ampicillin 125mg/5ml oral suspension | 100 ml
        - £29.86 DT price = £29.86
    - Ampicillin 50 mg per 1 ml
      - Ampicillin 250mg/5ml oral suspension | 100 ml
        - £38.86 DT price = £38.86

- **Powder for solution for injection**
  - **AMPICILLIN (Non-proprietary)**
    - Ampicillin (as Ampicillin sodium) 500 mg
      - Ampicillin 500mg powder for solution for injection vials | 10 vial
        - £76.30
Co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (sugar-free) | 10 ml (PoS) £35.00 DT price = £1.89
Amoxicillin (as Amoxicillin trihydrate) 80 mg per 1 ml, Clavulanic acid (as Potassium clavulanate) 1.4 mg per 1 ml Co-amoxiclav 400mg/57mg/5ml oral suspension sugar free (sugar-free) | 35 ml (PoS) £4.13 DT price = £1.13 (sugar-free) | 70 ml (PoS) £5.79 DT price = £1.79
Augmentin (GlaxoSmithKline UK Ltd) Amoxicillin (as Amoxicillin trihydrate) 25 mg per 1 ml, Clavulanic acid (as Potassium clavulanate) 6.2 mg per 1 ml Augmentin 125/31.5f oral suspension (sugar-free) | 100 ml (PoS) £3.54 DT price = £1.81
Amoxicillin (as Amoxicillin trihydrate) 50 mg per 1 ml, Clavulanic acid (as Potassium clavulanate) 12.5 mg per 1 ml Augmentin 250/62 5f oral suspension (sugar-free) | 100 ml (PoS) £3.60 DT price = £1.89
Augmentin-Duo (GlaxoSmithKline UK Ltd) Amoxicillin (as Amoxicillin trihydrate) 80 mg per 1 ml, Clavulanic acid (as Potassium clavulanate) 11.4 mg per 1 ml Augmentin-Duo 400/57 oral suspension (sugar-free) | 35 ml (PoS) £4.13 DT price = £1.13 (sugar-free) | 70 ml (PoS) £5.79 DT price = £1.79
Powder for solution for injection ELECTROLYTES: May contain Potassium, sodium
Co-amoxiclav (Non-proprietary) Amoxicillin (as Amoxicillin sodium) 500 mg, Clavulanic acid (as Potassium clavulanate) 100 mg Co-amoxiclav 500mg/100mg powder for solution for injection vials | 10 vial (PoS) £14.90 Amoxicillin (as Amoxicillin sodium) 1000 mg, Clavulanic acid (as Potassium clavulanate) 200 mg, Co-amoxiclav 1000mg/200mg powder for solution for injection vials | 10 vial (PoS) £29.70
Augmentin Intravenous (GlaxoSmithKline UK Ltd) Amoxicillin (as Amoxicillin sodium) 500 mg, Clavulanic acid (as Potassium clavulanate) 100 mg Augmentin Intravenous 600mg powder for solution for injection vials | 10 vial (PoS) £10.60 Amoxicillin (as Amoxicillin sodium) 1000 mg, Clavulanic acid (as Potassium clavulanate) 200 mg Augmentin Intravenous 1.2g powder for solution for injection vials | 10 vial (PoS) £10.60

Co-fluamcipil

INDICATIONS AND DOSE Mixed infections involving beta-lactamase-producing staphylococci
BY MOUTH
Child 1-9 years: 125/250 mg every 6 hours
Child 10-17 years: 250/500 mg every 6 hours
Adult: 500/1000 mg every 6 hours
BY INTRAMUSCULAR INJECTION OR BY SLOW INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION
Adult: 250/500 mg every 6 hours
Severe mixed infections involving beta-lactamase-producing staphylococci
BY MOUTH
Child 1-9 years: 250/500 mg every 6 hours
Child 10-17 years: 500/500 mg every 6 hours
Adult: 500/500 mg every 6 hours
BY INTRAMUSCULAR INJECTION OR BY SLOW INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION
Adult: 500/500 mg every 6 hours

Important safety information
HEPATIC DISORDERS
Cholestatic jaundice and hepatitis may occur very rarely, up to two months after treatment with flucloracill has been stopped. Administration for more than 2 weeks and increasing age are risk factors. Healthcare professionals are reminded that:
- Flucloracill should not be used in patients with a history of hepatic dysfunction associated with flucloracill;
- Flucloracill should be used with caution in patients with hepatic impairment;
CO-FLUAMPICIL (Non-proprietary)

Flucloxacillin sodium) 250 mg

There can be variation in the licensing of different medicines containing the same drug.

Tablet

<table>
<thead>
<tr>
<th>Indications and dose</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic or recurrent bacteriuria</td>
<td>Initial dose 400 mg every 6–8 hours for 3 days.</td>
</tr>
<tr>
<td>Urinary-tract infections</td>
<td>Initial dose 400 mg every 6–8 hours.</td>
</tr>
<tr>
<td>慢性 or recurrent bacteriuria</td>
<td>Child (body-weight up to 40 kg): 5–10 mg/kg daily in 3 divided doses</td>
</tr>
</tbody>
</table>

Flucloxacillin (as Flucloxacillin magnesium) 25 mg per 1 ml

CO-FLUAMPICIL (Non-proprietary)

Ampicillin 125mg/125mg/5ml oral suspension | 100 ml | £31.99 |

PENICILLINS (PENICILLINASE-RESISTANT)

Flucloxacillin

INDICATIONS AND DOSE

Infections due to beta-lactamase-producing staphylococci including otitis externa | Adjunct in pneumonia | Adjunct in impetigo | Adjunct in cellulitis

BY MOUTH

Child 1 month-1 year: 62.5–125 mg 4 times a day
Child 2–9 years: 125–250 mg 4 times a day
Temocillin

**INDICATIONS AND DOSE**

Septicaemia | Urinary-tract infections | Lower respiratory-tract infections caused by susceptible Gram-negative bacteria

**BY INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION**

- Adult: 1–2 g every 12 hours, give over 3–4 minutes when administered by intravenous injection

**CAUTIONS**

- Accumulation of sodium from injection can occur with high doses

**PREGNANCY**

- Not known to be harmful.

**BREAST FEEDING**

- Trace amounts in milk.

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**BREAST FEEDING**

- Common or very common
- Gastrointestinal disturbances
- Very rare
- Cholestatic jaundice - hepatitis
- Not known to be harmful.
- Trace amounts in milk, but appropriate to use.

**HEPATIC IMPAIRMENT**

- Use with caution.

**RENAL IMPAIRMENT**

- In adults: Reduce dose if eGFR less than 10 mL/minute/1.73 m². Accumulation of electrolytes can occur in patients with renal failure.

- In children: Use normal dose every 8 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m².

**EFFECT ON LABORATORY TESTS**

- False-positive urinary glucose (if tested for reducing substances).

**DIRECTIONS FOR ADMINISTRATION**

- For intravenous infusion (Fluropen®), give intermittently in Glucose 5% or Sodium chloride 0.9%; suggested volume 100 mL given over 30–60 minutes, via drip tubing in Glucose 5% or Sodium chloride 0.9%; continuous infusion not usually recommended.

**PATIENT AND CARER ADVICE**

- Medicines for Children leaflet: Flucloxacillin for bacterial infections www.medicinesforchildren.org.uk/ flucloxacillin-for-bacterial-infections

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: infusion

**Capsule**

- CAUTIONARY AND ADVISORY LABELS 9, 23

**Flucloxacillin**

- FLUCLOXACILLIN (Non-proprietary)

**Flucloxacillin (as Flucloxacillin sodium) 250 mg**

- Flucloxacillin 250mg capsules | 20 capsule (P) £0.58 | 28 capsule (P) £1.25 | 50 capsule (P) £1.14

- Flucloxacillin (as Flucloxacillin sodium) 500 mg

- Flucloxacillin 500mg capsules | 20 capsule (P) £1.50 | 28 capsule (P) £1.50 | 50 capsule (P) £2.00

**Flucloxacillin (as Flucloxacillin sodium) 1 g**

- Flucloxacillin 1g powder for solution for injection vials | 10 vial (P) £3.85

**Flucloxacillin (as Flucloxacillin sodium) 1 gram**

- Flucloxacillin 1g powder for solution for injection vials | 10 vial (P) £9.00

**Flucloxacillin (as Flucloxacillin sodium) 25 mg per 1 mL**

- Flucloxacillin 125mg/5ml oral solution | 100 ml (P) £2.85

- Flucloxacillin 125mg/5ml oral solution sugar free (sugar-free) | 100 ml (P) £2.85

- Flucloxacillin 250mg/5ml oral solution sugar free (sugar-free) | 100 ml (P) £5.00

**Flucloxacillin (as Flucloxacillin sodium) 50 mg per 1 mL**

- Flucloxacillin 250mg/5ml oral solution sugar free (sugar-free) | 100 ml (P) £3.50

- Flucloxacillin 500mg/5ml oral solution sugar free (sugar-free) | 100 ml (P) £6.50

**Flucloxacillin (as Flucloxacillin sodium) 125 mg per 5 mL**

- Flucloxacillin 125mg/5ml oral solution | 100 ml (P) £2.85

**Flucloxacillin (as Flucloxacillin sodium) 250 mg per 10 mL**

- Flucloxacillin 250mg/10ml oral solution | 100 ml (P) £5.00

- Flucloxacillin 500mg/10ml oral solution | 100 ml (P) £10.00

**重要的安全信息**

**HEPATIC DISORDERS**

- Cholestatic jaundice and hepatitis may occur very rarely, up to two months after treatment with flucloxacillin has been stopped. Administration for more than 2 weeks and increasing age are risk factors.

Healthcare professionals are reminded that:

- Flucloxacillin should not be used in patients with a history of hepatic dysfunction associated with flucloxacillin

- Flucloxacillin should be used with caution in patients with hepatic impairment

- Careful enquiry should be made about hypersensitivity reactions to beta-lactam antibacterials

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**Cautions**

- With intravenous use: Accumulation of electrolytes can occur with high doses.

**Side-effects**

- Common or very common: Gastrointestinal disturbances

- Very rare: Cholestatic jaundice - hepatitis

- Not known to be harmful.

- Trace amounts in milk, but appropriate to use.
**RENAL IMPAIRMENT** 1 g every 12 hours if eGFR 30–60 mL/minute/1.73 m². 1 g every 24 hours if eGFR 10–30 mL/minute/1.73 m². 1 g every 48 hours or 500 mg every 24 hours if eGFR less than 10 mL/minute/1.73 m². Accumulation of sodium from injection can occur in patients with renal failure.

**EFFECT ON LABORATORY TESTS** False-positive urinary glucose (if tested for reducing substances).

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Negaban®), give intermittently in Glucose 5% or 10% or Sodium chloride 0.9%. Reconstitute 1 g with 10 mL water for injections then dilute with 50–150 mL infusion fluid; give over 30–40 minutes.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**

**ELECTROLYTES:** May contain Sodium

- **Negaban** (Eumedica Pharmaceuticals)
  - Temocillin (as Temocillin sodium) 1 gram Negaban 1g powder for solution for injection vials | 1 vial (£0.30) no price available

**FOSPHONIC ACID ANTIBACTERIALS**

**Fosfomycin**

**DRUG ACTION** Fosfomycin, a phosphonic acid antibacterial, is active against a range of Gram-positive and Gram-negative bacteria including *Staphylococcus aureus* and Enterobacteriaceae.

**INDICATIONS AND DOSE**

Uncomplicated lower urinary-tract infections caused by multiple-antibacterial resistant organisms when other antibacterials cannot be used

**BY MOUTH**

- Adult (female): 3 g for 1 dose.
- Adult (male): 3 g for 1 dose, then 3 g after 3 days.

Osteomyelitis when first-line treatments are inappropriate or ineffective

Hospital-acquired lower respiratory-tract infections when first-line treatments are inappropriate or ineffective

**BY INTRAVENOUS INFUSION**

- Adult: 12–24 g once daily in 2–3 divided doses (max. per dose 8 g), use the high-dose regimen in severe infection suspected or known to be caused by less sensitive organisms

Complicated urinary-tract infections when first-line treatment ineffective or inappropriate

**BY INTRAVENOUS INFUSION**

- Adult: 12–16 g daily in 2–3 divided doses (max. per dose 8 g)

Bacterial meningitis when first-line treatment ineffective or inappropriate

**BY INTRAVENOUS INFUSION**

- Adult: 16–24 g daily in 3–4 divided doses (max. per dose 8 g), use the high-dose regimen in severe infection suspected or known to be caused by less sensitive organisms

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- Common or very common Gastro-intestinal disturbances • rash
- Uncommon Diarrhoea • nausea • vomiting
- Frequency not known Abdominal pain

**SPECIFIC SIDE-EFFECTS**

- With intravenous use Decreased appetite • dyspnoea • fatigue • headache • hyperpyrexia • hypokalaemia • taste disturbances • vertigo
- Rare
- With intravenous use Aplastic anaemia • blood disorders • eosinophilia
- Very rare
- With intravenous use Fatty liver • visual impairment
- Frequency not known
- With intravenous use Antibiotic-associated colitis • bronchospasm • confusion • hepatitis • jaundice • tachycardia

**PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING** Manufacturer advises use only if potential benefit outweighs risk—present in milk.

**RENA L IMPAIRMENT**

- With oral use Avoid if eGFR less than 10 mL/minute/1.73 m².
- With intravenous use Use with caution if eGFR 40–80 mL/minute/1.73 m² and consult product literature for dose if eGFR less than 40 mL/minute/1.73 m².

**MONITORING REQUIREMENTS**

- With intravenous use Monitor electrolytes and fluid balance.

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Fomicyt®), give intermittently in Glucose 5% or 10% or Water for Injections; reconstitute each 2-g vial with 50 mL infusion fluid; give 2 g over 15 minutes.

**PRESCRIBING AND DISPENSING INFORMATION** Although oral preparations containing fosfomycin are not marketed in the UK, they can be used, on the advice of a microbiologist, for the treatment of uncomplicated lower urinary tract infections caused by multiple-antibacterial resistant organisms when other antibacterials cannot be used.

Doses expressed as fosfomycin base.

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (February 2015) that Fosfomycin (Fomicyt®) is accepted for restricted use within NHS Scotland; initiation should be restricted to microbiologists or infectious disease specialists.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule

- **Granules**
  - CAUTIONARY AND ADVISORY LABELS 9, 13, 23
  - **FOSFOMYCIN** (Non-proprietary)
    - Fosfomycin (as Fosfomycin trometamol) 3 gram Monuril 3g granules sachets | 1 sachet (£0.45)
  - Powder for solution for infusion
    - **ELECTROLYTES:** May contain Sodium
      - **Fomicyt** (Nordic Pharma Ltd)
        - Fosfomycin (as Fosfomycin sodium) 2 gram Fomicyt 2g powder for solution for infusion vials | 10 vial (£0.37) £150.00
        - Fosfomycin (as Fosfomycin sodium) 4 gram Fomicyt 4g powder for solution for infusion vials | 10 vial (£0.70) £300.00

- **UNLICENSED USE** Oral preparations containing fosfomycin are not marketed in the UK and use of these preparations is unlicensed.

**CAUTIONS**

- With intravenous use Cardiac insufficiency • elderly (high doses) • hyperaldosteronism • hyperpyrexia • hypertension • pulmonary oedema

**INTERACTIONS** → Appendix 1 (fosfomycin).
POLYMIXYN ANTIBACTERIALS

Colistimethate sodium (Colistin sulphomethate sodium)

**DRUG ACTION** The polymyxin antibiotic, colistimethate sodium (colistin sulphomethate sodium), is active against Gram-negative organisms including *Pseudomonas aeruginosa*, *Acinetobacter baumanii*, and *Klebsiella pneumoniae*. It is not absorbed by mouth and thus needs to be given by injection for a systemic effect.

**INDICATIONS AND DOSE**
Gram-negative infections resistant to other antibacterials, including those caused by *Pseudomonas aeruginosa*, *Acinetobacter baumanii* and *Klebsiella pneumoniae*

**BY SLOW INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION**
- Adult (body-weight up to 59 kg): 50 000–75 000 units/kg daily in 3 divided doses, to be administered into a totally implantable venous access device when giving via slow intravenous injection
- Adult (body-weight 60 kg and above): 1–2 million units every 8 hours, to be administered into a totally implantable venous access device when giving via slow intravenous injection

**Adjunct to standard antibacterial therapy for *Pseudomonas aeruginosa* infection in cystic fibrosis**

**BY INHALATION OF NEBULISED SOLUTION**
- Adult: 1–2 million units twice daily; increased to 2 million units 3 times a day, dose only to be increased for subsequent respiratory isolates of *Pseudomonas aeruginosa*

**BY INHALATION OF POWDER**
- Adult: 1.66 million units twice daily

**CONTRA-INDICATIONS** Myasthenia gravis

**CAUTIONS**

**GENERAL CAUTIONS**
Acute porphyrias p. 864

**SPECIFIC CAUTIONS**
- When used by inhalation Severe haemoptysis — risk of further haemorrhage

**INTERACTIONS** → Appendix 1 (polymyxins).

**SIDE-EFFECTS**
- Common or very common
  - When used by inhalation Bronchospasm • cough • dysphonhia • nausea • sore mouth • sore throat • taste disturbances • vomiting
  - Uncommon
  - When used by inhalation Hyrosalivation • thirst
- Rare
  - With intravenous use Vasomotor instability
  - Frequency not known
  - With intravenous use Apnoea • confusion • headache • muscle weakness • nephrotoxicity • neurotoxicity reported especially with excessive doses • perioral paraesthesia • peripheral paraesthesia • psychosis • rash • slurred speech • vertigo • visual disturbances

**SIDE-EFFECTS, FURTHER INFORMATION**

**Dose-related side-effects** The major adverse effects are dose-related neurotoxicity and nephrotoxicity.

**PREGNANCY**
- When used by inhalation Clinical use suggests probably safe.
- With intravenous use Use only if potential benefit outweighs risk.

**BREAST FEEDING** Present in milk but poorly absorbed from gut; manufacturers advise avoid (or use only if potential benefit outweighs risk).

**RENAL IMPAIRMENT**
- With intravenous use Reduce dose. In renal impairment, monitor plasma colistimethate sodium concentration during parenteral treatment—consult product literature. Recommended ‘peak’ plasma colistimethate sodium concentration (approx. 1 hour after intravenous injection or infusion) 5–12 mg/litre; pre-dose (‘trough’) concentration 2–6 mg/litre.

**MONITORING REQUIREMENTS**
- With intravenous use Monitor renal function.
- When used by inhalation Measure lung function before and after initial dose of colistimethate sodium and monitor for bronchospasm; if bronchospasm occurs in a patient not using a bronchodilator, repeat test using a bronchodilator before the dose of colistimethate sodium.

**DIRECTIONS FOR ADMINISTRATION**
- When used by inhalation Other inhaled drugs should be administered before colistimethate sodium. For nebulisation administer required dose in 2–4 mL of sodium chloride 0.9% (or water for injections) or a 1:1 mixture of sodium chloride 0.9% and water for injection
- With intravenous use For intravenous infusion (Colomycin®, Promixin®), give intermittently in Sodium chloride 0.9% (or Glucose 5% for Promixin® brand only); dilute with 50 mL infusion fluid and give over 30 minutes.

**COLOMYCIN® POWDER FOR SOLUTION FOR INJECTION**
Colomycin® Injection may be used for nebulisation; administer required dose in 2–4 mL of sodium chloride 0.9%, (or water for injections) or a 1:1 mixture of sodium chloride 0.9% and water for injection.

**PRESCRIBING AND DISPENSING INFORMATION**
Colistimethate sodium is included in some preparations for topical application.

**PATIENT AND CARER ADVICE**
Patient should be advised to rinse mouth with water after each dose of dry powder inhalation.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**
Colistimethate sodium by dry powder inhalation for pseudomonal lung infection in cystic fibrosis (March 2013)
NICE TA276
Colistimethate sodium dry powder for inhalation is recommended for chronic pulmonary infection caused by *Pseudomonas aeruginosa* in patients with cystic fibrosis who would benefit from continued treatment, but do not tolerate the drug in its nebulised form. The manufacturer must provide colistimethate sodium dry powder for inhalation at the discount agreed as part of the patient access scheme to primary, secondary and tertiary care in the NHS. Patients currently receiving colistimethate sodium dry powder for inhalation can continue treatment until they and their clinician consider it appropriate to stop.

**www.nice.org.uk/TA276**

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ear drops, oral solution

**Tablet**
- Colomycin® (Forest Laboratories UK Ltd)
  - Colistin sulfate 1500000 unit Colomycin 1.5 million unit tablets | 50 tablet (PSt) £55.00

**Powder for solution for injection**

**ELECTROLYTES:** May contain Sodium
- **COLOMYCIN® SODIUM (Non-proprietary)**
  - Colistimethate sodium 1000000 unit Colistimethate 1 million unit powder for solution for injection vials | 10 vial (PSt) £18.00
  - 10 vial (Bo) £16.79 (Hospital only)
- Colomycin® (Forest Laboratories UK Ltd)
  - Colistimethate sodium 1000000 unit Colomycin 1 million unit powder for solution for injection vials | 10 vial (PSt) £18.00
  - Colistimethate sodium 2000000 unit Colomycin 2 million unit powder for solution for injection vials | 10 vial (Bo) £32.40

Bacterial infection 489
**Bacterial infection**

**Quinolones**

Nalidixic acid p. 493 and norfloxacin p. 493 are effective in uncomplicated urinary-tract infections.

Ciprofloxacin below is active against both Gram-positive and Gram-negative bacteria. It is particularly active against Gram-negative bacteria, including salmonella, shigella, campylobacter, neisseria, and pseudomonas. Ciprofloxacin has only moderate activity against Gram-positive bacteria such as *Streptococcus pneumoniae* and *Enterococcus faecalis*; it should not be used for pneumococcal pneumonia. It is active against chlamydia and some mycobacteria. Most anaerobic organisms are not susceptible. Ciprofloxacin can be used for respiratory tract infections (but not for pneumococcal pneumonia), urinary-tract infections, infections of the gastro-intestinal system (including typhoid fever), bone and joint infections, gonorrhoea and infections of the gastro-intestinal system (including typhoid fever). It is particularly active against Gram-negative organisms. It has greater activity against *Pneumococci* than ciprofloxacin. Moxifloxacin is not active against *Streptococcus pneumoniae* but it is more active against *Staphylococcus aureus* (MRSA).

Moxifloxacin should be reserved for the treatment of acute sinusitis, acute exacerbations of chronic bronchitis, and community-acquired pneumonia, but it should only be considered for these infections when first-line treatment cannot be used or is ineffective. Moxifloxacin is also licensed for the treatment of respiratory tract infections.

Although ciprofloxacin, levofloxacin, moxifloxacin p. 492, and ofloxacin are licensed for skin and soft-tissue infections, many staphylococci are resistant to the quinolones and their use should be avoided in MRSA infections.

**INDICATIONS AND DOSE**

**Fistulating Crohn’s disease**

- **BY MOUTH**
  - Adult: 500 mg twice daily

**Respiratory tract infections**

- **BY MOUTH**
  - Adult: 500–750 mg twice daily
  - **BY INTRAVENOUS INFUSION**
    - Adult: 400 mg every 8–12 hours, dose to be administered over 60 minutes

**CONTRA-INDICATIONS**

History of tendon disorders related to quinolone use.

**CAUTIONS**

Can prolong the QT interval · conditions that predispose to seizures · exposure to excessive sunlight should be avoided (discontinue if photosensitivity occurs) · G6PD deficiency · history of epilepsy · myasthenia gravis (risk of exacerbation)

**SIDE-EFFECTS**

- **Common or very common** Diarrhoea · dizziness · headache · nausea · vomiting
- **Uncommon** Abdominal pain · anorexia · anxiety · arthralgia · arthrosis · blood disorders · confusion · depression · disturbances in taste · disturbances in vision · dyspepsia · eosinophilia · hallucinations · leucopenia · myalgia · rash · sleep disturbances · thrombocytopenia · tremor
- **Rare** Antibiotic-associated colitis · convulsions · disturbances in hearing · disturbances in smell · dyspnoea · hepatic dysfunction · hepatitis · hypotension · interstitial nephritis · jaundice · photosensitivity · psychoses · renal failure · symptoms of peripheral neuropathy (sometimes irreversible) · tendon damage · tendon inflammation · vasculitis
- **Very rare** Stevens-Johnson syndrome · toxic epidermal necrolysis

**SIDE-EFFECTS, FURTHER INFORMATION**

The drug should be discontinued if psychiatric, neurological, or hypersensitivity reactions (including severe rash) occur.

**ALLERGY AND CROSS-SENSITIVITY**

Use of quinolones contraindicated in quinolone hypersensitivity.

**PREGNANCY**

Avoid in pregnancy—shown to cause arthropathy in animal studies; safer alternatives are available.

**Promixin (Profile Pharma Ltd)**

- Colistimethate sodium 1000000 unit Promixin 1mlln unit powder for solution for injection vials | 10 vial £30.00 (Hospital only)

**Inhalation powder**

- Colobreathe (Forest Laboratories UK Ltd)
  - Colistimethate sodium 1662500 unit Colobreathe 1,662,500 unit inhalation powder capsules | 56 capsule £968.80

**Powder for nebuliser solution**

- Promixin (Profile Pharma Ltd)
  - Colistimethate sodium 1000000 unit Promixin 1mlln unit powder for nebuliser solution unit dose vials | 30 unit dose £168.00

**CONTRA-INDICATIONS**

History of tendon disorders related to quinolone use.

**CAUTIONS**

Can prolong the QT interval · conditions that predispose to seizures · exposure to excessive sunlight should be avoided (discontinue if photosensitivity occurs) · G6PD deficiency · history of epilepsy · myasthenia gravis (risk of exacerbation)

**INTERACTIONS**

- Appendix 1 (quinolones).

**SIDE-EFFECTS**

- **Common or very common** Diarrhoea · dizziness · headache · nausea · vomiting
- **Uncommon** Abdominal pain · anorexia · anxiety · arthralgia · arthrosis · blood disorders · confusion · depression · disturbances in taste · disturbances in vision · dyspepsia · eosinophilia · hallucinations · leucopenia · myalgia · rash · sleep disturbances · thrombocytopenia · tremor
- **Rare** Antibiotic-associated colitis · convulsions · disturbances in hearing · disturbances in smell · dyspnoea · hepatic dysfunction · hepatitis · hypotension · interstitial nephritis · jaundice · photosensitivity · psychoses · renal failure · symptoms of peripheral neuropathy (sometimes irreversible) · tendon damage · tendon inflammation · vasculitis
- **Very rare** Stevens-Johnson syndrome · toxic epidermal necrolysis

**SIDE-EFFECTS, FURTHER INFORMATION**

The drug should be discontinued if psychiatric, neurological, or hypersensitivity reactions (including severe rash) occur.

**ALLERGY AND CROSS-SENSITIVITY**

Use of quinolones contraindicated in quinolone hypersensitivity.

**PREGNANCY**

Avoid in pregnancy—shown to cause arthropathy in animal studies; safer alternatives are available.

**Ciprofloxacin**

**INDICATIONS AND DOSE**

Fistulating Crohn’s disease

- **BY MOUTH**
  - Adult: 500 mg twice daily

Respiratory tract infections

- **BY MOUTH**
  - Adult: 500–750 mg twice daily
  - **BY INTRAVENOUS INFUSION**
    - Adult: 400 mg every 8–12 hours, dose to be administered over 60 minutes

**CONTRA-INDICATIONS**

History of tendon disorders related to quinolone use.

**CAUTIONS**

Can prolong the QT interval · conditions that predispose to seizures · exposure to excessive sunlight should be avoided (discontinue if photosensitivity occurs) · G6PD deficiency · history of epilepsy · myasthenia gravis (risk of exacerbation)

**INTERACTIONS**

- Appendix 1 (quinolones).

**SIDE-EFFECTS**

- **Common or very common** Diarrhoea · dizziness · headache · nausea · vomiting
- **Uncommon** Abdominal pain · anorexia · anxiety · arthralgia · arthrosis · blood disorders · confusion · depression · disturbances in taste · disturbances in vision · dyspepsia · eosinophilia · hallucinations · leucopenia · myalgia · rash · sleep disturbances · thrombocytopenia · tremor
- **Rare** Antibiotic-associated colitis · convulsions · disturbances in hearing · disturbances in smell · dyspnoea · hepatic dysfunction · hepatitis · hypotension · interstitial nephritis · jaundice · photosensitivity · psychoses · renal failure · symptoms of peripheral neuropathy (sometimes irreversible) · tendon damage · tendon inflammation · vasculitis
- **Very rare** Stevens-Johnson syndrome · toxic epidermal necrolysis

**SIDE-EFFECTS, FURTHER INFORMATION**

The drug should be discontinued if psychiatric, neurological, or hypersensitivity reactions (including severe rash) occur.

**ALLERGY AND CROSS-SENSITIVITY**

Use of quinolones contraindicated in quinolone hypersensitivity.

**PREGNANCY**

Avoid in pregnancy—shown to cause arthropathy in animal studies; safer alternatives are available.
Ciprofloxacin (as Ciprofloxacin hydrochloride) 750 mg Ciproxin

Ciprofloxacin (as Ciprofloxacin hydrochloride) 500 mg Ciproxin

Ciprofloxacin (as Ciprofloxacin hydrochloride) 250 mg Ciproxin

Ciprofloxacin (as Ciprofloxacin hydrochloride) 100 mg Ciproxin

Ciprofloxacin (as Ciprofloxacin lactate) 10 mg/ml Ciproxine

Ciprofloxacin (as Ciprofloxacin hydrochloride) 200 mg/ml Ciproxine

Ciprofloxacin 100 mg/ml Ciproxine

Ciprofloxacin 50 mg/ml Ciproxine

Ciprofloxacin 15 mg/ml Ciproxine

Ciprofloxacin 100 mg/ml Ciproxine
Solution for infusion

**ELECTROLYTES:** May contain Sodium

- **CIPROFLOXACIN (Non-proprietary)**
  - Ciprofloxacin (as Ciprofloxacin lactate) 2 mg per 1 ml Ciprofloxacin 200mg/100ml solution for infusion vials | 1 vial **PO** £14.78
  - Ciprofloxacin 200mg/100ml solution for infusion bottles | 10 bottle **PO** £144.45
  - Ciprofloxacin 100mg/50ml solution for infusion vials | 1 vial **PO** £7.57
  - Ciprofloxacin 400mg/200ml solution for infusion bottles | 5 bottle **PO** £97.05
  - Ciprofloxacin 400mg/200ml solution for infusion vials | 1 vial **PO** £19.79 (Hospital only)
  - **Ciproxin** (Bayer Plc)
    - Ciprofloxacin (as Ciprofloxacin lactate) 2 mg per 1 ml Ciproxin Infusion 100mg/50ml solution for infusion bottles | 1 bottle **PO** £7.61 (Hospital only)
    - Ciproxin Infusion 400mg/200ml solution for infusion bottles | 5 bottle **PO** £114.23 (Hospital only)
    - Ciproxin Infusion 200mg/100ml solution for infusion bottles | 5 bottle **PO** £75.06 (Hospital only)

**INDICATIONS AND DOSE**

**Acute sinusitis**
**BY MOUTH**
- Adult: 500 mg once daily for 10–14 days

**Acute exacerbation of chronic bronchitis**
**BY MOUTH**
- Adult: 500 mg once daily for 7–10 days

**Community-acquired pneumonia**
**BY MOUTH**
- Adult: 500 mg 1–2 times a day for 7–14 days
- Adult: 500 mg 1–2 times a day, to be given over at least 60 minutes

**Urinary-tract infections**
**BY MOUTH**
- Adult: 500 mg once daily for 7–14 days

**Urinary-tract infections (uncomplicated infection)**
**BY MOUTH**
- Adult: 250 mg once daily for 3 days

**Complicated urinary-tract infections**
**BY INTRAVENOUS INFUSION**
- Adult: 500 mg once daily, to be given over at least 60 minutes

**Chronic prostatitis**
**BY MOUTH**
- Adult: 500 mg once daily for 28 days
- Adult: 500 mg once daily, to be given over at least 60 minutes

**Complicated skin and soft tissue infections**
**BY MOUTH**
- Adult: 500 mg 1–2 times a day for 7–14 days
- Adult: 500 mg 1–2 times a day, to be given over at least 60 minutes

**Inhalation of anthrax (treatment and post-exposure prophylaxis)**
**BY MOUTH**
- Adult: 500 mg once daily for 8 weeks
- Adult: 500 mg once daily, to be given over at least 60 minutes

**CAUTIONS**
- Acute myocardial infarction (risk factor for QT interval prolongation)
- Bradycardia (risk factor for QT interval prolongation)
- Congenital long QT syndrome (risk factor for QT interval prolongation)
- Electrolyte disturbances (risk factor for QT interval prolongation)
- Heart failure with reduced left ventricular ejection fraction (risk factor for QT interval prolongation)
- History of psychiatric illness (risk factor for QT interval prolongation)
- History of symptomatic arrhythmias (risk factor for QT interval prolongation)
- Risk factors for QT interval prolongation

**INTERACTIONS**
- Caution if concomitant use with other drugs known to prolong the QT interval.

**SIDE-EFFECTS**
- **Common or very common** Constipation · flatulence · hyperhidrosis
- **Uncommon** Dysphagia · Rhabdomyolysis
- **Rare** Abnormal dreams · hypoglycaemia · palpitation · tachycardia · tinnitus
- **Frequency not known** Benign intracranial hypertension · extrapyramidal symptoms · hyperglycaemia · local reactions · peripheral neuropathy · pneumonitis · potentially life-threatening hepatic failure · rhabdomyolysis · stomatitis · syncope · transient hypotension

**BREAST FEEDING**
- Manufacturer advises avoid.

**RENAL IMPAIRMENT**
- Usual initial dose, then use half normal dose if eGFR 20–50 mL/minute/1.73 m²; consult product literature if eGFR less than 20 mL/minute/1.73 m².

**PATIENT AND CARER ADVICE**
- May impair performance of skilled tasks (e.g. driving).

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- CAUTIONARY AND ADVISORY LABELS 6, 9, 25

- **LEVOFLOXACIN (Non-proprietary)**
  - Levofloxacin (as Levofloxacin hemihydrate) 250 mg Levofloxacin 250mg tablets | 5 tablet **PO** £7.23 | 10 tablet **PO** £14.45 DT price + £11.36
  - Levofloxacin (as Levofloxacin hemihydrate) 500 mg Levofloxacin 500mg tablets | 5 tablet **PO** £12.93 | 10 tablet **PO** £25.85 DT price + £17.66
- **Tavanic** (Sanofi)
  - Levofloxacin (as Levofloxacin hemihydrate) 250 mg Tavanic 250mg tablets | 5 tablet **PO** £7.23 | 10 tablet **PO** £14.45 DT price + £11.36
  - Levofloxacin (as Levofloxacin hemihydrate) 500 mg Tavanic 500mg tablets | 5 tablet **PO** £12.93 | 10 tablet **PO** £25.85 DT price + £17.66
- Brands may include Evoxil

**Infusion**
- **LEVOFLOXACIN (Non-proprietary)**
  - Levofloxacin (as Levofloxacin hemihydrate) 5 mg per 1 ml Levofloxacin 500mg/100ml infusion bags | 20 bag **PO** £502.00

**Solution for infusion**
- **ELECTROLYTES:** May contain Sodium
- **LEVOFLOXACIN (Non-proprietary)**
  - Levofloxacin (as Levofloxacin hemihydrate) 5 mg per 1 ml Levofloxacin 500mg/100ml solution for infusion vials | 1 vial **PO** £25.00
  - Levofloxacin 500mg/100ml solution for infusion bottles | 10 bottle **PO** £224.00–£251.00
- Brands may include Evoxil

**Moxifloxacin**

**INDICATIONS AND DOSE**

**Sinusitis**
**BY MOUTH**
- Adult: 400 mg once daily for 7 days
Community-acquired pneumonia
BY MOUTH
- Adult: 400 mg once daily for 7–14 days
BY INTRAVENOUS INFUSION
- Adult: 400 mg once daily for 7–14 days, to be given over 60 minutes

Exacerbations of chronic bronchitis
BY MOUTH
- Adult: 400 mg once daily for 5–10 days

Mild to moderate pelvic inflammatory disease
BY MOUTH
- Adult: 400 mg once daily for 7–21 days

Complicated skin and soft-tissue infections which have failed to respond to other antibacterials or for patients who cannot be treated with other antibacterials
BY MOUTH
- Adult: 400 mg once daily for 7–21 days, to be given over 60 minutes

CONTRA-INDICATIONS
- Acute myocardial infarction (risk factor for QT interval prolongation) - bradycardia (risk factor for QT interval prolongation) - congenital long QT syndrome (risk factor for QT interval prolongation) - electrolyte disturbances (risk factor for QT interval prolongation) - heart failure with reduced left ventricular ejection fraction (risk factor for QT interval prolongation) - history of symptomatic arrhythmias (risk factor for QT interval prolongation)

INTERACTIONS
- + Appendix 1 (quinolones). Avoid concomitant use with other drugs known to prolong the QT interval.

SIDE-EFFECTS
- Common or very common Angina - arrhythmias - constipation - flatulence - gastritis - hyperlipidaemia - palpitation - sweating - vasodilatation
- Uncommon Dyspnoea
- Rare Abnormal dreams - anemia - dysphagia - hyperglycaemia - hypertension - hyperuricaemia - incoordination - myopathy - oedema - peripheral neuropathy - stomatitis - syncope
- Very rare Potentially life-threatening hepatic failure - rhabdomyolysis

SPECIFIC SIDE-EFFECTS
- With intravenous use Pain at injection site - phlebitis at injection site

BREAST FEEDING
Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT
Manufacturer advises avoid in severe impairment.

PATIENT AND CARER ADVICE
May impair performance of skilled tasks (e.g., driving).

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

### Tablet

**CAUTIONARY AND ADVISORY LABELS**
- **MOXIFLOXACIN (Non-proprietary)**
  - Moxifloxacin (as Moxifloxacin hydrochloride) 400 mg Moxifloxacin 400mg tablets | 5 tablet [POD] £8.05–£11.81
  - Avelox (Bayer Plc)

**Solution for infusion**

**ELECTROLYTES:** May contain Sodium
- **MOXIFLOXACIN (Non-proprietary)**
  - Moxifloxacin (as Moxifloxacin hydrochloride) 1.6 mg per 1 ml Moxifloxacin 400mg/250ml solution for infusion bottles | 1 bottle [POD] £39.95
  - Avelox (Bayer Plc)

**Nalidixic acid**

**INDICATIONS AND DOSE**

Urinary-tract infections
BY MOUTH
- Adult: 900 mg every 6 hours for 7 days, then reduced to 600 mg every 6 hours for prolonged therapy in chronic infections

CAUTIONS
- Acute myocardial infarction (risk factor for QT interval prolongation) - avoid in Acute porphyrias p. 864 - bradycardia (risk factor for QT interval prolongation) - congenital long QT syndrome (risk factor for QT interval prolongation) - electrolyte disturbances (risk factor for QT interval prolongation) - heart failure with reduced left ventricular ejection fraction (risk factor for QT interval prolongation) - history of symptomatic arrhythmias (risk factor for QT interval prolongation)

INTERACTIONS
- Caution if concomitant use with other drugs known to prolong the QT interval.

SIDE-EFFECTS
- Cranial nerve palsy - increased intracranial pressure - metabolic acidosis - peripheral neuropathy - toxic psychosis

BREAST FEEDING
Risk to infant very small but one case of haemolytic anaemia reported.

HEPATIC IMPAIRMENT
Manufacturer advises caution in liver disease.

RENAL IMPAIRMENT
Use with caution; avoid if eGFR less than 20 mL/minute/1.73 m².

MONITORING REQUIREMENTS
Monitor blood counts, renal and liver function if treatment exceeds 2 weeks.

EFFECT ON LABORATORY TESTS
False positive urinary glucose (if tested for reducing substances).

PRESCRIBING AND DISPENSING INFORMATION
Flavours of oral liquid formulations may include raspberry and strawberry.

MEDICINAL FORMS
Medicines not identified.

**Norfloxacin**

**INDICATIONS AND DOSE**

‘Lower’ urinary-tract infections
BY MOUTH
- Adult: 400 mg twice daily for 7–10 days (for 3 days for uncomplicated infections in women)

Chronic relapsing ‘lower’ urinary-tract infections
BY MOUTH
- Adult: 400 mg twice daily for up to 12 weeks; reduced to 400 mg once daily, if adequate suppression within first 4 weeks

Chronic prostatitis
BY MOUTH
- Adult: 400 mg twice daily for 28 days
**CAUTIONS** Acute myocardial infarction (risk factor for QT interval prolongation) · bradycardia (risk factor for QT interval prolongation) · congenital long QT syndrome (risk factor for QT interval prolongation) · heart failure with reduced left ventricular ejection fraction (risk factor for QT interval prolongation) · history of symptomatic arrhythmias (risk factor for QT interval prolongation)

**INTERACTIONS** Caution if concomitant use with other drugs known to prolong the QT interval.

**SIDE-EFFECTS**
- Frequency not known
- Rare
- Common or very common
- Epiphora · tinnitus
- Pancreatitis
- Extrapyramidal symptoms
- Hyperhidrosis
- Arrhythmias
- Tinnitus
- Nasopharyngitis
- Hot flushes
- Severe or complicated infections
- To be given over at least 30 minutes for each 200 mg

**SIDE-EFFECTS**
- Common or very common
- Epiphora · tinnitus
- Pancreatitis
- Extrapyramidal symptoms
- Hyperhidrosis
- Arrhythmias
- Tinnitus
- Nasopharyngitis
- Hot flushes
- Severe or complicated infections
- To be given over at least 30 minutes for each 200 mg

**MEDICINAL FORMS**

**INDICATIONS AND DOSE**

**Urinary-tract infections**
- Adult: 200–400 mg daily, preferably taken in the morning; increased if necessary to 400 mg twice daily, in upper urinary tract infections

**Complicated urinary-tract infection**
- Adult: 200 mg daily increased to 400 mg twice daily, for severe or complicated infections, to be given over at least 30 minutes for each 200 mg

**Acute or chronic prostatitis**
- Adult: 200 mg twice daily for 28 days

**Lower respiratory-tract infections**
- Adult: 400 mg daily, dose preferably taken in the morning, then increased if necessary to 400 mg twice daily

**Skin and soft-tissue infections**
- Adult: 400 mg twice daily

**Uncomplicated gonorrhoea**
- Adult: 400 mg once daily as a single dose

**Uncomplicated genital chlamydial infection | Non-gonococcal urethritis**
- Adult: 400 mg daily for 7 days, dose may be taken as a single daily dose or in divided doses

**Pelvic inflammatory disease**
- Adult: 400 mg twice daily for 14 days

**Septicaemia**
- Adult: 200 mg twice daily, increased to 400 mg twice daily, for severe or complicated infections. To be given over at least 30 minutes for each 200 mg

**INTERACTIONS** Caution if concomitant use with other drugs known to prolong the QT interval.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

| CAUTIONARY AND ADVISORY LABELS | NORFLOXACIN (Non-proprietary) | Norfloxacin 400 mg | Norfloxacin 400mg tablets | 6 tablet | P hire | £5.46 | 14 tablet | P hire | £8.90 |

**INDICATIONS AND DOSE**

**Urinary-tract infections**
- Adult: 200–400 mg daily, preferably taken in the morning; increased if necessary to 400 mg twice daily, in upper urinary tract infections

**Complicated urinary-tract infection**
- Adult: 200 mg daily increased to 400 mg twice daily, for severe or complicated infections, to be given over at least 30 minutes for each 200 mg

**Acute or chronic prostatitis**
- Adult: 200 mg twice daily for 28 days

**Lower respiratory-tract infections**
- Adult: 400 mg daily, dose preferably taken in the morning, then increased if necessary to 400 mg twice daily

**Skin and soft-tissue infections**
- Adult: 400 mg twice daily

**Uncomplicated gonorrhoea**
- Adult: 400 mg once daily as a single dose

**Uncomplicated genital chlamydial infection | Non-gonococcal urethritis**
- Adult: 400 mg daily for 7 days, dose may be taken as a single daily dose or in divided doses

**Pelvic inflammatory disease**
- Adult: 400 mg twice daily for 14 days

**Septicaemia**
- Adult: 200 mg twice daily, increased to 400 mg twice daily, for severe or complicated infections. To be given over at least 30 minutes for each 200 mg

**INTERACTIONS** Caution if concomitant use with other drugs known to prolong the QT interval.

**SIDE-EFFECTS**
- Common or very common
- Epiphora · tinnitus
- Pancreatitis
- Extrapyramidal symptoms
- Hyperhidrosis
- Arrhythmias
- Tinnitus
- Nasopharyngitis
- Hot flushes
- Severe or complicated infections
- To be given over at least 30 minutes for each 200 mg

**SIDE-EFFECTS**
- Common or very common
- Epiphora · tinnitus
- Pancreatitis
- Extrapyramidal symptoms
- Hyperhidrosis
- Arrhythmias
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- Nasopharyngitis
- Hot flushes
- Severe or complicated infections
- To be given over at least 30 minutes for each 200 mg

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

| CAUTIONARY AND ADVISORY LABELS | NORFLOXACIN (Non-proprietary) | Norfloxacin 400 mg | Norfloxacin 400mg tablets | 6 tablet | P hire | £5.46 | 14 tablet | P hire | £8.90 |

**INDICATIONS AND DOSE**

**Urinary-tract infections**
- Adult: 200–400 mg daily, preferably taken in the morning; increased if necessary to 400 mg twice daily, in upper urinary tract infections

**Complicated urinary-tract infection**
- Adult: 200 mg daily increased to 400 mg twice daily, for severe or complicated infections, to be given over at least 30 minutes for each 200 mg

**Acute or chronic prostatitis**
- Adult: 200 mg twice daily for 28 days

**Lower respiratory-tract infections**
- Adult: 400 mg daily, dose preferably taken in the morning, then increased if necessary to 400 mg twice daily

**Skin and soft-tissue infections**
- Adult: 400 mg twice daily

**Uncomplicated gonorrhoea**
- Adult: 400 mg once daily as a single dose

**Uncomplicated genital chlamydial infection | Non-gonococcal urethritis**
- Adult: 400 mg daily for 7 days, dose may be taken as a single daily dose or in divided doses

**Pelvic inflammatory disease**
- Adult: 400 mg twice daily for 14 days

**Septicaemia**
- Adult: 200 mg twice daily, increased to 400 mg twice daily, for severe or complicated infections. To be given over at least 30 minutes for each 200 mg

**INTERACTIONS** Caution if concomitant use with other drugs known to prolong the QT interval.

**SIDE-EFFECTS**
- Common or very common
- Epiphora · tinnitus
- Pancreatitis
- Extrapyramidal symptoms
- Hyperhidrosis
- Arrhythmias
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- Nasopharyngitis
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- Severe or complicated infections
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**SIDE-EFFECTS**
- Common or very common
- Epiphora · tinnitus
- Pancreatitis
- Extrapyramidal symptoms
- Hyperhidrosis
- Arrhythmias
- Tinnitus
- Nasopharyngitis
- Hot flushes
- Severe or complicated infections
- To be given over at least 30 minutes for each 200 mg

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

| CAUTIONARY AND ADVISORY LABELS | NORFLOXACIN (Non-proprietary) | Norfloxacin 400 mg | Norfloxacin 400mg tablets | 6 tablet | P hire | £5.46 | 14 tablet | P hire | £8.90 |
Rifaximin

- **DRUG ACTION** Rifaximin is a rifamycin that is poorly absorbed from the gastrointestinal tract, and, therefore, should not be used to treat systemic infections.

**INDICATIONS AND DOSE**

Travellers’ diarrhoea that is not associated with fever, bloody diarrhoea, blood or leucocytes in the stool, or 8 or more unformed stools in the previous 24 hours

**BY MOUTH**

- Adult: 200 mg every 8 hours for 3 days

**Reduction in recurrence of hepatic encephalopathy**

**BY MOUTH**

- Adult: 550 mg twice daily

- **CONTRA-INDICATIONS** Intestinal obstruction

- **INTERACTIONS** Rifamycins interactions in Appendix 1 do not apply to rifaximin.

- **SIDE-EFFECTS** Rifamycins interactions in Appendix 1 do not apply to rifaximin.

- **SIDE-EFFECTS**
  - Common or very common: Abdominal pain, depression, diarrhoea, dizziness, dyspnoea, flatulence, headache, muscle spasm, nausea, pruritus, rash, vomiting
  - Uncommon: Anorexia, antibiotic-associated colitis, anxiety, blood disorders, convulsions, dry mouth, dysuria, glycosuria, hyperkalaemia, hypoaesthesia, influenza-like symptoms, memory impairment, paraesthesia, peripheral oedema, polynephroaemia, polyuria, sleep disturbances, taste disturbances
  - Rare: Blood pressure changes, constipation, frequency not known: Syncope

- **ALLERGY AND CROSS-SENSITIVITY** Contraindicated if history of rifamycin hypersensitivity.

- **PREGNANCY** Manufacturer advises avoid—toxicity in animal studies.

- **BREAST FEEDING** Unlike to be present in milk in significant amounts, but manufacturer advises avoid.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution when used for hepatic encephalopathy in patients with severe hepatic impairment.

- **PRESCRIBING AND DISPENSING INFORMATION** Not recommended for diarrhoea associated with invasive organisms such as Campylobacter and Shigella.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - NICE technology appraisals (TAs)
    - Rifaximin for preventing episodes of overt hepatic encephalopathy (March 2015) NICE TA337
    - Rifaximin is recommended, within its marketing authorisation, as an option for reducing the recurrence of episodes of overt hepatic encephalopathy in adults.

  www.nice.org.uk/TA337

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**

  - CAUTIONARY AND ADVISORY LABELS 14, 9
    - Targaxan (Norgine Pharmaceuticals Ltd)
      - Rifaximin 550 mg Targaxan 550mg tablets | 56 tablet [POM] £259.23 DT price = £259.23
    - Xifaxanta (Norgine Pharmaceuticals Ltd)
      - Rifaximin 200 mg Xifaxanta 200mg tablets | 9 tablet [POM] £15.15

- **SULFONAMIDES**

  **Sulfadiazine** (Sulphadiazine)

  - **DRUG ACTION** Sulfadiazine is a short-acting sulfonamide with bacteriostatic activity against a broad spectrum of organisms. The importance of the sulfonamides has decreased as a result of increasing bacterial resistance and their replacement by antibacterials which are generally more active and less toxic.

  **INDICATIONS AND DOSE**

  Prevention of rheumatic fever recurrence

  **BY MOUTH**

  - Adult (body-weight up to 30 kg): 500 mg daily
  - Adult (body-weight 30 kg and above): 1 g daily

  - **UNLICENSED USE** Not licensed for use in toxoplasmosis.

  - **CONTRA-INDICATIONS** Acute porphyrias p. 864

  - **CAUTIONS** Asthma · avoid in blood disorders (unless under specialist supervision) · avoid in infants under 6 weeks (except for treatment or prophylaxis of pneumocystis pneumonia) because of the risk of kernicterus · elderly · G6PD deficiency (risk of haemolytic anaemia) · maintain adequate fluid intake · predisposition to folate deficiency · predisposition to hyperkalaemia

  - **INTERACTIONS** → Appendix 1 (sulfonamides).

  - **SIDE-EFFECTS**
    - Common or very common: Diarrhoea, headache, hyperkalaemia, nausea, rash
    - Uncommon: Vomiting
    - Rare: Agranulocytosis · bone marrow depression
    - Very rare: Anorexia, antibiotic-associated colitis, arthralgia, aseptic meningitis, ataxia, blood disorders, convulsions, cough, depression, esophagitis, glossitis, hallucinations, hepatic necrosis, hypoglycaemia, hyponatraemia, interstitial nephritis, jaundice, leucopenia, liver damage, megaloblastic anaemia, myocarditis, pancreatitis, peripheral neuropathy, photosensitivity, pulmonary infiltrates, renal disorders, shortness of breath, Stevens-Johnson syndrome, stomatitis, systemic lupus erythematosus, thrombocytopenia, tinnitus, toxic epidermal necrosis, uraemia, vasculitis, vertigo
    - Frequency not known: Benign intracranial hypertension, photophobia, optic neurapathy, rhabdomyolysis reported in HIV-infected patients

  - **SIDE-EFFECTS, FURTHER INFORMATION**

  - Blood disorders or rash: Discontinue immediately if blood disorders (including leucopenia, thrombocytopenia, megaloblastic anaemia, eosinophilia) or rash (including Stevens-Johnson syndrome, toxic epidermal necrosis, photosensitivity) develop.

  - **PREGNANCY** Risk of neonatal haemolyis and methaemoglobinemia in third trimester; fear of increased risk of kernicterus in neonates appears to be unfounded.

  - **BREAST FEEDING** Small risk of kernicterus in jaundiced infants and of haemolyis in G6PD-deficient infants.

  - **HEPATIC IMPAIRMENT** Use with caution in mild to moderate impairment; avoid in severe impairment.

  - **RENAL IMPAIRMENT** Use with caution in mild to moderate impairment; avoid in severe impairment; high risk of crystalluria.

  - **MONITORING REQUIREMENTS** Monitor blood counts on prolonged treatment.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

  **Tablet**

  - CAUTIONARY AND ADVISORY LABELS 9, 27
    - SULFADIAZINE (Non-proprietary)
      - Sulfadiazine 500 mg Sulfadiazine 500mg tablets | 56 tablet [POM] £78.59

- **Bacterial infection** 495
TETRACYCLINES AND RELATED DRUGS

Tetracyclines

The tetracyclines are broad-spectrum antibiotics whose value has decreased owing to increasing bacterial resistance. They remain, however, the treatment of choice for infections caused by chlamydia (trachoma, psittacosis, salpingitis, urethritis, and lymphogranuloma venereum), rickettsia (including Q-fever), brucella (doxycycline below with either streptomycin p. 451 or rifampicin p. 508), and the spirochaete, Borrelia burgdorferi (See Lyme disease). They are also used in respiratory and genital mycoplasma infections, in acne, in productive (refractory) periodontal disease, in exacerbations of chronic bronchitis (because of their activity against Haemophilus influenzae), and for leptospirosis in penicillin hypersensitivity (as an alternative to erythromycin p. 471).

Tetracyclines have a role in the management of meticillin-resistant Staphylococcus aureus (MRSA) infection. Microbiologically, there is little to choose between the various tetracyclines, the only exception being minocycline p. 498 which has a broader spectrum; it is active against Neisseria meningitidis and has been used for meningococcal prophylaxis but is no longer recommended because of side-effects including dizziness and vertigo. Compared to other tetracyclines, minocycline is associated with a greater risk of lupus-erythematosus-like syndrome. Minocycline sometimes causes irreversible pigmentation.

Tetracyclines

- **CONTRA-INDICATIONS** Children under 12 years (deposition in growing bone and teeth, by binding to calcium, causes staining and occasionally dental hypoplasia)
- **CAUTIONS** Myasthenia gravis (muscle weakness may be increased) - systemic lupus erythematosus (may be exacerbated)
- **INTERACTIONS** 
  - Appendix 1 (tetracyclines).
  - Antacids, and aluminium, calcium, iron, magnesium and zinc salts decrease the absorption of tetracyclines. Use with caution in those receiving potentially hepatotoxic drugs.
- **SIDE-EFFECTS**
  - **Rare** Anaphylaxis - angioedema - blood disorders - exfoliative dermatitis - hepatitis - hypersensitivity reactions - pancreatitis - pericarditis - photosensitivity (particularly with demeclocycline) - rash - Stevens-Johnson syndrome - urticaria
  - **Frequency not known** Antibiotic-associated colitis - benign intracranial hypertension - diarrhoea - dysphagia - headache - nausea - oesophageal irritation - visual disturbances - vomiting
- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Benign intracranial hypertension Headache and visual disturbances may indicate benign intracranial hypertension (discontinue treatment).
- **PREGNANCY** Should not be given to pregnant women; effects on skeletal development have been documented in the first trimester in animal studies. Administration during the second or third trimester may cause discoloration of the child’s teeth, and maternal hepatotoxicity has been reported with large parenteral doses.
- **BREAST FEEDING** Should not be given to women who are breast-feeding (although absorption and therefore discoloration of teeth in the infant is probably usually prevented by chelation with calcium in milk).

HEPATIC IMPAIRMENT Should be avoided or used with caution in patients with hepatic impairment.

Demeclocycline hydrochloride

**INDICATIONS AND DOSE**
Susceptible infections (e.g. chlamydia, rickettsia and mycoplasma)
- **BY MOUTH**
  - Adult: 150 mg 4 times a day, alternatively 300 mg twice daily

Treatment of hypoaesthesia resulting from inappropriate secretion of antidiuretic hormone, if fluid restriction alone does not restore sodium concentration or is not tolerable
- **BY MOUTH**
  - Adult: Initially 0.9–1.2 g daily in divided doses, maintenance 600–900 mg daily

- **CAUTIONS** Photosensitivity more common than with other tetracyclines
- **INTERACTIONS** Milk reduces absorption.
- **SIDE-EFFECTS** Acute renal failure - reversible nephrogenic diabetes insipidus
- **HEPATIC IMPAIRMENT** Max. 1 g daily in divided doses.
- **RENAL IMPAIRMENT** May exacerbate renal failure and should not be given to patients with renal impairment.
- **PATIENT AND CARER ADVICE** Patients should be advised to avoid exposure to sunlight or sun lamps.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

Capsule

CAUTIONARY AND ADVISORY LABELS 7, 9, 11, 23

**DEMECLOCYCLINE HYDROCHLORIDE (Non-proprietary)**

Demeclocycline hydrochloride 150 mg Demeclocycline 150mg capsules | 28 capsule [Pack] £81.49 DT price = £81.49

Doxycycline

**INDICATIONS AND DOSE**
Susceptible infections (e.g. chlamydia, rickettsia and mycoplasma)
- **BY MOUTH**
  - Child 12-17 years: Initially 200 mg daily for 1 dose, then 100 mg daily; 200 mg daily, increased dose used for severe infections including refractory urinary-tract infections
  - Adult: Initially 200 mg daily for 1 dose, then 100 mg daily; 200 mg daily, increased dose used for severe infections including refractory urinary-tract infections

Acne
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Child 12-17 years: 100 mg daily
  - Adult: 100 mg daily

Rosacea
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Adult: 100 mg daily

Papulopustular facial rosacea (without ocular involvement)
- **BY MOUTH USING MODIFIED-RELEASE MEDICINES**
  - Adult: 40 mg once daily for 16 weeks, dose to be taken in the morning, consider discontinuing treatment if no response after 6 weeks

Early syphilis
- **BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - Child 12-17 years: 100 mg twice daily for 14 days
  - Adult: 100 mg twice daily for 14 days
Late latent syphilis
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
▶ Child 12-17 years: 100 mg twice daily for 28 days
▶ Adult: 100 mg twice daily for 28 days

Neurosyphilis
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
▶ Adult: 200 mg twice daily for 28 days

Uncomplicated genital chlamydia | Non-gonococcal urethritis
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
▶ Child 12-17 years: 100 mg twice daily for 7 days
▶ Adult: 100 mg twice daily for 7 days

Pelvic inflammatory disease
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
▶ Child 12-17 years: 100 mg twice daily for 14 days
▶ Adult: 100 mg twice daily for 14 days

Lyme disease
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
▶ Child 12-17 years: 100 mg twice daily for 10–14 days (for 28 days in Lyme arthritis)
▶ Adult: 100 mg twice daily for 10–14 days (for 28 days in Lyme arthritis)

Anthrax (treatment or post-exposure prophylaxis)
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
▶ Child 12-17 years: 100 mg twice daily
▶ Adult: 100 mg twice daily

Prophylaxis of malaria
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
▶ Child 12-17 years: 100 mg once daily, to be started 1–2 days before entering endemic area and continued for 4 weeks after leaving, can be used for up to 2 years
▶ Adult: 100 mg once daily, to be started 1–2 days before entering endemic area and continued for 4 weeks after leaving

Adjunct to quinine in treatment of Plasmodium falciparum malaria
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
▶ Child 12-17 years: 200 mg daily for 7 days
▶ Adult: 200 mg daily for 7 days

Periodontitis (as an adjunct to gingival scaling and root planing)
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
▶ Child 12-17 years: 20 mg twice daily for 3 months
▶ Adult: 20 mg twice daily for 3 months


− CAUTIONS Alcohol dependence

− INTERACTIONS The metabolism of doxycycline may be influenced by antiepileptics.

− SIDE-EFFECTS Anorexia · anxiety · dry mouth · flushing · fungal superinfection (when used for periodontitis) · tinnitus

− PREGNANCY When travel to malarious areas is unavoidable during pregnancy, doxycycline can be used for malaria prophylaxis if other regimens are unsuitable, and if the entire course of doxycycline can be completed before 15 weeks’ gestation.

− RENAL IMPAIRMENT Use with caution (avoid excessive doses).

− MONITORING REQUIREMENTS When used for periodontitis, monitor for superficial fungal infection, particularly if predisposition to oral candidiasis.

− DIRECTIONS FOR ADMINISTRATION Capsules and tablets should be swallowed whole with plenty of fluid, while sitting or standing. Capsules should be taken during meals.

− PATIENT AND CARER ADVICE Counselling on administration advised (posture). Photosensitivity Patients should be advised to avoid exposure to sunlight or sun lamps.

− PROFESSION SPECIFIC INFORMATION

Dental practitioners’ formulary Doxycycline Capsules 100 mg may be prescribed. Dispersible tablets may be prescribed as Dispersible Doxycycline Tablets. Tablets may be prescribed as Doxycycline Tablets 20 mg.

− MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Dispersible tablet
CAUTIONARY AND ADVISORY LABELS 6, 9, 11, 13

▶ Vibramycin-D (Pfizer Ltd)

Doxycycline (as Doxycycline monohydrate) 100 mg Vibramycin-D

100 mg dispersible tablets (sugar-free) | 8 tablet £4.91 DT price

Capsule
CAUTIONARY AND ADVISORY LABELS 6, 9, 11, 27

▶ DOXCYCLINE (Non-proprietary)

Doxycycline (as Doxycycline hyclate) 50 mg Doxycycline 50mg capsules | 28 capsule £4.00 DT price = £1.67

Doxycycline (as Doxycycline hyclate) 100 mg Doxycycline 100mg capsules | 8 capsule £3.00 DT price = £1.13 | 50 capsule £7.06

Brands may include Vibrox

Modified-release capsule
CAUTIONARY AND ADVISORY LABELS 6, 11, 27

▶ Efracea (Galderma (UK) Ltd)

Doxycycline (as Doxycycline monohydrate) 40 mg Efracea 40mg modified-release capsules | 14 capsule £7.99 DT price = £1.79 | 56 capsule £21.71

Lymecycline

INDICATIONS AND DOSE
Susceptible infections (e.g. chlamydia, rickettsia and mycoplasma)
BY MOUTH
▶ Child 12-17 years: 408 mg twice daily, increased to 1.224–1.632 g daily, (in severe infection)
▶ Adult: 408 mg twice daily, increased to 1.224–1.632 g daily, (in severe infection)

Acne
BY MOUTH
▶ Child 12-17 years: 408 mg daily for at least 8 weeks
▶ Adult: 408 mg daily for at least 8 weeks

− RENAL IMPAIRMENT May exacerbate renal failure and should not be given to patients with renal impairment.

− MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Capsule
CAUTIONARY AND ADVISORY LABELS 6, 9

▶ LYMECYCLINE (Non-proprietary)

Lymecycline 408 mg Lymecycline 408mg capsules | 28 capsule £9.18 DT price = £0.95 | 56 capsule £18.36

▶ Tetralysal (Galderma (UK) Ltd)

Lymecycline 408 mg Tetralysal 300 capsules | 28 capsule £9.95 DT price = £0.95 | 56 capsule £11.53
**Minocycline**

**INDICATIONS AND DOSE**

Susceptible infections (e.g. chlamydia, rickettsia and mycoplasma)

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

- Child 12-17 years: 100 mg twice daily
- Adult: 100 mg twice daily

**Acne vulgaris**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

- Child 12-17 years: 100 mg once daily, alternatively 50 mg twice daily
- Adult: 100 mg once daily, alternatively 50 mg twice daily

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

- Child 12-17 years: 100 mg daily
- Adult: 100 mg daily

Prophylaxis of asymptomatic meningococcal carrier state (but no longer recommended)

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

- Adult: 100 mg twice daily for 5 days, minocycline treatment is usually followed by administration of rifampicin

**CAUTIONS** Systemic lupus erythematosus

**SIDE-EFFECTS**

- Rare Acute renal failure · alopecia · anorexia · hyperaesthesia · impaired hearing · paraesthesia · pigmentation (sometimes irreversible) · tinnitus
- Very rare Discoloration of conjunctiva · discoloration of sweat · discoloration of tears · systemic lupus erythematosus
- Frequency not known Dizziness (more common in women) · vertigo (more common in women)

**RENAI IMPAIRMENT** Use with caution (avoid excessive doses).

**MONITORING REQUIREMENTS** If treatment continued for longer than 6 months, monitor every 3 months for hepatoxicity, pigmentation and for systemic lupus erythematosus—discontinue if these develop or if pre-existing systemic lupus erythematosus worsens.

**DIRECTIONS FOR ADMINISTRATION** Tablets or capsules should be swallowed whole with plenty of fluid while sitting or standing.

**PATIENT AND CAREER ADVICE** Counselling on administration advised (posture).

**LESS SUITABLE FOR PRESCRIBING** Less suitable for prescribing (compared to other tetracyclines, minocycline is associated with a greater risk of lupus-erythematosus-like syndrome; it sometimes causes irreversible pigmentation).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

- CAUTIONARY AND ADVISORY LABELS 6, 9
- MINOCYCLINE (Non-proprietary)
  - Minocycline (as Minocycline hydrochloride) 50 mg  Minocycline 50mg tablets | 28 tablet [PST] £8.50 DT price + £6.19
  - Minocycline (as Minocycline hydrochloride) 100 mg Minocycline 100mg tablets | 28 tablet [PST] £14.50 DT price + £14.00

**Capsule**

- CAUTIONARY AND ADVISORY LABELS 6, 9
- Aknemin (Almirall Ltd)
  - Minocycline (as Minocycline hydrochloride) 50 mg Aknemin 50 capsules | 56 capsule [PST] £15.27 DT price + £15.27
  - Minocycline (as Minocycline hydrochloride) 100 mg Aknemin 100mg capsules | 28 capsule [PST] £13.09 DT price + £13.09

**Oxytetracycline**

**INDICATIONS AND DOSE**

Susceptible infections (e.g. chlamydia, rickettsia and mycoplasma)

**BY MOUTH**

- Child 12-17 years: 250–500 mg 4 times a day
- Adult: 250–500 mg 4 times a day

**Rosacea**

**BY MOUTH**

- Adult: 500 mg twice daily usually for 6–12 weeks (course may be repeated intermittently)

**INTERACTIONS** Milk reduces absorption.

**RENAI IMPAIRMENT** May exacerbate renal failure and should not be given to patients with renal impairment.

**PROFESSION SPECIFIC INFORMATION**

Dental practitioners’ formulary Oxytetracycline Tablets may be prescribed.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**

- CAUTIONARY AND ADVISORY LABELS 7, 9, 23
- OXYTETRACYCLINE (Non-proprietary)
  - Oxytetracycline (as Oxytetracycline dihydrate) 250 mg Oxytetracycline 250mg tablets | 28 tablet [PST] £12.50 DT price + £1.20 | 1000 tablet [PST] £33.93

**Tetracycline**

**INDICATIONS AND DOSE**

Susceptible infections (e.g. chlamydia, rickettsia, mycoplasma)

**BY MOUTH**

- Child 12-17 years: 250 mg 4 times a day, increased if necessary to 500 mg 3–4 times a day, increased dose used in severe infections
- Adult: 250 mg 4 times a day, increased if necessary to 500 mg 3–4 times a day, increased dose used in severe infections

**Rosacea**

**BY MOUTH**

- Adult: 500 mg twice daily usually for 6–12 weeks (course may be repeated intermittently)
2.2 Leprosy

Advice from a member of the Panel of Leprosy Opinion is essential for the treatment of leprosy (Hansen’s disease). Details can be obtained from the Hospital for Tropical Diseases, London (telephone (020) 3456 7890). The World Health Organization has made recommendations to overcome the problem of dapson p. 500 resistance and to prevent the emergence of resistance to other antileprotic drugs. Drugs recommended are dapson, rifampicin p. 508, and clofazimine p. 500. Other drugs with significant activity against Mycobacterium leprae include ofloxacin p. 494, minocycline p. 496 and clarithromycin p. 495. However, none of these are as active as rifampicin; at present they should be reserved for second-line drugs for leprosy.

A three-drug regimen is recommended for multidrug leprosy (lepromatous, borderline-lepromatous, and borderline leprosy) and a two-drug regimen for paucibacillary leprosy (borderline-tuberculoid, tuberculoid, and indeterminate).

Multibacillary leprosy should be treated with a combination of rifampicin, dapsone and clofazimine p. 500 for at least 2 years. Treatment should be continued unchanged during both type I (reversal) or type II (erythema nodosum leprosum) reactions. During reversal reactions neuritic pain or weakness can herald the rapid onset of permanent nerve damage. Treatment with prednisolone p. 585 should be instituted at once. Mild type II reactions may respond to aspirin. Severe type II reactions may require corticosteroids; thalidomide p. 798 [unlicensed] is also useful in patients who have become corticosteroid-dependent, but it should be used only under specialist supervision. Thalidomide is teratogenic and, therefore, contra-indicated in pregnancy; it must not be given to women of child-bearing potential unless they comply with a pregnancy prevention programme. Increased doses of clofazimine are also useful.

Paucibacillary leprosy should be treated with rifampicin and dapsone for 6 months. If treatment is interrupted the regimen should be recommenced where it was left off to complete the full course. Neither the multibacillary nor the paucibacillary antileprosy regimen is sufficient to treat tuberculosis.

2.1 Anthrax

Inhalation or gastro-intestinal anthrax should be treated initially with either ciprofloxacin [unlicensed indication] or doxycycline [unlicensed indication] for 7 days. Treatment may be switched to amoxicillin if the infecting strain is susceptible. Treatment may need to be extended to 60 days if exposure is due to aerosol. A combination of antibacterials for 14 days is recommended for cutaneous anthrax with systemic features, extensive oedema, or lesions of the head or neck.

Ciprofloxacin or doxycycline may be given for post-exposure prophylaxis. If exposure is confirmed, antibacterial prophylaxis should continue for 60 days. Antibacterial prophylaxis may be switched to amoxicillin after 10–14 days if the strain of B. anthracis is susceptible. Vaccination against anthrax may allow the duration of antibacterial prophylaxis to be shortened.
ANTIMYCOBACTERIALS

Clofazimine

INDICATIONS AND DOSE
Multibacillary leprosy in combination with rifampicin and dapsone (3-drug regimen)

BY MOUTH
Adult:
- Adult: 300 mg once a month, (supervised administration) and 50 mg daily, (self-administered), alternatively 100 mg once daily on alternate days, (self-administered)
Lepromatous lepra reactions

BY MOUTH
Adult: Increased to 300 mg daily for max. 3 months
Severe type II (erythema nodosum leprosum) reactions

BY MOUTH
Adult: Increased to 100 mg 3 times a day for the first month (with subsequent reductions), may take 4–6 weeks to attain full effect

CAUTIONS
Avoid if persistent abdominal pain and diarrhoea - may discolour soft contact lenses

SIDE-EFFECTS
Abdominal pain - acne-like eruptions - anorexia - bowel obstruction - brownish-black discoloration of lesions and skin including areas exposed to light - dimmed vision - dry eyes - dry skin - elevation of blood sugar - eosinophilic enteropathy - headache - lymphenadenopathy - macular corneal pigmentation - nausea - photosensitivity - pruritus - rash - red discoloration of body fluids - red discoloration of foaecees - red discoloration of urine - reversible hair discoloration - splenic infarction - subepithelial corneal pigmentation - tiredness - vomiting (hospitalise if persistent) - weight loss

PREGNANCY
Use with caution.

BREAST FEEDING
May alter colour of milk; skin discoloration of infant.

HEPATIC IMPAIRMENT
Use with caution.

RENAL IMPAIRMENT
Use with caution.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule

2.3 Lyme disease

Lyme disease

Lyme disease should generally be treated by those experienced in its management. Doxycycline p. 496, amoxicillin p. 482 [unlicensed indication] or cefuroxime p. 460 (as cefuroxime axetil) are the antibiotics of choice for early Lyme disease or Lyme arthritis. If these antibacterials are contra-indicated, a macrolide (e.g. clarithromycin p. 470) can be used for early Lyme disease. Intravenous administration of ceftriaxone p. 459, cefotaxime p. 457, or benzylpenicillin sodium p. 480 is recommended for Lyme disease associated with cardiac or neurological complications. The duration of treatment is usually 2–4 weeks; Lyme arthritis may require further treatment.
2.4 Methicillin-resistant staphylococcus aureus

MRSA

Infection from *Staphylococcus aureus* strains resistant to meticillin (now discontinued) (methicillin-resistant *Staph. aureus*, MRSA) and to flucloxacillin p. 486 can be difficult to manage. Treatment is guided by the sensitivity of the infecting strain.

Rifampicin p. 508 or fusidic acid p. 463 should not be used alone because resistance may develop rapidly. A tetracycline alone or a combination of rifampicin and fusidic acid can be used for skin and soft-tissue infections caused by MRSA; clindamycin p. 467 alone is an alternative. A glycopeptide (e.g. vancomycin p. 465) can be used for severe skin and soft-tissue infections associated with MRSA; if a glycopeptide is unsuitable, linezolid p. 477 can be used on expert advice. As linezolid is not active against Gram-negative organisms, it can be used for mixed skin and soft-tissue infections only when other treatments are not available; linezolid must be given with other antibacterials if the infection also involves Gram-negative organisms. A combination of a glycopeptide and fusidic acid or a glycopeptide and rifampicin can be considered for skin and soft-tissue infections that have failed to respond to a single antibacterial.

Tigecycline p. 466 and daptomycin p. 468 are licensed for the treatment of complicated skin and soft-tissue infections involving MRSA.

A tetracycline or clindamycin can be used for bronchiectasis caused by MRSA. A glycopeptide can be used for pneumonia associated with MRSA; if a glycopeptide is unsuitable, linezolid can be used on expert advice. Linezolid must be given with other antibacterials if the infection also involves Gram-negative organisms. A tetracycline can be used for urinary-tract infections caused by MRSA; trimethoprim p. 462 or nitrofurantoin p. 512 are alternatives. A glycopeptide can be used for urinary-tract infections that are severe or resistant to other antibacterials.

A glycopeptide can be used for septicaemia associated with MRSA.

See the management of endocarditis, osteomyelitis, or septic arthritis associated with MRSA.

Prophylaxis with vancomycin p. 465 or teicoplanin p. 464 (alone or in combination with another antibacterial active against other pathogens) is appropriate for patients undergoing surgery if:

- there is a history of MRSA colonisation or infection without documented eradication;
- there is a risk that the patient’s MRSA carriage has recurred;
- the patient comes from an area with a high prevalence of MRSA.

See eradication of nasal carriage of MRSA in Nose p. 980.

There are two regimens recommended for the treatment of tuberculosis in the UK; variations occur in other countries. Either the unsupervised regimen or the supervised regimen should be used; the two regimens should not be used concurrently. Compliance with therapy is a major determinant of its success.

**Initial phase**

The concurrent use of 4 drugs during the initial phase is designed to reduce the bacterial population as rapidly as possible and to prevent the emergence of drug-resistant bacteria. The drugs are best given as combination preparations unless one of the components cannot be given because of resistance or intolerance. The treatment of choice for the initial phase is the daily use of isoniazid p. 506, rifampicin p. 508, pyrazinamide p. 506 and ethambutol hydrochloride p. 505. Treatment should be started without waiting for culture results if clinical features or histology results are consistent with tuberculosis; treatment should be continued even if initial culture results are negative. The initial phase drugs should be continued for 2 months. Where a positive culture for *M. tuberculosis* has been obtained, but susceptibility results are not available after 2 months, treatment with rifampicin, isoniazid, pyrazinamide and ethambutol hydrochloride should be continued until full susceptibility is confirmed, even if this is for longer than 2 months.

Streptomycin p. 451 is rarely used in the UK but it may be used in the initial phase of treatment if resistance to isoniazid has been established before therapy is commenced.

**Continuation phase**

After the initial phase, treatment is continued for a further 4 months with isoniazid with rifampicin p. 510 (preferably given as a combination preparation). Longer treatment is necessary for meningitis, direct spinal cord involvement, and for resistant organisms which may also require modification of the regimen.

**Unsupervised treatment**

The unsupervised treatment regimen should be used for patients who are likely to take antituberculous drugs reliably without supervision. Patients who are unlikely to comply with daily administration of antituberculous drugs should be treated with the regimen described under Supervised Treatment.

**Pregnancy and breast-feeding**

The standard unsupervised 6-month treatment regimen may be used during pregnancy. Streptomycin should not be given in pregnancy.

The standard unsupervised 6-month treatment regimen may be used during breast-feeding.

**Supervised treatment**

Drug administration needs to be fully supervised (directly observed therapy, DOT) in patients who cannot comply reliably with the treatment regimen. These patients are given isoniazid, rifampicin, pyrazinamide and ethambutol hydrochloride (or streptomycin) 3 times a week under supervision for the first 2 months followed by isoniazid and rifampicin 3 times a week for a further 4 months.

**Immunocompromised patients**

Multi-resistant *Mycobacterium tuberculosis* may be present in immunocompromised patients. The organism should always be cultured to confirm its type and drug sensitivity. Confirmed *M. tuberculosis* infection sensitive to first-line drugs should be treated with a standard 6-month regimen; after completing treatment, patients should be closely monitored. The regimen may need to be modified if
### Recommended dosage for standard unsupervised 6-month treatment

#### 2-month initial phase

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Details</th>
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</table>
| **Rifater**<sup>®</sup> (isoniazid, pyrazinamide and rifampicin) | - Adult body-weight up to 40 kg: 3 tablets daily  
- Adult body-weight 40-49 kg: 4 tablets daily  
- Adult body-weight 50-64 kg: 5 tablets daily  
- Adult body-weight 65 kg and above: 6 tablets daily |
| Ethambutol hydrochloride       | - Adult: 15 mg/kg once daily                                                   |

#### 4-month continuation phase following initial treatment with Rifater<sup>®</sup> and ethambutol

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Details</th>
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</table>
| Isoniazid with rifampicin     | - Adult body-weight up to 50 kg: 450/300 mg daily, use Rifinah<sup>®</sup> 150/100 Tablets  
- Adult body-weight 50 kg and above: 600/300 mg daily, use Rifinah<sup>®</sup> 300/150 Tablets |

*or* (if combination preparations not appropriate):

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Details</th>
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</table>
| Isoniazid (for 6 months)      | - Child: 10 mg/kg once daily (max. 300 mg)  
- Adult: 300 mg daily |
| Rifampicin (for 6 months)     | - Child body-weight up to 50 kg: 15 mg/kg once daily (max. 450 mg)  
- Child body-weight 50 kg and above: 15 mg/kg daily (max. 600 mg)  
- Adult body-weight up to 50 kg: 450 mg daily  
- Adult body-weight 50 kg and above: 600 mg daily |
| Pyrazinamide (for 2-month initial phase only) | - Child body-weight up to 50 kg: 35 mg/kg once daily (max. 1.5 g)  
- Child body-weight 50 kg and above: 35 mg/kg once daily (max. 2 g)  
- Adult body-weight up to 50 kg: 1.5 g once daily  
- Adult body-weight 50 kg and above: 2 g once daily |
| Ethambutol hydrochloride (for 2-month initial phase only) | - Child: 20 mg/kg once daily  
- Adult: 15 mg/kg once daily |

### Recommended dosage for intermittent supervised 6-month treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Details</th>
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| Isoniazid (for 6 months)      | - Child: 15 mg/kg (max. 900 mg) 3 times a week  
- Adult: 15 mg/kg (max. 900 mg) 3 times a week |
| Rifampicin (for 6 months)     | - Child: 15 mg/kg (max. 900 mg) 3 times a week  
- Adult: 600-900 mg 3 times a week |
| Pyrazinamide (for 2-month initial phase only) | - Child body-weight up to 50 kg: 50 mg/kg 3 times a week (max. 2 g 3 times a week)  
- Child body-weight 50 kg and above: 50 mg/kg 3 times a week (max. 2.5 g 3 times a week)  
- Adult body-weight up to 50 kg: 2 g 3 times a week  
- Adult body-weight 50 kg and above: 2.5 g 3 times a week |
| Ethambutol hydrochloride (for 2-month initial phase only) | - Child: 30 mg/kg 3 times a week  
- Adult: 30 mg/kg 3 times a week |

Infection is caused by resistant organisms, and specialist advice is needed. Specialist advice should be sought about tuberculosis treatment or chemoprophylaxis in a HIV-positive individual; care is required in choosing the regimen and in avoiding potentially serious interactions. Starting antiretroviral treatment in the first 2 months of antituberculosis treatment increases the risk of immune reconstitution syndrome. Infection may also be caused by other mycobacteria e.g. *M. avium* complex in which case specialist advice on management is needed.

### Corticosteroids

In meningeal or pericardial tuberculosis, a corticosteroid should be started at the same time as antituberculosis therapy.

### Prevention of tuberculosis

Some individuals may develop tuberculosis owing to reactivation of previously latent disease. Chemoprophylaxis may be required in those who have evidence of latent tuberculosis and are receiving treatment with immunosuppressants (including cytotoxics and possibly long-term treatment with systemic corticosteroids). In these cases, chemoprophylaxis involves use of either isoniazid alone for 6 months or of isoniazid and rifampicin for 3 months; longer chemoprophylaxis is not recommended.

See prevention of tuberculosis in susceptible close contacts or those who have become tuberculin-positive. See advice on immunisation against tuberculosis.

#### Treatment failure

Major causes of treatment failure are incorrect prescribing by the physician and inadequate compliance by the patient. Monthly tablet counts and urine examination (rifampicin imparts an orange-red coloration) may be useful indicators of compliance with treatment. Avoid both excessive and inadequate dosage. Treatment should be supervised by a specialist physician.

### Antituberculosis drugs

Isoniazid is cheap and highly effective. Like rifampicin it should always be included in any antituberculous regimen unless there is a specific contra-indication.

Rifampicin, a rifamycin, is a key component of any antituberculous regimen. Like isoniazid it should always be included unless there is a specific contra-indication.

During the first two months (‘initial phase’) of rifampicin administration transient disturbance of liver function with elevated serum transaminases is common but generally does not require interruption of treatment. Occasionally more serious liver toxicity requires a change of treatment particularly in those with pre-existing liver disease.

On intermittent treatment six toxicity syndromes have been recognised—influenza-like, abdominal, and respiratory symptoms, shock, renal failure, and thrombocytopenic purpura—and can occur in 20 to 30% of patients.
Rifabutin, another rifamycin, is indicated for prophylaxis against *M. avium* complex infections in patients with a low CD4 count; it is also licensed for the treatment of non-tuberculous mycobacterial disease and pulmonary tuberculosis.

Pyrazinamide is a bactericidal drug only active against intracellular dividing forms of *Mycobacterium tuberculosis*; it exerts its main effect only in the first two or three months. It is particularly useful in tuberculous meningitis because of good meningeal penetration. It is not active against *M. bovis*.

Ethambutol hydrochloride is included in a treatment regime if isoniazid resistance is suspected; it can be omitted if the risk of resistance is low.

Streptomycin [unlicensed] is now rarely used in the UK except for resistant organisms.

Drug-resistant tuberculosis should be treated by a specialist physician with experience in such cases, and where appropriate facilities for infection-control exist. Second-line drugs available for infections caused by resistant organisms, or when first-line drugs cause unacceptable side-effects, include aminosalicylic acid below, amikacin p. 450, capreomycin p. 504, cyclodexine p. 594, newer macrolides (e.g. azithromycin p. 469 and clarithromycin p. 470), moxifloxacin p. 492 and prothionamide (prothionamide; no longer on UK market).

Bedaquiline below and delamanid p. 504 are licensed for the treatment of multiple-drug resistant pulmonary tuberculosis. Bedaquiline has a long half-life.

Management of tuberculosis in children

Children are given isoniazid, rifampicin, pyrazinamide, and ethambutol hydrochloride for the first 2 months followed by isoniazid and rifampicin during the next 4 months.

However, care is needed in young children receiving ethambutol hydrochloride because of the difficulty in testing eyesight and in obtaining reports of visual symptoms.

**Drugs used for Tuberculosis not listed below; Streptomycin, p. 451**

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**ANTIMYCOBACTERIALS**

**Aminosalicylic acid**

**INDICATIONS AND DOSE**

Multiple-drug resistant tuberculosis, in combination with other drugs

**BY MOUTH**

- Adult: 4 g every 8 hours for a usual treatment duration of 24 months; maximum 12 g per day

Desensitisation regimen

**BY MOUTH**

- Adult: (consult product literature)

- **CAUTIONS** Peptic ulcer
  - **SIDE-EFFECTS** Common or very common Abdominal pain - bloating - diarrhea - nausea - rash - vestibular syndrome - vomiting
  - **Uncommon** Anorexia
  - **Rare** Gastrointestinal bleeding - hypothyroidism - jaundice - malabsorption syndrome - metallic taste - peptic ulcer - urticaria
  - **Very rare** Agranulocytosis - anaemia - crystalluria - dizziness - headache - hypoglycaemia - leucopenia - methemoglobinemia - peripheral neuropathy - purpura - tendon pain - thrombocytopenia - visual abnormalities - weight loss
  - **Frequency not known** Hepatitis - hypersensitivity
information available. Avoid concomitant use of hepatotoxic drugs unless essential.

- **RENAL IMPAIRMENT** Manufacturer advises caution if eGFR less than 30 mL/minute/1.73 m².

- **MONITORING REQUIREMENTS**
  - Determine serum potassium, calcium, and magnesium before starting treatment (correct if abnormal)—remeasure if QT prolongation occurs during treatment.
  - Obtain ECG before starting treatment, and then at least monthly during treatment or more frequently if concomitant use with other drugs known to prolong the QT interval.
  - Monitor liver function before starting treatment and then at least monthly during treatment—discontinue treatment if severe abnormalities in liver function tests.

- **PATIENT AND CARER ADVICE** Dizziness may affect performance of skilled tasks (e.g. driving)

- **Missed doses** If a dose is missed during the first two weeks of treatment, the missed dose should not be taken and the next dose should be taken at the usual time; if a dose is missed during weeks 3–24 of treatment, the missed dose should be taken as soon as possible and then the usual regimen resumed.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**

  | CAUTIONARY AND ADVISORY LABELS 4, 8, 21 |
  | Sirturo (Janssen-Cilag Ltd) ▼ |
  | Bedaquiline (as Bedaquiline fumarate) 100 mg Sirturo 100mg tablets | 188 tablet (£0.07) £18,700.00

### Capreomycin

**INDICATIONS AND DOSE**

Tuberculosis resistant to first-line drugs in combination with other drugs

**BY DEEP INTRAMUSCULAR INJECTION**

- Adult: 1 g daily (max. per dose 20 mg/kg) for 2–4 months, then reduced to 1 g 2–3 times a week

- **CAUTIONS** Auditory impairment

- **INTERACTIONS** → Appendix 1 (capreomycin).

- **SIDE-EFFECTS** Induration at injection site — changes in liver function tests — electrolyte disturbances — hearing loss with tinnitus and vertigo — hypersensitivity reactions — leucocytosis — leucopenia — nephrotoxicity — neuromuscular block after large doses — pain at injection site — rashes — thrombocytopenia — urticaria

- **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk—teratogenic in animal studies.

- **BREAST FEEDING** Manufacturer advises caution—no information available.

- **HEPATIC IMPAIRMENT** Use with caution.

- **RENAL IMPAIRMENT** Reduce dose—consult product literature. Nephrotoxic; otoxic.

- **MONITORING REQUIREMENTS** Monitor renal, hepatic, auditory, and vestibular function and electrolytes.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Powder for solution for injection**

  | CAPREOMYCIN (Non-proprietary) |
  | Capreomycin (as Capreomycin sulfate) 1 gram Capreomycin 1g powder for solution for injection vials | 1 vial (£0.07) £28.61

### Cycloserine

**INDICATIONS AND DOSE**

Tuberculosis resistant to first-line drugs, in combination with other drugs

**BY MOUTH**

- Adult: Initially 250 mg every 12 hours for 2 weeks, then increased if necessary up to 500 mg every 12 hours, dose to be increased according to blood concentration and response

**PHARMACOKINETICS**

Cycloserine penetrates the CNS.

- **CONTRA-INDICATIONS** Alcohol dependence - depression - epilepsy - psychotic states - severe anxiety

- **INTERACTIONS** → Appendix 1 (cycloserine).

- **SIDE-EFFECTS** Allergic dermatitis — changes in liver function tests — confusion — convulsions — depression — dizziness — drowsiness — headache — heart failure at high doses — megaloblastic anaemia — psychosis — rashes — tremor — vertigo

**SIDE-EFFECTS, FURTHER INFORMATION**

CNS toxicity Discontinue or reduce dose if symptoms of CNS toxicity occur.

Rashes or allergic dermatitis Discontinue or reduce dose if rashes or allergic dermatitis develops.

**PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk—crosses the placenta.

**BREAST FEEDING** Present in milk—amount too small to be harmful.

**RENAL IMPAIRMENT** Increase interval between doses if creatinine clearance less than 50 mL/minute. Monitor blood-cycloserine concentration if creatinine clearance less than 50 mL/minute.

**MONITORING REQUIREMENTS**

- Blood concentration monitoring required especially in renal impairment or if dose exceeds 500 mg daily or if signs of toxicity; blood concentration should not exceed 30 mg/ litre.

- Monitor haematological, renal, and hepatic function.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Capsule**

  | CAUTIONARY AND ADVISORY LABELS 2, 8 |
  | CYCLOSERINE (Non-proprietary) |
  | Cycloserine 250 mg Cycloserine 250mg capsules | 100 capsule (£0.06) £402.63 DT price = £402.63

### Delamanid

**INDICATIONS AND DOSE**

Multiple-drug resistant pulmonary tuberculosis, in combination with other drugs

**BY MOUTH**

- Adult: 100 mg twice daily for 24 weeks, continue appropriate combination therapy after delamanid

- **CONTRA-INDICATIONS** QTc interval more than 500 milliseconds (derived using Fridericia’s formula) – serum albumin less than 28 g/litre

- **CAUTIONS** Risk factors for QT interval prolongation (e.g. electrolyte disturbances, acute myocardial infarction, heart failure with reduced left ventricular ejection fraction, severe hypertension, left ventricular hypertrophy, bradycardia, congenital long QT syndrome, history of symptomatic arrhythmias)

- **INTERACTIONS** → Appendix 1 (delamanid).
Caution when concomitant use with other drugs known to prolong the QT interval. Contra-indicated with concomitant use of potent CYP3A4 inducers.

- **SIDE-EFFECTS**
  - **Common or very common** Abdominal pain · acne · agitation · anxiety · chest pain · cough · decreased appetite · depression · dermatitis · dyspepsia · dyspnoea · earache · haemoptysis · headache · hyperhidrosis · hyperlipidaemia · hypertension · hypokalaemia · hypotension · insomnia · malaise · nausea · oropharyngeal pain · osteoarthritis · palpitation · peripheral neuropathy · photophobia · psychiatric disorder · QT interval prolongation · reticulocytosis · tinnitus · tremor · vomiting
  - **Uncommon** Arrhythmias · balance disorder · dehydration · dysphagia · herpes zoster · hypocalcaemia · leucopenia · nocturia · rash · thrombocytopenia · urinary retention

- **CONCEPTION AND CONTRACEPTION** Effective contraception required during treatment.

- **PREGNANCY** Manufacturer advises avoid—toxicity in animal studies.

- **BREAST FEEDING** Manufacturer advises avoid in milk in animal studies.

- **HEPATIC IMPAIRMENT** Manufacturer advises avoid in moderate to severe impairment.

- **RENAL IMPAIRMENT** Manufacturer advises avoid in severe impairment—no information available.

- **MONITORING REQUIREMENTS**
  - Monitor serum albumin and electrolytes before starting treatment and then during treatment—discontinue treatment if serum albumin less than 28 g/litre.
  - Obtain ECG before starting treatment and then monthly during treatment (more frequently if serum albumin 28–34 g/litre, or if concomitant use of potent CYP3A4 inhibitors, or if risk factors for QT interval prolongation, or if QTc interval 450–500 milliseconds in men or 470–500 milliseconds in women)—discontinue treatment if QTc interval more than 500 milliseconds (derived using Friderica’s formula).

- **HANDLING AND STORAGE** Dispense in original container (contains desiccant).

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**
  - **CAUTIONARY AND ADVISORY LABELS** 8, 21
  - Deltyba (Otsuka Novel Products GmbH) ▼ Delmaranid 50 mg Deltyba 50mg tablets | 48 tablet | £1,250.00

**Ethambutol hydrochloride**

### INDICATIONS AND DOSE

Tuberculosis, in combination with other drugs (standard unsupervised 6-month treatment)

**BY MOUTH**
- Child: 20 mg/kg once daily for 2 months (initial phase)
- Adult: 15 mg/kg once daily for 2 months (initial phase)

Tuberculosis, in combination with other drugs (intermittent supervised 6-month treatment) (under expert supervision)

**BY MOUTH**
- Child: 30 mg/kg 3 times a week for 2 months (initial phase)
- Adult: 30 mg/kg 3 times a week for 2 months (initial phase)

**CONTRA-INDICATIONS** Optic neuritis · poor vision

**CAUTIONS** Elderly · young children

**CAUTIONS, FURTHER INFORMATION**

**Understanding warnings** Patients who cannot understand warnings about visual side-effects should, if possible, be given an alternative drug. In particular, ethambutol should be used with caution in children until they are at least 5 years old and capable of reporting symptomatic visual changes accurately.

- **INTERACTIONS** → Appendix 1 (ethambutol).

- **SIDE-EFFECTS**
  - **Rare** Pruritus · rash · thrombocytopenia · urticaria
  - **Frequency not known** Colour blindness · loss of visual acuity · optic neuritis · peripheral neuritis · red/green colour blindness · restriction of visual fields · visual disturbances

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - **Ocular toxicity** Ocular toxicity is more common where excessive dosage is used or if the patient’s renal function is impaired. Early discontinuation of the drug is almost always followed by recovery of eyesight.

- **PREGNANCY** Not known to be harmful.

- **BREAST FEEDING** Amount too small to be harmful.

- **RENAL IMPAIRMENT** Risk of optic nerve damage. Should preferably be avoided in patients with renal impairment.

  If creatinine clearance less than 30 mL/minute, monitor plasma-ethambutol concentration.

  - In adults If creatinine clearance less than 30 mL/minute, use 15–25 mg/kg (max. 2.5 g) 3 times a week.
  - In children If creatinine clearance less than 30 mL/minute/1.73 m², use 15–25 mg/kg (max. 2.5 g) 3 times a week.

- **MONITORING REQUIREMENTS**
  - 'Peak' concentration (2–2.5 hours after dose) should be 2–6 mg/litre (7–22 micromol/litre); 'trough' (pre-dose) concentration should be less than 1 mg/litre (4 micromol/litre).
  - Renal function should be checked before treatment.
  - Visual acuity should be tested by Snellen chart before treatment with ethambutol.
  - In young children, routine ophthalmological monitoring recommended.

- **PATIENT AND CARER ADVICE**
  - Ocular toxicity The earliest features of ocular toxicity are subjective and patients should be advised to discontinue therapy immediately if they develop deterioration in vision and promptly seek further advice.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

  **Tablet**
  - **CAUTIONARY AND ADVISORY LABELS** 8
  - ETHAMBUTOL HYDROCHLORIDE (Non-proprietary)
    - Ethambutol hydrochloride 100 mg Ethambutol 100mg tablets | 56 tablet | £11.52 DT price = £11.52
    - Ethambutol hydrochloride 400 mg Ethambutol 400mg tablets | 56 tablet | £42.74 DT price = £42.74
  - Also available in combination with isoniazid, pyrazinamide and rifampicin, p. 509
Isoniazid

INDICATIONS AND DOSE
Tuberculosis, in combination with other drugs (standard unsupervised 6-month treatment)

BY MOUTH OR BY INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INJECTION
- Child: 10 mg/kg once daily (max. per dose 300 mg) for 6 months (initial and continuation phases)
- Adult: 300 mg daily for 6 months (initial and continuation phases)

Tuberculosis, in combination with other drugs (intermittent supervised 6-month treatment) (under expert supervision)

BY MOUTH OR BY INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INJECTION
- Child: 15 mg/kg 3 times a week (max. per dose 900 mg) for 6 months (initial and continuation phases)
- Adult: 15 mg/kg 3 times a week (max. per dose 900 mg) for 6 months (initial and continuation phases)

Prevention of tuberculosis in susceptible close contacts or those who have become tuberculin positive

BY MOUTH OR BY INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INJECTION
- Child 1 month–11 years: 10 mg/kg daily (max. per dose 300 mg) for 6 months, alternatively 10 mg/kg daily (max. per dose 300 mg) for 3 months, to be taken in combination with rifampicin
- Child 12–17 years: 300 mg daily for 6 months, alternatively 300 mg daily for 3 months, to be taken in combination with rifampicin
- Adult: 300 mg daily for 6 months, alternatively 300 mg daily for 3 months, to be taken in combination with rifampicin

CONTRA-INDICATIONS Drug-induced liver disease

CAUTIONS Acute porphyrias p. 864 - alcohol dependence - diabetes mellitus - epilepsy - history of psychosis - HIV infection - malnutrition - slow acetylator status (increased risk of side-effects)

CAUTIONS, FURTHER INFORMATION
Peripheral neuropathy Peripheral neuropathy is more likely to occur where there are pre-existing risk factors such as diabetes, alcohol dependence, chronic renal failure, pregnancy, malnutrition and HIV infection. In patients at increased risk of peripheral neuropathy, pyridoxine hydrochloride p. 882 should be given prophylactically from the start of treatment.

INTERACTIONS → Appendix 1 (isoniazid).
When used with tyramine or histamine rich foods, tachycardia, palpitation, hypotension, flushing, headache, dizziness, and sweating reported.

SIDE-EFFECTS
- Common or very common Peripheral neuropathy
- Rare Hepatitis - psychotic episodes

SIDE-EFFECTS, FURTHER INFORMATION
Hepatitis Hepatitis more common in those aged over 35 years.

PREGNANCY Not known to be harmful; prophylactic pyridoxine recommended.

- BREAST FEEDING Theoretical risk of convulsions and neuropathy; prophylactic pyridoxine advisable in mother. In breast-feeding, monitor infant for possible toxicity.
- HEPATIC IMPAIRMENT Use with caution. In patients with pre-existing liver disease or hepatic impairment monitor liver function regularly and particularly frequently in the first 2 months.
- RENAL IMPAIRMENT Risk of ototoxicity and peripheral neuropathy; prophylactic pyridoxine hydrochloride p. 882 recommended.
- MONITORING REQUIREMENTS
  - Renal function should be checked before treatment.
  - Hepatic function should be checked before treatment. If there is no evidence of liver disease (and pre-treatment liver function is normal), further checks are only necessary if the patient develops fever, malaise, vomiting, jaundice or unexplained deterioration during treatment.
  - Those with alcohol dependence should have frequent checks of hepatic function, particularly in the first 2 months.
- PRESCRIBING AND DISPENSING INFORMATION
  - In children In general, doses should be rounded up to facilitate administration of suitable volumes of liquid or an appropriate strength of tablet. Doses may need to be recalculated to allow for weight gain in younger children.
- PATIENT AND CARER ADVICE
  - Medicines for Children leaflet: Isoniazid for latent tuberculosis www.medicinesforchildren.org.uk/isoniazid-for-latent-tuberculosis
  - Hepatic disorders Patients or their carers should be told how to recognise signs of liver disorder, and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop.
- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

Table

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<thead>
<tr>
<th>Tablet</th>
<th>CAUTIONARY AND ADVISORY LABELS 8, 22</th>
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<tbody>
<tr>
<td>ISONIAZID (Non-proprietary)</td>
<td></td>
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<tr>
<td>Isoniazid 50 mg</td>
<td>Isoniazid 50mg tablets</td>
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<td>Isoniazid 100 mg</td>
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Solution for injection

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<tr>
<th>ISONIAZID (Non-proprietary)</th>
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<tr>
<td>Isoniazid 25 mg per 1 ml</td>
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Also available in combination with pyrazinamide and rifampicin, p. 510 - rifampicin, p. 510

Pyrazinamide

INDICATIONS AND DOSE
Tuberculosis in combination with other drugs (standard unsupervised 6-month treatment)

BY MOUTH
- Child (body-weight up to 50 kg): 35 mg/kg once daily for 2 months (initial phase); maximum 1.5 g per day
- Child (body-weight 50 kg and above): 35 mg/kg once daily for 2 months (initial phase); maximum 2 g per day
- Adult (body-weight up to 50 kg): 1.5 g once daily for 2 months (initial phase)
- Adult (body-weight 50 kg and above): 2 g once daily for 2 months (initial phase)
Tuberculosis in combination with other drugs (intermittent supervised 6-month treatment) (under expert supervision)

BY MOUTH
- Child (body-weight up to 50 kg): 50 mg/kg 3 times a week (max. per dose 2 g 3 times a week) for 2 months (initial phase)
- Child (body-weight 50 kg and above): 50 mg/kg 3 times a week (max. per dose 2.5 g 3 times a week) for 2 months (initial phase)
- Adult (body-weight up to 50 kg): 2 g 3 times a week for 2 months (initial phase)
- Adult (body-weight 50 kg and above): 2.5 g 3 times a week for 2 months (initial phase)

RENAL IMPAIRMENT
- Reduce dose if eGFR less than 30 mL/minute/1.73 m².
- Use half normal dose if eGFR less than 20 mL/minute/1.73 m².
- Use alternative family planning advice should be offered.
- Discontinue if serious side-effects develop.

INTERACTIONS
- Rifabutin induces hepatic enzymes and the effectiveness of hormonal contraceptives is reduced; alternative family planning advice should be offered.
- No information available.
- No information available.

SIDE-EFFECTS
- Rare
- Frequency not known
- Chest pain
- Dyspnoea
- Hepatitis
- Influenza-like symptoms
- No information available.

CONTRA-INDICATIONS
- No information available.

PATIENT AND CARER ADVICE
- Patients or their carers should be told how to recognise signs of liver disorder, and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

Tablet
- Pyrazinamide (Non-proprietary) Pyrazinamide 500 mg Pyrazinamide 500mg tablets | 30 tablet £38.34 | 50 tablet £52.25

Also available in combination with ethambutol with isoniazid and rifampicin, p. 509 · Isoniazid and rifampicin, p. 510

NITROIMIDAZO-OXAZOLE ANTIBACTERIALS

RIFAMYCINS

Rifabutin

INDICATIONS AND DOSE
- Prophylaxis of Mycobacterium avium complex infections in immuno-suppressed patients with low CD4 count

BY MOUTH
- Adult: 300 mg once daily, also consult product literature

Treatment of non-tuberculous mycobacterial disease, in combination with other drugs

BY MOUTH
- Adult: 450–600 mg once daily for up to 6 months after cultures negative

Treatment of pulmonary tuberculosis, in combination with other drugs

BY MOUTH
- Adult: 150–450 mg once daily for at least 6 months

CAUTIONS
- Acute porphyrias p. 864 · discolours soft contact lenses

INTERACTIONS
- Appendix 1 (rifamycins)

SIDE-EFFECTS
- Common or very common
- Anaemia, blood disorders, leucopenia, myalgia, nausea, pyrexia, rash, thrombocytopenia
- Uncommon
- Arthralgia, body secretions coloured orange-red, bronchospasm, corneal deposits, eosinophilia, hypersensitivity reactions, jaundice, raised liver enzymes, saliva coloured orange-red, skin coloured orange-red, urine coloured orange-red, uveitis (especially following high doses or concomitant use with drugs that increase plasma concentration), vomiting
- Rare
- Haemolysis
- Frequency not known
- Chest pain, dyspnoea, hepatitis, influenza-like symptoms

SIDE-EFFECTS, FURTHER INFORMATION
- Discontinue permanently if serious side-effects develop.

ALLERGY AND CROSS-SENSITIVITY
- Contra-indicated in patients with rifamycin hypersensitivity.

CONCEPTION AND CONTRACEPTION
- Important Rifabutin induces hepatic enzymes and the effectiveness of hormonal contraceptives is reduced; alternative family planning advice should be offered.

PREGNANCY
- No information available.

BREAST FEEDING
- No information available.

HEPATIC IMPAIRMENT
- Reduce dose in severe impairment.
- In patients with pre-existing liver disease or hepatic impairment monitor liver function regularly and particularly frequently in the first 2 months; blood counts should also be monitored in these patients.

RENAL IMPAIRMENT
- Use half normal dose if eGFR less than 30 mL/minute/1.73 m².

MONITORING REQUIREMENTS
- Those with alcohol dependence should have frequent checks of hepatic function, particularly in the first 2 months; blood counts should also be monitored in these patients.
Blood counts should be monitored on prolonged therapy.

Hepatic function should be checked before treatment. If increase gradually.

Adult (body-weight 50 kg and above):

\[ \text{Rifabutin 150 mg} \]

\[ \text{Capsule} \]

CAUTIONARY AND ADVISORY LABELS 8, 14

Mycobutin (Pfizer Ltd)

rifabutin 150 mg Mycobutin 150mg capsules | 30 capsule £30.38

Prevention of tuberculosis in susceptible close contacts or those who have become tuberculin positive, in combination with isoniazid

**BY MOUTH**

- Child 1 month-11 years (body-weight up to 50 kg): 15 mg/kg daily for 3 months; maximum 450 mg per day
- Child 1 month-11 years (body-weight 50 kg and above): 15 mg/kg daily for 3 months; maximum 600 mg per day
- Child 12-17 years (body-weight up to 50 kg): 450 mg daily for 3 months
- Adult (body-weight up to 50 kg): 450 mg daily for 3 months
- Adult (body-weight 50 kg and above): 600 mg daily for 3 months

Prevention of tuberculosis in susceptible close contacts or those who have become tuberculin positive, who are isoniazid-resistant

**BY MOUTH**

- Child 1 month-11 years (body-weight up to 50 kg): 15 mg/kg daily for 6 months; maximum 450 mg per day
- Child 1 month-11 years (body-weight 50 kg and above): 15 mg/kg daily for 6 months; maximum 600 mg per day
- Child 12-17 years (body-weight up to 50 kg): 450 mg daily for 6 months
- Child 12-17 years (body-weight 50 kg and above): 600 mg daily for 6 months

Prevention of tuberculosis in susceptible close contacts or those who have become tuberculin positive, under 35 years

**BY MOUTH**

- Adult 18–34 years (body-weight up to 50 kg): 450 mg daily for 6 months
- Adult 18–34 years (body-weight 50 kg and above): 600 mg daily for 6 months

Prevention of secondary case of Haemophilus influenzae type b disease

**BY MOUTH**

- Child 1-2 months: 10 mg/kg once daily for 4 days
- Child 3 months-11 years: 20 mg/kg once daily (max. per dose 600 mg) for 4 days
- Child 12-17 years: 600 mg once daily for 4 days
- Adult: 600 mg once daily for 4 days

Prevention of secondary case of meningococcal meningitis

**BY MOUTH**

- Child 1-11 months: 5 mg/kg every 12 hours for 2 days
- Child 1-11 years: 10 mg/kg every 12 hours (max. per dose 600 mg), for 2 days
- Child 12-17 years: 600 mg every 12 hours for 2 days

Multibacillary leprosy in combination with dapson and clofazimine (3-drug regimen) Paucibacillary leprosy in combination with dapson (2-drug regimen)

**BY MOUTH**

- Adult (body-weight up to 35 kg): 450 mg once a month, supervised administration
- Adult (body-weight 35 kg and above): 600 mg once a month, supervised administration

**CONTRA-INDICATIONS** Acute porphyrias p. 864 jaundice

**CAUTIONS** Discourages soft contact lenses

**INTERACTIONS** Appendix 1 (rifampicins).

Rifampicin induces hepatic enzymes which accelerate the metabolism of several drugs including oestrogens,
corticosteroids, phenytoin, sulfonylureas, and anticoagulants.

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

Acute renal failure • adrenal insufficiency • alterations of liver function • anorexia • antibiotic-associated colitis • body secretions coloured orange-red • collapse and shock • diarrhoea • disseminated intravascular coagulation • drowsiness • eosinophilia • exfoliative dermatitis • flushing • gastro-intestinal symptoms • haemolytic anaemia • headache • influenza-like symptoms • shortness of breath • Stevens-Johnson syndrome • thrombocytopenic purpura • toxic epidermal necrolysis • urine coloured orange-red • urticaria • vomiting

**SPECIFIC SIDE-EFFECTS**

- With intravenous use
  Thrombophlebitis reported if infusion used for prolonged period

**SIDE-EFFECTS, FURTHER INFORMATION**

Discontinue permanently if serious side-effects develop.

**Intermittent therapy**

Side-effects that mainly occur with intermittent therapy include influenza-like symptoms (with chills, fever, dizziness, bone pain), respiratory symptoms (including shortness of breath), collapse and shock, haemolytic anaemia, thrombocytopenic purpura, disseminated intravascular coagulation, and acute renal failure

**ALLERGY AND CROSS-SENSITIVITY**

Contra-indicated in patients with rifampicin hypersensitivity.

**CONCEPTION AND CONTRACEPTION**

Important

Effectiveness of hormonal contraceptives is reduced and alternative family planning advice should be offered.

**PREGNANCY**

Manufacturers advise very high doses teratogenic in animal studies in first trimester; risk of neonatal bleeding may be increased in third trimester.

**BREAST FEEDING**

Amount too small to be harmful.

**HEPATIC IMPAIRMENT**

Impaired elimination. Avoid or do not exceed 8 mg/kg daily. In patients with pre-existing liver disease or hepatic impairment, monitor liver function regularly and particularly frequently in the first 2 months; blood counts should also be monitored in these patients.

**RENAL IMPAIRMENT**

- In children Use with caution if doses above 10 mg/kg daily.
- In adults Use with caution if dose above 600 mg daily.

**MONITORING REQUIREMENTS**

- Renal function should be checked before treatment.
- Hepatic function should be checked before treatment. If there is no evidence of liver disease (and pre-treatment liver function is normal), further checks are only necessary if the patient develops fever, malaise, vomiting, jaundice or unexplained deterioration during treatment. However, liver function should be monitored on prolonged therapy.
- Blood counts should be monitored in patients on prolonged therapy.
- Those with alcohol dependence should have frequent checks of hepatic function, particularly in the first 2 months. Blood counts should also be monitored in these patients.

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use in adults
  For intravenous infusion (Rifadin®), give intermittently in Glucose 5% or Sodium chloride 0.9%; reconstitute with solvent provided then dilute with 500 mL infusion fluid; give over 2–3 hours.

- With intravenous use in children
  Displacement value may be significant, consult local reconstitution guidelines; reconstitute with solvent provided. May be further diluted with Glucose 5% or Sodium chloride 0.9% to a final concentration of 1.2 mg/mL. Infuse over 2–3 hours.

**PRESCRIBING AND DISPENSING INFORMATION**

If treatment interruption occurs, re-introduce with low dosage and increase gradually.

- With oral use in children In general, doses should be rounded up to facilitate administration of suitable volumes of liquid or an appropriate strength of tablet. Doses may also need to be recalculated to allow for weight gain in younger children. Flavours of syrup may include raspberry.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Rifampicin for meningococcal prophylaxis www.medicinesforchildren.org.uk/rifampicin-for-meningococcal-prophylaxis


Soft contact lenses Patients or their carers should be advised that rifampicin discolours soft contact lenses.

Hepatic disorders Patients or their carers should be told how to recognise signs of liver disorder, and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Capsule**

CAUTIONARY AND ADVISORY LABELS 8, 14, 23

- **RIFAMPICIN (Non-proprietary)**
  - Rifampicin 150 mg Rifampicin 150mg capsules | 100 capsule £47.10
  - Rifampicin 300 mg Rifampicin 300mg capsules | 100 capsule £47.33–£48.00
  - Rifadin (Sanofi) Rifampicin 150 mg Rifampicin 150mg capsules | 100 capsule £18.32 DT price = £15.75
  - Rifampicin 300 mg Rifampicin 300mg capsules | 100 capsule £36.63 DT price = £48.00
  - Rimactane (Sandoz Ltd) Rifampicin 300 mg Rimactane 300mg capsules | 60 capsule £25.92

Oral suspension

CAUTIONARY AND ADVISORY LABELS 8, 14, 23

EXCIPIENTS: May contain Sucrose

- Rifadin (Sanofi) Rifampicin 20 mg per 1 ml Rifampicin 100mg/5ml syrup | 120 ml £3.56

Powder and solvent for solution for infusion

ELECTROLYTES: May contain Sodium

- Rifadin (Sanofi) Rifampicin 600 mg Rifadin 600mg powder and solvent for solution for infusion vials | 1 vial £7.67

**Ethambutol with isoniazid, pyrazinamide and rifampicin**

The properties listed below are those particular to the combination only. For the properties of the components please consider, ethambutol hydrochloride p. 505, isoniazid p. 506, pyrazinamide p. 508, rifampicin p. 506.

**INDICATIONS AND DOSE**

Initial treatment of tuberculosis

**BY MOUTH**

- Adult (body-weight 30–39 kg): 2 tablets daily for 2 months (initial phase)
## Isoniazid with rifampicin

The properties listed below are those particular to the combination only. For the properties of the components please consider, isoniazid p. 506, rifampicin p. 508.

### INICATIONS AND DOSE

**Treatment of tuberculosis (continuation phase)**

**BY MOUTH**

- Adult (body-weight up to 50 kg): 450/300 mg daily for 4 months (continuation phase after 2-month initial phase), use Rifater® 150/100 Tablets, preferably taken before breakfast.
- Adult (body-weight above 50 kg): 600/300 mg daily for 4 months (continuation phase after 2-month initial phase), use Rifater® 300/150 Tablets, preferably taken before breakfast.

### Dose equivalence and conversion

Tablet quantities refer to the number of Voractiv® Tablets which should be taken. Each Voractiv® Tablet contains ethambutol hydrochloride 275 mg, isoniazid 75 mg, pyrazinamide 400 mg and rifampicin 150 mg.

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### 2.6 Urinary tract infections

**Urinary-tract infections**

Urinary-tract infection is more common in women than in men; when it occurs in men there is frequently an underlying abnormality of the renal tract. Recurrent episodes of infection are an indication for radiological investigation especially in children in whom untreated pyelonephritis may lead to permanent kidney damage.

*Escherichia coli* is the most common cause of urinary-tract infection; *Staphylococcus saprophyticus* is also common in sexually active young women. Less common causes include Proteus and Klebsiella spp. *Pseudomonas aeruginosa* infections usually occur in the hospital setting and may be associated with functional or anatomical abnormalities of the renal tract. *Staphylococcus epidermidis* and *Enterococcus faecalis* infection may complicate catheterisation or instrumentation.

A specimen of urine should be collected for culture and sensitivity testing before starting antibacterial therapy:

- in men;
- in pregnant women;
- in children under 3 years of age;
- in patients with suspected upper urinary-tract infection;
- complicated infection, or recurrent infection;
- if resistant organisms are suspected;
- if urine dipstick testing gives a single positive result for leucocyte esterase or nitrite;
- if clinical symptoms are not consistent with results of dipstick testing.
Treatment should not be delayed while waiting for results. The antibacterial chosen should reflect current local bacterial sensitivity to antibacterials.

**Antibacterial therapy for lower urinary-tract infections**

Uncomplicated lower urinary-tract infections often respond to trimethoprim p. 462 or nitrofurantoin p. 512, or alternatively, amoxicillin p. 482, ampicillin p. 483 or oral cephalosporin.

Suggested duration of treatment is 7 days, but a short course (e.g. 3 days) is usually adequate for uncomplicated urinary-tract infections in women.

Infections caused by fully sensitive bacteria respond to amoxicillin.

Widespread bacterial resistance to ampicillin, amoxicillin, and trimethoprim has been reported. Alternatives for resistant organisms include co-amoxiclav p. 484 (amoxicillin with clavulanic acid), an oral cephalosporin, nitrofurantoin, pivmecillinam hydrochloride p. 486, or a quinolone.

Fosfomycin [unlicensed] can be used, on the advice of a microbiologist, for the treatment of uncomplicated lower urinary-tract infections caused by multiple-antibacterial resistant organisms when other antibacterials cannot be used.

Long-term low dose therapy may be required in selected patients to prevent recurrence of infection; indications include frequent relapses and significant kidney damage. Trimethoprim, nitrofurantoin and cefalexin p. 456 have been recommended for long-term therapy.

Methenamine hippurate below (hexamine hippurate) should not generally be used because it requires an acidic urine for its antimicrobial activity and it is ineffective for upper urinary-tract infections; it may, however, have a role in the prophylaxis and treatment of chronic or recurrent uncomplicated lower urinary-tract infections.

**Antibacterial therapy for upper urinary-tract infections**

Acute pyelonephritis can lead to septicemia and is treated initially by injection of a broad-spectrum antibacterial such as a cephalosporin (e.g. cefuroxime p. 460) or a quinolone if the patient is severely ill; gentamicin p. 450 can also be used.

Suggested duration of treatment is 10–14 days (longer treatment may be necessary in complicated pyelonephritis).

Prostatitis can be difficult to cure and requires treatment for several weeks with an antibacterial which penetrates prostatic tissue such as some of the quinolones (ciprofloxacin p. 490 or ofloxacin p. 494), or alternatively, trimethoprim.

Suggested duration of treatment is 28 days. Where infection is localised and associated with an indwelling catheter, a bladder instillation is often effective.

**Pregnancy**

Urinary-tract infection in pregnancy may be asymptomatic and requires prompt treatment to prevent progression to acute pyelonephritis. Penicillins and cephalosporins are suitable for treating urinary-tract infection during pregnancy. Nitrofurantoin may also be used but it should be avoided at term. Sulfonamides and quinolones should be avoided during pregnancy; trimethoprim should also preferably be avoided particularly in the first trimester.

**Renal impairment**

In renal failure antibacterials normally excreted by the kidney accumulate with resultant toxicity unless the dose is reduced. This applies especially to the aminoglycosides which should be used with great caution; tetracyclines, methenamine hippurate, and nitrofurantoin should be avoided altogether.

**Urinary-tract infections in children**

Urinary-tract infections in children require prompt antibacterial treatment to minimise the risk of renal scarring. Uncomplicated ‘lower’ urinary-tract infections in children over 3 months of age can be treated with trimethoprim, nitrofurantoin, a first generation cephalosporin (e.g. cefalexin), or amoxicillin for 3 days; children should be reassessed if they continue to be unwell 24–48 hours after the initial assessment. Amoxicillin should only be used if the organism causing the infection is sensitive to it.

Acute pyelonephritis in children over 3 months of age can be treated with a first generation cephalosporin or co-amoxiclav for 7–10 days. If the patient is severely ill, then the infection is best treated initially by injection of a broad-spectrum antibacterial such as cefotaxime or co-amoxiclav; gentamicin is an alternative.

Children under 3 months of age should be transferred to hospital and treated initially with intravenous antibacterial drugs such as ampicillin with gentamicin, or cefotaxime alone, until the infection responds; full doses of oral antibacterials are then given for a further period.

Recurrent episodes of infection are an indication for imaging tests. **Antibacterial prophylaxis** with low doses of trimethoprim or nitrofurantoin may be considered for children with recurrent infection, significant urinary-tract anomalies, or significant kidney damage.

**Methenamine hippurate**

(Hexamine hippurate)

**INDICATIONS AND DOSE**

**Prophylaxis and long-term treatment of chronic or recurrent uncomplicated lower urinary-tract infections**

**BY MOUTH**

- Adult: 1 g every 12 hours

**Prophylaxis and long-term treatment of chronic or recurrent uncomplicated lower urinary-tract infections in patients with catheters**

**BY MOUTH**

- Adult: 1 g every 8–12 hours

- CONTRA-INDICATIONS
  - Gout
  - Metabolic acidosis
  - Severe dehydration

- INTERACTIONS
  - → Appendix 1 (methenamine).
  - Caution—avoid concurrent administration with sulfonamides (risk of crystalluria) or urinary alkalinising agents.

- SIDE-EFFECTS
  - Bladder irritation
  - Gastro-intestinal disturbances
  - Rash

- PREGNANCY
  - Use with caution.

- BREAST FEEDING
  - Amount too small to be harmful.

- HEPATIC IMPAIRMENT
  - Avoid.

- RENAL IMPAIRMENT
  - Avoid if eGFR less than 10 mL/minute/1.73 m²—risk of hippurate crystalluria.

- LESS SUITABLE FOR PRESCRIBING
  - Methenamine (hexamine) hippurate should not generally be used because it requires an acidic urine for its antimicrobial activity and it is ineffective for upper urinary-tract infections; it may, however, have a role in the prophylaxis and treatment of chronic or recurrent uncomplicated lower urinary-tract infections. It is considered less suitable for prescribing.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.
Nitrofurantoin

**INDICATIONS AND DOSE**

**Acute uncomplicated urinary-tract infections**

- Child 3 months–11 years: 750 micrograms/kg 4 times a day for 3–7 days
- Child 12–17 years: 50 mg 4 times a day for 3–7 days
- Adult: 50 mg 4 times a day for 3–7 days

**Severe chronic recurrent urinary-tract infections**

- Child 12–17 years: 100 mg twice daily, dose to be taken with food
- Adult: 100 mg twice daily, dose to be taken with food

**Prophylaxis of urinary-tract infection (considered for recurrent infection, significant urinary-tract anomalies, or significant kidney damage)**

- Child 3 months–11 years: 1 mg/kg once daily, dose to be taken at night
- Child 12–17 years: 50–100 mg once daily, dose to be taken at night
- Adult: 50–100 mg once daily, dose to be taken at night

**Genito-urinary surgical prophylaxis**

- Adult: 100 mg twice daily on day of procedure and for 3 days after

**CONTRA-INDICATIONS**

Acute porphyrias (exclude if G6PD-deficient infants).

**CAUTIONS**

Anaemia · diabetes mellitus · electrolyte imbalance · folate deficiency · pulmonary disease · susceptibility to peripheral neuropathy · urine may be coloured yellow or brown · vitamin B deficiency

**INTERACTIONS**

Appendix 1 (nitrofurantoin).

**SIDE-EFFECTS**

- Rare: Agranulocytosis · aplastic anaemia · arthralgia · benign intracranial hypertension · blood disorders · cholestatic jaundice · erythema multiforme · exfoliative dermatitis · hepatitis · pancreatitis · thrombocytopenia · transient alopecia
- Frequency not known: Acute pulmonary reactions · anaphylaxis · angioedema · anorexia · chronic pulmonary reactions (pulmonary fibrosis reported; possible association with lupus erythematosus-like syndrome) · diarrhoea · hypersensitivity reactions · nausea · peripheral neuropathy · pruritus · rash · sialadenitis · urticaria · vomiting

**PREGNANCY**

Avoid at term—may produce neonatal haemolysis.

**BREAST FEEDING**

Avoid; only small amounts in milk but enough to produce haemolysis in G6PD-deficient infants.

**HEPATIC IMPAIRMENT**

Use with caution; cholestatic jaundice and chronic active hepatitis reported.

**RENAL IMPAIRMENT**

Risk of peripheral neuropathy; antibacterial efficacy depends on renal secretion of the drug into urinary tract.

In adults: Avoid if eGFR less than 45 mL/minute/1.73 m²; may be used with caution if eGFR 30–44 mL/minute/1.73 m² as a short-course only (3 to 7 days), to treat uncomplicated lower urinary-tract infection caused by suspected or proven multidrug resistant bacteria and only if potential benefit outweighs risk.

In children: Avoid if estimated glomerular filtration rate less than 45 mL/minute/1.73 m²; may be used with caution if estimated glomerular filtration rate 30–44 mL/minute/1.73 m² as a short-course only (3 to 7 days), to treat uncomplicated lower urinary-tract infection caused by suspected or proven multidrug resistant bacteria and only if potential benefit outweighs risk.

**MONITORING REQUIREMENTS**

On long-term therapy, monitor liver function and monitor for pulmonary symptoms, especially in the elderly (discontinue if deterioration in lung function).

**EFFECT ON LABORATORY TESTS**

False positive urinary glucose (if tested for reducing substances).

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Nitrofurantoin for urinary tract infections www.medicinesforchildren.org.uk/nitrofurantoin-for-urinary-tract-infections

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

CAUTIONARY AND ADVISORY LABELS 9, 14, 21

- NITROFURANTOIN (Non-proprietary)

Nitrofurantoin 50 mg Nitrofurantoin 50mg tablets | 28 tablet | £35.00 DT price = £13.93 | 100 tablet | £111.89

Nitrofurantoin 100 mg Nitrofurantoin 100mg tablets | 28 tablet | £12.99 DT price = £12.29 | 100 tablet | £43.89

**Capsule**

CAUTIONARY AND ADVISORY LABELS 9, 14, 21

- NITROFURANTOIN (Non-proprietary)

Nitrofurantoin 50 mg Nitrofurantoin 50mg capsules | 30 capsule | £15.42 DT price = £15.42

Nitrofurantoin 100 mg Nitrofurantoin 100mg capsules | 30 capsule | £10.42 DT price = £10.42

**Modified-release capsule**

CAUTIONARY AND ADVISORY LABELS 9, 14, 21

- Macrobid (AMC)

Nitrofurantoin 100 mg Macrodantin 100mg modified-release capsules | 14 capsule | £9.90 DT price = £9.50

**Oral suspension**

CAUTIONARY AND ADVISORY LABELS 9, 14, 21

- NITROFURANTOIN (Non-proprietary)

Nitrofurantoin 3 mg per 1 ml Nitrofurantoin 25mg/5ml oral suspension sugar free (sugar-free) | 300 ml | £260.46 DT price = £260.46

3 Fungal infection

**Antifungals, systemic use**

The systemic treatment of common fungal infections is outlined below; specialist treatment is required in most forms of systemic or disseminated fungal infections. Local treatment is suitable for a number of fungal infections (genital, bladder, eye, ear, oropharynx, and skin).

**Aspergillosis**

Aspergillosis most commonly affects the respiratory tract but in severely immunocompromised patients, invasive forms can affect the heart, brain, and skin. Voriconazole p. 521 is the treatment of choice for aspergillosis; liposomal amphotericin p. 517 is an alternative first-line treatment.
when voriconazole cannot be used. Caspofungin p. 515, itraconazole p. 519, or posaconazole p. 521 can be used in patients who are refractory to, or intolerant of voriconazole and liposomal amphotericin. Itraconazole is also used for the treatment of chronic pulmonary aspergillosis or as an adjunct in the treatment of allergic bronchopulmonary aspergillosis [unlicensed indication].

Candidiasis

Many superficial candidal infections including infections of the skin are treated locally; widespread or intractable infection requires systemic antifungal treatment. Vaginal candidiasis may be treated with locally acting antifungals or with fluconazole p. 518 given by mouth; for resistant organisms in adults, itraconazole can be given by mouth.

Oral thrush (candidiasis) generally responds to topical therapy; fluconazole is given by mouth for unresponsive infections; it is effective and is reliably absorbed. Itraconazole may be used for infections that do not respond to fluconazole. Topical therapy may not be adequate in immunocompromised patients and an oral triazole antifungal is preferred.

For invasive or disseminated candidiasis, an echinocandin can be used. Fluconazole is an alternative for Candida albicans infection in clinically stable patients who have not received an azole antifungal recently. Amphotericin p. 517 is an alternative when an echinocandin or fluconazole cannot be used, however, amphotericin should be considered for the initial treatment of CNS candidiasis. Voriconazole can be used for infections caused by fluconazole-resistant Candida spp. when oral therapy is required, or in patients intolerant of amphotericin or an echinocandin. In refractory cases, flucytosine p. 516 can be used with intravenous amphotericin.

Cryptococcosis

Cryptococcosis is uncommon but infection in the immunocompromised, especially in HIV-positive patients, can be life-threatening; cryptococcal meningitis is the most common form of fungal meningitis. The treatment of choice in cryptococcal meningitis is amphotericin by intravenous infusion and flucytosine by intravenous infusion for 2 weeks, followed by fluconazole by mouth for 8 weeks or until cultures are negative. In cryptococcosis, fluconazole is sometimes given alone as an alternative in HIV-positive patients with mild, localised infections or in those who cannot tolerate amphotericin. Following successful treatment, fluconazole can be used for prophylaxis against relapse until immunity recovers.

Histoplasmosis

Histoplasmosis is rare in temperate climates; it can be life-threatening, particularly in HIV-infected persons. Itraconazole can be used for the treatment of immunocompetent patients with indolent non-meningeal infection, including chronic pulmonary histoplasmosis. Amphotericin by intravenous infusion is used for the initial treatment of fulminant or severe infections, followed by a course of itraconazole by mouth. Following successful treatment, itraconazole can be used for prophylaxis against relapse until immunity recovers.

Skin and nail infections

Mild localised fungal infections of the skin (including tinea corporis, tinea cruris, and tinea pedis) respond to topical therapy. Systemic therapy is appropriate if topical therapy fails, if many areas are affected, or if the site of infection is difficult to treat such as in infections of the nails (onychomycosis) and of the scalp (tinea capitis). Oral imidazole or triazole antifungals (particularly itraconazole) and terbinafine p. 514 are used more frequently than griseofulvin p. 514 because they have a broader spectrum of activity and require a shorter duration of treatment.

Tinea capitis is treated systemically; additional topical application of an antifungal may reduce transmission.

Griseofulvin is used for tinea capitis in adults and children; it is effective against infections caused by Trichophyton tonsurans and Microsporum spp. Terbinafine is used for tinea capitis caused by T. tonsurans [unlicensed indication]. The role of terbinafine in the management of Microsporum infections is uncertain.

Pityriasis versicolor may be treated with itraconazole by mouth if topical therapy is ineffective; fluconazole by mouth is an alternative. Oral terbinafine is not effective for pityriasis versicolor.

Antifungal treatment may not be necessary in asymptomatic patients with tinea infection of the nails. If treatment is necessary, a systemic antifungal is more effective than topical therapy. Terbinafine and itraconazole have largely replaced griseofulvin for the systemic treatment of onychomycosis, particularly of the toenail; terbinafine is considered to be the drug of choice.

Itraconazole can be administered as intermittent ‘pulse’ therapy. Topical antifungals also have a role in the treatment of onychomycosis.

Immunocompromised patients

Immunocompromised patients are at particular risk of fungal infections and may receive antifungal drugs prophylactically; oral triazole antifungals are the drugs of choice for prophylaxis. Fluconazole is more reliably absorbed than itraconazole p. 519, but fluconazole is not effective against Aspergillus spp. Itraconazole is preferred in patients at risk of invasive aspergillosis. Posaconazole p. 521 can be used for prophylaxis in patients who are undergoing haematopoietic stem cell transplantation or receiving chemotherapy for acute myeloid leukaemia and myelodysplastic syndrome, if they are intolerant of fluconazole or itraconazole. Micafungin p. 516 can be used for prophylaxis of candidiasis in patients undergoing haematopoietic stem cell transplantation when fluconazole, itraconazole or posaconazole cannot be used. Amphotericin p. 517 by intravenous infusion or caspofungin p. 515 is used for the empirical treatment of serious fungal infections; caspofungin is not effective against fungal infections of the CNS.

Triazole antifungals

Triazole antifungal drugs have a role in the prevention and systemic treatment of fungal infections. Fluconazole is very well absorbed after oral administration. It also achieves good penetration into the cerebrospinal fluid to treat fungal meningitis. Fluconazole is excreted largely unchanged in the urine and can be used to treat candiduria. Itraconazole is active against a wide range of dermatophytes. Itraconazole capsules require an acid environment in the stomach for optimal absorption. Itraconazole has been associated with liver damage and should be avoided or used with caution in patients with liver disease; fluconazole is less frequently associated with hepatotoxicity.

Posaconazole is licensed for the treatment of invasive fungal infections unresponsive to conventional treatment. Voriconazole p. 521 is a broad-spectrum antifungal drug which is licensed for use in life-threatening infections.

Imidazole antifungals

The imidazole antifungals include clotrimazole p. 712, econazole nitrate p. 712, ketoconazole p. 713, and tioconazole p. 1012. They are used for the local treatment of vaginal candidiasis and for dermatophyte infections. Miconazole p. 997 can be used locally for oral infections; it is also effective in intestinal infections. Systemic absorption may follow use of miconazole oral gel and may result in significant drug interactions.
Polyene antifungals

The polyene antifungals include amphotericin p. 517 and nystatin p. 997; neither drug is absorbed when given by mouth. Nystatin is used for oral, oropharyngeal, and perioral infections by local application in the mouth. Nystatin is also used for *Candida albicans* infection of the skin.

Amphotericin by intravenous infusion is used for the treatment of systemic fungal infections and is active against most fungi and yeasts. It is highly protein bound and penetrates poorly into body fluids and tissues. When given parenterally amphotericin is toxic and side-effects are common. Lipid formulations of amphotericin (Abelcet® and AmBisome®) are significantly less toxic and are recommended when the conventional formulation of amphotericin is contra-indicated because of toxicity, especially nephrotoxicity or when response to conventional amphotericin is inadequate; lipid formulations are more expensive.

Echinocandin antifungals

The echinocandin antifungals include anidulafungin p. 515, caspofungin p. 515 and micafungin p. 516. They are only active against *Aspergillus* spp. and *Candida* spp.; however, anidulafungin and micafungin are not used for the treatment of aspergillosis. Echinocandins are not effective against fungal infections of the CNS.

Other antifungals

Flucytosine p. 516 is used with amphotericin in a synergistic combination. Bone marrow depression can occur which limits its use, particularly in HIV-positive patients; weekly blood counts are necessary during prolonged therapy. Resistance to flucytosine can develop during therapy and sensitivity testing is essential before and during treatment. Flucytosine has a role in the treatment of systemic candidiasis and cryptococcal meningitis.

Griseofulvin below is effective for widespread or intractable dermatophyte infections but has been superseded by newer antifungals, particularly for nail infections. It is the drug of choice for trichophytosis in children. Duration of therapy is dependent on the site of the infection and may extend to a number of months.

Terbinafine below is the drug of choice for fungal nail infections and is also used for ringworm infections where oral treatment is considered appropriate.

**ANTIFUNGALS**

**Griseofulvin**

**INDICATIONS AND DOSE**

Dermatophyte infections where topical therapy has failed or is inappropriate

**BY MOUTH**

- **Child 1 month–11 years:** Usual dose 10 mg/kg daily (max. per dose 500 mg), alternatively 20 mg/kg daily, higher dose for severe infections; reduce dose when response occurs, daily dose may be taken once daily or in divided doses
- **Child 12–17 years:** 500 mg daily, alternatively 1 g daily, higher dose for severe infections; reduce dose when response occurs, daily dose may be taken once daily or in divided doses
- **Adult:** 500 mg daily, alternatively 1 g daily, higher dose for severe infections; reduce dose when response occurs, daily dose may be taken once daily or in divided doses

**Tinea capitis caused by *Trichophyton tonsurans***

**BY MOUTH**

- Child 1 month–11 years: 15–20 mg/kg once daily (max. per dose 1 g), alternatively 15–20 mg/kg daily in divided doses
- **Child 12–17 years:** 1 g once daily, alternatively 1 g daily in divided doses
- **Adult:** 1 g once daily, alternatively 1 g daily in divided doses

**SIDE-EFFECTS**

- **Rare** Erythema multiforme - toxic epidermal necrolysis
- **Very rare** Headache
- **Frequency not known** Abdominal pain - agitation - confusion - depression - diarrhoea - dizziness - dyspepsia - fatigue - glossitis - hepatotoxicity - impaired coordination - impaired hearing - leucopenia - menstrual disturbances - nausea - peripheral neuropathy - photosensitivity - rash - renal failure - sleep disturbances - systemic lupus erythematosus - taste disturbances - vomiting

**CONTRA-INDICATIONS**

- Acute porphyrias
- Systemic lupus erythematosus (risk of exacerbation)

**INTERACTIONS**

- **Effective** contraception required during and for at least 6 months after administration
- **PREGNANCY** Avoid (fetotoxicity and teratogenicity in animals)
- **HEPATIC IMPAIRMENT** Avoid in severe liver disease.
- **PATIENT AND CARER ADVICE** May impair performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

**MATERIAL HANDLING**

- Medicines for Children leaflet: Griseofulvin for fungal infections www.medicinesforchildren.org.uk/griseofulvin-for-fungal-infections

**TRENDS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>9, 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Griseofulvin (Non-proprietary)</td>
<td></td>
</tr>
<tr>
<td>Griseofulvin 125 mg Griseofulvin 125mg tablets</td>
<td>100 tablet</td>
</tr>
<tr>
<td>Griseofulvin 500 mg Griseofulvin 500mg tablets</td>
<td>90 tablet</td>
</tr>
</tbody>
</table>

**Terbinafine**

**INDICATIONS AND DOSE**

**Tinea pedis**

**BY MOUTH**

- **Adult:** 250 mg daily for 2–6 weeks

**Tinea corporis**

**BY MOUTH**

- **Adult:** 250 mg once daily for 4 weeks

**Tinea cruris**

**BY MOUTH**

- **Adult:** 250 mg once daily for 2–4 weeks
Dermatophyte infections of the nails

BY MOUTH
- Adult: 250 mg once daily for 6 weeks–3 months (occasionally longer in toenail infections)

- **CAUTIONS** Autoimmune disease (risk of lupus-erythematosus-like effect) • psoriasis (risk of exacerbation)
- **INTERACTIONS** → Appendix 1 (terbinafine).
- **SIDE-EFFECTS**
  - **Common or very common** Abdominal discomfort • anorexia • arthralgia • diarrhoea • dyspepsia • headache • myalgia • nausea • rash • urticaria
  - **Uncommon** Taste disturbance
  - **Rare** Cholestasis • dizziness • hepatitis • hypoaesthesia • jaundice • Liver toxicity • malaise • paraesthesia
  - **Very rare** Alopoeia • blood disorders • lupus erythematosus-like effect • neutropenia • photosensitivity • serious skin reactions • Stevens-Johnson syndrome • thrombocytopenia • toxic epidermal necrolysis

- **INTERACTIONS**
  - **Frequency not known** Disturbances in smell • exacerbation of psoriasis • hearing disturbances • influenza-like symptoms • pancreatitis • rhabdomyolysis • vasculitis

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - **Liver toxicity** Discontinue treatment if liver toxicity develops (including jaundice, cholestasis and hepatitis).
  - **Serious skin reactions** Discontinue treatment in progressive skin rash (including Stevens-Johnson syndrome and toxic epidermal necrolysis).

- **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk—no information available.
- **BREAST FEEDING** Manufacturer advises avoid—unless potential benefit outweighs risk—present in milk in animal studies.
- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Ecalta®), give intermittently in Glucose 5% or Sodium chloride 0.9%. Reconstitute each 100 mg with 30 mL water for injections and allow up to 5 minutes for reconstitution; dilute dose in infusion fluid to a concentration of 770 micrograms/mL; give at a rate not exceeding 1.1 mg/minute. Follow product information if using stock supplied with ethanol solvent.
- **MEDICINAL FORMS**
  - **Present in milk in animal**
  - **Contraindications** There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**
- **Ecalta** (Pfizer Ltd)
  - **Anidulafungin 100 mg** Ecalta 100mg powder for concentrate for solution for infusion vials | 1 vial | £295.99

### Caspofungin

**INDICATIONS AND DOSE**
- Invasive aspergillosis • Invasive candidiasis • Empirical treatment of systemic fungal infections in patients with neutropenia

**BY INTRAVENOUS INFUSION**
- Adult (body-weight up to 81 kg): 70 mg once daily for 1 day, then 50 mg once daily
- Adult (body-weight 81 kg and above): 70 mg once daily

- **INTERACTIONS** → Appendix 1 (caspofungin).
- **SIDE-EFFECTS**
  - **Common or very common** Arthralgia • diarrhoea • dyspnoea • headache • hypokalaemia • injection-site reactions • nausea • pruritus • rash • sweating • vomiting
  - **Uncommon** Abdominal pain • anaemia • anorexia • anxiety • arthralgia • ascites • blurred vision • bronchospasm • chest pain • cholestasis • constipation • cough • disorientation • dizziness • dry mouth • dyspepsia • dysphagia • erythema multiforme • fatigue • flatulence • flushing • heart failure • hepatic dysfunction • hyperglycaemia • hypertension • hypoaesthesia • hypocalcaemia • hypomagnesaemia • hypotension • leukopenia • metabolic acidosis • muscular weakness • myalgia • palpitation • paraesthesia • renal failure • sleep disturbances • taste disturbances • thrombocytopenia • thrombopelititis • tremor
  - **Frequency not known**
    - **Adult** Respiratory distress syndrome • anaphylaxis

- **PREGNANCY** Manufacturer advises avoid unless essential—toxicity in animal studies.
- **BREAST FEEDING** Present in milk in animal studies—manufacturer advises avoid.
- **HEPATIC IMPAIRMENT** 70 mg on first day then 35 mg once daily in moderate impairment. No information available for severe impairment.
- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Cancidas®), give intermittently in Sodium chloride 0.9%. Allow vial to reach room temperature, initially reconstitute each vial with 10.5 mL water for injections, mixing gently to dissolve then dilute requisite dose in 250 mL infusion fluid (35- or 50-mg doses may be diluted in 100 mL infusion fluid if necessary); give over 60 minutes; incompatible with glucose solutions.

### Echinocandin Antifungals

**Anidulafungin**

**INDICATIONS AND DOSE**
- Invasive candidiasis

**BY INTRAVENOUS INFUSION**
- Adult: Initially 200 mg once daily for 1 day, then 100 mg once daily

- **SIDE-EFFECTS**
  - **Common or very common** Coagulopathy • convulsion • diarrhoea • flushing • headache • hypokalaemia • nausea • pruritus • raised serum creatinine • rash • vomiting
  - **Uncommon** Abdominal pain • cholestasis • hyperglycaemia • hypertension • injection-site pain • urticaria

- **Frequency not known** Bronchospasm • dyspnoea • hepatitis • hypotension
- **PREGNANCY** Manufacturer advises avoid—no information available.
- **BREAST FEEDING** Manufacturer advises avoid unless potential benefit outweighs risk—present in milk in animal studies.
- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Ecalta®), give intermittently in Glucose 5% or Sodium chloride 0.9%. Reconstitute each 100 mg with 30 mL water for injections and allow up to 5 minutes for reconstitution; dilute dose in infusion fluid to a concentration of 770 micrograms/mL; give at a rate not exceeding 1.1 mg/minute. Follow product information if using stock supplied with ethanol solvent.
- **MEDICINAL FORMS**
  - **Present in milk in animal**
  - **Contraindications** There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**
- **Ecalta** (Pfizer Ltd)
  - **Anidulafungin 100 mg** Ecalta 100mg powder for concentrate for solution for infusion vials | 1 vial | £295.99
Micafungin

INDICATIONS AND DOSE

- **Invasive candidiasis**
  - **Adult (body-weight up to 40 kg):** 2 mg/kg once daily for at least 14 days; increased if necessary to 4 mg/kg once daily, increase dose if response inadequate
  - **Adult (body-weight 40 kg and above):** 150 mg once daily

- **Prophylaxis of candidiasis in patients undergoing bone-marrow transplantation or who are expected to become neutropenic for over 10 days**
  - **Adult (body-weight up to 40 kg):** 1 mg/kg once daily continue for at least 7 days after neutrophil count is desirable range
  - **Adult (body-weight 40 kg and above):** 50 mg once daily continue for at least 7 days after neutrophil count is desirable range

- **Blood disorders**

INTERACTIONS

→ Appendix 1 (micafungin).

SIDE-EFFECTS

- **Common or very common**
  - Abdominal pain - anaemia - diarrhoea - fever - headache - hypocalcaemia - hypokalaemia - hypomagnesaemia - leucopenia - nausea - phlebitis - rash - vomiting

- **Uncommon**

- **Rare**
  - Haemolytic anaemia

- **Frequency not known**
  - Disseminated intravascular coagulation - hepatoxicity (potentially life-threatening) - renal failure - Stevens-Johnson syndrome - toxic epidermal necrolysis

PREGNANCY

Manufacturer advises avoid unless essential—toxicity in animal studies.

BREAST FEEDING

Manufacturer advises use only if potential benefit outweighs risk.

HEPATIC IMPAIRMENT

Use with caution in mild to moderate impairment. Avoid in severe impairment.

RENAL IMPAIRMENT

Use with caution; renal function may deteriorate.

MONITORING REQUIREMENTS

- Monitor renal function.
- Monitor liver function—discontinue if significant and persistent abnormalities in liver function tests develop.

DIRECTIONS FOR ADMINISTRATION

For intravenous infusion (Mycamine®), give intermittently in Glucose 5% or Sodium chloride 0.9%. Reconstitute each vial with 5 mL infusion fluid; gently rotate vial, without shaking, to dissolve; dilute requisite dose with infusion fluid to 100 mL (final concentration of 0.5–2 mg/mL); protect infusion from light; give over 60 minutes.

FLUORONATED PYRIMIDINE ANTIFUNGALS

Flucytosine

INDICATIONS AND DOSE

- **Systemic yeast and fungal infections**
  - Adjunct to amphotericin in severe systemic candidiasis and in other severe or long-standing infections

BY INTRAVENOUS INFUSION

- **Adult:** Usual dose 200 mg/kg daily in 4 divided doses usually for not more than 7 days, alternatively 100–150 mg/kg daily in 4 divided doses, lower dose may be sufficient for sensitive organisms

- **Cryptococcal meningitis (adjunct to amphotericin)**
  - **Adult:** 100 mg/kg daily in 4 divided doses for 2 weeks

UNLICENSED USE

Use in cryptococcal meningitis for 2 weeks is an unlicensed duration.

CAUTIONS

- Blood disorders - elderly

INTERACTIONS

→ Appendix 1 (flucytosine).

SIDE-EFFECTS

- **Common or very common**
  - Diarrhoea - nausea - rash - vomiting

- **Uncommon**
  - Alterations in liver function tests

- **Frequency not known**
  - Aplastic anaemia - blood disorders - hepatic necrosis - hepatitis - leucopenia - thrombocytopenia

PREGNANCY

Teratogenic in animal studies; manufacturer advises use only if potential benefit outweighs risk.

BREAST FEEDING

Manufacturer advises avoid.

RENAL IMPAIRMENT

Use 50 mg/kg every 12 hours if creatinine clearance 20–40 mL/minute; use 50 mg/kg every 24 hours if creatinine clearance 10–20 mL/minute; use initial dose of 50 mg/kg if creatinine clearance less than 10 mL/minute and then adjust dose according to plasma-flucytosine concentration. In renal impairment liver- and kidney-function tests and blood counts required weekly.

MONITORING REQUIREMENTS

- For plasma concentration monitoring, blood should be taken shortly before starting the next infusion; plasma concentration for optimum response 25–50 mg/litre (200–400 micromol/litre)—should not be allowed to exceed 80 mg/litre (620 micromol/litre).
- Liver- and kidney-function tests and blood counts required (weekly in blood disorders).

DIRECTIONS FOR ADMINISTRATION

For intravenous infusion, give over 20–40 minutes.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution.
Solution for infusion  
ELECTROLYTES: May contain Sodium  
- Ancotil (Medica Pharmaceuticals Ltd)  
- Fluocytosine 10 mg per 1 ml Ancotil 2.5g/250ml solution for infusion bottles | 5 bottle pack £151.67 (Hospital only)

POLYENE ANTIFUNGALS

Amphotericin (Amphotericin B)

**INDICATIONS AND DOSE**

**AMBISOME®**  
Severe systemic or deep mycoses where toxicity (particularly nephrotoxicity) precludes use of conventional amphotericin | Suspected or proven infection in febrile neutropenic patients unresponsive to broad-spectrum antibacterials

**BY INTRAVENOUS INFUSION**
- Adult: Test dose 1 mg, to be given over 10 minutes, then 3 mg/kg once daily; maximum 5 mg/kg per day
- Aspergillosis
  - Adult: Test dose 1 mg, to be given over 10 minutes, then 3 mg/kg once daily; maximum 5 mg/kg per day
- Visceral leishmaniasis (unresponsive to the antimonial alone)
  - Adult: 1–3 mg/kg daily for 10–21 days to a cumulative dose of 21–30 mg/kg, alternatively 3 mg/kg for 5 consecutive days, followed by 3 mg/kg after 6 days for 1 dose

**FUNGIZONE®**  
Systemic fungal infections

**BY INTRAVENOUS INFUSION**
- Adult: Test dose 1 mg, to be given over 20–30 minutes, then 250 micrograms/kg daily, gradually increased over 2–4 days, increased if tolerated to 1 mg/kg daily, max. (severe infection) 1.5 mg/kg daily or on alternate days. Prolonged treatment usually necessary; if interrupted for longer than 7 days recommence at 250 micrograms/kg daily and increase gradually

**ABELCET®**  
Severe invasive candidiasis  | Severe systemic fungal infections in patients not responding to conventional amphotericin or to other antifungal drugs or where toxicity or renal impairment precludes conventional amphotericin, including invasive aspergillosis, cryptococcal meningitis and disseminated cryptococcosis in HIV patients

**BY INTRAVENOUS INFUSION**
- Adult: Test dose 1 mg, to be given over 15 minutes, then 5 mg/kg once daily for at least 14 days

**UNLICENSED USE**

**AMBISOME®** Use at the maximum dose of 5 mg/kg once daily is an unlicensed dose.

**CAUTIONS**  
Avoid rapid infusion (risk of arrhythmias) - when given parenterally, toxicity common (close supervision necessary and close observation required for at least 30 minutes after test dose)

**CAUTIONS, FURTHER INFORMATION**

Anaphylaxis  
Anaphylaxis can occur with any intravenous amphotericin product and a test dose is advisable before the first infusion; the patient should be carefully observed for at least 30 minutes after the test dose. Phrophylactic antipyretics or hydrocortisone should only be used in patients who have previously experienced acute adverse reactions (in whom continued treatment with amphotericin is essential).

**INTERACTIONS**  
- Appendix 1 (amphotericin). Caution—corticosteroids (avoid except to control reactions).

**SIDE-EFFECTS**

- **Common or very common**  
  Abdominal pain  | abnormal liver function (discontinue treatment)  | anaemia  | arrhythmias  | blood disorders  | blood pressure changes  | cardiovascular effects  | chest pain  | diarrhoea  | disturbances in renal function  | dyspnoea  | electrolyte disturbances  | febrile reactions  | headache  | hypokalaemia  | hypomagnesaemia  | nausea  | rash  | renal tubular acidosis  | thrombocytopoenia  | vomiting

- **Uncommon**  
  Anaphylactoid reactions  | bronchospasm  | convulsions  | diplopia  | encephalopathy  | hearing loss  | neurological disorders  | peripheral neuropathy  | tremor

- **Frequency not known**  
  Anorexia  | arthralgia  | myalgia  | Stevens–Johnson syndrome  | toxic epidermal necrolysis

**PREGNANCY**  
Not known to be harmful but manufacturers advise avoid unless potential benefit outweighs risk.

**BREAST FEEDING**  
No information available.

**RENAL IMPAIRMENT**  
Use only if no alternative; nephrotoxicity may be reduced with use of lipid formulation.

**MONITORING REQUIREMENTS**  
Hepatic and renal function tests, blood counts, and plasma electrolyte (including plasma-potassium and magnesium concentration) monitoring required.

**DIRECTIONS FOR ADMINISTRATION**

**AMBISOME®**

Amphotericin (liposomal)  
For intravenous infusion (Ambisome®), give intermittently in Glucose 5% or 10%. Reconstitute each vial with 12 mL water for injections and shake vigorously to produce a preparation containing 4 mg/mL; withdraw requisite dose from vial and introduce into infusion fluid through the 5 micron filter provided to produce a final concentration of 0.2–2 mg/mL; infuse over 30–60 minutes, or if non-anaphylactic infusion-related reactions occur infuse over 2 hours (initial test dose of 1 mg over 10 minutes); an in-line filter (pore size no less than 1 micron) may be used; incompatible with sodium chloride solutions, flush existing intravenous line with glucose 5% or 10%, or use separate line.

**FUNGIZONE®**

Amphotericin (as sodium deoxycholate complex)  
For intravenous infusion (Fungizone®), give intermittently in Glucose 5%. Reconstitute each vial with 10 mL water of injections and shake immediately to produce a 5 mg/mL colloidal solution; dilute further in infusion fluid to a concentration of 100 micrograms/mL; pH of the glucose must not be below 4.2 (check each container—consult product literature for details of the buffer); infuse over 2–4 hours, or longer if not tolerated (initial test dose of 1 mg over 20–30 minutes); begin infusion immediately after dilution; protect from light; incompatible with sodium chloride solutions, flush existing intravenous line with glucose 5% or use separate line; an in-line filter (pore size no less than 1 micron) may be used.

**ABELCET®**

Amphotericin (lipid complex)  
For intravenous infusion, give intermittently in Glucose 5%. Allow suspension to reach room temperature, shake gently to ensure no yellow settlement, withdraw requisite dose (using 17–19 gauge needle) into one or more 20–20 mL syringes; replace needle on syringe with a 5-micron filter needle provided (fresh needle for each syringe) and dilute to a concentration of 1 mg/mL (2 mg/mL can be used in fluid restriction and in children); preferably give via an infusion pump at a rate of 2.5 mg/kg/hour (initial test dose of 1 mg over 15 minutes); an in-line filter (pore size no less than 15 micron) may be used; do not use sodium
518 Fungal infection

Infection

chlordane or other electrolyte solutions, flush existing intravenous line with glucose 5% or use separate line.

- **PRESCRIBING AND DISPENSING INFORMATION** Different preparations of intravenous amphotericin vary in their pharmacodynamics, pharmacokinetics, dosage, and administration; these preparations should not be considered interchangeable. To avoid confusion, prescribers should specify the brand to be dispensed.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops, oral solution, lozenge

**Powder for solution for infusion**

- **Excipients**: May contain Sodium Chloride or other electrolyte solutions, flush existing intravenous line with glucose 5% or use separate line.

**Vulvovaginal candidiasis (recurrent)** Considered interchangeable. To avoid confusion, preparations of intravenous amphotericin vary in their licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops, oral solution, lozenge

**INDICATIONS AND DOSE**

- **BY MOUTH**
  - Child 12–16 years: 150 mg for 1 dose
  - Adult: 150 mg for 1 dose

- **Vaginal candidiasis**
  - Child 12–16 years: 150 mg for 1 dose
  - Adult: 150 mg for 1 dose

- **Vulvovaginal candidiasis (recurrent)**
  - Adult: Initially 150 mg every 72 hours for 3 doses, then 150 mg once weekly for 6 months

**Mucosal candidiasis (except genital)**

- **BY MOUTH OR BY INTRAVENOUS INFUSION**
  - Child 1 month–11 years: 3–6 mg/kg, dose to be given on first day, then 3 mg/kg daily (max. per dose 100 mg) for 7–14 days in oropharyngeal candidiasis (max. 14 days except in severely immunocompromised patients); for 14–30 days in other mucosal infections (e.g. oesophagitis, candiduria, non-invasive bronchopulmonary infections)
  - Child 12–17 years: 50 mg for 7–14 days in oropharyngeal candidiasis (max. 14 days except in severely immunocompromised patients); for 14–30 days in other mucosal infections (e.g. oesophagitis, candiduria, non-invasive bronchopulmonary infections); increased to 100 mg daily, increased dose only for unusually difficult infections

- **BY MOUTH**
  - Adult: 50 mg daily given for 7–14 days in oropharyngeal candidiasis (max. 14 days except in severely immunocompromised patients); for 14 days in atrophic oral candidiasis associated with dentures; for 14–30 days in other mucosal infections (e.g. oesophagitis, candiduria, non-invasive bronchopulmonary infections); increased to 100 mg daily, increased dose only for unusually difficult infections

**Amphotericin**

- **Child 12–16 years**: 100 mg/kg daily (max. per dose 400 mg), commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range, dose given according to extent and duration of neutropenia
- **Adult**: 400 mg daily, commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range, dose adjusted according to risk

**Prevention of fungal infections in immunocompromised patients** (for patients with high risk of systemic infections e.g. following bone-marrow transplantation)

- **BY MOUTH OR BY INTRAVENOUS INFUSION**
  - Adult: 400 mg daily, commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range

**Prevention of relapse of cryptococcal meningitis in HIV-infected patients after completion of primary therapy**

- **BY MOUTH OR BY INTRAVENOUS INFUSION**
  - Adult: 200 mg daily

- **CONTRA-INDICATIONS** Acute porphyrias p. 864
- **CAUTIONS** Susceptibility to QT interval prolongation
- **INTERACTIONS** → Appendix 1 (antifungals, triazole); in general, fluconazole interactions in Appendix 1 relate to multiple-dose treatment. Caution with concomitant use of hepatotoxic drugs.

- **SIDE-EFFECTS**
  - Common or very common Abdominal discomfort, diarrhoea, flatulence, headache, nausea, rash
  - Uncommon Alopecia, anaphylaxis, angioedema (in children), dizziness, dyspepsia, hepatic disorders, hyperlipidaemia, hypersensitivity reactions (in adults), pruritus, seizures, Stevens-Johnson syndrome, taste disturbance, toxic epidermal necrolysis, vomiting
  - Frequency not known Hypokalaemia, leucopenia, thrombocytopenia

**SIDE-EFFECTS, FURTHER INFORMATION**

If rash occurs, discontinue treatment (or monitor closely if infection invasive or systemic); severe cutaneous reactions are more likely in patients with AIDS.

- **PREGNANCY** Manufacturer advises avoid—multiple congenital abnormalities reported with long-term high doses.
- **BREAST FEEDING** Present in milk but amount probably too small to be harmful.
- **HEPATIC IMPAIRMENT** Toxicity with related drugs.
**Itraconazole**

**INDICATIONS AND DOSE**

**Vulvovaginal candidiasis**
- **BY MOUTH**
  - Adult: 200 mg twice daily for 1 day

**Vulvovaginal candidiasis (recurrent)**
- **BY MOUTH**
  - Adult: 50–100 mg daily for 6 months

**Oral or oesophageal candidiasis that has not responded to fluconazole**
- **BY MOUTH USING ORAL SOLUTION**
  - Adult: 100–200 mg twice daily for 2 weeks (continue for another 2 weeks if no response; the higher dose should not be used for longer than 2 weeks if no signs of improvement)

**Oral or oesophageal candidiasis in HIV-positive or other immunocompromised patients**
- **BY MOUTH USING ORAL SOLUTION**
  - Adult: 200 mg daily in 1–2 divided doses for 1 week (continue for another week if no response)

**Systemic candidiasis where other antifungal drugs inappropriate or ineffective**
- **BY MOUTH**
  - Adult: 100–200 mg once daily

**BY INTRAVENOUS INFUSION**
- Adult: 200 mg every 12 hours for 2 days, then 200 mg once daily for max. 12 days

**Pityriasis versicolor**
- **BY MOUTH**
  - Adult: 200 mg once daily for 7 days

**Tinea pedis | Tinea manuum**
- **BY MOUTH**
  - Adult: 100 mg once daily for 30 days, alternatively 200 mg twice daily for 7 days

**Tinea corporis | Tinea cruris**
- **BY MOUTH**
  - Adult: 100 mg once daily for 15 days, alternatively 200 mg once daily for 7 days

**Onychomycosis**
- **BY MOUTH**
  - Adult: 200 mg once daily for 3 months, alternatively 200 mg twice daily for 7 days, subsequent courses repeated after 21-day intervals; fingernails 2 courses, toenails 3 courses

**Aspergillosis**
- **BY MOUTH**
  - Adult: 200 mg twice daily

**Systemic aspergillosis where other antifungal drugs inappropriate or ineffective**
- **BY INTRAVENOUS INFUSION**
  - Adult: 200 mg every 12 hours for 2 days, then 200 mg once daily for max. 12 days

**Histoplasmosis**
- **BY MOUTH**
  - Adult: 200 mg 3 times a day for 3 days, then 200 mg 1–2 times a day

**BY INTRAVENOUS INFUSION**
- Adult: 200 mg every 12 hours for 2 days, then 200 mg once daily for max. 12 days

**Systemic cryptococcosis including cryptococcal meningitis where other antifungal drugs inappropriate or ineffective**
- **BY MOUTH**
  - Adult: 200 mg once daily, dose increased in invasive or disseminated disease and in cryptococcal meningitis, increased to 200 mg twice daily continued**
Infection

520  Fungal infection

BY INTRAVENOUS INFUSION
• Adult: 200 mg every 12 hours for 2 days, then 200 mg once daily for max. 12 days

Maintenance in HIV-infected patients to prevent relapse of underlying fungal infection and prophylaxis in neutropenia when standard therapy inappropriate

BY MOUTH
• Adult: 200 mg once daily, then increased to 200 mg twice daily, dose increased only if low plasma-itraconazole concentration

Prophylaxis of deep fungal infections (when standard therapy inappropriate) in patients with haematological malignancy or undergoing bone-marrow transplantation who are expected to become neutropenic
• Adult: 5 mg/kg daily in 2 divided doses, to be started before transplantation or before chemotherapy (taking care to avoid interaction with cytotoxic drugs) and continued until neutrophil count recovers, safety and efficacy not established in elderly patients

UNLICENSED USE Itraconazole doses in BNF may differ from those in product literature.

Important safety information

HEART FAILURE
Following reports of heart failure, caution is advised when prescribing itraconazole to patients at high risk of heart failure. Those at risk include:
• patients receiving high doses and longer treatment courses;
• older adults and those with cardiac disease;
• patients with chronic lung disease (including chronic obstructive pulmonary disease) associated with pulmonary hypertension;
• patients receiving treatment with negative inotropic drugs, e.g. calcium channel blockers.

Itraconazole should be avoided in patients with ventricular dysfunction or a history of heart failure unless the infection is serious.

CONTRA-INDICATIONS Acute porphyrias p. 864

CAUTIONS Active liver disease • history of hepatotoxicity with other drugs • susceptibility to congestive heart failure

INTERACTIONS → Appendix 1 (antifungals, triazole).

SIDE-EFFECTS

GENERAL SIDE-EFFECTS
• Common or very common Abdominal pain • diarrhoea • dyspnoea • headache • hepatitis • hyponatraemia • nausea • rash • taste disturbances • vomiting
• Uncommon Constipation • dizziness • dyspepsia • flatulence • menstrual disorder • myalgia • oedema • peripheral neuropathy (discontinue treatment)
• Rare Alopecia • deafness • erectile dysfunction • heart failure • hypertriglyceridaemia • leucopenia • pancreatitis • photosensitivity • Stevens-Johnson syndrome • tinnitus • toxic epidermal necrolysis • urinary frequency • visual disturbances
• Frequency not known Arthralgia • blood pressure changes • confusion • drowsiness • hepatotoxicity • renal impairment • thrombocytopenia • tremor

SPECIFIC SIDE-EFFECTS
• With intravenous use Hyperglycaemia

SIDE-EFFECTS, FURTHER INFORMATION

Hepatotoxicity Potentially life-threatening hepatotoxicity reported very rarely—discontinue if signs of hepatitis develop.

CONCEPTION AND CONTRACEPTION Ensure effective contraception during treatment and until the next menstrual period following end of treatment.

PREGNANCY Manufacturer advises use only in life-threatening situations (toxicity at high doses in animal studies).

BREAST FEEDING Small amounts present in milk—may accumulate; manufacturer advises avoid.

HEPATIC IMPAIRMENT Dose reduction may be necessary. Use only if potential benefit outweighs risk of hepatotoxicity.

RENAL IMPAIRMENT Risk of congestive heart failure.
• With oral use Bioavailability of oral formulations possibly reduced.
• With intravenous use Use intravenous infusion with caution if eGFR 30–80 mL/minute/1.73 m²; avoid intravenous infusions if eGFR less than 30 mL/minute/1.73 m².

MONITORING REQUIREMENTS
• Absorption reduced in AIDS and neutropenia (monitor plasma-itraconazole concentration and increase dose if necessary).
• Monitor liver function if treatment continues for longer than one month, if receiving other hepatotoxic drugs, if history of hepatotoxicity with other drugs, or in hepatic impairment.

DIRECTIONS FOR ADMINISTRATION
• With intravenous use For intravenous infusion (Sporanox®), give intermittently in Sodium Chloride 0.9%; dilute 250 mg in 50 mL infusion fluid and infuse only 60 mL through an in-line filter (0.2 micron) over 60 minutes.
• With oral use For oral liquid, do not take with food; swish around mouth and swallow, do not rinse afterwards.

PRESCRIBING AND DISPENSING INFORMATION Flavours of oral liquid formulations may include cherry.

PATIENT AND CARER ADVICE Patients should be told how to recognise signs of liver disorder and advised to seek prompt medical attention if symptoms such as anorexia, nausea, vomiting, fatigue, abdominal pain or dark urine develop. Patients or carers should be given advice on how to administer itraconazole oral liquid.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

Capsule

CAUTIONARY AND ADVISORY LABELS 5, 9, 21, 25

Itraconazole 100 mg Itraconazole 100mg capsules | 4 capsule [POM] £3.75 | 15 capsule [POM] £21.50 DT price = £4.57 | 60 capsule [POM] £17.74/£56.21

Sporanox (Janssen-Cilag Ltd)
Itraconazole 100 mg Sporanox-Pulse 100mg capsules | 28 capsule [POM] £25.72
Sporanox 100mg capsules | 4 capsule [POM] £3.67 | 15 capsule [POM] £13.77 DT price = £4.57 | 60 capsule [POM] £55.10

Oral solution

CAUTIONARY AND ADVISORY LABELS 5, 9, 23

Itraconazole 10 mg per 1 ml Itraconazole 50mg/5ml oral solution sugar free (sugar-free) | 150 ml [POM] £58.34 DT price = £58.34

Sporanox (Janssen-Cilag Ltd)
Itraconazole 10 mg per 1 ml Sporanox 50mg/5ml oral solution (sugar-free) | 150 ml [POM] £58.34 DT price = £58.34

Solution for infusion

EXCipients: May contain Propylene glycol

Sporanox (Janssen-Cilag Ltd)
Itraconazole 10 mg per 1 ml Sporanox IV 250mg/25ml solution for infusion ampoules and diluent | 1 ampoule [POM] £79.71
Posaconazole

**INDICATIONS AND DOSE**

Invasive aspergillosis in patients who are refractory to, or intolerant of voriconazole and liposomal amphotericin | Fusariosis either unresponsive to, or in patients intolerant of, amphotericin | Chromoblastomycosis and mycetoma either unresponsive to, or in patients intolerant of, itraconazole (occasionally unresponsive to, or in patients intolerant of, amphotericin, itraconazole, or fluconazole)

**BY MOUTH USING ORAL SUSPENSION**
- Adult: 400 mg twice daily, to be taken with food, alternatively 200 mg 4 times a day, dose if food not tolerated

**BY MOUTH USING TABLETS**
- Adult: 300 mg twice daily on first day, then 300 mg once daily

Oropharyngeal candidiasis (severe infection or in immunocompromised patients only)

**BY MOUTH USING ORAL SUSPENSION**
- Adult: 200 mg on first day, then 100 mg once daily for 13 days, dose if not tolerated

Prophylaxis of invasive fungal infections in patients undergoing bone-marrow transplantation or receiving chemotherapy for acute myeloid leukaemia and myelodysplastic syndrome who are expected to become neutropenic, and who are intolerant of fluconazole or itraconazole

**BY MOUTH USING ORAL SUSPENSION**
- Adult: 200 mg 3 times a day start before transplantation or before chemotherapy and continued until neutrophil count recovers, dose to be taken with food

**BY MOUTH USING TABLETS**
- Adult: 300 mg twice daily on first day, then 300 mg once daily start before transplantation or before chemotherapy and continued until neutrophil count recovers

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain | anaemia | anorexia | blood disorders | constipation | diarrhea | dizziness | drowsiness | dry mouth | dyspepsia | electrolyte disturbances | fatigue | fever | flatulence | gastro-intestinal disturbances | headache | nausea | neutropenia | paraesthesia | pruritus | rash | thrombocytopaenia | vomiting
- **Uncommon** Alopecia | aphasia | arthralgia | bradycardia | cholestasis | convulsions | cough | gastroesophageal reflux | hepatic disorders | hiccups | hyperglycaemia | insomnia | menorrhagia | mouth ulcers | musculoskeletal pain | neuropathy | oedema | palpitation | pancreatitis | renal failure | tachycardia | tremor | vasculitis | visual disturbances
- **Rare** Adrenal insufficiency | breast pain | cardiac failure | depression | encephalopathy | hearing impairment | ileus | myocardial infarction | pneumonitis | psychosis | Stevens-Johnson syndrome | stroke | syncope | thrombosis

**CONTRA-INDICATIONS**

- Acute porphyrias

**PRECAUTIONS AND DISPENSING INFORMATION**

Where possible, Noxafil® tablets should be used in preference to the suspension because the tablets have a higher bioavailability; the suspension is not interchangeable with the tablets on a milligram-for-milligram basis. Flavours of oral liquid formulations may include cherry.

**CONCEPTION AND CONTRACEPTION**

Manufacturer recommends effective contraception during treatment.

**PREGNANCY**

Manufacturer advises avoid unless potential benefit outweighs risk; toxicity in animal studies.

**BREAST FEEDING**

Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**

Monitor liver function in hepatic impairment.

**MONITORING REQUIREMENTS**

- Monitor electrolytes (including potassium, magnesium, and calcium) before and during therapy.
- Monitor liver function before and during therapy.

**GASTRO-RESISTANT TABLET**

**CAUTIONARY AND ADVISORY LABELS** 3, 9, 25

Posaconazole 100 mg | Novofox 100mg gastro-resistant tablets | 24 tablet (PMS) £596.96 | 96 tablet (PMS) £2,387.85

**Oral suspension**

**CAUTIONARY AND ADVISORY LABELS** 3, 9, 21

Posaconazole 40 mg per 1 ml | Novofox 40mg/ml oral suspension | 105 ml (PMS) £491.20 (Hospital only)

Voriconazole

**INDICATIONS AND DOSE**

Invasive aspergillosis | Serious infections caused by Scedosporium spp., Fusarium spp., or invasive fluconazole-resistant Candida spp. (including C. krusei)

**BY MOUTH**
- Adult (body-weight up to 40 kg): 200 mg every 12 hours for 2 doses, then 100 mg every 12 hours, (by mouth) increased if necessary to 150 mg every 12 hours
- Adult (body-weight 40 kg and above): 400 mg every 12 hours, then 200 mg every 12 hours, increased if necessary to 300 mg every 12 hours

**BY INTRAVENOUS INFUSION**
- Adult: Initially 6 mg/kg every 12 hours for 2 doses, then 4 mg/kg every 12 hours for max. 6 months; reduced if not tolerated to 3 mg/kg every 12 hours

**CONTRA-INDICATIONS**

- Acute porphyrias

**CAUTIONS**

Avoid exposure to sunlight | bradycardia | cardiomyopathy | electrolyte disturbances | history of QT interval prolongation | patients at risk of pancreatitis | symptomatic arhythmias

**INTERACTIONS**

- Appendix 1 (antifungals, triazole). Caution with concomitant use with other drugs known to cause QT-interval prolongation.

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain | acute renal failure | agitation | alopecia | altered perception | anaemia | anxiety | asthenia | blood disorders | blurred vision | chest pain | confusion | depression | diarrhoea | dizziness | encephalopathy | hallucinations | headache | hypertensive encephalopathy | hypokalaemia | hypoglycaemia | hypothyroidism | influenza-like symptoms | jaundice | leucopenia | nausea | oedema | pancytopenia | paraesthesia | photophobia | photosensitivity | pruritus | rash | respiratory distress

**GENERAL SIDE-EFFECTS**
syndrome · sinusitis · thrombocytopenia · tremor · visual disturbances · vomiting

- **Uncommon** Adrenocortical insufficiency · arrhythmias · arthritis · ataxia · blepharitis · cholecystitis · constipation · duodenitis · dyspepsia · flushing · fulminant hepatic failure · gingivitis · glossitis · hepatitis · hypersensitivity reactions · hypoglycaemia · hypotension · hypoxia · optic neuritis · pancreatitis · psoriasis · QT interval prolongation · raised serum cholesterol · scleritis · Stevens-Johnson syndrome · syncope

- **Rare** Convulsions · discoid lupus erythematosus · extrapyramidal effects · hearing disturbances · hyperthyroidism · hypertension · hypothyroidism · insomnia · optic atrophy · pseudomembranous colitis · pseudoporphyria · retinal haemorrhage · taste disturbances (more common with oral suspension) · tinnitus · toxic epidermal necrolysis

- **Frequency not known** On long term treatment, squamous cell carcinoma of skin (particularly in presence of phototoxicity) · periostitis (particularly in transplant patients)

### SPECIFIC SIDE-EFFECTS

- **Common or very common**
- **With intravenous use** Injection-site reactions

### SIDE-EFFECTS, FURTHER INFORMATION

- **Hepatotoxicity** Hepatitis, cholestasis, and fulminant hepatic failure usually occur in the first 10 days; risk of hepatotoxicity increased in patients with haematological malignancy. Consider treatment discontinuation if severe abnormalities in liver function tests.

- **Phototoxicity** Phototoxicity occurs commonly. If phototoxicity occurs, consider treatment discontinuation; if treatment is continued, monitor for pre-malignant skin lesions and squamous cell carcinoma, and discontinue treatment if they occur.

### CONCEPTION AND CONTRACEPTION

Effective contraception required during treatment.

### PREGNANCY

Toxicity in animal studies—manufacturer advises avoid unless potential benefit outweighs risk.

### BREAST FEEDING

Manufacturer advises avoid—no information available.

### HEPATIC IMPAIRMENT

In mild to moderate hepatic cirrhosis use usual initial dose then halve maintenance dose. No information available for severe hepatic cirrhosis—manufacturer advises use only if potential benefit outweighs risk.

### RENAL IMPAIRMENT

Intravenous vehicle may accumulate if eGFR less than 50 mL/minute/1.73 m²—use intravenous infusion only if potential benefit outweighs risk, and monitor renal function; alternatively, use tablets or oral suspension (no dose adjustment required).

### MONITORING REQUIREMENTS

- Monitor renal function.
- Monitor liver function before starting treatment, then at least weekly for 1 month, and then monthly during treatment.

### DIRECTIONS FOR ADMINISTRATION

For intravenous infusion, reconstitute each 200 mg with 19 mL Water for Injections or Sodium Chloride 0.9% to produce a 10 mg/mL solution; dilute dose to concentration of 0.5–5 mg/mL with Glucose 5% or Sodium Chloride 0.9% and give at a rate not exceeding 3 mg/kg/hour.

### PRESCRIBING AND DISPENSING INFORMATION

Flavours of oral liquid formulations may include orange.

### PATIENT AND CARER ADVICE

Patients and their carers should be advised to keep the Alert Card with them at all times. Patients and their carers should be told how to recognise symptoms of liver disorder, and advised to seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop.

Patients and their carers should be advised that patients should avoid intense or prolonged exposure to direct sunlight, and to avoid the use of sunbeds. In sunlight, patients should cover sun-exposed areas of skin and use a sunscreen with a high sun protection factor. Patients should seek medical attention if they experience sunburn or a severe skin reaction following exposure to light or sun.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **CAFÉTORY AND ADVISORY LABELS 9, 11, 23**
- **VFEND (Pfizer Ltd)**
  - **Voriconazole 50 mg** VFEND 50mg tablets | 28 tablet £27.68
  - **Voriconazole 200 mg** VFEND 200mg tablets | 28 tablet £110.74

**Oral suspension**

- **CAFÉTORY AND ADVISORY LABELS 9, 11, 23**
- **VFEND (Pfizer Ltd)**
  - Voriconazole 40 mg per 1 ml VFEND 40mg/ml oral suspension | 75 ml [Post] £51.37

**Powder for solution for infusion**

EXCIPIENTS: May contain Sulfobutylether beta cyclodextrin sodium

- **VFEND (Pfizer Ltd)**
  - Voriconazole 200 mg VFEND 200mg powder for solution for infusion vials | 1 vial [Post] £77.14

**Powder and solvent for solution for infusion**

EXCIPIENTS: May contain Sulfobutylether beta cyclodextrin sodium

- **VFEND (Pfizer Ltd)**
  - Voriconazole 200 mg VFEND 200mg powder and solvent for solution for infusion vials | 1 vial [Post] £77.14

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### 3.1 Pneumocystis pneumonia

**Pneumocystis pneumonia**

Pneumonia caused by *Pneumocystis jirovecii (Pneumocystis carinii)* occurs in immunosuppressed patients; it is a common cause of pneumonia in AIDS. Pneumocystis pneumonia should generally be treated by those experienced in its management. Blood gas measurement is used to assess disease severity.

**Treatment**

**Mild to moderate disease**

Co-trimoxazole p. 461 in high dosage is the drug of choice for the treatment of mild to moderate pneumocystis pneumonia.

Atovaquone p. 523 is licensed for the treatment of mild to moderate pneumocystis infection in patients who cannot tolerate co-trimoxazole. A combination of dapsone p. 500 with trimethoprim p. 462 is given by mouth for the treatment of mild to moderate disease [unlicensed indication].

A combination of clindamycin p. 467 and primaquine p. 538 by mouth is used in the treatment of mild to moderate disease [unlicensed indication]; this combination is associated with considerable toxicity.

**Severe disease**

Co-trimoxazole in high dosage, given by mouth or by intravenous infusion, is the drug of choice for the treatment of severe pneumocystis pneumonia. Pentamidine isetionate p. 523 given by intravenous infusion is an alternative for patients who cannot tolerate co-trimoxazole, or who have not responded to it. Pentamidine isetionate is a potentially toxic drug that can cause severe hypotension during or immediately after infusion.
Corticosteroid treatment can be lifesaving in those with severe pneumocystis pneumonia.

**Adjunctive therapy**
In moderate to severe infections associated with HIV infection, prednisolone p. 585 is given by mouth for 5 days (alternatively, hydrocortisone p. 583 may be given parenterally); the dose is then reduced to complete 21 days of treatment. Corticosteroid treatment should ideally be started at the same time as the anti-pneumocystis therapy and certainly no later than 24–72 hours afterwards. The corticosteroid should be withdrawn before anti-pneumocystis treatment is complete.

**Prophylaxis**
Prophylaxis against pneumocystis pneumonia should be given to all patients with a history of the infection. Prophylaxis against pneumocystis pneumonia should also be considered for severely immunocompromised patients. Prophylaxis should continue until immunity recovers (alternatively, dapsone p. 500 can be used. Atovaquone below has also been used for prophylaxis [unlicensed indication].

**Pentamidine isetionate**

**INDICATIONS AND DOSE**
Treatment of *Pneumocystis jirovecii* (*Pneumocystis carinii*) pneumonia (specialist use only)
- **BY INTRAVENOUS INFUSION**
  - Adult: 4 mg/kg once daily for at least 14 days
- **Prophylaxis of *Pneumocystis jirovecii* (*Pneumocystis carinii*) pneumonia (specialist use only)**
  - **BY INHALATION OF NEBULISED SOLUTION**
    - Adult: 300 mg every 4 weeks, alternatively 150 mg every 2 weeks, using suitable equipment—consult product literature
- **Visceral leishmaniasis**
  - **BY DEEP INTRAMUSCULAR INJECTION**
    - Adult: 3–4 mg/kg once daily on alternate days, maximum total of 10 injections, course may be repeated if necessary
- **Cutaneous leishmaniasis**
  - **BY DEEP INTRAMUSCULAR INJECTION**
    - Adult: 3–4 mg/kg 1–2 times a week until condition resolves
- **Trypanosomiasis**
  - **BY DEEP INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INFUSION**
    - Adult: 4 mg/kg once daily or on alternate days for a total of 7–10 injections

**Atovaquone**

**INDICATIONS AND DOSE**
Treatment of mild to moderate *Pneumocystis jirovecii* (*Pneumocystis carinii*) pneumonia in patients intolerant of co-trimoxazole
- **BY MOUTH**
  - Adult: 750 mg twice daily for 21 days, dose to be taken with food, particularly high fat food
- **Prophylaxis against pneumocystis pneumonia**
  - **BY MOUTH**
    - Adult: 750 mg twice daily

**UNLICENSED USE**
Not licensed for primary prevention of *Pneumocystis jirovecii* (*Pneumocystis carinii*) pneumonia by inhalation of nebulised solution

**CAUTIONS**
Other causes of pulmonary disease should be sought and treated - elderly - initial diarrhoea and difficulty in taking with food may reduce absorption (and require alternative therapy)

**INTERACTIONS**
Appendix 1 (atovaquone).

**SIDE-EFFECTS**
**GENERAL SIDE-EFFECTS**
Abnormal liver-function tests - acute renal failure - anaemia - arrhythmias (can be severe and sometimes fatal) - azotaemia - dizziness - flushing - hyperglycaemia - hyperkalaemia - hypoglycaemia - hypokalaemia - hypomagnesaemia - hypotension - leucopenia - risk of severe hypotension following administration - thrombocytopenia

**SPECIFIC SIDE-EFFECTS**
- **When used by inhalation**
  - Bronchoconstriction (may be prevented by prior use of bronchodilators) - cough - shortness of breath
- **With intramuscular use**
  - Injection site reactions (muscle necrosis, discomfort, pain, induration, abscess formation)
- **With intravenous use**
  - Injection site reactions (muscle necrosis, discomfort, pain, induration, abscess formation)

**PREGNANCY**
Manufacturer advises avoid unless essential.
524 Helminth infection

Helminth infections

Advice on prophylaxis and treatment of helminth infections is available from the following specialist centres:

<table>
<thead>
<tr>
<th>Location</th>
<th>Contact Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birmingham</td>
<td>(0121) 424 0357</td>
</tr>
<tr>
<td>Scotland</td>
<td>Contact local Infectious Diseases Unit</td>
</tr>
<tr>
<td>Liverpool</td>
<td>(0151) 705 3100</td>
</tr>
<tr>
<td>London</td>
<td>0845 155 5000 (treatment)</td>
</tr>
</tbody>
</table>

Drugs for threadworms

Anthelmintics are effective in threadworm (pinworms, Enterobius vermicularis) infections, but their use needs to be combined with hygienic measures to break the cycle of auto-infection. All members of the family require treatment. Adult threadworms do not live for longer than 6 weeks and for development of fresh worms, ova must be swallowed and exposed to the action of digestive juices in the upper intestinal tract. Direct multiplication of worms does not take place in the large bowel. Adult female worms lay ova on the perianal skin which causes pruritus; scratching the area then leads to ova being transmitted on fingers to the mouth, often via food eaten with unwashed hands. Washing hands and scrubbing nails before each meal and after each visit to the toilet is essential. A bath taken immediately after rising will remove ova laid during the night.

Mebendazole p. 526 is the drug of choice for treating threadworm infection in patients of all ages over 6 months. It is given as a single dose; as reinfection is very common, a second dose may be given after 2 weeks.

Ascaricides (common roundworm infections)

Mebendazole is effective against Ascaris lumbricoides and is generally considered to be the drug of choice.

Drugs for tapeworm infections

Taenicides

Niclosamide [unlicensed] (available from ‘special-order’ manufacturers or specialist importing companies) is the most widely used drug for tapeworm infections and side-effects are limited to occasional gastro-intestinal upset, lightheadedness, and pruritus; it is not effective against larval worms. Fears of developing cysticercosis in Taenia solium infections have proved unfounded. All the same, an antiemetic can be given before treatment and a laxative can be given 2 hours after niclosamide.

Praziquantel p. 526 [unlicensed] (available from ‘special-order’ manufacturers or specialist importing companies) is as effective as niclosamide.

Hydatid disease

Cysts caused by Echinococcus granulosus grow slowly and asymptomatic patients do not always require treatment. Surgical treatment remains the method of choice in many situations. Albendazole p. 525 [unlicensed] (available from ‘special-order’ manufacturers or specialist importing companies) is used in conjunction with surgery to reduce the risk of recurrence or as primary treatment in inoperable cases. Alveolar echinococcosis due to E. multilocularis is usually fatal if untreated. Surgical removal with albendazole cover is the treatment of choice, but where effective surgery is impossible, repeated cycles of albendazole (for a year or more) may help. Careful monitoring of liver function is particularly important during drug treatment.

Drugs for hookworms

Hookworms (ancylostomiasis, necatoriasis) live in the upper small intestine and draw blood from the point of their attachment to their host. An iron-deficiency anaemia may occur and, if present, effective treatment of the infection requires not only expulsion of the worms but treatment of the anaemia.

Mebendazole p. 526 has a useful broad-spectrum activity, and is effective against hookworms. Albendazole p. 525 [unlicensed] (available from ‘special-order’ manufacturers or specialist importing companies) is an alternative. Levamisole p. 525 is also also effective in children.

Schistosomicides (bilharziasis)

Adult Schistosoma haematobium worms live in the genito-urinary veins and adult S. mansoni in those of the colon and mesentery. S. japonicum is more widely distributed in veins of the alimentary tract and portal system. Praziquantel p. 526 [unlicensed] is available from Merck Serono (Cysticide®) and is effective against all human schistosomes. No serious adverse effects have been reported. Of all the available schistosomicides, it has the most attractive combination of effectiveness, broad-spectrum activity, and low toxicity.

Filaricides

Diethylcarbamazine [unlicensed] (available from ‘special-order’ manufacturers or specialist importing companies) is
Diethylcarbamazine

**INDICATIONS AND DOSE**

- *Wuchereria bancrofti* infections | *Brugia malayi* infections

**BY MOUTH**

- Adult: Initially 1 mg/kg daily in divided doses on the first day, then increased to 6 mg/kg daily in divided doses, dose to be increased gradually over 3 days

- *Loa loa* infections

**BY MOUTH**

- Adult: Initially 1 mg/kg daily in divided doses on the first day, then increased to 6 mg/kg daily in divided doses, dose to be increased gradually over 3 days; maximum 9 mg/kg per day

**INTERACTIONS** → Appendix 1 (diethylcarbamazine).

**MEDICINAL FORMS**

Medicines are available from importing manufacturers.

Ivermectin

**INDICATIONS AND DOSE**

- Chronic *Strongyloides* infection

**BY MOUTH**

- Adult: 200 micrograms/kg daily for 2 days

- *Onchocerciasis*

**BY MOUTH**

- Adult: 150 micrograms/kg for 1 dose, retreatment at intervals of 6 to 12 months may be required depending on symptoms

- Scabies, in combination with topical drugs, for the treatment of hyperkeratotic (crusted or ‘Norwegian’) scabies that does not respond to topical treatment alone

**BY MOUTH**

- Adult: 200 micrograms/kg for 1 dose, further doses of 200 micrograms/kg may be required

**UNLICENSED USE** Ivermectin is an unlicensed drug.

**INTERACTIONS** → Appendix 1 (ivermectin).

**SIDE-EFFECTS** Aggravation of itching - aggravation of rash

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet

Levamisole

**INDICATIONS AND DOSE**

- Roundworm infections

**BY MOUTH**

- Adult: 120–150 mg for 1 dose

**UNLICENSED USE** Not licensed.

**CONTRA-INDICATIONS** Blood disorders

**CAUTIONS** Epilepsy - Sjögren’s syndrome

**INTERACTIONS** → Appendix 1 (levamisole).

**SIDE-EFFECTS** Arthralgia (on prolonged treatment) - blood disorders (on prolonged treatment) - convulsions (on prolonged treatment) - diarrhoea - dizziness - headache - influenza-like syndrome (on prolonged treatment) - insomnia (on prolonged treatment) - myalgia (on prolonged treatment) - nausea - rash (on prolonged treatment) - taste disturbances (on prolonged treatment) - vasculitis (on prolonged treatment) - vomiting

**PREGNANCY** Embryotoxic in animal studies, avoid if possible.

**ANNEXES**

**MEDICATION**

- Albendazole
- Ivermectin
- Levamisole

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effective against microfilariae and adults of *Loa loa*, *Wuchereria bancrofti*, and *Brugia malayi*. To minimise reactions, treatment in adults and children over 1 month, is commenced with a dose of diethylcarbamazine citrate on the first day and increased gradually over 3 days. Length of treatment varies according to infection type, and usually gives a radical cure for these infections. Close medical supervision is necessary particularly in the early phase of treatment.

In heavy infections there may be a febrile reaction, and in heavy *Loa loa* infection there is a small risk of encephalopathy. In such cases specialist advice should be sought, and treatment must be given under careful in-patient supervision and stopped at the first sign of cerebral involvement.

Ivermectin below [unlicensed] (available from ‘special-order’ manufacturers or specialist importing companies) is very effective in *onchocerciasis* and it is now the drug of choice; reactions are usually slight. Diethylcarbamazine or suramin should no longer be used for *onchocerciasis* because of their toxicity.

**Drugs for cutaneous larva migrans (creeping eruption)**

Dog and cat hookworm larvae may enter human skin where they produce slowly extending itching tracks usually on the foot. Single tracks can be treated with topical thiabendazole (no commercial preparation available). Multiple infections respond to ivermectin, albendazole or thiabendazole (thiabendazole) by mouth [all unlicensed] (available from ‘special-order’ manufacturers or specialist importing companies).

**Drugs for strongyloidiasis**

Adult *Strongyloides stercoralis* live in the gut and produce larvae which penetrate the gut wall and invade the tissues, setting up a cycle of auto-infection. Ivermectin [unlicensed] (available from ‘special-order’ manufacturers or specialist importing companies) is the treatment of choice for chronic *Strongyloides* infection in adults and children over 5 years. Albendazole [unlicensed] (available from ‘special order’ manufacturers or specialist importing companies) is an alternative given to adults and children over 2 years.

**ANTHELMIINTICS**

**Albendazole**

**INDICATIONS AND DOSE**

- Chronic *Strongyloides* infection

**BY MOUTH**

- Adult: 400 mg twice daily for 3 days, dose may be repeated after 3 weeks if necessary

- Hydatid disease, in conjunction with surgery to reduce the risk of recurrence or as primary treatment in inoperable cases

**BY MOUTH**

- Adult: (consult product literature)

- Hookworm infections

**BY MOUTH**

- Adult: 400 mg for 1 dose

**UNLICENSED USE** Albendazole is an unlicensed drug.

**INTERACTIONS** → Appendix 1 (albendazole).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, chewable tablet
### Mebendazole

**INDICATIONS AND DOSE**

#### Threadworm infections

**BY MOUTH**
- Child 6 months-17 years: 100 mg for 1 dose, if reinfection occurs, second dose may be needed after 2 weeks
- Adult: 100 mg for 1 dose, if reinfection occurs, second dose may be needed after 2 weeks

#### Whipworm infections | Hookworm infections

**BY MOUTH**
- Child 1-17 years: 100 mg twice daily for 3 days
- Adult: 100 mg twice daily for 3 days

#### Roundworm infections

**BY MOUTH**
- Child 1 year: 100 mg twice daily for 3 days
- Child 2-17 years: 100 mg twice daily for 3 days, alternatively 500 mg for 1 dose
- Adult: 100 mg twice daily for 3 days, alternatively 500 mg for 1 dose

**SIDE-EFFECTS**
- Common or very common Abdominal pain
- Uncommon Diarrhoea; flatulence
- Rare Alopecia; convulsions; dizziness; neutropenia; rash; Stevens-Johnson syndrome; toxic epidermal necrolysis; urticaria

**PREGNANCY**
- Manufacturer advises avoid—toxicity in animal studies.

**BREAST FEEDING**
- Amount present in milk too small to be harmful but manufacturer advises avoid.

**PRESCRIBING AND DISPENSING INFORMATION**
- Flavours of oral liquid formulations may include banana.

**PATIENT AND CARER ADVICE**
- Medicines for Children leaflet: Mebendazole for worm infections www.medicinesforchildren.org.uk/mebendazole-for-worm-infections

**EXCEPTIONS TO LEGAL CATEGORY**
- Mebendazole tablets can be sold to the public if supplied for oral use in the treatment of enterobiasis in adults and children over 2 years provided its container or package is labelled to show a max. single dose of 100 mg and it is supplied in a container or package containing not more than 800 mg.

**UNLICENSED USE**
- Not licensed for use in children under 2 years. Treatment of roundworm infections with mebendazole 500 mg as a single dose is an unlicensed dose.

**INTERACTIONS** → Appendix 1 (mebendazole).

### Antiprotozoal drugs

#### Amoebicides

**Mebendazole**

- Brands may include: Ovex

- **Vermox** (Janssen-Cilag Ltd)
  - Mebendazole 100 mg
  - Mebendazole 20 mg per 1 ml
  - Vermox 100mg/5ml oral suspension | 30 ml (£0.53) £1.59 DT price = £1.59

**Praziquantel**

- **INDICATIONS AND DOSE**
  - **Tapeworm infections (Taenia solium)**
    - **BY MOUTH**
    - Adult: 5–10 mg/kg for 1 dose, to be taken after a light breakfast

- **Tapeworm infections (Hymenolepis nana)**
  - **BY MOUTH**
  - Adult: 25 mg/kg for 1 dose, to be taken after a light breakfast

- **Schistosoma haematobium** worm infections | **Schistosoma mansoni** worm infections
  - **BY MOUTH**
  - Adult: 20 mg/kg, followed by 20 mg/kg after 4–6 hours

- **Schistosoma japonicum** worm infections
  - **BY MOUTH**
  - Adult: 20 mg/kg 3 times a day for 1 day

**UNLICENSED USE**
- Praziquantel is an unlicensed drug.

**INTERACTIONS** → Appendix 1 (praziquantel).

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet

#### Metronidazole

- **INDICATIONS AND DOSE**
  - **Diloxanide furoate**
    - **Tapeworm infections (Taenia solium)**
      - **BY MOUTH**
      - Adult: 36–59 mg/kg 20 times daily for 20–30 days, alternatively 20 mg/kg 36 times a day for 10 days

- **Amoebicides**
  - **Entamoeba histolytica**
    - Adult: 5–10 mg/kg for 1 dose, to be taken after a light breakfast

**SIDE-EFFECTS**
- **Common or very common** Abdominal pain

**PRESCRIBING AND DISPENSING INFORMATION**
- Flavours of oral liquid formulations may include banana.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet

**Unlicensed use**
- Praziquantel is an unlicensed drug.

**INTERACTIONS** → Appendix 1 (praziquantel).

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet

**5 Protozoal infection**
Trichomonacides
Metronidazole is the treatment of choice for *Trichomonas vaginalis* infection. Contact tracing is recommended and sexual contacts should be treated simultaneously. If metronidazole is ineffective, tinidazole may be tried.

Antigiardial drugs
Metronidazole is the treatment of choice for *Giardia lamblia* infections. Alternative treatments are tinidazole or mepacrine hydrochloride p. 438.

Leishmaniacides
Cutaneous leishmaniasis frequently heals spontaneously but if skin lesions are extensive or unsightly, treatment is indicated, as it is in visceral leishmaniasis (kala-azar). Leishmaniasis should be treated under specialist supervision.

Sodium stibogluconate below, an organic pentavalent antimony compound, is used for visceral leishmaniasis. The dosage varies with different geographical regions and expert advice should be obtained. Some early non-inflamed lesions of cutaneous leishmaniasis can be treated with intralesional injections of sodium stibogluconate below under specialist supervision.

Amphotericin p. 517 is used with or after an antimony compound for visceral leishmaniasis unresponsive to the antimonial alone; side-effects may be reduced by using liposomal amphotericin (AmBisome®). Abelcet® is also likely to be effective but less information is available.

Pentamidine isetionate p. 523 has been used in antimony-resistant visceral leishmaniasis, but although the initial response is often good, the relapse rate is high; it is associated with serious side-effects. Other treatments include paromomycin [unlicensed] (available from ‘special-order’ manufacturers or specialist importing companies).

Trypanocides
The prophylaxis and treatment of trypanosomiasis is difficult and differs according to the strain of organism. Expert advice should therefore be obtained.

Drugs for toxoplasmosis
Most infections caused by *Toxoplasma gondii* are self-limiting, and treatment is not necessary. Exceptions are patients with eye involvement (toxoplasma chorioretinitis), and those who are immunosuppressed. Toxoplasmic encephalitis is a common complication of AIDS. The treatment of choice is a combination of pyrimethamine p. 539 and sulfadiazine p. 495, given for several weeks (expert advice essential). Pyrimethamine is a folate antagonist, and adverse reactions to this combination are relatively common (folic acid supplements and weekly blood counts needed). Alternative regimens use combinations of pyrimethamine p. 539 with clindamycin p. 467 or clarithromycin p. 470 or azithromycin p. 469. Long-term secondary prophylaxis is required after treatment of toxoplasmosis in immunocompromised patients; prophylaxis should continue until immunity recovers.

If toxoplasmosis is acquired in pregnancy, transplacental infection may lead to severe disease in the fetus; specialist advice should be sought on management. Spiramycin [unlicensed] (available from ‘special-order’ manufacturers or specialist importing companies) may reduce the risk of transmission of maternal infection to the fetus.

5.1 Leishmaniasis

Sodium stibogluconate

<table>
<thead>
<tr>
<th>INDICATIONS AND DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral leishmaniasis (specialist use only)</td>
</tr>
<tr>
<td>BY INTRAVENOUS INJECTION OR BY INTRAMUSCULAR INJECTION</td>
</tr>
<tr>
<td>▶ Adult: 20 mg/kg daily for 28 days</td>
</tr>
<tr>
<td>Cutaneous leishmaniasis (specialist use only)</td>
</tr>
<tr>
<td>BY INTRAVENOUS INJECTION OR BY INTRAMUSCULAR INJECTION</td>
</tr>
<tr>
<td>▶ Adult: 20 mg/kg daily for 20 days</td>
</tr>
</tbody>
</table>

- **CAUTIONS** Heart disease (withdraw if conduction disturbances occur) · mucocutaneous disease · predisposition to QT interval prolongation · treat intercurrent infection (e.g. pneumonia)
- **CAUTIONS, FURTHER INFORMATION**
  - Mucocutaneous disease Successful treatment of mucocutaneous leishmaniasis may induce severe inflammation around the lesions (may be life-threatening if pharyngeal or tracheal involvement)—may require corticosteroid.
- **INTERACTIONS** > Appendix 1 (sodium stibogluconate). Caution with concomitant use of drugs that prolong QT interval.
- **SIDE-EFFECTS**
  - Rare Bleeding from gums · bleeding from nose · fever · flushing · jaundice · rash · substernal pain · sweating · vertigo
  - Frequency not known Abdominal pain · anaphylaxis · anorexia · arthralgia · coughing · diarrhoea · ECG changes · headache · lethargy · myalgia · nausea · pain on intramuscular injection · pain on intravenous administration · pancreatitis · thrombosis on intravenous administration · vomiting
- **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.
- **BREAST FEEDING** Amount probably too small to be harmful.
- **HEPATIC IMPAIRMENT** Use with caution.
- **RENAL IMPAIRMENT** Avoid in significant impairment.
- **MONITORING REQUIREMENTS** Monitor ECG before and during treatment.
- **DIRECTIONS FOR ADMINISTRATION** Intravenous injections must be given slowly over 5 minutes (to reduce risk of local thrombosis) and stopped if coughing or substernal pain occur. Injection should be filtered immediately before administration using a filter of 5 microns or less.

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5.2 Malaria

Antimalarials

*Artemether with lumefantrine*

*Artemether with lumefantrine* p. 534 is licensed for the treatment of acute non-complicated *falciparum* malaria.
Chloroquine
Chloroquine p. 536 is used for the prophylaxis of malaria in areas of the world where the risk of chloroquine-resistant *falciparum* malaria is still low. It is also used with proguanil hydrochloride p. 539 when chloroquine-resistant *falciparum* malaria is present but this regimen may not give optimal protection (see recommended regimens for prophylaxis against malaria in Malaria, prophylaxis below).

Chloroquine is no longer recommended for the treatment of *falciparum* malaria owing to widespread resistance, nor is it recommended if the infective species is not known or if the infection is mixed; in these cases treatment should be with quinine p. 540, Malarone®, or Riamet®. It is still recommended for the treatment of non-*falciparum* malaria.

Mefloquine
Mefloquine p. 537 is used for the prophylaxis of malaria in areas of the world where there is a high risk of chloroquine-resistant *falciparum* malaria (for details, see recommended regimens for prophylaxis against malaria in Malaria, prophylaxis below).

Mefloquine is now rarely used for the treatment of *falciparum* malaria because of increased resistance. It is rarely used for the treatment of non-*falciparum* malaria because better tolerated alternatives are available.

Mefloquine should not be used for treatment if it has been used for prophylaxis.

Piperaquine with artenimol
Arténimol with piperaquine phosphate p. 535 is not recommended for the first-line treatment of acute uncomplicated *falciparum* malaria because there is limited experience of its use in travellers who usually reside in areas where malaria is not endemic. Piperaquine has a long half-life.

Primamaquine
Primamaquine p. 538 is used to eliminate the liver stages of *P. vivax* or *P. ovale* following chloroquine treatment.

Proguanil
Proguanil hydrochloride p. 539 is used (usually with chloroquine, but occasionally alone) for the prophylaxis of malaria, (for details, see Recommended regimens for prophylaxis against malaria p. 530).

Proguanil hydrochloride used alone is not suitable for the treatment of malaria; however, Malarone® (a combination of atovaquone with proguanil hydrochloride p. 536) is licensed for the treatment of acute uncomplicated *falciparum* malaria. Malarone® is also used for the prophylaxis of *falciparum* malaria in areas of widespread mefloquine or chloroquine resistance. Malarone® is also used as an alternative to mefloquine or doxycycline p. 496. Malarone® is particularly suitable for short trips to highly chloroquine-resistant areas because it needs to be taken only for 7 days after leaving an endemic area.

Pyrimethamine
Pyrimethamine p. 539 should not be used alone, but is used with sulfadoxine.

Pyrimethamine with sulfadoxine is not recommended for the prophylaxis of malaria, but can be used in the treatment of *falciparum* malaria with (or following) quinine.

Quinine
Quinine is not suitable for the prophylaxis of malaria.

Quinine is used for the treatment of *falciparum* malaria or if the infective species is not known or if the infection is mixed (for details see Malaria, treatment p. 529).

Tetracyclines
Doxycycline p. 496 is used in adults and children over 12 years for the prophylaxis of malaria in areas of widespread mefloquine or chloroquine resistance. Doxycycline is also used as an alternative to mefloquine or Malarone® (for details, see Recommended regimens for prophylaxis against malaria p. 530).

Malaria, prophylaxis

Prophylaxis
The recommendations on prophylaxis reflect guidelines agreed by UK malaria specialists; the advice is aimed at residents of the UK who travel to endemic areas. The choice of drug for a particular individual should take into account:

- risk of exposure to malaria
- extent of drug resistance
- efficacy of the recommended drugs
- side-effects of the drugs
- patient-related factors (e.g. age, pregnancy, renal or hepatic impairment, compliance with prophylactic regimen)

Protection against bites

Prophylaxis is not absolute, and breakthrough infection can occur with any of the drugs recommended. Personal protection against being bitten is very important. Mosquito nets impregnated with permethrin p. 1015 provide the most effective barrier protection against insects; mats and vapourised insecticides are also useful. Diethyltoluamide (DEET) 20–50% in lotions, sprays, or roll-on formulations is safe and effective when applied to the skin of adults and children over 2 months of age. It can also be used during pregnancy and breast-feeding. The duration of protection varies according to the concentration of DEET and is longest for DEET 50%. When sunscreen is also required, DEET should be applied after the sunscreen. Long sleeves and trousers worn after dusk also provide protection against bites.

Length of prophylaxis

In order to determine tolerance and to establish habit, prophylaxis should generally be started one week (2–3 weeks in the case of mefloquine p. 537) before travel into an endemic area; Malarone® or doxycycline p. 496 prophylaxis should be started 1–2 days before travel. Prophylaxis should be continued for 4 weeks after leaving (except for Malarone® prophylaxis which should be stopped 1 week after leaving).

In those requiring long-term prophylaxis, chloroquine p. 536 and proguanil hydrochloride p. 539 may be used for periods of over 5 years. Mefloquine is licensed for up to 1 year (although, if it is tolerated in the short term, there is no evidence of harm when it is used for up to 3 years). Doxycycline can be used for up to 2 years. Malarone® can be used for up to 1 year. Prophylaxis with mefloquine, doxycycline, or Malarone® may be considered for longer durations if it is justified by the risk of exposure to malaria. Specialist advice should be sought for long-term prophylaxis.

Return from malarial region

It is important to be aware that any illness that occurs within 1 year and especially within 3 months of return might be malaria even if all recommended precautions against malaria were taken. Travellers should be warned of this and told that if they develop any illness particularly within 3 months of their return they should go immediately to a doctor and specifically mention their exposure to malaria.

Epilepsy

Both chloroquine p. 536 and mefloquine are unsuitable for malaria prophylaxis in individuals with a history of epilepsy. In areas without chloroquine resistance proguanil alone is recommended; in areas with chloroquine resistance, doxycycline or Malarone® may be considered.
Asplenia
Asplenic individuals (or those with severe splenic dysfunction) are at particular risk of severe malaria. If travel to malarious areas is unavoidable, rigorous precautions are required against contracting the disease.

Renal impairment
Avoidance (or dosage reduction) of proguanil hydrochloride p. 539 is recommended since it is excreted by the kidneys. Malarone® should not be used for prophylaxis in patients with estimated glomerular filtration rate less than 30 mL/minute/1.73m². Chloroquine p. 536 is only partially excreted by the kidneys and reduction of the dose for prophylaxis is not required except in severe impairment. Mefloquine is considered to be appropriate to use in renal impairment and does not require dosage reduction. Doxycycline is also considered to be appropriate.

Pregnancy
Travel to malarious areas should be avoided during pregnancy; if travel is unavoidable, effective prophylaxis must be used. Chloroquine and proguanil hydrochloride can be given in the usual doses during pregnancy, but these drugs are not appropriate for most areas because their effectiveness has declined, particularly in Sub-Saharan Africa; in the case of proguanil hydrochloride, folic acid p. 836 (dosed as a pregnancy at ‘high-risk’ of neural tube defects) should be given for at least the first trimester. The centres listed (see Malaria, treatment below) should be consulted for advice on prophylaxis in chloroquine-resistant areas. Although the manufacturer advises that mefloquine should not be used during pregnancy, particularly in the first trimester, unless the potential benefit outweighs the risk, studies of mefloquine in pregnancy (including use in the first trimester) indicate that it can be considered for travel to chloroquine-resistant areas. Doxycycline p. 496 is contra-indicated during pregnancy; however, it can be used for malaria prophylaxis if other regimens are unsuitable, and if the entire course of doxycycline can be completed before 15 weeks’ gestation [unlicensed]. Malarone® should be avoided during pregnancy, however, it can be considered during the second and third trimesters if there is no suitable alternative.

Breast-feeding
Prophylaxis is required in breast-fed infants; although antimalarials are present in milk, the amounts are too variable to give reliable protection.

Anticoagulants
Travellers taking warfarin sodium p. 121 should begin chemoprophylaxis 2–3 weeks before departure. The INR should be stable before departure. It should be measured before starting chemoprophylaxis, 7 days after starting, and after completing the course. For prolonged stays, the INR should be checked at regular intervals.

Standby treatment
Travellers visiting remote, malarious areas for prolonged periods should carry standby treatment if they are likely to be more than 24 hours away from medical care. Self-medication should be avoided if medical help is accessible. In order to avoid excessive self-medication, the traveller should be provided with written instructions that urgent medical attention should be sought if fever (38°C or more) develops 7 days (or more) after arriving in a malarious area and that self-treatment is indicated if medical help is not available within 24 hours of fever onset.

In view of the continuing emergence of resistant strains and of the different regimens required for different areas expert advice should be sought on the best treatment course for an individual traveller. A drug used for chemoprophylaxis should not be considered for standby treatment for the same traveller.

Specific recommendations
Where a journey requires two regimens, the regimen for the higher risk area should be used for the whole journey. Those travelling to remote or little-visited areas may require expert advice. See also Recommended regimens for prophylaxis against malaria p. 530

Important
Settled immigrants (or long-term visitors) to the UK may be unaware that any immunity they may have acquired while living in malarious areas is lost rapidly after migration to the UK, or that any non-malarious areas where they lived previously may now be malarious.

Malaria, treatment
A number of specialist centres are able to provide advice on specific problems.

Advice for healthcare professionals
PHE (Public Health England) Malaria Reference Laboratory (020) 7637 0248 (fax) (prophylaxis only) www.malaria-reference.co.uk
National Travel Health Network and Centre 0845 602 6712
Travel Medicine Team, Health Protection Scotland (registered users of Travax only) www.travax.nhs.uk (for registered users of the NHS Travax website only) (0141) 300 1100 (weekdays 2–4 p.m. only)
Birmingham (0121) 424 03587
Liverpool (0151) 705 3100
London 0845 155 5000 (treatment)
Oxford (01865) 225 430

Advice for travellers
Hospital for Tropical Diseases Travel Healthline (020) 7950 7799 www.fitfortravel.nhs.uk
WHO advice on international travel and health www.who.int/ith
National Travel Health Network and Centre (NaTHNaC) www.nathnac.org/travel/index.htm

Treatment of malaria
Recommendations on the treatment of malaria reflect guidelines agreed by UK malaria specialists.

If the infective species is not known, or if the infection is mixed, initial treatment should be for falciparum malaria with quinine p. 540, Malarone® (atovaquone with proguanil hydrochloride p. 536), or Riamet® (artemether with lumefantrine p. 534). Falciparum malaria can progress rapidly in unprotected individuals and antimalarial treatment should be considered in those with features of severe malaria and possible exposure, even if the initial blood tests for the organism are negative.

Falciparum malaria (treatment)
Falciparum malaria (malignant malaria) is caused by Plasmodium falciparum. In most parts of the world P. falciparum is now resistant to chloroquine p. 536 which should not therefore be given for treatment.

Quinine, Malarone® (atovaquone with proguanil hydrochloride p. 536), or Riamet® (artemether with lumefantrine) can be given by mouth if the patient can swallow and retain tablets and there are no serious manifestations (e.g. impaired consciousness); quinine should be given by intravenous infusion if the patient is seriously ill or unable to take tablets. Mefloquine p. 537 is now rarely used for treatment because of concerns about resistance.

Oral quinine is given by mouth for 5–7 days, together with or followed by either doxycycline p. 496 for 7 days or
### Key to recommended regimens for prophylaxis against malaria

<table>
<thead>
<tr>
<th>Codes for regimens</th>
<th>Details of regimens for prophylaxis against malaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chemoprophylaxis not recommended, but avoid mosquito bites and consider malaria if fever presents</td>
</tr>
<tr>
<td>2</td>
<td>Chloroquine only</td>
</tr>
<tr>
<td>3</td>
<td>Chloroquine with proguanil</td>
</tr>
<tr>
<td>4</td>
<td>Atovaquone with proguanil hydrochloride or doxycycline or mefloquine</td>
</tr>
<tr>
<td>5</td>
<td>Atovaquone with proguanil hydrochloride or doxycycline</td>
</tr>
</tbody>
</table>

### Specific recommendations

<table>
<thead>
<tr>
<th>Country</th>
<th>Comments on risk of malaria and regional or seasonal variation</th>
<th>Codes for regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afghanistan</td>
<td>Risk below 2000 m from May–November</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Low risk below 2000 m from December–April</td>
<td>1</td>
</tr>
<tr>
<td>Algeria</td>
<td>Very low risk in Illizi department only</td>
<td>1</td>
</tr>
<tr>
<td>Andaman and Nicobar Islands</td>
<td>Risk present</td>
<td>1</td>
</tr>
<tr>
<td>Angola</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Argentina</td>
<td>Low risk in low altitude areas of Salta provinces bordering Bolivia and in Chaco, Corrientes, and Misiones provinces close to border with Paraguay and Brazil</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No risk in Iguazu Falls and areas other than those above</td>
<td>1</td>
</tr>
<tr>
<td>Armenia</td>
<td>No risk</td>
<td>1</td>
</tr>
<tr>
<td>Azerbaijan</td>
<td>Low to no risk</td>
<td>1</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>High risk in Chittagong Hill Tract districts (but not Chittagong city)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Low to no risk in Chittagong city and other areas, except Chittagong Hill Tract districts</td>
<td>1</td>
</tr>
<tr>
<td>Belize</td>
<td>Low risk in rural areas</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No risk in Belize district (including Belize city and islands)</td>
<td>1</td>
</tr>
<tr>
<td>Benin</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Bhutan</td>
<td>Risk in southern belt districts, along border with India: Chukha, Geyleg-phug, Samchi, Samdrup Jonkar, and Shemgang</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Low to no risk in areas other than those above</td>
<td>1</td>
</tr>
<tr>
<td>Bolivia</td>
<td>High risk in Amazon basin</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Risk in rural areas below 2500 m (other than above)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No risk above 2500 m</td>
<td>1</td>
</tr>
<tr>
<td>Botswana</td>
<td>High risk from November–June in northern half, including Okavango Delta area</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Low risk from July–October in northern half; low to no risk all year in southern half</td>
<td>1</td>
</tr>
<tr>
<td>Brazil</td>
<td>Risk in Amazon basin, including city of Manaus</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Very low risk in areas other than those above, and no risk in Iguazu Falls</td>
<td>1</td>
</tr>
<tr>
<td>Brunei Darussalam</td>
<td>Very low risk</td>
<td>1</td>
</tr>
<tr>
<td>Burkina Faso</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Burundi</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Cambodia</td>
<td>High risk, with widespread chloroquine and mefloquine resistance, in western provinces bordering Thailand</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>High risk in areas other than those above and below</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Very low risk in Angkor Wat and Lake Tonle Sap, including Siem Reap; no risk in Phnom Penh</td>
<td>1</td>
</tr>
<tr>
<td>Cameroon</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Cape Verde</td>
<td>Very low risk on island of Santiago (Sao Tiago) and Boa Vista</td>
<td>1</td>
</tr>
<tr>
<td>Central African Republic</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Chad</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>China</td>
<td>High risk in Yunnan and Hainan provinces</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Very low risk in areas other than those above and below</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No risk in Hong Kong</td>
<td>1</td>
</tr>
<tr>
<td>Colombia</td>
<td>High risk in rural areas below 1600 m</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Low to no risk above 1600 m and in Cartagena</td>
<td>1</td>
</tr>
<tr>
<td>Country</td>
<td>Comments on risk of malaria and regional or seasonal variation</td>
<td>Codes for regimens</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Comoros</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Congo</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Costa Rica</td>
<td>Risk in Limon province (but not city of Limon)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Very low risk in areas other than those above</td>
<td>1</td>
</tr>
<tr>
<td>Côte d’Ivoire (Ivory Coast)</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Democratic Republic of the Congo</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Djibouti</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>Risk in all areas except cities of Santiago and Santo Domingo</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Cities of Santiago and Santo Domingo</td>
<td>1</td>
</tr>
<tr>
<td>East Timor (Timor-Leste)</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Ecuador</td>
<td>Risk in areas below 1500 m including coastal provinces and Amazon basin (no risk in Galapagos islands or city of Guayaquil)</td>
<td>4</td>
</tr>
<tr>
<td>Egypt</td>
<td>No risk</td>
<td>1</td>
</tr>
<tr>
<td>El Salvador</td>
<td>Low risk in rural areas of Santa Ana, Ahuachapán, and La Unión provinces in western part of country; low to no risk in other areas</td>
<td>1</td>
</tr>
<tr>
<td>Equatorial Guinea</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Eritrea</td>
<td>High risk below 2200 m</td>
<td>4</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>High risk below 2000 m</td>
<td>4</td>
</tr>
<tr>
<td>French Guiana</td>
<td>High risk (particularly in border areas) except city of Cayenne or Devil’s Island (Île du Diable)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>No risk in city of Cayenne or Devil’s Island (Île du Diable)</td>
<td>1</td>
</tr>
<tr>
<td>Gabon</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Gambia</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Georgia</td>
<td>Very low risk in rural south east from June–October</td>
<td>1</td>
</tr>
<tr>
<td>Ghana</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Guatemala</td>
<td>Low risk below 1500 m</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No risk in Guatemala City, Antigua, or Lake Atitlan</td>
<td></td>
</tr>
<tr>
<td>Guinea</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Guinea-Bissau</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Guyana</td>
<td>High risk in all interior regions</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Very low risk in Georgetown and coastal region</td>
<td></td>
</tr>
<tr>
<td>Haiti</td>
<td>Risk present</td>
<td>2</td>
</tr>
<tr>
<td>Honduras</td>
<td>Risk below 1000 m and in Roatán and other Bay Islands (no risk in San Pedro Sula or Tegucigalpa)</td>
<td>2</td>
</tr>
<tr>
<td>India</td>
<td>High risk in states of Assam and Orissa, districts of East Godavari, Srikakulam, Vishakhapatnam, and Vizianagaram in the state of Andhra Pradesh, and districts of Balaghat, Dindori, Mandla, and Seoni in the state of Madhya Pradesh</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Risk in areas other than those above or below (including Goa, Andaman and Nicobar islands)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No risk in Lakshadweep islands</td>
<td></td>
</tr>
<tr>
<td>Indonesia</td>
<td>High risk in Lombok and Irian Jaya (Papua)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Risk in areas other than those above or below</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Very low risk in Bali, and cities on islands of Java and Sumatra</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No risk in city of Jakarta</td>
<td></td>
</tr>
<tr>
<td>Indonesia (Borneo)</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Iran</td>
<td>Risk from March–November in rural south eastern provinces and in north, along Azerbaijan border in Ardabil, and near Turkmenistan border in North Khorasan</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Low to no risk in areas other than those above</td>
<td>1</td>
</tr>
<tr>
<td>Iraq</td>
<td>Very low risk from May–November in rural northern area below 1500 m</td>
<td>1</td>
</tr>
<tr>
<td>Kenya</td>
<td>High risk below 2500 m (except city of Nairobi)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Very low risk in the highlands above 2500 m and in city of Nairobi</td>
<td>1</td>
</tr>
<tr>
<td>Kyrgyzstan</td>
<td>Very low risk from June–October in southwest areas bordering Tajikistan and Uzbekistan</td>
<td>1</td>
</tr>
</tbody>
</table>
### Key to recommended regimens for prophylaxis against malaria

<table>
<thead>
<tr>
<th>Codes for regimens</th>
<th>Details of regimens for prophylaxis against malaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chemoprophylaxis not recommended, but avoid mosquito bites and consider malaria if fever presents</td>
</tr>
<tr>
<td>2</td>
<td>Chloroquine only</td>
</tr>
<tr>
<td>3</td>
<td>Chloroquine with proguanil</td>
</tr>
<tr>
<td>4</td>
<td>Atovaquone with proguanil hydrochloride or doxycycline or mefloquine</td>
</tr>
<tr>
<td>5</td>
<td>Atovaquone with proguanil hydrochloride or doxycycline</td>
</tr>
</tbody>
</table>

### Specific recommendations

<table>
<thead>
<tr>
<th>Country</th>
<th>Comments on risk of malaria and regional or seasonal variation</th>
<th>Codes for regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laos</td>
<td>High risk along the border with Myanmar in the provinces of Bokeo and Louang Namtha, and along the border with Thailand in the province of Champasak and Saravan; High risk in areas other than those above or below</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Low to no risk in city of Vientiane</td>
<td>1</td>
</tr>
<tr>
<td>Liberia</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Libya</td>
<td>No risk</td>
<td>1</td>
</tr>
<tr>
<td>Madagascar</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Malawi</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Malaysia</td>
<td>Risk in inland forested areas of peninsular Malaysia; Very low risk in rest of peninsular Malaysia, including Cameron Highlands and city of Kuala Lumpur</td>
<td>4</td>
</tr>
<tr>
<td>Mauritania</td>
<td>High risk all year in southern provinces, and from July-October in the north; Low risk from November-June in north</td>
<td>4</td>
</tr>
<tr>
<td>Mauritius</td>
<td>No risk</td>
<td>1</td>
</tr>
<tr>
<td>Mayotte</td>
<td>Risk present</td>
<td>4</td>
</tr>
<tr>
<td>Mexico</td>
<td>Low risk in Oaxaca and Chiapas</td>
<td>2</td>
</tr>
<tr>
<td>Mozambique</td>
<td>Very low risk in areas other than those above</td>
<td>1</td>
</tr>
<tr>
<td>Myanmar</td>
<td>High risk (but not in cities of Mandalay and Yangon); No risk in cities of Mandalay and Yangon</td>
<td>5</td>
</tr>
<tr>
<td>Namibia</td>
<td>High risk all year in regions of Caprivi Strip, Kavango, and Kunene river, and from November-June in northern third of country; Low to no risk in areas other than those above; low risk from July-October in northern third of country</td>
<td>4</td>
</tr>
<tr>
<td>Nepal</td>
<td>Risk below 1500 m, particularly in Terai district; No risk in city of Kathmandu and on typical Himalayan treks</td>
<td>3</td>
</tr>
<tr>
<td>Nicaragua</td>
<td>Low risk (except Managua); Very low risk in Managua</td>
<td>2</td>
</tr>
<tr>
<td>Niger</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>Nigeria</td>
<td>High risk</td>
<td>4</td>
</tr>
<tr>
<td>North Korea</td>
<td>Very low risk in some southern areas</td>
<td>1</td>
</tr>
<tr>
<td>Pakistan</td>
<td>Risk below 2000 m</td>
<td>3</td>
</tr>
<tr>
<td>Panama</td>
<td>Risk east of Canal Zone; Low risk west of Canal Zone; No risk in Panama City or Canal Zone itself</td>
<td>3</td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>High risk below 1800 m; Low to no risk above 1800 m</td>
<td>4</td>
</tr>
<tr>
<td>Paraguay</td>
<td>Low risk in departments of Alto Paraná and Caaguazú; Very low risk in areas other than those above</td>
<td>2</td>
</tr>
</tbody>
</table>

### Protozoal infection

<table>
<thead>
<tr>
<th>BNF 70</th>
<th>Protozoal infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>532</td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td>Comments on risk of malaria and regional or seasonal variation</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Peru</td>
<td>High risk in Amazon basin along border with Brazil, particularly in Loreto province. Risk in rural areas below 2000 m (other than those above and below) and in part of the Amazon basin that borders Bolivia. No risk in city of Lima and coastal region south of Chiclayo.</td>
</tr>
<tr>
<td>Philippines</td>
<td>Risk in rural areas below 600 m on islands of Luzon, Mindanao, Mindoro, and Palawan. No risk in cities or on islands of Boracay, Bohol, Catanduanes, Cebu, or Leyte.</td>
</tr>
<tr>
<td>Rwanda</td>
<td>High risk</td>
</tr>
<tr>
<td>São Tomé and Príncipe</td>
<td>High risk</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>Risk in south-western provinces along border with Yemen, including below 2000 m in Asir province. No risk in cities of Jeddah, Makkah (Mecca), Medina, Riyadh, or Ta’īl, or above 2000 m in Asir province.</td>
</tr>
<tr>
<td>Senegal</td>
<td>High risk</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>High risk</td>
</tr>
<tr>
<td>Solomon Islands</td>
<td>High risk</td>
</tr>
<tr>
<td>Somalia</td>
<td>High risk</td>
</tr>
<tr>
<td>South Africa</td>
<td>Moderate risk from September–May in low altitude areas of Mpumalanga and Limpopo, which border Mozambique and Zimbabwe (including Kruger National Park). Low risk in north-east KwaZulu-Natal. Low risk in areas bordering those above.</td>
</tr>
<tr>
<td>South Korea</td>
<td>Very low risk in northern areas, in Gangwon-do and Gyeonggi-do provinces, and Incheon city (towards Demilitarized Zone).</td>
</tr>
<tr>
<td>South Sudan</td>
<td>High risk</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>Low risk north of Vavuniya</td>
</tr>
<tr>
<td>Sudan</td>
<td>Very low risk in areas other than those above and below. No risk in Colombo or Kandy.</td>
</tr>
<tr>
<td>Sudan</td>
<td>High risk in central and southern areas; risk also present in rest of country (except Khartoum). Very low risk in Khartoum.</td>
</tr>
<tr>
<td>Suriname</td>
<td>High risk (except coastal districts or city of Paramaribo). Very low risk in coastal districts; no risk in city of Paramaribo.</td>
</tr>
<tr>
<td>Swaziland</td>
<td>High risk in northern and eastern regions bordering Mozambique and South Africa, including all of Lubombo district and Big Bend, Mhluwe, Simunye, and Tshaneni regions. Very low risk in the areas other than those above.</td>
</tr>
<tr>
<td>Syria</td>
<td>Very low risk in small, remote foci of El Hasakah.</td>
</tr>
<tr>
<td>Tajikistan</td>
<td>Risk below 2000 m from June–October. Low risk below 2000 m from November–May.</td>
</tr>
<tr>
<td>Tanzania</td>
<td>High risk below 1800 m; risk also in Zanzibar.</td>
</tr>
<tr>
<td>Thailand</td>
<td>High risk, with chloroquine and mefloquine resistance, in rural forested borders with Cambodia, Laos, and Myanmar. Very low risk in areas other than those above, including Kanchanaburi (Kwai Bridge); no risk in cities of Bangkok, Chiang Mai, Chiang Rai, Koh Phangam, Koh Samui, and Pattaya.</td>
</tr>
<tr>
<td>Togo</td>
<td>High risk</td>
</tr>
<tr>
<td>Turkey</td>
<td>Low risk from May–October along the border plain with Syria, around Adana and east of Adana.</td>
</tr>
<tr>
<td>Uganda</td>
<td>High risk</td>
</tr>
<tr>
<td>Uzbekistan</td>
<td>Very low risk in extreme south-east.</td>
</tr>
<tr>
<td>Vanuatu</td>
<td>Risk present</td>
</tr>
<tr>
<td>Venezuela</td>
<td>High risk in all areas south of, and including, the Orinoco river and Angel Falls. Risk in rural areas of Apure, Monagas, Sucre, and Zulia states. No risk in city of Caracas or on Margarita Island.</td>
</tr>
</tbody>
</table>
clindamycin p. 467 for 7 days [unlicensed].

If the parasite is likely to be sensitive, pyrimethamine with sulfadoxine p. 540 as a single dose [unlicensed] may be given (instead of either clindamycin p. 467 or doxycycline p. 496) together with, or after, a course of quinine. Alternatively, Malarone® or Riamet® may be given instead of quinine. It is not necessary to give clindamycin, doxycycline, or pyrimethamine with sulfadoxine after Malarone® or Riamet® treatment.

If the patient is seriously ill or unable to take tablets, or if more than 2% of red blood cell are parasitized, quinine should be given by intravenous infusion [unlicensed] (until patient can swallow tablets to complete the 7-day course together with or followed by either doxycycline p. 496 or clindamycin p. 467).

Specialist advice should be sought in difficult cases (e.g. very high parasite count, deterioration on optimal doses of quinine p. 540, infection acquired in quinine-resistant areas of south east Asia) because intravenous artesunate may be available for ‘named-patient’ use.

Pregnancy
Falciparum malaria is particularly dangerous in pregnancy, especially in the last trimester. The adult treatment doses or oral and intravenous quinine (including the loading dose) can safely be given to pregnant women. Clindamycin should be given after quinine [unlicensed indication]. Doxycycline should be avoided in pregnancy (affects teeth and skeletal development); pyrimethamine with sulfadoxine, Malarone®, and Riamet® are also best avoided without more information is available. Specialist advice should be sought in difficult cases (e.g. very high parasite count, deterioration on optimal doses of quinine, infection acquired in quinine-resistant areas of south east Asia) because intravenous artesunate may be available for ‘named patient’ use.

Non-falciparum malaria (treatment)
Non-falciparum malaria is usually caused by Plasmodium vivax and less commonly by P. ovale and P. malariae. P. knowlesi is also present in the Asia-Pacific region. Chloroquine p. 536 is the drug of choice for the treatment of non-falciparum malaria (but chloroquine-resistant P. vivax has been reported in the Indonesian archipelago, the Malay Peninsula, including Myanmar, and eastward to Southern Vietnam).

For the treatment of chloroquine-resistant non-falciparum malaria, Malarone® [unlicensed indication], quinine, or Riamet® [unlicensed indication] can be used; as with chloroquine p. 536, primaquine p. 538 should be given for radical cure. Chloroquine p. 536 alone is adequate for P. malariae and P. knowlesi infections but in the case of P. vivax and P. ovale, a radical cure (to destroy parasites in the liver and thus prevent relapses) is required. This is achieved with primaquine p. 538 [unlicensed] given after chloroquine, with the dose dependent on the infecting organism. For a radical cure, primaquine [unlicensed] is then given for 14 days, with the dose also dependent on the infecting organism.

Parenteral
Parenteral If the patient is unable to take oral therapy, quinine p. 540 can be given by intravenous infusion [unlicensed], changed to oral chloroquine p. 536 as soon as the patient’s condition permits.

Pregnancy
The adult treatment doses of chloroquine p. 536 can be given for non-falciparum malaria. In the case of P. vivax or P. ovale, however, the radical cure with primaquine p. 538 should be postponed until the pregnancy is over; instead chloroquine p. 536 should be continued, given weekly during the pregnancy.

Artemether with lumefantrine

INDICATIONS AND DOSE
Treatment of acute uncomplicated falciparum malaria | Treatment of chloroquine-resistant non-falciparum malaria

BY MOUTH

Adult (body-weight 35 kg and above): Initially 4 tablets, followed by 4 tablets for 5 doses each given at 8, 24, 36, 48, and 60 hours (total 24 tablets over 60 hours)
UNLICENSED USE Use in treatment of non-falciparum malaria is an unlicensed indication.

CONTRA-INDICATIONS Family history of congenital QT interval prolongation · family history of sudden death · history of arrhythmias · history of clinically relevant bradycardia · history of congestive heart failure accompanied by reduced left ventricular ejection fraction

CAUTIONS Avoid in Acute porphyrias p. 864 · electrolyte disturbances

INTERACTIONS → Appendix 1 (artemether with lumefantrine). Caution if concomitant use with other drugs known to cause QT-interval prolongation.

SIDE-EFFECTS

Common or very common Abdominal pain · anorexia · arthralgia · asthma · cough · diarrhoea · dizziness · headache · malaise · palpitation · paraesthesia · prolonged QT interval · pruritus · rash · sleep disturbances · vomiting

Uncommon Ataxia · clonus · hypoaesthesia

PREGNANCY Toxicity in animal studies with artemether. Manufacturer advises use only if potential benefit outweighs risk.

BRIOSEEDING Manufacturer advises avoid breastfeeding for at least 1 week after last dose. Present in milk in animal studies.

HEPATIC IMPAIRMENT Manufacturer advises caution in severe impairment.

RENAL IMPAIRMENT Manufacturer advises caution in severe impairment. In severe renal impairment monitor ECG and plasma potassium concentration.

MONITORING REQUIREMENTS Monitor patients unable to take food (greater risk of recrudescence).

DIRECTIONS FOR ADMINISTRATION Tablets may be crushed just before administration.

PATIENT AND CARER ADVICE Dizziness may affect performance of skilled tasks (e.g. driving).

MEDICINAL FORMS

Tablet

CAUTIONARY AND ADVISORY LABELS 21

Riamet (Nouartis Pharmaceuticals UK Ltd)

Artemether 20 mg, Lumefantrine 120 mg

Riamet tablets £22.50

Artemol with piperaquine phosphate (Piperaquine tetraphosphate with dihydroartemisinin)

INDICATIONS AND DOSE Treatment of uncomplicated falciparum malaria

BY MOUTH

→ Child 6 months-17 years (body-weight 7-12 kg): 0.5 tablet once daily for 3 days, max. 2 courses in 12 months; second course given at least 2 months after first course

→ Child 6 months-17 years (body-weight 13-23 kg): 1 tablet once daily for 3 days, max. 2 courses in 12 months; second course given at least 2 months after first course

→ Child 6 months-17 years (body-weight 24-35 kg): 2 tablets once daily for 3 days, max. 2 courses in 12 months; second course given at least 2 months after first course

→ Child 6 months-17 years (body-weight 36-74 kg): 3 tablets once daily for 3 days, max. 2 courses in 12 months;

second course given at least 2 months after first course

→ Adult (body-weight 36-74 kg): 3 tablets once daily for 3 days, max. 2 courses in 12 months; second course given at least 2 months after first course

→ Adult (body-weight 75 kg and over): 4 tablets once daily for 3 days, max. 2 courses in 12 months; second course given at least 2 months after first course

CONTRA-INDICATIONS Acute myocardial infarction · bradycardia · congenital long QT syndrome · electrolyte disturbances · family history of sudden death · heart failure with reduced left ventricular ejection fraction · history of symptomatic arrhythmias · left ventricular hypertrophy · risk factors for QT interval prolongation · severe hypertension

INTERACTIONS → Appendix 1 (artemol with piperaquine).

Piperaquine has a long half-life; there is a potential for drug interactions to occur for up to 3 months after treatment has been stopped. Concomitant use with other drugs known to prolong the QT interval contra-indicated.

SIDE-EFFECTS

Common or very common Abdominal pain (in children) · anaemia · blood disorders (in children) · conjunctivitis (in children) · cough (in children) · diarrhoea (in children) · headache (in adults) · irregular heart rate (in children) · leucopenia (in children) · malaise · QT interval prolonged · rash (in children) · tachycardia (in adults) · thrombocytopenia (in children) · vomiting (in children)

Uncommon Abdominal pain (in adults) · acanthosis (in children) · anaemia (in adults) · arthralgia · arthralgia · bradycardia (in adults) · convulsions · cough (in adults) · diarrhoea (in adults) · dizziness (in adults) · headache (in children) · heart murmur (in children) · hepatitis · hepatomegaly · influenza-like symptoms · jaundice (in children) · malathy (in adults) · nausea · pruritus (in adults) · stomatitis (in children) · vomiting (in adults)

PREGNANCY Teratogenic in animal studies—manufacturer advises use only if other antimalarials cannot be used.

BREAST FEEDING Manufacturer advises avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT No information available in moderate to severe impairment. Manufacturer advises monitor ECG and plasma-potassium concentration in moderate to severe hepatic impairment.

RENAL IMPAIRMENT No information available in moderate to severe impairment. Manufacturer advises monitor ECG and plasma-potassium concentration in moderate to severe renal impairment.

MONITORING REQUIREMENTS Obtain ECG as soon as possible after starting treatment then continue monitoring in those taking medicines that increase plasma-piperaquine concentration, in children who are vomiting, in females, or in the elderly.

Consider obtaining ECG in all patients before third dose and 4–6 hours after third dose.

If QTc interval more than 500 milliseconds, discontinue treatment and monitor ECG for a further 24–48 hours.

DIRECTIONS FOR ADMINISTRATION Tablets to be taken at least 3 hours before and at least 3 hours after food. Tablets may be crushed and mixed with water immediately before administration.

PATIENT AND CARER ADVICE Patients or carers should be given advice on how to administer tablets containing piperaquine phosphate with artemol.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.
Atovaquone with proguanil hydrochloride

INDICATIONS AND DOSE
MALARONE®

Prophylaxis of falciparum malaria, particularly where resistance to other antimalarial drugs suspected

BY MOUTH
- Adult (body-weight 11-20 kg): 1 tablet once daily for 3 days
- Adult (body-weight 21-30 kg): 2 tablets once daily for 3 days
- Adult (body-weight 31-40 kg): 3 tablets once daily for 3 days
- Adult (body-weight 41 kg and above): 4 tablets once daily for 3 days

Common or very common
- Headache
- Nausea
- Vomiting
- Abdominal pain
- Diarrhoea
- Rash
- Anosmia
- Dizziness
- Fever
- Tachycardia
- Hallucinations
- Hypersensitivity reactions
- Seizures
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis

Other
- Anemia
- Blood disorders
- Alopecia
- Anaphylaxis
- Anaphylactoid reactions
- Anorexia
- Anuria
- Arthralgia
- Arthritis
- Blood disorders
- Bone marrow depression
- Bronchitis
- Cough
- Dysuria
- Dyspepsia
- Erythematous rash
- Fever
- Headache
- Hypersensitivity reactions
- Itching
- Pruritus
- Tachycardia
- Vomiting

INTERACTIONS
- Avoid for malaria prophylaxis (and if eGFR less than 30 mL/minute/1.73m²).
- Treatment of non-falciparum malaria
- Initialy by mouth using syrup
- Child 6-11 months (body-weight 8-11 kg): 75 mg once weekly, started 1 week before entering endemic area and continued for 4 weeks after leaving
- Child 1-2 years (body-weight 11-15 kg): 100 mg once weekly, started 1 week before entering endemic area and continued for 4 weeks after leaving
- Child 3-4 years (body-weight 15-16.5 kg): 125 mg once weekly, started 1 week before entering endemic area and continued for 4 weeks after leaving
- Child 4-7 years (body-weight 16.5-25 kg): 150 mg once weekly, alternatively (by mouth using tablets) 155 mg once weekly, started 1 week before entering endemic area and continued for 4 weeks after leaving
- Child 8-12 years (body-weight 25-45 kg): 225 mg once weekly, alternatively (by mouth using tablets) 232.5 mg once weekly, started 1 week before entering endemic area and continued for 4 weeks after leaving
- Child 13-17 years (body-weight 45 kg and above): 310 mg once weekly, started 1 week before entering endemic area and continued for 4 weeks after leaving
- Adult (body-weight 45 kg and above): 310 mg once weekly, started 1 week before entering endemic area and continued for 4 weeks after leaving

Doses at extremes of body-weight
- Initialy by mouth using syrup
- Child: Initially 10 mg/kg (max. per dose 620 mg), then 5 mg/kg after 6–8 hours (max. per dose 310 mg), then 5 mg/kg daily (max. per dose 310 mg) for 2 days
- Adult: Initially 620 mg, then 310 mg after 6–8 hours, then 310 mg daily for 2 days, approximate total cumulative dose of 25 mg/kg of base

R. vivax or P. ovale infection during pregnancy while radical cure is postponed

Tablet
- Aspirin 325 mg
- Paracetamol 125 mg

Chloroquine

INDICATIONS AND DOSE

Active rheumatoid arthritis (administered on expert advice)
- Systemic and discoid lupus erythematosus (administered on expert advice)

BY MOUTH
- Adult: 150 mg daily; maximum 2.5 mg/kg per day

Prophylaxis of malaria

INITIALLY BY MOUTH USING SYRUP
- Child 6 weeks–5 months (body-weight 4.5-8 kg): 50 mg once weekly, started 1 week before entering endemic area and continued for 4 weeks after leaving
- Child 6-11 months (body-weight 8-11 kg): 75 mg once weekly, started 1 week before entering endemic area and continued for 4 weeks after leaving
- Child 1-2 years (body-weight 11-15 kg): 100 mg once weekly, started 1 week before entering endemic area and continued for 4 weeks after leaving
- Child 3-4 years (body-weight 15-16.5 kg): 125 mg once weekly, started 1 week before entering endemic area and continued for 4 weeks after leaving
- Child 4-7 years (body-weight 16.5-25 kg): 150 mg once weekly, alternatively (by mouth using tablets) 155 mg once weekly, started 1 week before entering endemic area and continued for 4 weeks after leaving
- Child 8-12 years (body-weight 25-45 kg): 225 mg once weekly, alternatively (by mouth using tablets) 232.5 mg once weekly, started 1 week before entering endemic area and continued for 4 weeks after leaving
- Child 13-17 years (body-weight 45 kg and above): 310 mg once weekly, started 1 week before entering endemic area and continued for 4 weeks after leaving
- Adult (body-weight 45 kg and above): 310 mg once weekly, started 1 week before entering endemic area and continued for 4 weeks after leaving

TREATMENT OF NON-FALCIPARUM MALARIA

BY MOUTH
- Child: Initially 10 mg/kg (max. per dose 620 mg), then 5 mg/kg after 6–8 hours (max. per dose 310 mg), then 5 mg/kg daily (max. per dose 310 mg) for 2 days
- Adult: Initially 620 mg, then 310 mg after 6–8 hours, then 310 mg daily for 2 days, approximate total cumulative dose of 25 mg/kg of base

Doses at extremes of body-weight

In active rheumatoid arthritis and systemic and discoid lupus erythematosus, to avoid excessive dosage in obese patients, the daily maximum dose should be calculated on the basis of ideal body weight.

Dose equivalence and conversion
- Doses expressed as chloroquine base. Chloroquine base 150 mg = chloroquine sulfate 200 mg = chloroquine phosphate 250 mg (approx).
UNLICENSED USE Chloroquine doses for the treatment and prophylaxis of malaria in BNF publications may differ from those in product literature.

**Important safety information**
Ocular toxicity is unlikely if the adult dose of chloroquine phosphate does not exceed 4 mg/kg daily (equivalent to chloroquine base approx. 2.5 mg/kg daily).

**CAUTIONS** Acute porphyrias p. 864 - elderly · G6PD deficiency · long-term therapy (regular ophthalmic examination recommended by manufacturers) - may aggravate myasthenia gravis · may exacerbate psoriasis · neurological disorders, especially epilepsy (avoid for prophylaxis of malaria if history of epilepsy) · severe gastro-intestinal disorders

**CAUTIONS, FURTHER INFORMATION**
Screening for ocular toxicity A review group convened by the Royal College of Ophthalmologists has updated guidelines for screening adults to prevent ocular toxicity on long-term treatment with chloroquine and hydroxychloroquine (*Hydroxychloroquine and Ocular Toxicity: Recommendations on Screening 2009*).

Chloroquine should be considered (for treating chronic inflammatory conditions) only if other drugs have failed. All patients taking chloroquine should receive ophthalmic examination according to a protocol arranged locally between the prescriber and the ophthalmologist.

**INTERACTIONS → Appendix 1 (chloroquine, hydroxychloroquine).**
Avoid concurrent therapy with hepatotoxic drugs.

**SIDE-EFFECTS**
- **Common or very common** Gastro-intestinal disturbances · headache · pruritus · rashes · skin reactions
- **Uncommon** Convulsions · discoloration of mucous membranes · discoloration of nails · discoloration of skin · ECG changes · hair depigmentation · hair loss · keratopathy · otoxicity · retinal damage · visual changes
- **Rare** Acute generalised exanthematous pustulosis · agranulocytosis · angioedema · aplastic anaemia · blood disorders · bone marrow suppression · cardiomyopathy · emotional disturbances · exfoliative dermatitis · hepatic damage · hypersensitivity reactions · mental changes · myopathy · neuromyopathy · photosensitivity · psychosis · Stevens-Johnson syndrome · thrombocytopenia · urticaria
- **Frequency not known** Diffuse parenchymal lung disease · drug rash with eosinophilia and systemic symptoms · extrapyramidal symptoms (associated with use in malaria) · hypotension · visual disturbances · bronchospasm (in children)

**SIDE-EFFECTS, FURTHER INFORMATION**
**Malaria prophylaxis and treatment** Serious skin reactions, ECG changes, visual effects, otoxicity, blood disorders, mental changes, myopathies and hepatic damage are not usually associated with malaria prophylaxis or treatment.

**Overdose** Chloroquine is very toxic in overdosage; overdosage is extremely hazardous and difficult to treat. Urgent advice from the National Poisons Information Service is essential. Life-threatening features include arrhythmias (which can have a very rapid onset) and convulsions (which can be intractable).

**PREGNANCY** Benefit of use in prophylaxis and treatment in malaria outweighs risk. For rheumatoid disease, it is not necessary to withdraw an antimalarial drug during pregnancy if the disease is well controlled.

**BREAST FEEDING** Present in breast milk and breast-feeding should be avoided when used to treat rheumatic disease. Amount in milk probably too small to be harmful when used for malaria.

**HEPATIC IMPAIRMENT** Use with caution in moderate to severe impairment.

**RENAL IMPAIRMENT** Only partially excreted by the kidneys and reduction of the dose is not required for prophylaxis of malaria except in severe impairment. For rheumatoid arthritis and lupus erythematosus, reduce dose. Manufacturers advise caution.

**MONITORING REQUIREMENTS**
- in adults Manufacturers recommend regular ophthalmological examination but the evidence of practical value is unsatisfactory.
- in children Ophthalmic examination with long-term therapy.

**PATIENT AND CARER ADVICE** Warn travellers going to malaria-prone areas about importance of avoiding mosquito bites, importance of taking prophylaxis regularly, and importance of immediate visit to doctor if ill within 1 year and especially within 3 months of return.

**NATIONAL FUNDING/ACCESS DECISIONS**
NHS restrictions Drugs for malaria prophylaxis not prescribable on the NHS; health authorities may investigate circumstances under which antimalarials are prescribed.

**EXCEPTIONS TO LEGAL CATEGORY** Can be sold to the public provided it is licensed and labelled for the prophylaxis of malaria.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
CAUTIONARY AND ADVISORY LABELS 5
- **Avloclor** (Alliance Pharmaceuticals Ltd) Chloroquine phosphate 250 mg Avloclor 250mg tablets | 20 tablet [Pack] £4.90 DT price = £4.90

**Oral solution**
CAUTIONARY AND ADVISORY LABELS 5
- **Malarivon** (Wallace Manufacturing Chemists Ltd) Chloroquine phosphate 16 mg per 1 ml Malarivon 80mg/5ml syrup | 75 ml [Pack] £10.85

**Chloroquine with proguanil**
The properties listed below are those particular to the combination only. For the properties of the components please consider, proguanil hydrochloride p. 539, chloroquine p. 536.

**INDICATIONS AND DOSE**
Prophylaxis of malaria
BY MOUTH
- Adult: (consult product literature)

**EXCEPTIONS TO LEGAL CATEGORY** Can be sold to the public provided it is licensed and labelled for the prophylaxis of malaria.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablets**
CAUTIONARY AND ADVISORY LABELS 5, 21
- **CHLOROQUINE WITH PROGUANIL** (Non-proprietary) Paludrine/Avloclor tablets anti-malarial travel pack | 112 tablet [Pack] £11.75

**Mefloquine**

**INDICATIONS AND DOSE**
Treatment of malaria
BY MOUTH
- Adult: (consult product literature)
## Prophylaxis of malaria

### BY MOUTH
- **Child (body-weight 5-15 kg):** 62.5 mg once weekly, dose to be started 2–3 weeks before entering endemic area and continued for 4 weeks after leaving.
- **Child (body-weight 16-24 kg):** 125 mg once weekly, dose to be started 2–3 weeks before entering endemic area and continued for 4 weeks after leaving.
- **Child (body-weight 25-44 kg):** 187.5 mg once weekly, dose to be started 2–3 weeks before entering endemic area and continued for 4 weeks after leaving.
- **Child 1-17 years (body-weight 45 kg and above):** 250 mg once weekly, dose to be started 2–3 weeks before entering endemic area and continued for 4 weeks after leaving.
- **Adult (body-weight 45 kg and above):** 250 mg once weekly, dose to be started 2–3 weeks before entering endemic area and continued for 4 weeks after leaving.

### UNLICENSED USE
Mefloquine doses in BNF Publications may differ from those in product literature. Not licensed for use in children under 5 kg body-weight and under 3 months.

### CONTRA-INDICATIONS
Avoid for prophylaxis if history of psychiatric disorders (including depression) or convulsions - avoid for standby treatment if history of convulsions - history of blackwater fever.

### CAUTIONS
Cardiac conduction disorders - epilepsy (avoid for prophylaxis) - not recommended in infants under 3 months (5 kg) - traumatic brain injury.

### CAUTIONS, FURTHER INFORMATION

#### Neuropsychiatric reactions
Mefloquine is associated with potentially serious neuropsychiatric reactions. Abnormal dreams, insomnia, anxiety, and depression occur commonly. Psychosis, suicidal ideation, and suicide have also been reported. Psychiatric symptoms such as nightmares, acute anxiety, depression, restlessness, or confusion should be regarded as potentially prodomal for a more serious event. If neuropsychiatric symptoms occur, patients should be advised to discontinue mefloquine and to seek immediate medical attention so that mefloquine can be replaced with an alternative antimalarial. Adverse reactions may occur and persist up to several months after discontinuation because mefloquine has a long half-life. Mefloquine is contraindicated for malaria prophylaxis in those with a history of psychiatric disorders or convulsions.

### INTERACTIONS
- Appendix 1 (mefloquine).

### SIDE-EFFECTS
- **Common or very common**
  - Abdominal pain
  - Diarrhoea
  - Dizziness
  - Headache
  - Nausea
  - Neuropsychiatric reactions
  - Pruritus
  - Visual disturbances
  - Vomiting
- **Very rare**
  - Optic neuropathy
  - Frequency not known
  - Alopecia
  - Anemia
  - Anorexia
  - Arthralgia
  - Ataxia
  - Blood disorders
  - Bradycardia
  - Cataract
  - Chest pain
  - Confusion
  - Drowsiness
  - Dyspepsia
  - Dysphonia
  - Encephalopathy
  - Fever
  - Flushing
  - Hepatic failure
  - Hyperhidrosis
  - Hypertension
  - Hypotension
  - Leucocytosis
  - Malaria
  - Motor neuropathies
  - Muscle weakness
  - Myalgia
  - Oedema
  - Palpitation
  - Panic attacks
  - Pneumonitis
  - Rash
  - Seizures
  - Sensory neuropathies
  - Speech disturbances
  - Stevens-Johnson syndrome
  - Syncpe
  - Tachycardia
  - Thrombocytopenia
  - Tremor
  - Vestibular disorders

### ALLERGY AND CROSS-SENSITIVITY
Contra-indicated in patients with hypersensitivity to quinine.

### CONCEPTION AND CONTRACEPTION
Manufacturer advises adequate contraception during prophylaxis and for 3 months after stopping (teratogenicity in animal studies).

### PREGNANCY
Manufacturer advises avoid (particularly in the first trimester) unless the potential benefit outweighs the risk; however, studies of mefloquine in pregnancy (including use in the first trimester) indicate that it can be considered for travel to chloroquine-resistant areas.

### BREAST FEEDING
Present in milk but risk to infant minimal.

### HEPATIC IMPAIRMENT
Elimination may be prolonged; avoid in severe impairment.

### RENAL IMPAIRMENT
Manufacturer advises caution.

### DIRECTIONS FOR ADMINISTRATION
Tablet may be crushed and mixed with food such as jam or honey just before administration.

### PATIENT AND CARER ADVICE
Inform travellers about adverse reactions of mefloquine and, if they occur, to seek medical advice on alternative antimalarials before the next dose is due. Also warn travellers about importance of avoiding mosquito bites, importance of taking prophylaxis regularly, and importance of immediate visit to doctor if ill within 1 year and especially within 3 months of return. Dizziness or a disturbed sense of balance may affect performance of skilled tasks (e.g. driving); effects may occur and persist up to several months after stopping mefloquine.

### NATIONAL FUNDING/ACCESS DECISIONS
NHS restrictions
- Drugs for malaria prophylaxis not prescribable on the NHS; health authorities may investigate circumstances under which antimalarials prescribed.

### MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

#### Tablet
- **CAUTIONARY AND ADVISORY LABELS** 21, 27
- **Lariam (Roche Products Ltd)**
  - **Mefloquine** (as Mefloquine hydrochloride) 250 mg
  - Lariam 250mg tablets | 8 tablet [Pack] £14.53

## Primquine

### INDICATIONS AND DOSE
Adjunct in the treatment of non-falciparum malaria caused by *P. vivax* infection

#### BY MOUTH
- **Adult:** 30 mg daily for 14 days

Adjunct in the treatment of non-falciparum malaria caused by *P. ovale* infection

#### BY MOUTH
- **Adult:** 15 mg daily for 14 days

### CONTRA-INDICATIONS
Adjunct in the treatment of non-falciparum malaria caused by *P. vivax* infection in patients with mild 6GPD deficiency (administered on expert advice)

### BY MOUTH
- **Adult:** 45 mg once weekly for 8 weeks

Treatment of mild to moderate pneumocystis infection (in combination with clindamycin)

#### BY MOUTH
- **Adult:** 30 mg daily, this combination is associated with considerable toxicity

### UNLICENSED USE
Not licensed.

### CAUTIONS
- 6GPD deficiency - systemic diseases associated with granulocytopenia (e.g. juvenile idiopathic arthritis, rheumatoid arthritis, lupus erythematosus)

### INTERACTIONS
- Appendix 1 (primquine).
Proguanil hydrochloride

INDICATIONS AND DOSE
Prophylaxis of malaria

BY MOUTH
- Child up to 11 weeks (body-weight up to 6 kg): 25 mg once daily, dose to be started 1 week before entering endemic area and continued for 4 weeks after leaving
- Child 3-11 months (body-weight 6-9 kg): 50 mg once daily, dose to be started 1 week before entering endemic area and continued for 4 weeks after leaving
- Child 1-3 years (body-weight 10-16 kg): 75 mg once daily, dose to be started 1 week before entering endemic area and continued for 4 weeks after leaving
- Child 4-7 years (body-weight 16-25 kg): 100 mg once daily, dose to be started 1 week before entering endemic area and continued for 4 weeks after leaving
- Child 8-12 years (body-weight 25-45 kg): 150 mg once daily, dose to be started 1 week before entering endemic area and continued for 4 weeks after leaving
- Child 13-17 years (body-weight 46 kg and above): 200 mg once daily, dose to be started 1 week before entering endemic area and continued for 4 weeks after leaving
- Adult 200 mg once daily, dose to be started 1 week before entering endemic area and continued for 4 weeks after leaving

UNLICENSED USE
Proguanil doses in BNF Publications may differ from those in product literature.

INTERACTIONS
- Appendix 1 (proguanil).

SIDE-EFFECTS
- Common or very common Abdominal pain, nausea, vomiting
- Uncommon Haemolytic anaemia especially in G6PD deficiency, leucopenia, thrombocytopenia
- PREGNANCY Risk of neonatal haemolysis and methaemoglobinaemia
- BREAST FEEDING Risk of haemolysis in G6PD-deficient infants
- PRE-TREATMENT SCREENING Before starting primaquine, blood should be tested for glucose-6-phosphate dehydrogenase (G6PD) activity since the drug can cause haemolysis in G6PD-deficient patients. Specialist advice should be obtained in G6PD deficiency.

INTERACTIONS
- Primaquine (as Primaquine phosphate) 7.5 mg tablets | 100 tablet no price available

Pyrimethamine

INDICATIONS AND DOSE
Toxoplasmosis in pregnancy (in combination with sulfadiazine and folic acid)

BY MOUTH
- Adult: 50 mg once daily until delivery

Congenital toxoplasmosis (in combination with sulfadiazine and folic acid)

BY MOUTH
- Adult 18-28 years: 1 mg/kg twice daily for 2 days, then 1 mg/kg once daily for 5 months, then 1 mg/kg 3 times a week for 6 months
- Malaria
- Adult: No dose stated because not recommended alone

CAUTIONS
- History of seizures—avoid large loading doses · predisposition to folate deficiency

INTERACTIONS
- Appendix 1 (pyrimethamine).

SIDE-EFFECTS
- Common or very common Anaemia (with high doses) · blood disorders (with high doses) · diarrhea · dizziness · headache · leucopenia · nausea · rash · thrombocytopenia · vomiting
- Uncommon Abnormal skin pigmentation · fever · Very rare Buccal ulceration · colic · convulsions
- PREGNANCY Theoretical teratogenic risk in first trimester (folate antagonist). Adequate folate supplements should be given to the mother.

BREAST FEEDING
- Significant amount in milk—avoid administration of other folate antagonists to infant. Avoid breast-feeding during toxoplasmosis treatment.

HEPATIC IMPAIRMENT
- Manufacturer advises caution.

RENAL IMPAIRMENT
- Manufacturer advises caution.
**Pyrimethamine with sulfadoxine**

**INDICATIONS AND DOSE**

Adjunct to quinine in treatment of Plasmodium falciparum

**Adults**

- Oral: 500 mg daily for 3 days (max. 1500 mg total).
- Intravenous: 75 mg/m² body surface area per day (max. 3000 mg total).

**Children**

- Oral: 40 mg/m² body surface area per day (max. 1000 mg total).
- Intravenous: 60 mg/m² body surface area per day (max. 1500 mg total).

**SIDE-EFFECTS**

- Acute agranulocytosis, aplastic anaemia, aplastic crisis, aplastic crisis on long-term use.
- Convulsions (severe side-effects on long-term use).
- Photosensitivity.
- Interstitial nephritis.
- Pulmonary infiltrates.
- Aseptic meningitis.
- Aseptic meningitis.
- Arthralgia.
- Headache.
- Rash.
- Vertigo.
- Hypoglycaemia.
- Hepatic necrosis.
- Pancreatitis.
- Megaloblastic anaemia.
- Megaloblastic anaemia.
- Vertigo.
- Hypoglycaemia.
- Hepatic necrosis.
- Pancreatitis.
- Megaloblastic anaemia.
- Megaloblastic anaemia.
- Vertigo.
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- Hepatic necrosis.
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- Megaloblastic anaemia.
- Megaloblastic anaemia.
- Vertigo.
- Hypoglycaemia.
- Hepatic necrosis.
- Pancreatitis.
- Megaloblastic anaemia.
- Megaloblastic anaemia.
- Vertigo.
- Hypoglycaemia.
6 Viral infection

6.1 Hepatitis

Hepatitis

Treatment for viral hepatitis should be initiated by a specialist. The management of uncomplicated acute viral hepatitis is largely symptomatic. Early treatment of acute hepatitis C with interferon alfa p. 794 [unlicensed indication] may reduce the risk of chronic infection. Hepatitis B and hepatitis C viruses are major causes of chronic hepatitis. Active or passive immunisation against hepatitis A and B infections can be given.

Hepatitis B, chronic

Peginterferon alfa p. 542 is an option for the initial treatment of chronic hepatitis B and may be preferable to interferon alfa. The use of peginterferon alfa and interferon alfa is limited by a response rate of 30–40% and relapse is frequent. Treatment should be discontinued if no improvement occurs after 4 months. The manufacturers of peginterferon alfa-2a and interferon alfa contraindicate use in decompensated liver disease, but low doses can be used with great caution in these patients. Although interferon alfa is contra-indicated in patients receiving immunosuppressant treatment (or who have received it recently), caution of peginterferon alfa-2a may be justified in some cases.

Entecavir p. 543 or tenofovir disoproxil p. 564 are options for the initial treatment of chronic hepatitis B. If the response is inadequate after 6–9 months of treatment, a change in treatment should be considered. Other drugs that are licensed for the treatment of chronic hepatitis B include adefovir dipivoxil p. 544, lamivudine p. 563, or telbivudine p. 544.

Entecavir p. 543 alone, tenofovir disoproxil p. 564 alone, or a combination of lamivudine with either adefovir dipivoxil or tenofovir disoproxil can be used in patients with decompensated liver disease.

If drug-resistant hepatitis B virus emerges during treatment, another antiviral drug to which the virus is sensitive should be added. Hepatitis B viruses with reduced susceptibility to lamivudine have emerged following extended therapy. Adefovir dipivoxil or tenofovir disoproxil can be given with lamivudine in lamivudine-resistant chronic hepatitis B; telbivudine p. 544 or entecavir p. 543 should not be used because cross-resistance can occur.

If there is no toxicity or loss of efficacy, treatment with adefovir dipivoxil, entecavir, lamivudine, telbivudine, or tenofovir disoproxil is usually continued until 6 months after adequate seroconversion has occurred. Treatment is usually continued long-term in patients with decompensated liver disease.

Tenofovir disoproxil, or a combination of tenofovir disoproxil with either emtricitabine p. 563 or lamivudine may be used with other antiretrovirals, as part of ‘highly active antiretroviral therapy’ in patients who require treatment for both HIV and chronic hepatitis B. If patients infected with both HIV and chronic hepatitis B only require treatment for chronic hepatitis B, they should receive antivirals that are not active against HIV, such as peginterferon alfa p. 542 or adefovir dipivoxil. Treatment may be continued long-term, even if adequate seroconversion occurs. Management of these patients should be coordinated between HIV and hepatology specialists.

Hepatitis C, chronic

Before starting treatment, the genotype of the infecting hepatitis C virus should be determined and the viral load...
measured as this may affect the choice and duration of treatment. A combination of ribavirin p. 545 and peginterferon alpha below is used for the treatment of chronic hepatitis C. The combination of ribavirin and interferon alpha is less effective than the combination of peginterferon alpha and ribavirin. Peginterferon alpha alone should be used if ribavirin is contra-indicated or not tolerated. Ribavirin monotherapy is ineffective.

Boceprevir p. 547 and telaprevir p. 548 are protease inhibitors that inhibit the replication of hepatitis C virus genotype 1, but they are less effective against other genotypes of the virus. Monotherapy is not recommended because there is a high likelihood of resistance developing. Either boceprevir or telaprevir is licensed for use in combination with ribavirin and peginterferon alpha for the treatment of chronic hepatitis C infection of genotype 1 in patients with compensated liver disease; these combinations are more effective than dual therapy with ribavirin and peginterferon alpha. However, triple therapy is associated with a higher incidence and greater severity of anaemia than dual therapy. Neutropenia seems to be more frequent during treatment with regimens containing boceprevir than with those containing telaprevir. Rash is a particular concern with telaprevir, and to a lesser extent with boceprevir.

Daclatasvir p. 544 is licensed for use in combination with sofosbuvir p. 546 for the treatment of chronic hepatitis C infection of genotypes 1 or 4, with or without compensated cirrhosis; the addition of ribavirin should be considered for patients with advanced liver disease or with other negative prognostic factors, such as prior treatment experience. It is also licensed in combination with sofosbuvir and ribavirin for the treatment of chronic hepatitis C infection of genotype 3 in patients who are treatment experienced, with or without compensated cirrhosis, and in combination with peginterferon alpha and ribavirin for the treatment of chronic hepatitis C infection of genotype 4. Daclatasvir p. 544 must not be given as monotherapy.

Sofosbuvir is a pro-drug of a nucleoside inhibitor that is effective against hepatitis C virus polymerase NS5B. It is licensed for use in combination with ribavirin, with or without peginterferon alpha, for the treatment of chronic hepatitis C infection of genotypes 1, 2, 3, 4, 5, or 6 in patients with compensated liver disease. Sofosbuvir monotherapy is not recommended because it is less effective than combination therapy.

Simeprevir p. 548 is licensed for use in combination with ribavirin and peginterferon alfa for the treatment of chronic hepatitis C infection of genotype 1 or 4; regimens containing peginterferon alfa-2b are less effective than those containing peginterferon alfa-2a. Simeprevir may also be used in combination with sofosbuvir, with or without ribavirin p. 545, for the urgent treatment of chronic hepatitis C infection of genotypes 1 or 4 only when peginterferon alfa cannot be used because of intolerance or contra-indications. Simeprevir monotherapy is not recommended.

6.2 **Hepatitis B, chronic**

**INTERFERONS**

**Peginterferon alfa**

- **Drug action** Polyethylene glycol-conjugated ('pegylated') derivatives of interferon alfa (peginterferon alfa-2a and peginterferon alfa-2b) are available; pegylation increases the persistence of the interferon in the blood.

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**INDICATIONS AND DOSE**

**PEGASYS®**

Combined with ribavirin for chronic hepatitis C | Monotherapy for chronic hepatitis C if ribavirin not tolerated or contra-indicated | Monotherapy for chronic hepatitis B

**BY SUBCUTANEOUS INJECTION**

- Adults: (consult product literature)

**VIRAFERONPEG®**

Combined with ribavirin for chronic hepatitis C | Combined with ribavirin and boceprevir for chronic hepatitis C infection of genotype 1 in patients with compensated liver disease | Monotherapy for chronic hepatitis C if ribavirin not tolerated or contra-indicated

**BY SUBCUTANEOUS INJECTION**

- Adults: (consult product literature)
● treated previously with interferon alfa alone or in combination with ribavirin;
● whose condition did not respond to peginterferon alfa alone or to a combination of peginterferon alfa and ribavirin, or responded but subsequently relapsed;
● co-infected with HIV.

Peginterferon alfa alone should be used if ribavirin is contra-indicated or not tolerated. Interferon alfa for either monotherapy or combined therapy should be used only if neutropenia and thrombocytopenia are a particular risk. Patients receiving interferon alfa may be switched to peginterferon alfa. www.nice.org.uk/TA200

● MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

EXCIPIENTS: May contain Benzyl alcohol

▶ Peginterferon alfa-2a 180 microgram per 1 ml Pegasis 90micrograms/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (PO) £66.46
Peginterferon alfa-2a 270 microgram per 1 ml Pegasis 135micrograms/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (PO) £107.76
Pegasis 135micrograms/0.5ml solution for injection pre-filled pen | 1 pre-filled disposable injection (PO) £107.76
Peginterferon alfa-2a 360 microgram per 1 ml Pegasis 180micrograms/0.5ml solution for injection pre-filled syringes | 4 pre-filled disposable injection (PO) £497.60
Pegasis 180micrograms/0.5ml solution for injection pre-filled pen | 4 pre-filled disposable injection (PO) £497.60

Powder and solvent for solution for injection

▶ ViraferonPeg (Mercer Sharp & Dohme Ltd)
Peginterferon alfa-2b 50 microgram ViraferonPeg 50microgram powder and solvent for solution for injection pre-filled disposable devices | 1 pre-filled disposable injection (PO) £66.46
ViraferonPeg 50microgram powder and solvent for solution for injection pre-filled disposable devices CLEARCLICK | 1 pre-filled disposable injection (PO) £66.46
Peginterferon alfa-2b 80 microgram ViraferonPeg 80microgram powder and solvent for solution for injection pre-filled disposable devices CLEARCLICK | 1 pre-filled disposable injection (PO) £106.34
ViraferonPeg 80microgram powder and solvent for solution for injection pre-filled disposable devices CLEARCLICK | 1 pre-filled disposable injection (PO) £106.34
Peginterferon alfa-2b 100 microgram ViraferonPeg 100microgram powder and solvent for solution for injection pre-filled disposable devices CLEARCLICK | 1 pre-filled disposable injection (PO) £132.92
ViraferonPeg 100microgram powder and solvent for solution for injection pre-filled disposable devices | 1 pre-filled disposable injection (PO) £132.92
Peginterferon alfa-2b 120 microgram ViraferonPeg 120microgram powder and solvent for solution for injection pre-filled disposable devices CLEARCLICK | 1 pre-filled disposable injection (PO) £159.51
ViraferonPeg 120microgram powder and solvent for solution for injection pre-filled disposable devices CLEARCLICK | 1 pre-filled disposable injection (PO) £159.51
Peginterferon alfa-2b 150 microgram ViraferonPeg 150microgram powder and solvent for solution for injection pre-filled disposable devices CLEARCLICK | 1 pre-filled disposable injection (PO) £199.38

NUCLEOSIDE ANALOGUES

Entecavir

INDICATIONS AND DOSE

Chronic hepatitis B in patients with compensated liver disease (with evidence of viral replication, and histologically documented active liver inflammation or fibrosis) is not previously treated with nucleoside analogues

BY MOUTH

▶ Adult: 500 micrograms once daily

Chronic hepatitis B in patients with decompensated liver disease

BY MOUTH

▶ Adult: 1 mg once daily

● CAUTIONS

HIV infection—risk of HIV resistance in patients not receiving ‘highly active antiretroviral therapy’ - lamivudine-resistant chronic hepatitis B—risk of entecavir resistance

CAUTIONS, FURTHER INFORMATION
Discontinue if deterioration in liver function, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis.

SIDE-EFFECTS

▶ Common or very common Diarrhoea - dizziness - dyspepsia - fatigue - headache - nausea - raised serum amylase - raised serum lipase - sleep disturbances - vomiting

▶ Uncommon Alopecia - rash - thrombocytopenia

CONCEPTION AND CONTRACEPTION
Effective contraception required during treatment.

PREGNANCY

Toxicty in animal studies—manufacturer advises use only if potential benefit outweighs risks.

BREAST FEEDING

Manufacturer advises avoid—present in milk in animal studies.

RENAL IMPAIRMENT

Reduce dose if eGFR less than 50 mL/minute/1.73 m². Consult product literature.

MONITORING REQUIREMENTS

Monitor liver function tests every 3 months, and viral markers for hepatitis B every 3–6 months during treatment (continue monitoring for at least 1 year after discontinuation—recurgent hepatitis may occur on discontinuation).

DIRECTIONS FOR ADMINISTRATION

To be taken at least 2 hours before or 2 hours after food.

PRESCRIBING AND DISPENSING INFORMATION

Flavours of oral liquid formulations may include orange.

PATIENT AND CARER ADVICE

Patients or carers should be counselled on the administration of entecavir tablets and oral solution.

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

Entecavir for chronic hepatitis B (August 2008) NICE TA153
Entecavir is an option for the treatment of chronic hepatitis B. www.nice.org.uk/TA153

● MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

▶ Baraclude (Bristol-Myers Squibb Pharmaceuticals Ltd)
Entecavir (as Entecavir monohydrate) 500 microgram Baraclude 0.5mg tablets | 30 tablet (PO) £363.26
Entecavir (as Entecavir monohydrate) 1 mg Baraclude 1mg tablets | 30 tablet (PO) £363.26

Oral solution

▶ Baraclude (Bristol-Myers Squibb Pharmaceuticals Ltd)
Entecavir (as Entecavir monohydrate) 50 microgram per 1 ml Baraclude 0.05mg/ml oral solution (sugar-free) | 210 ml (PO) £423.80
Telbivudine

INDICATIONS AND DOSE
Chronic hepatitis B infection with compensated liver disease, evidence of viral replication, and histologically documented active liver inflammation or fibrosis, when other treatment is not appropriate

BY MOUTH
- Adult: 600 mg once daily

- CAUTIONS Lamivudine-resistant chronic hepatitis B—risk of telbivudine resistance
- CAUTIONS, FURTHER INFORMATION Discontinue if deterioration in liver function, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis.
- INTERACTIONS → Appendix 1 (telbivudine).
- SIDE-EFFECTS
  - Common or very common Abdominal pain - cough - diarrhea - dizziness - fatigue - headache - nausea - raised serum amylase - raised serum lipase - rash
  - Uncommon Arthralgia - myalgia - myopathy (discontinue treatment) - peripheral neuropathy - taste disturbance
- Rare Lactic acidosis - rhabdomyolysis
- PREGNANCY Manufacturer advises use only if potential benefit outweighs risk.
- BREAST FEEDING Manufacturer advises avoid—present in milk in animal studies.
- RENAL IMPAIRMENT 600 mg every 48 hours if eGFR 30–49 mL/minute/1.73 m²; 600 mg every 72 hours if eGFR less than 30 mL/minute/1.73 m².
- MONITORING REQUIREMENTS Monitor liver function tests every 3 months and viral markers for hepatitis B every 3–6 months during treatment (continue monitoring for at least 1 year after discontinuation—recurrent hepatitis may occur on discontinuation).
- PATIENT AND CARER ADVICE
  - Muscle effects and peripheral neuropathy Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, or numbness, tingling or burning sensations.
- NATIONAL FUNDING/ACCESS DECISIONS
- NICE technology appraisals (TAs)
  - Telbivudine for chronic hepatitis B (August 2008) NICE TA154
  - Telbivudine is not recommended for the treatment of chronic hepatitis B. Patients currently receiving telbivudine can continue treatment until they and their clinician consider it appropriate to stop. www.nice.org.uk/TA154

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.
  - Tablet
    - Sebivo (Novartis Pharmaceuticals UK Ltd)
    - Telbivudine 600 mg Sebivo 600mg tablets | 28 tablet £290.33

NUCLEOTIDE ANALOGUES

Adefovir dipivoxil

INDICATIONS AND DOSE
Chronic hepatitis B infection with either compensated liver disease with evidence of viral replication, and histologically documented active liver inflammation and fibrosis, when other treatment not appropriate or decompensated liver disease in combination with another antiviral for chronic hepatitis B that has no cross-resistance to adefovir

BY MOUTH
- Adult: 10 mg once daily

- CAUTIONS Elderly
- CAUTIONS, FURTHER INFORMATION Discontinue if deterioration in liver function, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis.
- SIDE-EFFECTS Abdominal pain - asthenia - diarrhea - dyspepsia - flatulence - headache - hypophosphataemia - nausea - pancreatitis - pruritus - rash - renal failure - vomiting
- CONCEPTION AND CONTRACEPTION Effective contraception required during treatment.
- PREGNANCY Toxicity in animal studies—manufacturer advises use only if potential benefit outweighs risk.
- BREAST FEEDING Manufacturer advises avoid—no information available.
- RENAL IMPAIRMENT 10 mg every 48 hours if eGFR 30–50 mL/minute/1.73 m²; 10 mg every 72 hours if eGFR 10–30 mL/minute/1.73 m².
  - No information available if eGFR less than 10 mL/minute/1.73 m². Monitor renal function more frequently in patients with renal impairment.
- MONITORING REQUIREMENTS
  - Monitor liver function tests every 3 months, and viral markers for hepatitis B every 3–6 months during treatment (continue monitoring for at least 1 year after discontinuation—recurrent hepatitis may occur on discontinuation).
  - Monitor renal function before treatment then every 3 months, more frequently in patients receiving nephrotoxic drugs.
- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.
  - Tablet
    - Hepsera (Gilead Sciences International Ltd)
    - Adefovir dipivoxil 10 mg Hepsera 10mg tablets | 30 tablet £252.22

6.3 Hepatitis C, chronic

NON-STRUCTURAL PROTEIN 5A INHIBITORS

Daclatasvir

- DRUG ACTION Daclatasvir is an inhibitor of the multifunctional protein NS5A, which is an essential component of the hepatitis C virus replication process.

INDICATIONS AND DOSE
In combination with sofosbuvir for the treatment of chronic hepatitis C infection of genotypes 1 or 4, with or without compensated cirrhosis | In combination with sofosbuvir and ribavirin for the treatment of chronic hepatitis C infection of genotype 3 in patients who are treatment experienced, with or without compensated cirrhosis | In combination with peginterferon alfa and ribavirin for the treatment of chronic hepatitis C infection of genotype 4

BY MOUTH
- Adult: Usual dose 60 mg once daily (for duration of treatment consult product literature)

Dose adjustments due to interactions
Reduce dose to 30 mg once daily with concomitant use of potent CYP3A4 inhibitors (e.g. atazanavir boosted with ritonavir, boceprevir, clarithromycin, cobicistat, itraconazole, ketoconazole, posaconazole, telaprevir, telithromycin, and voriconazole). Increase dose to 90 mg once daily with concomitant use of moderate CYP3A4 inducers (e.g. efavirenz).
Chronic hepatitis C genotype 2 or 3 (not previously treated), or patients infected with HIV and hepatitis C (in combination with peginterferon alfa)

**BY MOUTH**
- Adult: Usual dose 400 mg twice daily

**REBETOL® CAPSULES**

Chronic hepatitis C (in combination with interferon alfa 2b, or peginterferon alfa 2b with or without boceprevir)
- Adult (body-weight up to 64 kg): 400 mg twice daily
- Adult (body-weight 65-80 kg): 400 mg, dose to be given in the morning and 600 mg, dose to be given in the evening
- Adult (body-weight 81-104 kg): 600 mg twice daily
- Adult (body-weight 105 kg and above): 600 mg, dose to be given in the morning and 800 mg, dose to be given in the evening

**REBETOL® ORAL SOLUTION**

Chronic hepatitis C (in combination with interferon alfa or peginterferon alfa)
- Adult (body-weight up to 64 kg): 400 mg twice daily
- Adult (body-weight 65-80 kg): 400 mg daily, dose to be given in the morning and 600 mg daily, dose to be given in the evening
- Adult (body-weight 81-104 kg): 600 mg twice daily
- Adult (body-weight 105 kg and above): 600 mg daily, dose to be given in the morning and 800 mg daily, dose to be given in the evening

**CONTRA-INDICATIONS** Consult product literature for specific contra-indications when ribavirin used in combination with other medicinal products - haemoglobinopathies - severe cardiac disease - severe debilitating medical conditions - unstable or uncontrolled cardiac disease in previous 6 months

**CAUTIONS** Anaemia (haemoglobin concentration should be monitored during the treatment and corrective action taken) - cardiac disease (assessment including ECG recommended before and during treatment—discontinue if deterioration) - consult product literature for specific cautions when ribavirin used in combination with other medicinal products - gout - haemolyisis (haemoglobin concentration should be monitored during the treatment and corrective action taken) - patients with a transplant—risk of rejection - severe dental disorders - severe ocular disorders - severe periodontal disorders - severe psychiatric effects

**INTERACTIONS** → Appendix 1 (ribavirin).


**SIDE-EFFECTS, FURTHER INFORMATION** Side-effects listed are reported when daclatasvir is used in combination with sofosbuvir with or without ribavirin or with ribavirin and peginterferon alfa

**CONCEPTION AND CONTRACEPTION** Highly effective contraception required during and for 5 weeks after treatment.

**PREGNANCY** Manufacturer advises avoid (toxicity in animal studies).

**BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

**PATIENT AND CARER ADVICE**

- **Missed doses** If a dose is more than 20 hours late, the missed dose should not be taken and the next dose should be taken at the normal time. May affect performance of skilled tasks (e.g. driving)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 25**
- Daklinza (Bristol-Myers Squibb Pharmaceuticals Ltd) ▼
  - Daclatasvir (as Daclatasvir dihydrochloride) 30 mg Daklinza 30mg tablets | 28 tablet (PO) £8.172.61
  - Daclatasvir (as Daclatasvir dihydrochloride) 60 mg Daklinza 60mg tablets | 28 tablet (PO) £8.172.61

**NUCLEOSIDE ANALOGUES**

Ribavirin (Tribavirin)

**INDICATIONS AND DOSE COPEGUS® TABLETS**

Chronic hepatitis C (in combination with direct acting antivirals, or interferon alfa 2a, or peginterferon alfa 2a with or without direct acting antivirals)

**BY MOUTH**
- Adult (body-weight up to 74 kg): 400 mg, dose to be taken in the morning and 600 mg, dose to be taken in the evening
- Adult (body-weight 75 kg and above): 600 mg twice daily

Chronic hepatitis C (in combination with peginterferon alfa 2b with or without direct acting antivirals)

**BY MOUTH**
- Adult (body-weight up to 64 kg): 400 mg twice daily
- Adult (body-weight 65-80 kg): 400 mg, to be taken in the morning and 600 mg, to be taken in the evening
- Adult (body-weight 81-105 kg): 600 mg twice daily
- Adult (body-weight 106 kg and above): 600 mg, to be taken in the morning and 800 mg, to be taken in the evening
Infection
paraesthesia · peptic ulcer · pericarditis · peripheral neuropathy · peripheral oedema · photosensitivity · prostatitis · pruritus · psoriasis · psychotic disorders · pulmonary embolism · rash · renal failure · respiratory infections · retinal detachment · retinal haemorrhage · rhabdomyolysis · rheumatoid arthritis · sarcoidosis · seizures · sexual dysfunction · sinus congestion · skin discoloration · sleep disturbances · sore throat · Stevens-Johnson syndrome · stomatitis · suicidal ideation (more frequent in children) · syncope · systemic lupus erythematosus · tachycardia · taste disturbance · thrombocytopenia · thrombocytopenia purpura · thyroid disorders · tinnitus · tongue pigmentation · toxic epidermal necrolysis; tremor · urinary tract infections · vertigo · visual disturbances · vomiting · weight loss · wheezing

**CONCEPTION AND CONTRACEPTION** Exclude pregnancy before treatment in females of childbearing age. Effective contraception essential during treatment and for 4 months after treatment in females and for 7 months after treatment in males of childbearing age. Routine monthly pregnancy tests recommended. Condoms must be used if partner of male patient is pregnant (ribavirin excrated in semen).

**PREGNANCY** Avoid; teratogenicity in animal studies.

**BREAST FEEDING** Avoid—no information available.

**HEPATIC IMPAIRMENT** No dosage adjustment required. Avoid oral ribavirin in severe hepatic dysfunction or decompensated cirrhosis.

**RENAL IMPAIRMENT** Plasma-ribavirin concentration increased.

Manufacturer advises avoid oral ribavirin unless essential if eGFR less than 50 mL/minute/1.73 m²—monitor haemoglobin concentration closely.

**MONITORING REQUIREMENTS** Determine full blood count, platelets, electrolytes, glucose, serum creatinine, liver function tests and uric acid before starting treatment and then on weeks 2 and 4 of treatment, then as indicated clinically—adjust dose if adverse reactions or laboratory abnormalities develop (consult product literature).

**PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid formulations may include bubble-gum.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Peginterferon alfa and ribavirin for mild chronic hepatitis C (August 2006 and September 2010) NICE TA200
  
  The combination of peginterferon alfa and ribavirin can be used for treating mild chronic hepatitis C in patients over 18 years. Alternatively, treatment can be delayed until the disease has reached a moderate stage (‘watchful waiting’). www.nice.org.uk/TA200

- Peginterferon alfa, interferon alfa, and ribavirin for moderate to severe chronic hepatitis C (January 2004 and September 2010) NICE TA200
  
  The combination of peginterferon alfa and ribavirin should be used for treating moderate to severe chronic hepatitis C in patients aged over 18 years:

  - not previously treated with interferon alfa or peginterferon alfa;
  - treated previously with interferon alfa alone or in combination with ribavirin;
  - whose condition did not respond to peginterferon alfa alone or to a combination of peginterferon alfa and ribavirin, or responded but subsequently relapsed;
  - co-infected with HIV.

Peginterferon alfa alone should be used if ribavirin is contra-indicated or not tolerated. Interferon alfa for either monotherapy or combined therapy should be used only if neutropenia and thrombocytopenia are a particular risk. Patients receiving interferon alfa may be switched to peginterferon alfa. www.nice.org.uk/TA200

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- RIBAVIRIN (Non-proprietary)
  - Ribavirin 200 mg Ribavirin 200mg tablets | 42 tablet £92.50 | 112 tablet £246.65 | 168 tablet £369.98
  - Copegus (Roche Products Ltd)
    - Ribavirin 200 mg Copegus 200mg tablets | 42 tablet £92.50 | 112 tablet £246.65 | 168 tablet £369.98
  - Ribavirin 400 mg Copegus 400mg tablets | 56 tablet £246.65

**Capsule**

- RIBAVIRIN (Non-proprietary)
  - Ribavirin 200 mg Ribavirin 200mg capsules | 84 capsule £160.69 | 140 capsule £267.81 | 168 capsule £321.38
  - Rebetol (Merck Sharp & Dohme Ltd)
    - Ribavirin 200 mg Rebetol 200mg capsules | 84 capsule £160.69 | 140 capsule £267.81 | 168 capsule £321.38

**Oral solution**

- Rebetol (Merck Sharp & Dohme Ltd)
  - Ribavirin 40 mg per 1 ml Rebetol 40mg/ml oral solution | 100 ml £87.08

**NUCLEOTIDE ANALOGUES**

**Sofosbuvir**

**INDICATIONS AND DOSE**

In combination with ribavirin (Copegus®), with or without peginterferon alfa, for chronic hepatitis C infection of genotypes 1, 3, 4, 5, or 6 in patients with compensated liver disease | In combination with ribavirin (Copegus®) for chronic hepatitis C infection of genotype 2 in patients with compensated liver disease | In combination with daclatasvir for chronic hepatitis C infection of genotype 1, 3, or 4

**BY MOUTH**

- Adult: 400 mg once daily, for duration of treatment consult product literature

**CAUTIONS, FURTHER INFORMATION**

In chronic hepatitis C of genotype 1, 4, 5, or 6, only use sofosbuvir with ribavirin in those with intolerance or contra-indications to peginterferon alfa who require urgent treatment.

- INTERACTIONS → Appendix 1 (sofosbuvir).

- SIDE-EFFECTS Abdominal discomfort · agitation · alopecia · anaemia · anxiety · arthralgia · asthenia · blurred vision · chest pain · constipation · cough · decreased appetite · depression · diarrhoea · disturbance in attention · dizziness · dry mouth · dyspnoea · gastro-oesophageal reflux · headache · influenza-like symptoms · insomnia · irritability · memory impairment · migraine · myalgia · nausea · neutropenia · rash · vomiting · weight loss

- SIDE-EFFECTS, FURTHER INFORMATION

Side-effects listed are reported when sofosbuvir is used in combination with ribavirin or with ribavirin and peginterferon alfa

- PREGNANCY Manufacturer advises avoid.

- BREAST FEEDING Manufacturer advises avoid—metabolites present in milk in animal studies.
CONTRA-INDICATIONS

PROTEASE INHIBITORS (HEPATITIS)

**Sofosbuvir**

**INDICATIONS AND DOSE**

Chronic hepatitis C infection of genotype 1 in patients with compensated liver disease

**BY MOUTH**

- Adult: 800 mg 3 times a day, for duration of treatment consult product literature

**CONTRA-INDICATIONS**

- Autoimmune hepatitis
- CAUTIONS Coagulopathy - hypoalbuminaemia - low platelets - predisposition to QT interval prolongation

**CAUTIONS, FURTHER INFORMATION**

Low platelets, hypoalbuminaemia, or coagulopathy Not recommended in patients with low platelets, hypoalbuminaemia, or coagulopathy—if initiated in these patients monitor closely for signs of infection, worsening liver impairment and anaemia (increased risk of severe morbidity and mortality).

**INTERACTIONS** → Appendix 1 (boceprevir). Caution with concomitant use of other drugs known to prolong QT interval.

**SIDE-EFFECTS**

- **Common or very common** Abdominal pain · agitation · alopecia · amnesia · anaemia · anxiety · arthralgia · asthenia · blood pressure changes · changes in libido · constipation · cough · decreased appetite · depression · diarrhoea · disturbances in smell · disturbances in taste · dizziness · dry eyes · dry mouth · dysphonia · erectile dysfunction · flatulence · gastro-oesophageal reflux · haemorrhoids · headache · hyperglycaemia · hyperhidrosis · hyperglyceridaemia · hyperuricaemia · hypoaesthesia · hypothyroidism · influenza-like symptoms · insomnia · leucopenia · mouth ulcers · muscle spasm · myalgia · nausea · palpitation · pancytopenia · paraesthesia · peripheral oedema · polyuria · pruritus · psoriasis · rash · stomatitis · syncope · thrombocytopaenia · tinnitus · tooth disorder · tremor · visual disturbances · vomiting · weight loss

- **Uncommon** Aneurorrhoea · arrhythmias · colitis · conjunctival haemorrhage · dysphagia · dysphonia · dysuria · eye pain · flushing · gingivitis · gut · hearing impairment · homicidal ideation · hypoaesthesia · hyperbilirubinaemia · hypercalcaemia · hypercalciuria · hypergammaglobulinaemia · hyperkalaemia · hyperlipidaemia · hyperparathyroidism · hypokalaemia · increased laceration · pancreatitis · photophobia · polymyalgia · photophobia · sensitivity · retinal ischaemia · retinopathy · skin ulceration · suicidal ideation · tongue discoloration · venous thromboembolism

- **Rare** Acute myocardial infarction · asthma · bipolar disorder · cholestatic jaundice · coronary artery disease · encephalopathy · hallucinations · pericarditis · pleural fibrosis · respiratory failure · sarcoidosis · thyroid neoplasms

- **Frequency not known** Rash with eosinophilia and systemic symptoms · Stevens-Johnson syndrome

**SIDE-EFFECTS, FURTHER INFORMATION**

Side-effects listed are reported when boceprevir is used in combination with ribavirin and peginterferon alfa.

**PREGNANCY**

Manufacturer advises avoid.

**BREAST FEEDING**

Manufacturer advises avoid; present in milk in animal studies.

**MONITORING REQUIREMENTS**

Monitor full blood count before starting treatment and then on weeks 2, 4, 8, and 12 of treatment, then as indicated clinically.

**PATIENT AND CARER ADVICE**

Missed doses If a dose is more than 6 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

**NATIONAL FUNDING/ACCESS DECISIONS**

NICE technology appraisals (TAs)

- Boceprevir for chronic hepatitis C infection of genotype 1 (April 2012) NICE TA253

Boceprevir in combination with ribavirin and peginterferon alfa is an option for the treatment of chronic hepatitis C infection of genotype 1 in adults with compensated liver disease:

- who have not been treated previously;
- in whom previous treatment (e.g. with peginterferon alfa in combination with ribavirin) has failed.

www.nice.org.uk/TA253

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (June 2014) that sofosbuvir (Sovaldi)® is accepted for use within NHS Scotland for the treatment of chronic hepatitis C infection of genotypes 1 to 6; its use in combination with ribavirin as dual therapy for chronic hepatitis C infection of either genotype 2 (in treatment naive patients) or genotype 3 is restricted to those who cannot use peginterferon alfa because of intolerance or contra-indications.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

CAUTIONARY AND ADVISORY LABELS 21, 25

- **Sofosbuvir 400 mg** Sovaldi 400mg tablets | 28 tablet pack £11.660.98

**PROTEASE INHIBITORS (HEPATITIS)**

**Boceprevir**

- **RENA L IMPAIRMENT** Safety and efficacy not established if eGFR less than 30 mL/minute/1.73 m²—accumulation may occur.

**PRESCRIBING AND DISPENSING INFORMATION**

Dispense in original container (contains desiccant).

**PATIENT AND CARER ADVICE**

Missed doses If a dose is more than 18 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

**NATIONAL FUNDING/ACCESS DECISIONS**

NICE technology appraisals (TAs)

- Boceprevir for treating chronic hepatitis C (February 2015) NICE TA330

Sofosbuvir in combination with peginterferon alfa and ribavirin is an option for treating adults with chronic hepatitis C infection:

- of genotype 1
- of genotype 3 with cirrhosis (treatment naive patients)
- of genotype 3 that has not adequately responded to interferon-based treatment
- of genotype 4, 5, or 6 with cirrhosis

Sofosbuvir in combination with ribavirin is an option for treating adults with chronic hepatitis C infection:

- of genotype 2 who are intolerant to or ineligible for interferon (treatment naive patients)
- of genotype 2 that has not adequately responded to interferon-based treatment
- of genotype 3 with cirrhosis who are intolerant to or ineligible for interferon (treatment naive patients)
- of genotype 3 that has not adequately responded to interferon-based treatment

NICE technology appraisals (TAs)

- Sofosbuvir for treating chronic hepatitis C (February 2015) NICE TA330

Sofosbuvir in combination with ribavirin is not recommended for the treatment of adults with chronic hepatitis C infection of genotypes 1, 4, 5, or 6.

www.nice.org.uk/TA330

www.nice.org.uk/TA253

NICE technology appraisals (TAs)

- Sovaldi (Gilead Sciences International Ltd) ▼

Sofosbuvir 400 mg Sovaldi 400mg tablets | 28 tablet pack £11.660.98
Simeprevir

INDICATIONS AND DOSE
In combination with ribavirin and peginterferon alfa for chronic hepatitis C infection of genotype 1 or 4. In combination with sofosbuvir (with or without ribavirin) for urgent treatment of chronic hepatitis C infection of genotype 1 or 4 when peginterferon alfa cannot be used because of intolerance or contra-indications.

BY MOUTH
Adult: 150 mg once daily (for duration of treatment consult product literature).

CAUTIONS
Consider alternative treatment in presence of NS3 Q80K polymorphism—efficacy of simeprevir is reduced—patients of East Asian origin.

INTERACTIONS
Appendix 1 (simeprevir).

SIDE-EFFECTS
Constipation; dyspepsia; fatigue (in combination with sofosbuvir); headache (in combination with sofosbuvir); insomnia (in combination with sofosbuvir); nausea; photoanisotropia; pruritus; raised bilirubin concentration—rash.

SIDE-EFFECTS, FURTHER INFORMATION
Rash Monitor for deterioration if mild or moderate; discontinue if severe.

CONCEPTION AND CONTRACEPTION
Effective contraception essential during treatment.

PREGNANCY
Manufacturer advises use only if potential benefit outweighs risk—toxicity in animal studies.

BREAST FEEDING
Manufacturer advises avoid—present in plasma of breast-fed animals.

HEPATIC IMPAIRMENT
Manufacturer advises caution in moderate to severe impairment—elimination reduced in severe impairment. Manufacturer advises caution in decompensated cirrhosis—elimination reduced in severe impairment.

RENAL IMPAIRMENT
Manufacturer advises caution if eGFR less than 30 mL/minute/1.73 m—elimination may be reduced.

PRE-TREATMENT SCREENING
Test for NS3 Q80K polymorphism before combination treatment with ribavirin and peginterferon alfa in patients with chronic hepatitis C infection of genotype 1a. Consider testing for NS3 Q80K polymorphism before combination treatment with sofosbuvir (with or without ribavirin) in patients with chronic hepatitis C infection of genotype 1a.

PATIENT AND CARER ADVICE
Missed doses If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

NATIONAL FUNDING/ACCESS DECISIONS
NICE technology appraisals (TAs)
Simeprevir in combination with peginterferon alfa and ribavirin for treating genotypes 1 and 4 chronic hepatitis C (February 2015) NICE TA331 Simeprevir in combination with peginterferon alfa and ribavirin is recommended within its marketing authorisation, as an option for the treatment of chronic hepatitis C infection of genotype 1 and 4 in adults. www.nice.org.uk/TA331

Telaprevir

INDICATIONS AND DOSE
In combination with ribavirin and peginterferon alfa for chronic hepatitis C infection of genotype 1 in patients with compensated liver disease.

BY MOUTH
Adult: 1.125 g every 12 hours, alternatively 750 mg every 8 hours, for duration of treatment consult product literature.

CAUTIONS
Bradycardia—congenital or family history of QT interval prolongation—electrolyte disturbances—family history of sudden death—heart failure with reduced left ventricular ejection fraction—hypoaalbuminaemia—low platelets—prolongation of QT interval

INTERACTIONS
Appendix 1 (telaprevir). Caution in concomitant use with other drugs known to prolong QT interval.

SIDE-EFFECTS
Common or very common Anaemia—anal fissure—diarrhoea—eczema—haemorrhoids—hyperuricaemia—hyperuricaemia—hypokalaemia—hyperthyroidism—lymphopenia—nausea—peripheral oedema—pruritus—rash—syncope—taste disturbances—thrombocytopenia—vomiting
Uncommon Gout—proctitis—retinopathy—urticaria
Rare Stevens-Johnson syndrome—toxic epidermal necrolysis

SIDE-EFFECTS, FURTHER INFORMATION
Side-effects listed are reported when telaprevir is used in combination with ribavirin and peginterferon alfa.
Varicella–zoster infections

Regardless of immune function and the use of any immunoglobulins, neonates with chickenpox should be treated with a parenteral antiviral to reduce the risk of severe disease. Oral therapy in children is not recommended as absorption is variable. Chickenpox in otherwise healthy children between 1 month and 12 years is usually mild and antiviral treatment is not usually required.

Chickenpox is more severe in adolescents and adults than in children; antiviral treatment started within 24 hours of the onset of rash may reduce the duration and severity of symptoms in otherwise healthy adults and adolescents. Antiviral treatment is generally recommended in immunocompromised patients and those at special risk (e.g. because of severe cardiovascular or respiratory disease or chronic skin disorder); in such cases, an antiviral is given for 10 days with at least 7 days of parenteral treatment.

Pregnant women who develop severe chickenpox may be at risk of complications, especially varicella pneumonia. Specialist advice should be sought for the treatment of chickenpox during pregnancy.

Those who have been exposed to chickenpox and are at special risk of complications may require prophylaxis with varicella–zoster immunoglobulin (see under Disease Specific Immunoglobulins).

In herpes zoster (shingles) systemic antiviral treatment can reduce the severity and duration of pain, reduce complications, and reduce viral shedding. Treatment with the antiviral should be started within 72 hours of the onset of rash and is usually continued for 7–10 days. Immunocompromised patients at high risk of disseminated or severe infection should be treated with a parenteral antiviral drug.

Chronic pain which persists after the rash has healed (postherpetic neuralgia) requires specific management.

Choice

Aciclovir p. 550 is active against herpesviruses but does not eradicate them. Uses of aciclovir include systemic treatment of varicella–zoster and the systemic and topical treatment of herpes simplex infections of the skin and mucous membranes. It is used by mouth for severe herpetic stomatitis. Aciclovir eye ointment is used for herpes simplex infections of the eye; it is combined with systemic treatment for ophthalmic zoster. Famiciclovir p. 552, a prodrug of penciclovir, is similar to aciclovir and is licensed for use in herpes zoster and genital herpes.

Valaciclovir p. 552 is an ester of aciclovir, licensed for herpes zoster and herpes simplex infections of the skin and mucous membranes (including genital herpes); it is also licensed for preventing cytomegalovirus disease following solid organ transplantation. Famiciclovir or valaciclovir are suitable alternatives to aciclovir for oral lesions associated with herpes zoster. Valaciclovir once daily may reduce the risk of transmitting genital herpes to heterosexual partners—specialist advice should be sought.

Foscarnet sodium p. 553 is used for mucocutaneous herpes simplex virus infection unresponsive to aciclovir in immunocompromised patients; it is toxic and can cause renal impairment.

Inosine pranobex p. 550 has been used by mouth for herpes simplex infections; its effectiveness remains unproven.

Cytomegalovirus infection

Ganciclovir p. 554 is related to aciclovir but it is more active against cytomegalovirus (CMV); it is also much more toxic than aciclovir and should therefore be prescribed only when the potential benefit outweighs the risks. Ganciclovir is administered by intravenous infusion for the initial treatment of CMV infection. Ganciclovir causes profound myelosuppression when given with zidovudine p. 566; the
Infection

Acyclovir (Aciclovir)

MEDICINAL FORMS

- Not suitable for prescribing

RENAL IMPAIRMENT

PREGNANCY

- Manufacturer advises caution

SIDE-EFFECTS

- Common or very common: Reversible increase in serum uric acid; reversible increase in urinary uric acid

- Uncommon: Arthralgia, epigastric discomfort, fatigue, headache, itching, nausea, rash, vertigo, vomiting

- Rare: Anxiety, constipation, diarrhoea, polyuria, sleep disturbances

PREGNANCY

- Manufacturer advises caution

RESEARCH IMPAIRED

LESS SUITABLE FOR PRESCRIBING

- Inosine pranobex is less suitable for prescribing

CAUTIONS

History of gout; history of hyperuricaemia

INDICATIONS AND DOSE

Mucocutaneous herpes simplex

- Adult: 1 g 4 times a day for 7–14 days

Adjuvant treatment of genital warts

- Adult: 1 g 3 times a day for 14–28 days

Subacute sclerosing panencephalitis

- Adult: 50–100 mg/kg daily in 6 divided doses

CAUTIONARY AND ADVISORY LABELS

- Manufacturer advises caution; metabolised to uric acid

INOSINE COMPLEXES

Inosine pranobex (inosine acedoben dimepranol)

NUCLEOSIDE ANALOGUES

Aciclovir (Acyclovir)

INDICATIONS AND DOSE

Herpes simplex, suppression

- Adult: 400 mg twice daily, alternatively 200 mg 4 times a day; increased to 400 mg 3 times a day. Dose may be increased if recurrences occur on standard suppressive therapy or for suppression of genital herpes during late pregnancy (from 36 weeks gestation), therapy interrupted every 6–12 months to reassess recurrence frequency—consider restarting after two or more recurrences

- Adult: 200–400 mg 4 times a day

- Adult: 5 mg/kg every 8 hours

Herpes simplex, treatment (non-genital)

- Adult: 100 mg 5 times a day usually for 5 days (longer if new lesions appear during treatment or if healing incomplete)

- Adult: 400 mg 5 times a day usually for 5 days (longer if new lesions appear during treatment or if healing incomplete)

Genital herpes simplex, treatment of severe, initial infection

- Adult: Initially 5 mg/kg every 8 hours usually for 5 days; increased to 10 mg/kg every 8 hours for at least 14 days in encephalitis (at least 21 days if also immunocompromised)—confirm cerebrospinal fluid negative for herpes simplex virus before stop-ping treatment, to be increased only if resistant organisms suspected or in simplex encephalitis

- Adult: 400 mg 5 times a day for 7–10 days

Herpes simplex, treatment of recurrent infection

- Adult: 400 mg 5 times a day for 2 days, alternatively 200 mg 5 times a day for 5 days, alternatively 400 mg 3 times a day for 3–5 days

- Adult: 400 mg 3 times a day for 5–10 days

- Adult: 5 mg/kg every 8 hours

Children

- Adult: 200 mg 3 times per day for 2 weeks; increased to 400 mg 3 times per day for 2 weeks (longer if new lesions appear during treatment or if healing incomplete)

- Adult: 400 mg 3 times a day for 5–10 days

- Adult: 5 mg/kg every 8 hours

Children

- Adult: 200 mg 3 times per day for 2 weeks; increased to 400 mg 3 times per day for 2 weeks (longer if new lesions appear during treatment or if healing incomplete)

- Adult: 5 mg/kg every 8 hours

Children

- Adult: 200 mg 3 times per day for 2 weeks; increased to 400 mg 3 times per day for 2 weeks (longer if new lesions appear during treatment or if healing incomplete)

- Adult: 5 mg/kg every 8 hours

Children

- Adult: 200 mg 3 times per day for 2 weeks; increased to 400 mg 3 times per day for 2 weeks (longer if new lesions appear during treatment or if healing incomplete)

- Adult: 5 mg/kg every 8 hours

Children

- Adult: 200 mg 3 times per day for 2 weeks; increased to 400 mg 3 times per day for 2 weeks (longer if new lesions appear during treatment or if healing incomplete)

- Adult: 5 mg/kg every 8 hours

Children

- Adult: 200 mg 3 times per day for 2 weeks; increased to 400 mg 3 times per day for 2 weeks (longer if new lesions appear during treatment or if healing incomplete)

- Adult: 5 mg/kg every 8 hours

Children

- Adult: 200 mg 3 times per day for 2 weeks; increased to 400 mg 3 times per day for 2 weeks (longer if new lesions appear during treatment or if healing incomplete)

- Adult: 5 mg/kg every 8 hours

Children

- Adult: 200 mg 3 times per day for 2 weeks; increased to 400 mg 3 times per day for 2 weeks (longer if new lesions appear during treatment or if healing incomplete)

- Adult: 5 mg/kg every 8 hours

Children

- Adult: 200 mg 3 times per day for 2 weeks; increased to 400 mg 3 times per day for 2 weeks (longer if new lesions appear during treatment or if healing incomplete)

- Adult: 5 mg/kg every 8 hours

Children

- Adult: 200 mg 3 times per day for 2 weeks; increased to 400 mg 3 times per day for 2 weeks (longer if new lesions appear during treatment or if healing incomplete)

- Adult: 5 mg/kg every 8 hours

Children

- Adult: 200 mg 3 times per day for 2 weeks; increased to 400 mg 3 times per day for 2 weeks (longer if new lesions appear during treatment or if healing incomplete)

- Adult: 5 mg/kg every 8 hours

Children

- Adult: 200 mg 3 times per day for 2 weeks; increased to 400 mg 3 times per day for 2 weeks (longer if new lesions appear during treatment or if healing incomplete)

- Adult: 5 mg/kg every 8 hours

Children

- Adult: 200 mg 3 times per day for 2 weeks; increased to 400 mg 3 times per day for 2 weeks (longer if new lesions appear during treatment or if healing incomplete)

- Adult: 5 mg/kg every 8 hours

Children

- Adult: 200 mg 3 times per day for 2 weeks; increased to 400 mg 3 times per day for 2 weeks (longer if new lesions appear during treatment or if healing incomplete)

- Adult: 5 mg/kg every 8 hours
Varicella zoster (chickenpox), treatment | Herpes zoster, treatment

**BY MOUTH**
- Child 1 month—1 year: 200 mg 4 times a day for 5 days
- Child 2—5 years: 400 mg 4 times a day for 5 days
- Child 6—11 years: 800 mg 4 times a day for 5 days
- Child 12—17 years: 800 mg 5 times a day for 7 days
- Adult: 800 mg 5 times a day for 7 days

**BY INTRAVENOUS INFUSION**
- Adult: 5 mg/kg every 8 hours usually for 5 days

Herpes zoster, treatment in immunocompromised

**BY MOUTH**
- Child 1 month—1 year: 200 mg 4 times a day continue for 2 days after crusting of lesions
- Child 2—5 years: 400 mg 4 times a day continue for 2 days after crusting of lesions
- Child 6—12 years: 800 mg 4 times a day continue for 2 days after crusting of lesions
- Child 12—17 years: 800 mg 5 times a day continue for 2 days after crusting of lesions
- Adult: 800 mg 5 times a day continue for 2 days after crusting of lesions

**BY INTRAVENOUS INFUSION**
- Adult: 10 mg/kg every 8 hours given for 10—14 days in encephalitis, possibly longer if also immunocompromised

Varicella zoster (chickenpox) attenuation of infection if varicella-zoster immunoglobulin not indicated

**BY MOUTH**
- Child: 10 mg/kg 4 times a day for 7 days, to be started 1 week after exposure
- Adult: 10 mg/kg 4 times a day for 7 days, to be started 1 week after exposure

**Doses at extremes of body-weight**
To avoid excessive dosage in obese patients parenteral dose should be calculated on the basis of ideal weight for height.

- **UNLICENSED USE** Attenuation of chickenpox is an unlicensed indication. Tablets and suspension not licensed for suppression of herpes simplex or for treatment of herpes zoster in children (age range not specified by manufacturer)

- **CAUTIONS** Elderly (risk of neurological reactions) (in adults) • maintain adequate hydration (especially with infusion or high doses)

- **INTERACTIONS** → Appendix 1 (aciclovir).

- **SIDE-EFFECTS**
  - **GENERAL SIDE-EFFECTS**
    - Abdominal pain • diarrhoea • fatigue • headache • nausea • photosensitivity • pruritus • rash • urticaria • vomiting
  - **Very rare** Acute renal failure • anaemia • ataxia • confusion • convulsions • dizziness • drowsiness • dysarthria • dyspnoea • hallucinations • hepatitis • jaundice • leucopenia • neurological reactions • thrombocytopenia
  - **SPECIFIC SIDE-EFFECTS**
    - **Very rare**
      - With intravenous use • agitation • fever • psychosis • severe local inflammation (sometimes leading to ulceration) • tremors
    - **PREGNANCY** Not known to be harmful—manufacturers advise use only when potential benefit outweighs risk.
    - **BREAST FEEDING** Significant amount in milk after systemic administration—not known to be harmful but manufacturer advises caution.
    - **Renal Impairment** Risk of neurological reactions increased. Maintain adequate hydration (especially during renal impairment).

- With intravenous use in adults Use normal intravenous dose every 12 hours if eGFR 25—50 mL/minute/1.73 m² (every 24 hours if eGFR 10—25 mL/minute/1.73 m²). Consult product literature for intravenous dose if eGFR less than 10 mL/minute/1.73 m².

- With oral use in adults For herpes zoster, use normal oral dose every 8 hours if eGFR 10—25 mL/minute/1.73 m² (every 12 hours if eGFR less than 10 mL/minute/1.73 m²).

- For herpes simplex, use normal oral dose every 12 hours if eGFR less than 10 mL/minute/1.73 m².

- With oral use in children For herpes zoster, use normal oral dose every 8 hours if estimated glomerular filtration rate 10—25 mL/minute/1.73 m² (every 12 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²).

- For herpes simplex, use normal dose every 12 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m².

- **DIRECTIONS FOR ADMINISTRATION**
  - **For intravenous infusion** Zovirax IV®; Aciclovir IV (Genus), give intermittently in Sodium chloride 0.9% or Sodium chloride and glucose; initially reconstitute to 25 mg/mL in water for injection or sodium chloride 0.9% then dilute to not more than 5 mg/mL with the infusion fluid; to be given over 1 hour; alternatively, may be administered in a concentration of 25 mg/mL using a suitable infusion pump and given over 1 hour; For Aciclovir IV ( Hospira) dilute to not more than 5 mg/mL with infusion fluid; give over 1 hour.

- **PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid preparations may include banana, or orange.

- **PATIENT AND CARER ADVICE**
  - Medicines for Children leaflet: Aciclovir (oral) for viral infections www.medicinesforchildren.org.uk/aciclovir-for-viral-infections

- **PROFESSION SPECIFIC INFORMATION**
  - Dental practitioners’ formulation: Aciclovir Tablets 200 mg or 800 mg may be prescribed. Aciclovir Oral Suspension 200 mg/5mL may be prescribed. Aciclovir Cream may be prescribed.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**
  - **CAUTIONARY AND ADVISORY LABELS** 9
    - **ACICLOVIR (Non-proprietary)**
      - Aciclovir 200 mg Aciclovir 200mg tablets | 25 tablet (£0.50) DT price = £1.77
      - Aciclovir 400 mg Aciclovir 400mg tablets | 56 tablet (£0.75) DT price = £4.05
      - Aciclovir 800 mg Aciclovir 800mg tablets | 35 tablet (£0.75) DT price = £4.24

  **Dispersible tablet**
  - **CAUTIONARY AND ADVISORY LABELS** 9
    - **ACICLOVIR (Non-proprietary)**
      - Aciclovir 200 mg Aciclovir 200mg dispersible tablets | 25 tablet (£0.75) DT price = £1.88
      - Aciclovir 400 mg Aciclovir 400mg dispersible tablets | 56 tablet (£0.75) DT price = £2.75
      - Aciclovir 800 mg Aciclovir 800mg dispersible tablets | 35 tablet (£0.75) DT price = £6.00
    - Zovirax (GlaxoSmithKline UK Ltd)
      - Aciclovir 200 mg Zovirax 200mg dispersible tablets | 25 tablet (£0.85) DT price = £1.88
      - Aciclovir 800 mg Zovirax 800mg dispersible tablets | 35 tablet (£0.85) DT price = £6.75

  **Oral suspension**
  - **CAUTIONARY AND ADVISORY LABELS** 9
    - **ACICLOVIR (Non-proprietary)**
      - Aciclovir 40 mg per 1 ml Aciclovir 200mg/5ml oral suspension sugar free (sugar-free) | 125 ml (£0.50) DT price = £3.75
      - Aciclovir 80 mg per 1 ml Aciclovir 400mg/5ml oral suspension sugar free (sugar-free) | 100 ml (£0.50) DT price = £3.97
Famciclovir

**INDICATIONS AND DOSE**

**Herpes zoster infection, treatment**

**BY MOUTH**

- Adult: 500 mg 3 times a day for 7 days, alternatively 750 mg 1–2 times a day for 7 days

**Herpes zoster infection, treatment in immunocompromised patients**

**BY MOUTH**

- Adult: 500 mg 3 times a day for 10 days, continue for 2 days after crusting of lesions

**Genital herpes, suppression**

**BY MOUTH**

- Adult: 250 mg twice daily, therapy to be interrupted every 6–12 months to reassess recurrence frequency—consider restarting after two or more recurrences

**Genital herpes, suppression in immunocompromised or HIV-positive patients**

**BY MOUTH**

- Adult: 500 mg twice daily, therapy to be interrupted every 6–12 months to reassess recurrence frequency—consider restarting after two or more recurrences

**Valaciclovir**

**INDICATIONS AND DOSE**

**Herpes zoster infection, treatment**

**BY MOUTH**

- Adult: 1 g 3 times a day for 7 days

**Herpes zoster infection, treatment in immunocompromised patients**

**BY MOUTH**

- Adult: 1 g 3 times a day for at least 7 days and continued for 2 days after crusting of lesions

**Herpes simplex, treatment of first infective episode**

**BY MOUTH**

- Adult: 500 mg twice daily for 5 days (longer if new lesions appear during treatment or if healing incomplete)

**Herpes simplex infections treatment of first episode in immunocompromised or HIV-positive patients**

**BY MOUTH**

- Adult: 1 g twice daily for 5–10 days

**Herpes simplex infection (non-genital), treatment in immunocompromised patients**

**BY MOUTH**

- Adult: 500 mg twice daily for 5–10 days

**INTERACTIONS**

→ Appendix 1 (famciclovir).

**SIDE-EFFECTS**

- Common or very common: Headache, nausea, vomiting

- Rare: Confusion

- Very rare: Dizziness, drowsiness, hallucinations, jaundice, rash, Stevens-Johnson syndrome, thrombocytopenia

- Frequency not known: Constipation, abdominal pain, diarrhoea, fatigue, fever, pruritus, sweating

- Pregnancy: Manufacturers advise avoid unless potential benefit outweighs risk.

- Breast feeding: No information available—present in milk in animal studies.

- Hepatic impairment: Usual dose in well compensated liver disease (information not available on decompensated).

- Renal impairment: Reduce dose; consult product literature.

**PRESCRIBING AND DISPENSING INFORMATION**

Famciclovir is a pro-drug of penciclovir.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: table.
Herpes virus infections, cytomegalovirus

6.5 Herpesvirus infections, cytomegalovirus

NON-NUCLEOSIDE PYROPHOSPHATE ANALOGUES

Foscarnet sodium

INDICATIONS AND DOSE

Cytomegalovirus disease

BY INTRAVENOUS INFUSION

Adult: Initially 60 mg/kg every 8 hours for 2–3 weeks, alternatively initially 90 mg/kg every 12 hours for 2–3 weeks, then maintenance 60 mg/kg daily, then increased if tolerated to 90–120 mg/kg daily, if disease progresses on maintenance dose, repeat induction regimen

Mucocutaneous herpes simplex virus infections

unresponsive to aciclovir in immunocompromised patients

BY INTRAVENOUS INFUSION

Adult: 40 mg/kg every 8 hours for 2–3 weeks or until lesions heal
NUCLEOSIDE ANALOGUES

Ganciclovir

**INDICATIONS AND DOSE**
Prevention of cytomegalovirus disease during immunosuppressive therapy following organ transplantation

**BY INTRAVENOUS INFUSION**
- Adult: 5 mg/kg every 12 hours for 7–14 days

Treatment of life-threatening or sight-threatening cytomegalovirus infections in immunocompromised patients only

**BY INTRAVENOUS INFUSION**
- Adult: 5 mg/kg every 12 hours for 14–21 days, followed by maintenance 6 mg/kg daily on 5 days of the week, alternatively 5 mg/kg daily until adequate recovery of immunity, maintenance only for patients at risk of relapse of retinitis, if retinitis progresses initial induction treatment may be repeated

**SIDE-EFFECTS**
- Common or very common Abdominal pain - acute renal failure - aggravation - agitation - anaemia - arthralgia - asthenia - changes in blood pressure - changes in ECG - confusion - constipation - convulsions - depression - diarrhoea - dizziness - dyspepsia - dysuria - electrolyte disturbances - genitourinary irritation and ulceration (due to high concentrations excreted in urine) - granulocytopenia - headache - hepatic dysfunction - hypocalcaemia - hypokalaemia - hypomagnesaemia - leucopenia - malaise - myalgia - nausea (reduce infusion rate) - neurological disorders - oedema - palpititation - pancreatitis - paraesthesia (reduce infusion rate) - polyuria - pruritus - rash - renal impairment - thrombocytopenia - thrombophlebitis if given undiluted by peripheral vein - tremor - vomiting

- Uncommon Acidosis

- Frequency not known Diabetes insipidus - myasthenia - myositis - oesophageal ulceration - rhabdomyolysis - ventricular arrhythmias

**CONCEPTION AND CONTRACEPTION**
Men should avoid fathering a child during and for 6 months after treatment.

**PREGNANCY**
Manufacturer advises avoid.

**BREAST FEEDING**
Avoid — present in milk in animal studies.

**RENAI IMPAIRMENT**
Reduce dose; consult product literature.

**MONITORING REQUIREMENTS**
- Monitor electrolytes, particularly calcium and magnesium.
- Monitor serum creatinine every second day during induction and every week during maintenance.

**DIRECTIONS FOR ADMINISTRATION**
- Avoid rapid infusion.
- For intravenous infusion (Foscavir®), give intermittently in Glucose 5% or Sodium Chloride 0.9%; dilute to a concentration of 12 mg/mL for infusion into peripheral vein (undiluted solution via central venous line only); infuse over at least 1 hour (infuse doses greater than 60 mg/kg over 2 hours).

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**SOLUION FOR INFUSION**
**ELECTROLYTES:** May contain Sodium
- *Foscavir* (Cipligen Healthcare Ltd)
  - Foscarnet sodium 24 mg per 1 ml
  - Foscovir 6g/250ml solution for infusion bottles | 1 bottle £30 £119.85 (Hospital only)

**CONTRA-INDICATIONS**
- Abnormally low haemoglobin count (consult product literature) - abnormally low neutrophil count (consult product literature) - abnormally low platelet count (consult product literature)

**CAUTIONS**
Children (possible risk of long-term carcinogenic or reproductive toxicity) - ensure adequate hydration - history of cytopenia - potential carcinogen - potential teratogen - radiotherapy - vesicant

**INTERACTIONS**
- Appendix 1 (foscarnet).
- Increased risk of myelosuppression with other myelosuppressive drugs - consult product literature.

**SIDE-EFFECTS**

- Uncommon Alopecia - anaphylactic reactions - arrhythmias - disturbances in hearing and vision - haematuria - hypotension - male infertility - mouth ulcers - pancreatitis - psychosis - tremor

**ALLERGY AND CROSS-SENSITIVITY**
Contra-indicated in patients hypersensitive to valganciclovir, aciclovir, or valaciclovir.

**CONCEPTION AND CONTRACEPTION**
Ensure effective contraception during treatment and barrier contraception for men during and for at least 90 days after treatment.

**PREGNANCY**
Avoid — teratogenic risk.

**BREAST FEEDING**
Avoid — no information available.

**RENAI IMPAIRMENT**
Reduce dose if eGFR less than 70 mL/minute/1.73 m²; consult product literature.

**MONITORING REQUIREMENTS**
Monitor full blood count closely (severe deterioration may require correction and possibly treatment interruption).

**DIRECTIONS FOR ADMINISTRATION**
Infuse into vein with adequate flow preferably using plastic cannula. For intravenous infusion (Cyveine®) give intermittently in Glucose 5% or Sodium chloride 0.9%. Reconstitute initially in water for injections (500 mg/10 mL then dilute to not more than 10 mg/mL with infusion fluid (usually 100 mL); give over 1 hour.

**HANDLING AND STORAGE**
Caution in handling. Ganciclovir is toxic and personnel should be adequately protected during handling and administration; if solution comes into contact with skin or mucosa, wash off immediately with soap and water.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**
- **ELECTROLYTES:** May contain Sodium
  - *Cyveine* (Roche Products Ltd)
  - Ganciclovir (as Ganciclovir sodium) 500 mg
  - Cyveine 500mg powder for solution for infusion vials | 5 vial £30 £148.83
Valganciclovir

**INDICATIONS AND DOSE**

**Cytomegalovirus retinitis, induction**

**BY MOUTH**

- Adult: Initially 900 mg twice daily for 21 days, then 900 mg daily, induction regimen may be repeated if retinitis progresses

**Prevention of cytomegalovirus disease following solid organ transplantation**

**BY MOUTH**

- Adult: 900 mg daily for 100 days (for 100–200 days following kidney transplantation), to be started within 10 days of transplantation

**Dose equivalence and conversion**

Oral valganciclovir 900 mg twice daily is equivalent to intravenous ganciclovir 5 mg/kg twice daily.

- **CONTRA-INDICATIONS** Abnormally low haemoglobin count (consult product literature) • abnormally low neutrophil count (consult product literature) • abnormally low platelet count (consult product literature)

- **CAUTIONS** Children (possible risk of long-term carcinogenic or reproductive toxicity) • history of cytopenia • potential carcinogen • potential teratogen • radiotherapy

- **INTERACTIONS** → Appendix 1 (valganciclovir).

- **SIDE-EFFECTS**
  - Common or very common Abdominal pain • abnormal thinking • anaemia • anorexia • anxiety • arthralgia • chest pain • confusion • constipation • convulsions • cough • depression • dermatitis • diarrhoea • dizziness • dyspepsia • dysphagia • dyspepsia • ear pain • eye pain • fatigue • flatulence • headache • hepatic dysfunction • infection • insomnia • leucopenia • macular oedema • myalgia • nausea • night sweats • pancytopenia • peripheral neuropathy • pruritus • pyrexia • renal impairment • retinal detachment • taste disturbance • thrombocytopenia • vitreous floaters • vomiting • weight loss
  - Uncommon Alopecia • anaphylactic reactions • arrhythmias • disturbances in hearing • disturbances in vision • haematuria • hypotension • male infertility • mouth ulcers • pancreatitis • psychosis • tremor

- **ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in patients hypersensitive to ganciclovir, aciclovir, or valaciclovir.

- **CONCEPTION AND CONTRACEPTION** Ensure effective contraception during treatment and barrier contraception for men during and for at least 90 days after treatment.

- **PREGNANCY** Avoid—teratogenic risk.

- **BREAST FEEDING** Avoid—no information available.

- **RENAL IMPAIRMENT** Reduce dose, consult product literature.

- **MONITORING REQUIREMENTS** Monitor full blood count closely (severe deterioration may require correction and possibly treatment interruption).

- **PRESCRIBING AND DISPENSING INFORMATION**

  Valganciclovir is a pro-drug of ganciclovir. Flavours of oral liquid formulations may include tutti-frutti.

- **HANDLING AND STORAGE**

  Caution in handling Valganciclovir is a potential teratogen and carcinogen and caution is advised when handling the powder, reconstituted solution, or broken tablets; if these come into contact with skin or mucosa, wash off immediately with water; avoid inhalation of powder.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS 21</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Valcyte</strong> (Roche Products Ltd)</td>
</tr>
<tr>
<td>Valganciclovir (as Valganciclovir hydrochloride) 450 mg Valcyte 30mg tablets</td>
</tr>
</tbody>
</table>

**Oral solution**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS 21</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Valcyte</strong> (Roche Products Ltd)</td>
</tr>
<tr>
<td>Valganciclovir (as Valganciclovir hydrochloride) 50 mg per 1 ml Valcyte 50mg/ml oral solution (sugar-free)</td>
</tr>
</tbody>
</table>

### 6.6 HIV infection

**HIV infection**

There is no cure for infection caused by the human immunodeficiency virus (HIV) but a number of drugs slow or halt disease progression. Drugs for HIV infection (antiretrovirals) may be associated with serious side-effects. Although antiretrovirals increase life expectancy considerably and decrease the risk of complications associated with premature ageing, mortality and morbidity remain slightly higher than in uninfected individuals. Treatment should be undertaken only by those experienced in their use.

**Principles of treatment**

Treatment aims to prevent the mortality and morbidity associated with chronic HIV infection whilst minimising drug toxicity. Although it should be started before the immune system is irreversibly damaged, the need for early drug treatment should be balanced against the risk of toxicity. Commitment to treatment and strict adherence over many years are required; the regimen chosen should take into account convenience and patient tolerance. The development of drug resistance is reduced by using a combination of drugs; such combinations should have synergistic or additive activity while ensuring that their toxicity is not additive. It is recommended that viral sensitivity to antiretroviral drugs is established before starting treatment or before switching drugs if the infection is not responding.

Treatment also reduces the risk of HIV transmission to sexual partners, but the risk is not eliminated completely; this risk and strategies to reduce HIV transmission should be discussed with patients and their sexual partners.

**Initiation of treatment**

The optimum time for initiating antiretroviral treatment depends primarily on the CD4 cell count. The timing and choice of treatment should also take account of clinical symptoms, comorbidities, and the possible effect of antiretroviral drugs on factors such as the risk of cardiovascular events. Treatment includes a combination of drugs known as "highly active antiretroviral therapy". Treatment of HIV-1 infection is initiated with 2 nucleoside reverse transcriptase inhibitors and either a non-nucleoside reverse transcriptase inhibitor, or a boosted protease inhibitor, or an integrase inhibitor; the regimens of choice contain tenofovir disoproxil and emtricitabine with either efavirenz or ritonavir-boosted atazanavir, or ritonavir-boosted darunavir, or raltegravir. Alternative regimens contain abacavir and lamivudine with either lopinavir with ritonavir, or ritonavir-boosted fosamprenavir, or nevirapine, or rilpivirine. Patients who require treatment for both HIV
and chronic hepatitis B should be treated with antivirals active against both diseases.

Switching therapy
Deterioration of the condition (including clinical and virological changes) may require a change in therapy. The choice of an alternative regimen depends on factors such as the response to previous treatment, tolerance and the possibility of cross-resistance.

Pregnancy
Treatment of HIV infection in pregnancy aims to reduce the risk of toxicity to the fetus (although information on the teratogenic potential of most antiretroviral drugs is limited), to minimise the viral load and disease progression in the mother, and to prevent transmission of infection to the neonate. All treatment options require careful assessment by a specialist. Combination antiretroviral therapy maximises the chance of preventing transmission and represents optimal therapy for the mother. However, it may be associated with a greater risk of preterm delivery. Pregnancies in HIV-positive women and babies born to them should be reported prospectively to the National Study of HIV in Pregnancy and Childhood at www.ucl.ac.uk/ bbhp/ and to the Antiretroviral Pregnancy Registry at www.apregistry.com.

Breast-feeding
Breast-feeding by HIV-positive mothers may cause HIV infection in the infant and should be avoided.

Post-exposure prophylaxis
Prophylaxis with antiretroviral drugs [unlicensed indication] may be appropriate following exposure to HIV-contaminated material. Immediate expert advice should be sought in such cases; national guidelines on post-exposure prophylaxis for healthcare workers have been developed (by the Chief Medical Officer’s Expert Advisory Group on AIDS), www.gov.uk/dh and local ones may also be available. Antiretrovirals for prophylaxis are chosen on the basis of efficacy and potential for toxicity. Prompt prophylaxis with antiretroviral drugs [unlicensed indication] is also appropriate following potential sexual exposure to HIV; recommendations have been developed by the British Association for Sexual Health and HIV, www.bashh.org.

Drugs for HIV infection
Zidovudine p. 566, a nucleoside reverse transcriptase inhibitor (or ‘nucleoside analogue’), was the first anti-HIV drug to be introduced. Other nucleoside reverse transcriptase inhibitors include abacavir p. 561, didanosine p. 562, emtricitabine p. 563, lamivudine p. 563, stavudine p. 564, and tenofovir disoproxil p. 564.

The protease inhibitors include atazanavir p. 567, darunavir p. 568, fosamprenavir p. 568 (a pro-drug of amprenavir), indinavir p. 569, lopinavir (available as lopinavir with ritonavir), ritonavir p. 570, saquinavir p. 570, and tipranavir p. 571. Indinavir is rarely used in the treatment of HIV-infection because it is associated with nephrolithiasis. Ritonavir in low doses boosts the activity of atazanavir, darunavir, fosamprenavir, indinavir, lopinavir (available as lopinavir with ritonavir), saquinavir, and tipranavir increasing the persistence of plasma concentrations of these drugs; at such a low dose, ritonavir has no intrinsic antiviral activity. The protease inhibitors are metabolised by cytochrome P450 enzyme systems and therefore have a significant potential for drug interactions. Protease inhibitors are associated with lipodystrophy and metabolic effects.

The non-nucleoside reverse transcriptase inhibitors efavirenz p. 558, etravirine p. 559, nevirapine p. 560, and rilpivirine p. 561 are used in the treatment of HIV-1 infection, but not against the subtype HIV-2, a subtype that is rare in the UK. Nevirapine is associated with a high incidence of rash (including Stevens-Johnson syndrome) and occasionally fatal hepatitis. Rash is also associated with efavirenz and etravirine but it is usually milder. Psychiatric or CNS disturbances are common with efavirenz; CNS disturbances are often self-limiting and can be reduced by taking the dose at bedtime (especially in the first 2–4 weeks of treatment). Efavirenz has also been associated with an increased plasma-cholesterol concentration. Etravirine is used in regimens containing a boosted protease inhibitor for HIV infection resistant to other non-nucleoside reverse transcriptase inhibitors and protease inhibitors.

Enfuvirtide p. 557, which inhibits the fusion of HIV to the host cell, is licensed for managing infection that has failed to respond to a regimen of other antiretroviral drugs; enfuvirtide should be combined with other potentially active antiretroviral drugs.

Maraviroc p. 557 is an antagonist of the CCR5 chemokine receptor. It is licensed for patients exclusively infected with CCR5-tropic HIV.

Dolutegravir p. 557 and raltegravir p. 558 are inhibitors of HIV integrase. They are licensed for the treatment of HIV infection in combination with other antiretroviral drugs.

Elvitegravir is also an inhibitor of HIV integrase that is only available as a component of a fixed-dose combination product (cobicistat with elvitegravir, emtricitabine and tenofovir). Cobicistat p. 567 is a pharmacokinetic enhancer that boosts the concentrations of other antiretrovirals, but it has no antiretroviral activity itself.

Immune reconstitution syndrome
Improvement in immune function as a result of antiretroviral treatment may provoke a marked inflammatory reaction against residual opportunistic organisms; these reactions may occur within the first few weeks or months of initiating treatment. Autoimmune disorders (such as Graves’ disease) have also been reported many months after initiation of treatment.

Lipodystrophy syndrome
Metabolic effects associated with antiretroviral treatment include fat redistribution, insulin resistance, and dyslipidaemia; collectively these have been termed lipodystrophy syndrome. The usual risk factors for cardiovascular disease should be taken into account before starting antiretroviral therapy and patients should be advised about lifestyle changes to reduce their cardiovascular risk. Plasma lipids and blood glucose should be measured before starting antiretroviral therapy, after 3–6 months of treatment, and then annually.

Fat redistribution (with loss of subcutaneous fat, increased abdominal fat, ‘buffalo hump’ and breast enlargement) is associated with regimens containing protease inhibitors and nucleoside reverse transcriptase inhibitors. Stavudine (especially in combination with didanosine), and to a lesser extent zidovudine, are associated with a higher risk of lipodystrophy and should be used only if alternative regimens are not suitable.

Dyslipidaemia is associated with antiretroviral treatment, particularly with protease inhibitors. Protease inhibitors and some nucleoside reverse transcriptase inhibitors are associated with insulin resistance and hyperglycaemia. Of the protease inhibitors, atazanavir and darunavir may be less likely to cause dyslipidaemia, while saquinavir and atazanavir may be less likely to impair glucose tolerance.

Osteonecrosis
Osteonecrosis has been reported in patients with advanced HIV disease or following long-term exposure to combination antiretroviral therapy.
HIV infection in children
HIV disease in children has a different natural progression to adults. Children infected with HIV should be managed within a formal paediatric HIV clinical network by specialists with access to guidelines and information on antiretroviral drugs for children.

CCRS CHEMOKINE RECEPTOR ANTAGONISTS

Maraviroc
- **DRUG ACTION** Maraviroc is an antagonist of the CCR5 chemokine receptor.

**INDICATIONS AND DOSE**
CCR5-tropic HIV infection in combination with other antiretroviral drugs in patients previously treated with antiretrovirals

- **BY MOUTH**
  - Adult: 300 mg twice daily

- **CAUTIONS** Cardiovascular disease
- **INTERACTIONS** → Appendix 1 (maraviroc).
- **SIDE-EFFECTS**
  - Common or very common Abdominal pain, anaemia, anorexia, depression, diarrhoea, flattulence, headache, insomnia, malaise, nausea, rash
  - Uncommon Myositis, proteinuria, renal failure, seizures
  - Rare Angina, granulocytopenia, hepatitis, pancytopenia, Stevens-Johnson syndrome, toxic epidermal necrolysis
  - Frequency not known Eosinophilia, fever, hepatic reactions, hypersensitivity reactions, osteonecrosis, rash

**SIDE-EFFECTS, FURTHER INFORMATION**
Osteonecrosis
For further information see HIV infection p. 555.

- **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risks.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution—no information available; chronic hepatitis B or C (possibly greater risk of hepatic side-effects).
- **DIRECTIONS FOR ADMINISTRATION** For subcutaneous injection, reconstitute with 1.1 mL Water for Injections and allow to stand (for up to 45 minutes) to dissolve; do not shake or invert vial.
- **PATIENT AND CARER ADVICE** Hypersensitivity reactions Patients or carers should be told how to recognise signs of hypersensitivity, and advised to discontinue treatment and seek immediate medical attention if symptoms develop.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- Celsentri (ViiV Healthcare UK Ltd)
  - Maraviroc 150 mg Celsentri 150mg tablets | 60 tablet pack £441.27
  - Maraviroc 300 mg Celsentri 300mg tablets | 60 tablet pack £441.27

HIV-FUSION INHIBITORS

Enfuvirtide
- **DRUG ACTION** Enfuvirtide inhibits the fusion of HIV to the host cell.

**INDICATIONS AND DOSE**
HIV infection in combination with other antiretroviral drugs for resistant infection or for patients intolerant to other antiretroviral regimens

- **BY SUBCUTANEOUS INJECTION**
  - Adult: 90 mg twice daily

**INTERACTIONS** → Appendix 1 (enfuvirtide).

**SIDE-EFFECTS**
- Common or very common Acne, anorexia, anxiety, asthenia, conjunctivitis, diabetes mellitus, dry skin, erythema, gastrointestinal reflux disease, haematuria, hypertriglyceridaemia, impaired concentration, influenza-like illness, injection-site reactions, irritability, lymphaedema, myalgia, nightmares, pancreatitis, peripheral neuropathy, pneumonia, renal calculi, sinusitis, skin papilloma, tremor, vertigo, weight loss
- Uncommon Hypersensitivity reactions
- Frequency not known Osteonecrosis

**SIDE-EFFECTS, FURTHER INFORMATION**
Hypersensitivity reactions
Hypersensitivity reactions including rash, fever, nausea, vomiting, chills, rigors, low blood pressure, respiratory distress, glomerulonephritis, and raised liver enzymes reported; discontinue immediately if any signs or symptoms of systemic hypersensitivity develop and do not rechallenge.

**Osteonecrosis**
For further information see HIV infection p. 555.

- **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risks.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution—no information available; chronic hepatitis B or C (possibly greater risk of hepatic side-effects).
- **DIRECTIONS FOR ADMINISTRATION** For subcutaneous injection, reconstitute with 1.1 mL Water for Injections and allow to stand (for up to 45 minutes) to dissolve; do not shake or invert vial.
- **PATIENT AND CARER ADVICE** Hypersensitivity reactions Patients or carers should be told how to recognise signs of hypersensitivity, and advised to discontinue treatment and seek immediate medical attention if symptoms develop.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for solution for injection**

**ELECTROLYTES:** May contain Sodium

- Fuzeon (Roche Products Ltd)
  - Enfuvirtide 108 mg Fuzeon 108mg powder and solvent for solution for injection vials | 60 vial pack £1,081.57

HIV-INTEGRASE INHIBITORS

Dolutegravir
- **DRUG ACTION** Dolutegravir is an inhibitor of HIV integrase.

**INDICATIONS AND DOSE**
HIV infection without resistance to other inhibitors of HIV integrase, in combination with other antiretroviral drugs

- **BY MOUTH**
  - Adult: 50 mg once daily

HIV infection in patients where resistance to other inhibitors of HIV integrase suspected, in combination with other antiretroviral drugs

- **BY MOUTH**
  - Adult: 50 mg twice daily, dose to be taken with food

HIV infection in combination with other antiretroviral drugs (with concomitant efavirezin, nevirapine, tipranavir, or rifampicin)

- **BY MOUTH**
  - Adult: 50 mg twice daily, avoid concomitant use with these drugs if resistance to other inhibitors of HIV integrase suspected

**INTERACTIONS** → Appendix 1 (dolutegravir).
Caution—avoid concomitant use with etravirine, unless used in combination with atazanavir, darunavir, or lopinavir.

**SIDE-EFFECTS**
- **Common or very common** Abdominal pain · abnormal dreams · diarrhoea · dizziness · fatigue · flatulence · headache · insomnia · nausea · pruritus · raised creatine kinase · rash · vomiting
- **Uncommon** Hepatitis · hypersensitivity reactions
- **Frequency not known** Osteonecrosis

**SIDE-EFFECTS, FURTHER INFORMATION**

Hypersensitivity reactions
- Hypersensitivity reactions (including severe rash, or rash accompanied by fever, malaise, arthralgia, myalgia, blistering, oral lesions, conjunctivitis, angioedema, eosinophilia, or raised liver enzymes) reported uncommonly. Discontinue immediately if any sign or symptoms of hypersensitivity reactions develop.

Osteonecrosis
- For further information see HIV infection p. 555

**PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in severe impairment—no information available.

**DIRECTIONS FOR ADMINISTRATION** Avoid antacids 6 hours before or 2 hours after taking dolutegravir.

**PATIENT AND CARER ADVICE**
- **Missed doses** If a dose is more than 2 hours late on the once daily regimen (or more than 8 hours late on the twice daily regimen), the missed dose should not be taken and the next dose should be taken at the normal time. Patients or carers should be given advice on how to administer dolutegravir tablets.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Tivicay** (ViiV Healthcare UK Ltd) ▼
  - Dolutegravir (as Dolutegravir sodium) 50 mg Tivicay 50mg tablets | 30 tablet | £49.87

Also available in combination with abacavir and lamivudine, p. 562

**Draltegravir**

**DRUG ACTION** Draltegravir is an inhibitor of HIV integrase.

**INDICATIONS AND DOSE**

**HIV infection in combination with other antiretroviral drugs**

**BY MOUTH USING TABLETS**
- **Adult:** 400 mg twice daily

**Dose equivalence and conversion**

The bioavailability of Isentress® chewable tablets is higher than that of the ’standard’ 400 mg tablets; the chewable tablets are not interchangeable with the ’standard’ tablets on a milligram-for-milligram basis.

**CAUTIONS**

Psychiatric illness (may exacerbate underlying illness including depression) · risk factors for myopathy · risk factors for rhabdomyolysis

**INTERACTIONS** → Appendix 1 (raltegravir).

**SIDE-EFFECTS**
- **Common or very common** Abdominal pain · abnormal dreams · anaemia · anxiety · appetite changes · arthralgia · bradycardia · carpal tunnel syndrome · chest pain · chills · confusion · constipation · drowsiness · dry mouth · dry skin · dysphonia · epistaxis · erectile dysfunction · flushing · gastritis · gingivitis · glossitis · gynaecomastia · hepatitis · hyperhidrosis · hypertension · impaired memory and attention · lipodystrophy · Lipodystrophy Syndrome · menopausal symptoms · myalgia · nasal congestion · neutropenia · nocturia · oedema · osteopenia · pain on swallowing · palpitation · pancreatitis · peptic ulcer · peripheral neuropathy · polydipsia · pruritus · pyrexia · rash with eosinophilia and systemic symptoms · rectal bleeding · renal failure · rhabdomyolysis · skin papilloma · Stevens-Johnson syndrome · suicidal ideation · taste disturbances · thrombocytopenia · tinnitus · tremor · ventricular extrasystoles · visual disturbances
- **Uncommon** Angina · angioedema · hepatitis · or eosinophilia.

**Frequency not known** Osteonecrosis

**SIDE-EFFECTS, FURTHER INFORMATION**

Rash
- Rash occurs commonly. Discontinue if severe rash or rash accompanied by fever, malaise, arthralgia, myalgia, blistering, mouth ulceration, conjunctivitis, angioedema, hepatitis, or eosinophilia.

Lipodystrophy syndrome
- For further information see HIV infection p. 555

**PREGNANCY** Manufacturer advises avoid—toxicity in animal studies.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in severe impairment—no information available. Use with caution in patients with chronic hepatitis B or C (at greater risk of hepatic side-effects).

**PRESCRIBING AND DISPENSING INFORMATION** Dispense raltegravir chewable tablets in original container (contains desiccant).

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) Decisions
- The Scottish Medicines Consortium has advised (April 2010) that raltegravir (Isentress®) is accepted for restricted use within NHS Scotland for the treatment of HIV infection when non-nucleoside reverse transcriptase inhibitors or protease inhibitors cannot be used because of intolerance, drug interactions, or resistance.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- CAUTIONARY AND ADVISORY LABELS 25
  - **Isentress** (Merck Sharp & Dohme Ltd)
    - **Raltegravir 400 mg** Isentress 400mg tablets | 60 tablet | £471.41

**Chewable tablet**
- CAUTIONARY AND ADVISORY LABELS 24
  - EXCIPIENTS: May contain Aspartame
  - **Isentress** (Merck Sharp & Dohme Ltd)
    - **Raltegravir 25 mg** Isentress 25mg chewable tablets | 60 tablet | £29.46 | DT price = £29.46
    - **Raltegravir 100 mg** Isentress 100mg chewable tablets | 60 tablet | £117.85 | DT price = £117.85

**Granules**
- **RALTEGRAVIR (Non-proprietary)**
  - **Raltegravir 100 mg** Isentress 100mg granules sachets | 60 sachet | £213.02

**NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS**

**Efavirenz**

**INDICATIONS AND DOSE**

HIV infection in combination with other antiretroviral drugs

**BY MOUTH USING CAPSULES**
- **Adult:** 600 mg once daily
Etravirine

**INDICATIONS AND DOSE**
HIV infection resistant to other non-nucleoside reverse transcriptase inhibitor and protease inhibitors in combination with other antiretroviral drugs (including a boosted protease inhibitor)

**BY MOUTH**

- Adult: 200 mg twice daily, to be taken after food

**SIDE-EFFECTS**

- Common or very common Abdominal pain · abnormal dreams · anxiety · depression · diarrhoea · diziness · fatigue · headache · impaired concentration · nausea · pruritus · rash · sleep disturbances · Stevens-Johnson syndrome · vomiting
- Uncommon Amnesia · ataxia · blurred vision · convulsions · flushing · gynaecomastia · hepatitis · mania · pancreatitis · psychosis · suicidal ideation · tinnitus · tremor
- Rare Hepatic failure · photosensitivity · suicide
- Frequency not known Lipodystrophy Syndrome · osteonecrosis · raised serum cholesterol

**SIDE-EFFECTS, FURTHER INFORMATION**

**Common** Rash
Rash, usually in the first 2 weeks, is the most common side-effect; discontinue if severe rash with blistering, desquamation, mucosal involvement or fever; if rash mild or moderate, may continue without interruption—usually resolves within 1 month.

**CNS effects** Administration at bedtime especially in first 2–4 weeks reduces CNS effects.

**Lipodystrophy Syndrome** For further information see HIV infection, p. 555.

**Osteonecrosis** For further information see HIV infection, p. 555.

**Pregnancy** Reports of neural tube defects when used in first trimester.

**Hepatic impairment** Greater risk of hepatic side-effects in chronic hepatitis B or C. Avoid in moderate to severe impairment. In mild liver disease, monitor for dose related side-effects (e.g. CNS effects) and monitor liver function.

**Renal impairment** Manufacturer advises caution in severe renal failure—no information available.

**Monitoring requirements** Monitor liver function if receiving other hepatotoxic drugs.

**Directions for administration** Capsules may be opened and contents added to food (contents have a peppery taste).

**Prescribing and dispensing information** Flavours of oral liquid formulations may include strawberry and mint.

**Patient and carer advice** Psychiatric disorders. Patients or their carers should be advised to seek immediate medical attention if symptoms such as severe depression, psychosis or suicidal ideation occur.

**Medicinal forms**

- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- CAUTIONARY AND ADVISORY LABELS 23
- Efavirenz (Non-proprietary) Efavirenz 600 mg Efavirenz 600 mg tablets | 30 tablet (£102.79) (Hospital only)
PATIENT AND CARER ADVICE

Missed doses If a dose is more than 6 hours late, the missed dose should not be taken and the next dose should be taken at the normal time. Hypersensitivity reactions Patients or carers should be told how to recognise hypersensitivity reactions and advised to seek immediate medical attention if hypersensitivity reaction or severe rash develop.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet CAUTIONARY AND ADVISORY LABELS 21

Intolerance (Janssen-Cilag Ltd) Etravirine 25 mg Intolerance 25mg tablets | 120 tablet £75.32
Etravirine 100 mg Intolerance 100mg tablets | 120 tablet £130.27
Etravirine 200 mg Intolerance 200mg tablets | 60 tablet £203.27

Nevirapine

INDICATIONS AND DOSE

HIV infection in combination with other antiretroviral drugs (initial dose)

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

Adult: Initially 200 mg once daily for first 14 days, initial dose titration using 'immediate-release' preparation should not exceed 28 days; if rash occurs and is not resolved within 28 days, alternative treatment should be sought. If treatment interrupted for more than 7 days, restart using the lower dose of the 'immediate-release' preparation for the first 14 days as for new treatment

HIV infection in combination with other antiretroviral drugs (maintenance dose following initial dose titration if no rash present)

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

Adult: 400 mg once daily

CONTRA-INDICATIONS Acute porphyrias p. 864 • post-exposure prophylaxis

CAUTIONS Females (at greater risk of hepatic side effects) • high CD4 cell count (at greater risk of hepatic side effects)

CAUTIONS, FURTHER INFORMATION

Hepatic effects Patients with chronic hepatitis B or C, high CD4 cell count, and women are at increased risk of hepatic side effects— if plasma HIV-1 RNA detectable, manufacturer advises avoid in women with CD4 cell count greater than 250 cells/mm³ or in men with CD4 cell count greater than 400 cells/mm³ unless potential benefit outweighs risk.

INTERACTIONS → Appendix 1 (nevirapine).

SIDE-EFFECTS

Common or very common Abdominal pain • diarrhoea • fatigue • fever • granulocytopenia • headache • hepatitis • hypersensitivity reactions (may involve hepatic reactions and rash) • nausea • rash • Stevens-Johnson syndrome • toxic epidermal necrolysis • vomiting

Uncommon Anaemia • arthralgia • myalgia

Frequency not known Osteonecrosis

SIDE-EFFECTS, FURTHER INFORMATION

Hepatic effects Potentially life-threatening hepatotoxicity including fatal fulminant hepatitis reported usually in first 5 weeks; discontinue permanently if abnormalities in liver function tests accompanied by hypersensitivity reaction (rash, fever, arthralgia, myalgia, lymphadenopathy, hepatitis, renal impairment, eosinophilia, granulocytopenia); suspend if severe abnormalities in liver function tests but no hypersensitivity reaction—discontinue permanently if significant liver function abnormalities recur; monitor patient closely if mild to moderate abnormalities in liver function tests with no hypersensitivity reaction.

Rash Rash, usually in first 5 weeks, is most common side-effect; incidence reduced if introduced at low dose and dose increased gradually (after 14 days); discontinue permanently if severe rash or if rash accompanied by blistering, oral lesions, conjunctivitis, facial oedema, general malaise or hypersensitivity reactions; if rash mild or moderate may continue without interruption but dose should not be increased until rash resolves.

Osteonecrosis For more information see HIV infection p. 555.

HEPATIC IMPAIRMENT Manufacturer advises avoid modified-release preparation—no information available; use 'immediate-release' preparation with caution in moderate impairment and avoid in severe impairment. Use with caution in patients with chronic hepatitis B or C (at greater risk of hepatic side effects).

RENAL IMPAIRMENT Manufacturer advises avoid modified-release preparation—no information available.

MONITORING REQUIREMENTS

Hepatic disease Close monitoring of liver function required during first 18 weeks; monitor liver function before treatment then every 2 weeks for 2 months then after 1 month and then regularly.

Rash Monitor closely for skin reactions during first 18 weeks.

PATIENT AND CARER ADVICE

Missed doses If a dose is more than 8 hours late with the 'immediate-release' preparation or more than 12 hours late with the modified-release preparation, the missed dose should not be taken and the next dose should be taken at the usual time.

Hypersensitivity reactions Patients or carers should be told how to recognise hypersensitivity reactions and advised to discontinue treatment and seek immediate medical attention if severe skin reaction, hypersensitivity reactions, or symptoms of hepatitis develop.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

NEVIRAPINE (Non-proprietary)

Nevirapine 200 mg Nevirapine 200mg tablets | 60 tablet £170.00

VIRAMUNE (Boehringer Ingelheim Ltd)

Nevirapine 200 mg Viramune 200mg tablets | 14 tablet £39.67 | 60 tablet £170.00

Modified-release tablet CAUTIONARY AND ADVISORY LABELS 25

VIRAMUNE (Boehringer Ingelheim Ltd)

Nevirapine 50 mg Viramune 50mg modified-release tablets | 180 tablet £127.50 (Hospital only)

Nevirapine 100 mg Viramune 100mg modified-release tablets | 90 tablet £127.50 (Hospital only)

Nevirapine 400 mg Viramune 400mg modified-release tablets | 30 tablet £170.00 (Hospital only)

Oral suspension

VIRAMUNE (Boehringer Ingelheim Ltd)

Nevirapine (as Nevirapine hemihydrate) 10 mg per 1 ml Viramune 50mg/5ml oral suspension | 240 ml £50.40
Rilpivirine

**INDICATIONS AND DOSE**

HIV infection in combination with other antiretroviral drugs in patients not previously treated with antiretroviral therapy and if plasma HIV-1 RNA concentration less than 100 000 copies/mL

**BY MOUTH**
- Adult: 25 mg once daily

**INTERACTIONS** → Appendix 1 (rilpivirine).

Caution if concomitant use with drugs that prolong QT interval.

**SIDE-EFFECTS** Abdominal pain - abnormal dreams - anorexia - depression - dizziness - dry mouth - headache - hyperlipidaemia - Lipodystrophy Syndrome - malaise - nausea - osteonecrosis - raised serum amylase - raised serum lipase - rash - sleep disturbances - vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

Lipodystrophy For further information see HIV infection p. 555.

Osteonecrosis For further information see HIV infection p. 555.

**PREGNANCY**

Manufacturer advises avoid unless essential — no information available.

**HEPATIC IMPAIRMENT**

Manufacturer advises caution in moderate impairment; avoid in severe impairment — no information available; greater risk of hepatic side-effects in chronic hepatitis B or C.

**RENAL IMPAIRMENT**

Manufacturer advises caution in severe impairment.

**DIRECTIONS FOR ADMINISTRATION** Avoid antacids 2 hours before or 4 hours after taking rilpivirine.

**PATIENT AND CARER ADVICE**

Missed doses If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time. Patients or carers should be given advice on how to administer rilpivirine tablets.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

CAUTIONARY AND ADVISORY LABELS 21, 25
- Edurant (Janssen-Cilag Ltd) ▼
- Rilpivirine (as Rilpivirine hydrochloride) 25 mg Edurant 25 mg tablets | 30 tablet | £20.27

Also available in combination with emtricitabine and tenofovir, p. 565

**NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS**

Nucleoside reverse transcriptase inhibitors

**CAUTIONS**

- Alcohol abuse (increased risk of lactic acidosis)
- Obese women (increased risk of lactic acidosis) - patients at risk of lactic acidosis

**CAUTIONS, FURTHER INFORMATION**

Lactic acidosis Life-threatening lactic acidosis associated with hepatomegaly and hepatic steatosis has been reported with nucleoside reverse transcriptase inhibitors. They should be used with caution in patients with hepatomegaly, hepatitis (especially hepatitis C treated with interferon alfa and ribavirin), liver-enzyme abnormalities and with other risk factors for liver disease and hepatic steatosis. Treatment with the nucleoside reverse transcriptase inhibitor should be discontinued in case of symptomatic hyperlactataemia, lactic acidosis, progressive hepatomegaly or rapid deterioration of liver function.

**SIDE-EFFECTS**


**SIDE-EFFECTS, FURTHER INFORMATION**

Lipodystrophy syndrome For further information see HIV infection p. 555.

Osteonecrosis For further information see HIV infection p. 555.

**PREGNANCY** Mitochondrial dysfunction has been reported in infants exposed to nucleoside reverse transcriptase inhibitors in utero; the main effects include haematological, metabolic, and neurological disorders; all infants whose mothers received nucleoside reverse transcriptase inhibitors during pregnancy should be monitored for relevant signs or symptoms.

**HEPATIC IMPAIRMENT** Use with caution in patients with chronic hepatitis B or C (greater risk of hepatic side-effects).

Abacavir

**INDICATIONS AND DOSE**

HIV infection in combination with other antiretroviral drugs

**BY MOUTH**
- Adult: 600 mg daily in 1–2 divided doses

**CAUTIONS**

- HIV load greater than 100 000 copies/mL in patients at high risk of cardiovascular disease (especially if 10-year cardiovascular risk greater than 20%)

**INTERACTIONS** → Appendix 1 (abacavir).

**SIDE-EFFECTS**

- Very rare Stevens-Johnson syndrome - toxic epidermal necrolysis
- Frequency not known Hypersensitivity reactions

**SIDE-EFFECTS, FURTHER INFORMATION**

Hypersensitivity reactions Life-threatening hypersensitivity reactions reported—characterised by fever or rash and possibly nausea, vomiting, diarrhoea, abdominal pain, dyspnoea, cough, lethargy, malaise, headache, and myalgia; less frequently mouth ulceration, oedema, hypotension, sore throat, acute respiratory distress syndrome, anaphylaxis, paraesthesia, arthralgia, conjunctivitis, lymphadenopathy, lymphocytopenia and renal failure; rarely myolysis; laboratory abnormalities may include raised liver function tests and creatine kinase; symptoms usually appear in the first 6 weeks, but may occur at any time. Discontinue immediately if any symptom of hypersensitivity develops and do not rechallenge (risk of more severe hypersensitivity reaction); discontinue if hypersensitivity cannot be ruled out, even when other diagnoses possible — if rechallenge necessary it must be carried out in hospital setting; if abacavir is stopped for any reason other than hypersensitivity, exclude hypersensitivity reaction as the cause and rechallenge only if medical assistance is readily available; care needed with concomitant use of drugs which cause skin toxicity.

**Gastro-intestinal disturbances** More common in children.

**Rash** More common in children.
Abacavir with lamivudine and zidovudine

The properties listed below are those particular to the combination only. For the properties of the components please consider, abacavir p. 561, lamivudine p. 563, zidovudine p. 566.

INDICATIONS AND DOSE
HIV infection (use only if patient is stabilised for 6–8 weeks on the individual components in the same proportions)
BY MOUTH
» Adult: 1 tablet twice daily

RENAL IMPAIRMENT Avoid Trizivir® if estimated glomerular filtration rate less than 50 mL/minute/1.73 m². (consult product literature).
MEDIcular FORMS
There can be variation in the licensing of different medicines containing the same drug.
Tablet
» Trizivir® (ViiV Healthcare UK Ltd)
Abacavir (as Abacavir sulfate) 300 mg, Lamivudine 150 mg, Zidovudine 300 mg Trizivir tablets | 60 tablet £432.70

Abacavir with dolutegravir and lamivudine

The properties listed below are those particular to the combination only. For the properties of the components please consider, abacavir p. 561, lamivudine p. 563, dolutegravir p. 557.

INDICATIONS AND DOSE
HIV infection
BY MOUTH
» Adult (body-weight 40 kg and above): 1 tablet once daily

RENAL IMPAIRMENT Avoid Triumeq® if eGFR less than 50 mL/minute/1.73 m² (consult product literature).
PATIENT AND CARER ADVICE
Missed doses If a dose is more than 24 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

MEDIcular FORMS
There can be variation in the licensing of different medicines containing the same drug.
Tablet
» Triumeq® (ViiV Healthcare UK Ltd)
Abacavir (as Abacavir sulfate) 600 mg, Dolutegravir (as Dolutegravir sodium) 50 mg, Lamivudine 300 mg Triumeq 50mg/600mg/300mg tablets | 30 tablet £798.16

Didanosine
(ddi; DDI)

INDICATIONS AND DOSE
HIV infection in combination with other antiretrovirals
BY MOUTH
» Adult (body-weight up to 60 kg): 250 mg daily in 1–2 divided doses
» Adult (body-weight 60 kg and above): 400 mg daily in 1–2 divided doses

CAUTIONS History of pancreatitis (preferably avoid, otherwise extreme caution) · hyperuricaemia · peripheral neuropathy
INTERACTIONS → Appendix 1 (didanosine).
Antacids in tablet formulation may affect absorption of other drugs—give at least 2 hours apart.
SIDE-EFFECTS Acute renal failure · alopecia · anaphylactic reactions · diabetes mellitus · dry eyes · dry mouth · hyperuricaemia (suspend if raised significantly) · hypoglycaemia · liver failure · non-cirrhotic portal hypertension · optic nerve changes · pancreatitis (less
common in children) - parotid gland enlargement - peripheral neuropathy (switch to another antiretroviral if peripheral neuropathy develops) - retinal changes - rhombomylolysis - siadadenitis

**SIDE-EFFECTS, FURTHER INFORMATION**

**Pancreatitis** Suspend treatment if serum lipase raised (even if asymptomatic) or if symptoms of pancreatitis develop; discontinue if pancreatitis confirmed. Whenever possible avoid concomitant treatment with other drugs known to cause pancreatic toxicity (e.g. intravenous pentamidine isetionate); monitor closely if concomitant therapy unavoidable. Since significant elevations of triglycerides cause pancreatitis monitor closely if elevated.

**PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.

**HEPATIC IMPAIRMENT** Insufficient information. In hepatic impairment, monitor for toxicity. **RENAL IMPAIRMENT** Reduce dose if eGFR less than 60 mL/minute/1.73 m²; consult product literature.

**MONITORING REQUIREMENTS** Ophthalmological examination (including visual acuity, colour vision, and dilated fundus examination) recommended annually or if visual changes occur.

**DIRECTIONS FOR ADMINISTRATION** With chewable tablets, to ensure sufficient antacid, each dose to be taken as at least 2 tablets (child under 1 year 1 tablet) chewed thoroughly, crushed or dispersed in water; clear apple juice may be added for flavouring; tablets to be taken 2 hours after food. With chewable dispersible tablets (sugar-free) /oral liquid formulations may include candy.

**SIDE-EFFECTS, FURTHER INFORMATION**

**Abnormal dreams** - hyperpigmentation - pruritus

**INTERACTIONS** → Appendix 1 (emtricitabine).

**SIDE-EFFECTS** Abnormal dreams - hyperpigmentation - pruritus

**HEPATIC IMPAIRMENT** On discontinuation, monitor patients with hepatitis B (risk of exacerbation of hepatitis).

**RENAL IMPAIRMENT** Reduce dose if eGFR less than 50 mL/minute/1.73 m²; consult product literature.

**PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral liquid formulations may include candy.

**PATIENT AND CARER ADVICE** Missed doses. If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

- Emtriva (Gilead Sciences International Ltd)
  - Emtricitabine 200 mg Emtriva 200mg capsules | 30 capsule £138.96

**Oral solution**

- Emtriva (Gilead Sciences International Ltd)
  - Emtricitabine 10 mg per 1 ml Emtriva 10mg/ml oral solution (sugar-free) | 170 ml (PO) £39.53

Also available in combination with cobicistat with elvitegravir, tenofovir, p. 565 · efavirenz with tenofovir, p. 565 · rilpivirine and tenofovir, p. 565 · tenofovir, p. 566

**Lamivudine (3TC)**

**INDICATIONS AND DOSE**

**ZEFFIX**

Chronic hepatitis B infection either with compensated liver disease (with evidence of viral replication and histology of active liver inflammation or fibrosis) when first-line treatments cannot be used, or (in combination with another antiviral drug without cross-resistance to lamivudine) with decompensated liver disease

**BY MOUTH**

- Adult: 100 mg once daily, patients receiving lamivudine for concomitant HIV infection should continue to receive lamivudine in a dose appropriate for HIV infection

**EPIVIR® TABLETS**

HIV infection in combination with other antiretroviral drugs

**BY MOUTH**

- Adult: 150 mg every 12 hours, alternatively 300 mg once daily

**EPIVIR® ORAL SOLUTION**

HIV infection in combination with other antiretroviral drugs

**BY MOUTH**

- Adult: 150 mg every 12 hours, alternatively 300 mg once daily

**CAUTIONS** Recurrent hepatitis in patients with chronic hepatitis B may occur on discontinuation of lamivudine

**INTERACTIONS** → Appendix 1 (lamivudine).

**SIDE-EFFECTS** Alopecia - muscle disorders - nasal symptoms - peripheral neuropathy - rhombomylolysis

**BREAST FEEDING** Can be used with caution in women infected with chronic hepatitis B alone, providing that adequate measures are taken to prevent hepatitis B infection in infants.

**RENAL IMPAIRMENT** Reduce dose if eGFR less than 50 mL/minute/1.73 m²; consult product literature.
Infection

564 Viral infection

• MONITORING REQUIREMENTS When treating chronic hepatitis B with lamivudine, monitor liver function tests every 3 months, and viral markers of hepatitis B every 3–6 months, more frequently in patients with advanced liver disease or following transplantation (monitoring to continue for at least 1 year after discontinuation—recurrent hepatitis may occur on discontinuation).

• PRESCRIBING AND DISPENSING INFORMATION Flavours of oral liquid formulations may include banana and strawberry.

• MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet
- **LAMIVUDINE (Non-proprietary)**
  - Lamivudine 100 mg: Lamivudine 100mg tablets | 28 tablet [POM] £74.19–£78.09 DT price = £74.55
  - Lamivudine 150 mg: Lamivudine 150mg tablets | 60 tablet [POM] £85.80–£136.15
  - Lamivudine 300 mg: Lamivudine 300mg tablets | 30 tablet [POM] £54.98–£149.63
- **Epivir** (ViiV Healthcare UK Ltd)
  - Lamivudine 150 mg: Epivir 150mg tablets | 60 tablet [POM] £121.82
  - Lamivudine 300 mg: Epivir 300mg tablets | 30 tablet [POM] £133.89
- **Zefix** (GlaxoSmithKline UK Ltd)
  - Lamivudine 100 mg: Zefix 100mg tablets | 28 tablet [POM] £78.09 DT price = £74.55

Oral solution
- **EXCIPIENTS:** May contain Sucrose
- **Epivir** (ViiV Healthcare UK Ltd)
  - Lamivudine 10 mg per 1 ml: Epivir 50mg/5ml oral solution | 240 ml [POM] £33.16

Also available in combination with abacavir and dolutegravir, p. 562.

Stavudine (d4T)

INDICATIONS AND DOSE
HIV infection in combination with other antiretroviral drugs
when no suitable alternative available and when prescribed for shortest period possible BY MOUTH
- Adult (body-weight up to 60 kg): 30 mg every 12 hours, to be taken preferably at least 1 hour before food
- Adult (body-weight 60 kg and above): 40 mg every 12 hours, to be taken preferably at least 1 hour before food

- CAUTIONS Excessive alcohol intake - higher risk of lactic acidosis than other nucleoside reverse transcriptase inhibitors (especially when used in combination with didanosine)—use only if alternative regimens are not suitable - history of pancreatitis - history of peripheral neuropathy

- INTERACTIONS → Appendix 1 (stavudine). Caution with concomitant use of isoniazid—risk of peripheral neuropathy. Caution with concomitant use with other drugs associated with pancreatitis.

- SIDE-EFFECTS
  - Common or very common Abnormal dreams - cognitive dysfunction - depression - drowsiness - peripheral neuropathy (switch to another antiretroviral if peripheral neuropathy develops) - pruritus
  - Uncommon Anxiety - gynaecomastia
  - PREGNANCY Manufacturer advises use only if potential benefit outweighs risk.

- RENAL IMPAIRMENT Use half normal dose every 12 hours if eGFR 25–50 mL/minute/1.73 m². Use half normal dose every 24 hours if eGFR less than 25 mL/minute/1.73 m². Risk of peripheral neuropathy.

- PRESCRIBING AND DISPENSING INFORMATION Flavours of oral liquid formulations may include cherry.

- LESS SUITABLE FOR PRESCRIBING Stavudine (especially in combination with didanosine) is associated with a higher risk of lipatrophy and should be used only if alternative regimens are not suitable; it is considered to be less suitable for prescribing.

- MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Capsule
- **Zerit** (Bristol-Myers Squibb Pharmaceuticals Ltd)
  - Stavudine 20 mg: Zerit 20mg capsules | 56 capsule [POM] £139.46 (Hospital only)
  - Stavudine 30 mg: Zerit 30mg capsules | 56 capsule [POM] £146.25 (Hospital only)
  - Stavudine 40 mg: Zerit 40mg capsules | 56 capsule [POM] £150.66 (Hospital only)

Oral solution
- **Zerit** (Bristol-Myers Squibb Pharmaceuticals Ltd)
  - Stavudine 1 mg per 1 ml: Zerit 1mg/ml oral solution | 200 ml [POM] £22.94 (Hospital only)

Tenofovir disoproxil

INDICATIONS AND DOSE
HIV infection in combination with other antiretroviral drugs
| Chronic hepatitis B infection with compensated liver disease (with evidence of viral replication, and histologically documented active liver inflammation or fibrosis) | Chronic hepatitis B infection with decompensated liver disease |
| BY MOUTH |
- Adult: 245 mg once daily

Dose equivalence and conversion
7.5 scoops of granules contains approx. 245 mg tenofovir disoproxil (as fumarate).

INTERACTIONS → Appendix 1 (tenofovir). Use with caution if concomitant or recent use of nephrotoxic drugs.

- SIDE-EFFECTS
  - Rare Nephrogenic diabetes insipidus - proximal renal tubulopathy - renal failure
  - Frequency not known Hypophosphataemia - reduced bone density

- RENAL IMPAIRMENT Granules: 132 mg once daily if eGFR 30–50 mL/minute/1.73 m²; 66 mg once daily if eGFR 20–30 mL/minute/1.73 m²; 33 mg once daily if eGFR 10–20 mL/minute/1.73 m². Tablets: 245 mg every 2 days if eGFR 30–50 mL/minute/1.73 m²; 245 mg every 3–4 days if eGFR 10–30 mL/minute/1.73 m². Monitor renal function—interrupt treatment if further deterioration.

MONITORING REQUIREMENTS
- Test renal function and serum phosphate before treatment, then every 4 weeks (more frequently if at increased risk of renal impairment) for 1 year and then every 3 months, interrupt treatment if renal function deteriorates or serum phosphate decreases.
- When treating chronic hepatitis B with tenofovir, monitor liver function tests every 3 months and viral markers for hepatitis B every 3–6 months during treatment (continue monitoring for at least 1 year after discontinuation—recurrent hepatitis may occur on discontinuation).

DIRECTIONS FOR ADMINISTRATION Granules: mix 1 scoop of granules with 1 tablespoon of soft food (e.g. yoghurt, apple sauce) and take immediately without chewing. Do not mix granules with liquids.
Cobicistat with elvitegravir, emtricitabine and tenofovir

The properties listed below are those particular to the combination only. For the properties of the components please consider, emtricitabine p. 563, tenofovir disoproxil p. 564, cobicistat p. 567.

INDICATIONS AND DOSE

HIV infection
BY MOUTH
- Adult: 1 tablet once daily

INTERACTIONS
- Appendix 1 (cobicistat, elvitegravir, emtricitabine, tenofovir).

SIDE-EFFECTS
- Uncommon Depression and suicidal ideation (in patients with a history of psychiatric illness)
- CONCEPTION AND CONCEPTION Women of childbearing potential should use effective contraception during treatment (if using a hormonal contraceptive, it must contain norgestimate as the progestogen and at least 30 micrograms ethinylestradiol).
- PREGNANCY Manufacturer advises use only if potential benefit outweighs risk.
- HEPATIC IMPAIRMENT Avoid Strild ® in severe impairment.
- RENAL IMPAIRMENT If eGFR less than 90 mL/minute/1.73 m², only initiate Strild ® if other treatments cannot be used (avoid initiating Strild ® if eGFR less than 70 mL/minute/1.73 m²); if eGFR less than 70 mL/minute/1.73 m², only continue Strild ® if potential benefit outweighs risk (discontinue Strild ® if eGFR less than 50 mL/minute/1.73 m²).
- MONITORING REQUIREMENTS Test urine glucose before treatment, then every 4 weeks for 1 year and then every 3 months.

INDICATIONS AND DOSE

HIV infection stabilised on antiretroviral therapy for more than 3 months
BY MOUTH
- Adult: 1 tablet once daily

HEPATIC IMPAIRMENT Manufacturer of Atripla ® advises caution in mild impairment; avoid Atripla ® in moderate to severe impairment.

RENAL IMPAIRMENT Avoid Atripla ® if eGFR less than 50 mL/minute/1.73 m².

PATIENT AND CARER ADVICE
Missed doses If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
CAUTIONARY AND ADVISORY LABELS 21
- Atripla (Gilead Sciences International Ltd)
- Emtricitabine with rilpivirine and tenofovir

Tablet
CAUTIONARY AND ADVISORY LABELS 21
- Stribild (Gilead Sciences International Ltd)
- Strild
- Efavirenz 600 mg, Emtricitabine 200 mg, Tenofovir disoproxil (as Tenofovir disoproxil fumarate) 245 mg Strild 150mg/150mg/200mg/245mg tablets | 30 tablet 
- 19
- 58
- 87
- 13

Efavirenz with emtricitabine and tenofovir

The properties listed below are those particular to the combination only. For the properties of the components please consider, efavirenz p. 558, emtricitabine p. 563, tenofovir disoproxil p. 564.

INDICATIONS AND DOSE

HIV infection in patients with plasma HIV-1 RNA concentration less than 100 000 copies/mL
BY MOUTH
- Adult: 1 tablet once daily

Emtricitabine with rilpivirine and tenofovir

The properties listed below are those particular to the combination only. For the properties of the components please consider, emtricitabine p. 563, rilpivirine p. 561, tenofovir disoproxil p. 564.

INDICATIONS AND DOSE

HIV infection in patients with plasma HIV-1 RNA concentration less than 100 000 copies/mL
BY MOUTH
- Adult: 1 tablet once daily

@drmyothethan
Emtricitabine with tenofovir

The properties listed below are those particular to the combination only. For the properties of the components please consider, emtricitabine p. 563, tenofovir disoproxil p. 564.

INDICATIONS AND DOSE

HIV infection in combination with other antiretroviral drugs

BY MOUTH

► Adult: 1 tablet once daily

RENAL IMPAIRMENT

Use normal dose of Truvada® every 2 days if eGFR 30–50 mL/minute/1.73 m².

Avoid Truvada® if eGFR less than 30 mL/minute/1.73 m².

DIRECTIONS FOR ADMINISTRATION

Patients with swallowing difficulties may disperse tablet in half a glass of water, orange juice, or grape juice (but bitter taste).

PATIENT AND CARER ADVICE

Missed doses

If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time. Patients or carers should be given advice on how to administer Eviplera®.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 21, 25

► Eviplera (Gilead Sciences International Ltd) ▼

Emtricitabine 200 mg, Rilpivirine (as Rilpivirine hydrochloride) 25 mg, Tenofovir disoproxil (as Tenofovir disoproxil fumarate) 245 mg Eviplera 200mg/25mg/245mg tablets | 30 tablet £525.95

Zidovudine

(Azidothymidine; AZT)

INDICATIONS AND DOSE

HIV infection in combination with other antiretroviral drugs

BY MOUTH

► Adult: 250–300 mg twice daily

Prevention of maternal-fetal HIV transmission

BY MOUTH OR BY INTRAVENOUS INFUSION

► Adult: Seek specialist advice (combination therapy preferred) (consult local protocol)

CONTRA-INDICATIONS

Acute porphyrias p. 864 • abnormally low haemoglobin concentration (consult product literature) • abnormally low neutrophil counts (consult product literature)

CAUTIONS

Elderly • risk of haematological toxicity particularly with high dose and advanced disease • vitamin B₁₂ deficiency (increased risk of neutropenia)

INTERACTIONS

Appendix 1 (zidovudine).

SIDE-EFFECTS

Anaemia and myelosuppression If anaemia or myelosuppression occur, reduce dose or interrupt treatment according to product literature, or consider other treatment

Lipoatrophy Zidovudine is associated with a higher risk of lipoatrophy than other antiretrovirals and should be used only if alternative regimens are not suitable.

HEPATIC IMPAIRMENT

Accumulation may occur.

RENAL IMPAIRMENT

Reduce oral dose to 300–400 mg daily in divided doses or intravenous dose to 1 mg/kg 3–4 times daily if eGFR is less than 10 mL/minute/1.73 m².

MONITORING REQUIREMENTS

Monitor full blood count after 4 weeks of treatment, then every 3 months.

DIRECTIONS FOR ADMINISTRATION

Avoid antacids

BY INTRAVENOUS INFUSION

► Adult: 0.8–1 mg/kg every 4 hours usually for not more than 2 weeks, dose approximating to 1.2–1.5 mg/kg every 4 hours by mouth

CONTRA-INDICATIONS

Acute porphyrias p. 864 • abnormally low haemoglobin concentration (consult product literature) • abnormally low neutrophil counts (consult product literature)

CAUTIONS

Elderly • risk of haematological toxicity particularly with high dose and advanced disease • vitamin B₁₂ deficiency (increased risk of neutropenia)

INTERACTIONS

Appendix 1 (zidovudine).

SIDE-EFFECTS

Anaemia and myelosuppressive drugs—for further details consult product literature.

SIDE-EFFECTS, FURTHER INFORMATION

Anaemia and myelosuppression If anaemia or myelosuppression occur, reduce dose or interrupt treatment according to product literature, or consider other treatment

Lipoatrophy Zidovudine is associated with a higher risk of lipoatrophy than other antiretrovirals and should be used only if alternative regimens are not suitable.

HEPATIC IMPAIRMENT

Accumulation may occur.

RENAL IMPAIRMENT

Reduce oral dose to 300–400 mg daily in divided doses or intravenous dose to 1 mg/kg 3–4 times daily if eGFR is less than 10 mL/minute/1.73 m².

MONITORING REQUIREMENTS

Monitor full blood count after 4 weeks of treatment, then every 3 months.

DIRECTIONS FOR ADMINISTRATION

For intermittent intravenous infusion, dilute to a concentration of 2 mg/mL or 4 mg/mL with Glucose 5% and give over 1 hour.

PRESCRIBING AND DISPENSING INFORMATION

The abbreviation AZT which is sometimes used for zidovudine has also been used for another drug.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Capsule

► ZIDOVUDINE (Non-proprietary)

Zidovudine 100 mg Zidovudine 100mg capsules | 60 capsule £40.41

Zidovudine 250 mg Zidovudine 250mg capsules | 60 capsule £96.36

► Retrovir (ViiV Healthcare UK Ltd)

Zidovudine 100 mg Retrovir 100mg capsules | 100 capsule £88.86

Zidovudine 250 mg Retrovir 250mg capsules | 40 capsule £88.86

Oral solution

► Retrovir (ViiV Healthcare UK Ltd)

Zidovudine 10 mg per 1 ml Retrovir 50mg/5ml oral solution (sugar-free) | 200 ml (PO) £17.78

Solution for infusion

► Retrovir (ViiV Healthcare UK Ltd)

Zidovudine 10 mg per 1 ml Retrovir IV 200mg/20ml concentrate for solution for infusion vials | 5 vial (PO) £44.61

HIV infection in combination with other antiretroviral drugs in patients temporarily unable to take zidovudine by mouth

BY INTRAVENOUS INFUSION

► Adult: 0.8–1 mg/kg every 4 hours usually for not more than 2 weeks, dose approximating to 1.2–1.5 mg/kg every 4 hours by mouth
Abacavir with lamivudine and zidovudine

The properties listed below are those particular to the combination only. For the properties of the components please consider, abacavir p. 561, lamivudine p. 563, zidovudine p. 566.

**INDICATIONS AND DOSE**

HIV infection (use only if patient is stabilised for 6–8 weeks on the individual components in the same proportions)

**BY MOUTH**

- Adult: 1 tablet twice daily

- **RENAL IMPAIRMENT** Avoid Trizivir® if eGFR less than 50 mL/minute/1.73 m² (consult product literature).
- Avoid Trizivir® if estimated glomerular filtration rate less than 50 mL/minute/1.73 m².

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - Tablet
    - Trizivir (ViiV Healthcare UK Ltd)
    - Abacavir (as Abacavir sulfate) 300 mg, Lamivudine 150 mg, Zidovudine 300 mg

Lamivudine with zidovudine

The properties listed below are those particular to the combination only. For the properties of the components please consider, lamivudine p. 563, zidovudine p. 566.

**INDICATIONS AND DOSE**

HIV infection in combination with other antiretrovirals

**BY MOUTH**

- Adult: 1 tablet twice daily

- **RENAL IMPAIRMENT** Avoid if eGFR less than 50 mL/minute/1.73 m² (consult product literature).

- **DIRECTIONS FOR ADMINISTRATION**
  - **COMBIVIR® TABLETS** Tablets may be crushed and mixed with semi-solid food or liquid just before administration.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  - Tablet
    - Lamivudine with zidovudine (Non-proprietary)
      - Lamivudine 150 mg, Zidovudine 300 mg
      - Lamivudine 150mg tablets | 60 tablet (Po) £70.61–£80.12
    - Combivir (ViiV Healthcare UK Ltd)
      - Lamivudine 150 mg, Zidovudine 300 mg
      - Combivir 150mg/300mg tablets | 60 tablet (Po) £255.10

**PHARMACOKINETIC ENHANCERS**

**Cobicistat**

**INDICATIONS AND DOSE**

Pharmacokinetic enhancer used to increase the effect of atazanavir or darunavir

**BY MOUTH**

- Adult: 150 mg once daily

- **INTERACTIONS** → Appendix 1 (cobicistat).
- **PREGNANCY** Manufacturer advises avoid unless essential.
- **HEPATIC IMPAIRMENT** Manufacturer advises avoid in severe impairment—no information available.
- **RENAL IMPAIRMENT** No dose adjustment required; inhibits tubular secretion of creatinine; when any co-administered drug requires dose adjustment based on renal function, avoid initiating cobicistat if eGFR less than 70 mL/minute/1.73 m².

- **PRESCRIBING AND DISPENSING INFORMATION** Disperse in original container (contains desiccant).
- **PATIENT AND CARER ADVICE**
  - **Missed doses** If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - Tablet
    - CAUTIONARY AND ADVISORY LABELS 21
      - Tybost (Gilead Sciences International Ltd)
        - Cobicistat 150 mg
      - Tybost 150mg tablets | 30 tablet (Po) £21.38

Also available in combination with elvitegravir, emtricitabine and tenofovir, p. 565

**PROTEASE INHIBITORS (HIV)**

**Protease inhibitors**

- **CONTRA-INDICATIONS** Acute porphyrias p. 864
- **CAUTIONS** Diabetes - haemophilia (increased risk of bleeding)
- **SIDE-EFFECTS, FURTHER INFORMATION** Lipodystrophy Syndrome For further information see HIV infection p. 555. Osteonecrosis For further information see HIV infection p. 555.
- **HEPATIC IMPAIRMENT** Use with caution in patients with chronic hepatitis B or C (increased risk of hepatic side-effects).

**Atazanavir**

**INDICATIONS AND DOSE**

HIV infection in combination with other antiretroviral drugs—with low-dose ritonavir

**BY MOUTH**

- Adult: 300 mg once daily

- HIV infection in combination with other antiretroviral drugs—with cobicistat

- **BY MOUTH**
  - Adult: 300 mg daily

- **CAUTIONS** Cardiac conduction disorders - electrolyte disturbances - predisposition to QT interval prolongation

- **INTERACTIONS** → Appendix 1 (atazanavir).
  - Caution if concomitant use with drugs that prolong PR interval. Caution with concomitant use of drugs that prolong QT interval.

- **SIDE-EFFECTS**
  - **Uncommon** Abnormal dreams - alopecia - amnesia - anxiety - arthralgia - chest pain - cholelithiasis - depression - disorientation - dry mouth - dyspnoea - gynaecomastia - haematuria - hypertension - increased appetite - mouth
ulcers · nephrolithiasis · peripheral neuropathy · proteinuria · syncope · tarsode de pointes · urinary frequency · weight changes

- Rare Abnormal gait · cholecystitis · hepatosplenomegaly · oedema · palpitation

SIDE-EFFECTS, FURTHER INFORMATION

Rash Mild to moderate rash occurs commonly, usually within the first 3 weeks of therapy. Severe rash occurs less frequently and may be accompanied by systemic symptoms. Discontinue if severe rash develops.

- PREGNANCY Theoretical risk of hyperbilirubinaemia in neonate if used at term. In pregnancy, monitor viral load and plasma-atazanavir concentration during third trimester.

- HEPATIC IMPAIRMENT Manufacturer advises caution in mild impairment; avoid in moderate to severe impairment.

- MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS 5, 21

- Reyataz (Bristol-Myers Squibb Pharmaceuticals Ltd)
  Atazanavir (as Atazanavir sulfate) 150 mg Reyataz 150mg capsules | 60 capsule £303.38 (Hospital only)
  Atazanavir (as Atazanavir sulfate) 200 mg Reyataz 200mg capsules | 60 capsule £303.38 (Hospital only)
  Atazanavir (as Atazanavir sulfate) 300 mg Reyataz 300mg capsules | 30 capsule £303.38 (Hospital only)

Darunavir

INDICATIONS AND DOSE

HIV infection in combination with other antiretroviral drugs in patients previously treated with antiretroviral therapy—

with low-dose ritonavir

BY MOUTH

- Adult: 600 mg twice daily, alternatively 800 mg once daily if no resistance to darunavir, if plasma HIV-RNA concentration less than 100 000 copies/ml, and if CD4 cell count greater than 100 cells × 10⁹/litre

HIV infection in combination with other antiretroviral drugs in patients previously treated with antiretroviral therapy—

with cobicistat

BY MOUTH

- Adult: 800 mg once daily, if no resistance to darunavir, if plasma HIV-RNA concentration less than 100 000 copies/mL, and if CD4 cell count greater than 100 cells × 10⁹/litre

HIV infection in combination with other antiretroviral drugs in patients not previously treated with antiretroviral therapy—

with low-dose ritonavir

BY MOUTH

- Adult: 800 mg once daily

HIV infection in combination with other antiretroviral drugs in patients not previously treated with antiretroviral therapy—

with cobicistat

BY MOUTH

- Adult: 800 mg once daily

INTERACTIONS → Appendix 1 (darunavir).

SIDE-EFFECTS

- Common or very common Peripheral neuropathy · rash
- Uncommon Abnormal dreams · acne · alopecia · angina · anxiety · arthralgia · conjunctival hyperaemia · cough · depression · dry eyes · dry mouth · dyspnoea · dysuria · eczema · erectile dysfunction · flushing · gynaecomastia · hypertension · hypothyroidism · increased appetite · increased sweating · memory impairment · myocardial infarction · nail discoloration · nephrolithiasis · osteoporosis · peripheral oedema · polyuria · pyrexia · QT interval prolongation · reduced libido · renal failure · severe skin rash · Stevens-Johnson syndrome · stomatitis · tachycardia · throat irritation · toxic epidermal necrolysis · weight changes

- Rare Bradycardia · confusion · convulsions · haematemesis · palpitation · rhinorrhea · seborrhoeic dermatitis · syncope · visual disturbances

SIDE-EFFECTS, FURTHER INFORMATION

Rash Mild to moderate rash occurs commonly, usually within the first 4 weeks of therapy and resolves without stopping treatment. Severe skin rash (including Stevens-Johnson syndrome and toxic epidermal necrolysis) occurs less frequently and may be accompanied by fever, malaise, arthralgia, myalgia, oral lesions, conjunctivitis, hepatitis, or eosinophilia; treatment should be stopped if severe rash develops.

ALLERGY AND CROSS-SENSITIVITY Use with caution in patients with sulphonamide sensitivity.

- PREGNANCY Manufacturer advises use only if potential benefit outweighs risk; if required, use the twice daily dose regimen.

- HEPATIC IMPAIRMENT Manufacturer advises caution in mild to moderate impairment; avoid in severe impairment—no information available.

- MONITORING REQUIREMENTS Monitor liver function before and during treatment.

- PRESCRIBING AND DISPENSING INFORMATION Flavours of oral liquid formulations may include strawberry.

- PATIENT AND CARER ADVICE

Missed doses

If a dose is more than 6 hours late on the twice daily regimen (or more than 12 hours late on the once daily regimen), the missed dose should not be taken and the next dose should be taken at the normal time.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 21

- Prezista (Janssen-Cilag Ltd)
  Darunavir (as Darunavir ethanolate) 75 mg Prezista 75mg tablets | 480 tablet £446.70
  Darunavir (as Darunavir ethanolate) 150 mg Prezista 150mg tablets | 240 tablet £446.70
  Darunavir (as Darunavir ethanolate) 400 mg Prezista 400mg tablets | 60 tablet £297.80
  Darunavir (as Darunavir ethanolate) 600 mg Prezista 600mg tablets | 60 tablet £446.70
  Darunavir (as Darunavir ethanolate) 800 mg Prezista 800mg tablets | 30 tablet £297.80

Oral suspension

CAUTIONARY AND ADVISORY LABELS 21

- Prezista (Janssen-Cilag Ltd)
  Darunavir (as Darunavir ethanolate) 100 mg per 1 ml Prezista 100mg/ml oral suspension (sugar-free) | 200 ml £248.17

Fosamprenavir

- DRUG ACTION Fosamprenavir is a pro-drug of ampranavir.

INDICATIONS AND DOSE

HIV infection in combination with other antiretroviral drugs—

with low-dose ritonavir

BY MOUTH

- Adult: 700 mg twice daily

Dose equivalence and conversion

700 mg fosamprenavir is equivalent to approximately 600 mg ampranavir.

- INTERACTIONS → Appendix 1 (fosamprenavir).
INDICATIONS AND DOSE
HIV infection in combination with other antiretroviral drugs
INITIALLY BY MOUTH USING TABLETS
- Adult: 400/100 mg twice daily, alternatively (by mouth) 800/200 mg once daily in adults with a HIV strain that has less than 3 mutations to protease inhibitors
-成人：每日2次，每次400/100mg，或800/200mg一次，用于成人对HIV的株，该株对蛋白酶抑制剂有3个或3个以下的突变。

Dose equivalence and conversion
The proportions are expressed in the form x/y where x and y are the strengths in milligrams of lopinavir and ritonavir respectively.

CAUTIONS
Cardiac conduction disorders · pancreatitis · patients at high risk of cardiovascular disease (especially if 10-year cardiovascular risk greater than 20%) · structural heart disease

INTERACTIONS → Appendix 1 (lopinavir, ritonavir).
Caution if concomitant use with drugs that prolong QT or PR interval.

SIDE-EFFECTS
- Common or very common Amenorrhea · anxiety · arthralgia · colitis · hypertension · menorrhagia · neuropathy · night sweats · sexual dysfunction · weight changes
- Uncommon Abnormal dreams · alopecia · AV block · cerebrovascular accident · convulsions · deep vein thrombosis · dry mouth · gastro-intestinal ulcer · haematuria · myocardial infarction · nephritis · rectal bleeding · stomatitis · tinnitus · tremor · visual disturbances

SIDE-EFFECTS, FURTHER INFORMATION
Pancreatitis Signs and symptoms suggestive of pancreatitis (including raised serum lipase) should be evaluated—discontinue if pancreatitis diagnosed

PREGNANCY
Avoid oral solution due to high propylene glycol content; use tablets only if potential benefit outweighs risk (toxicity in animal studies)
Ritonavir

INDICATIONS AND DOSE
HIV infection in combination with other antiretrovirals in patients previously treated with antiretroviral therapy—with low-dose ritonavir
BY MOUTH
> Adult: 1 g every 12 hours
HIV infection in combination with other antiretrovirals in patients not previously treated with antiretroviral therapy—with low-dose ritonavir
BY MOUTH
> Adult: 500 mg every 12 hours for 7 days, then increased to 1 g every 12 hours

CAUTIONS
Cardiac conduction disorders · pancreatitis · structural heart disease

INTERACTIONS → Appendix 1 (ritonavir).
Caution if concomitant use with drugs that prolong PR interval.

SIDE-EFFECTS
> Common or very common Acne · anxiety · arthralgia · blood pressure changes · blurred vision · confusion · cough · decreased blood thyroxine concentration · fever · flushing · gastro-intestinal haemorrhage · menorrhagia · mouth ulcers · oedema · peripheral neuropathy · pharyngitis · renal impairment · seizures · syncope
> Uncommon Electrolyte disturbances · myocardial infarction
> Rare Toxic epidermal necrolysis

SIDE-EFFECTS, FURTHER INFORMATION
Pancreatitis Signs and symptoms suggestive of pancreatitis (including raised serum lipase) should be evaluated—discontinue if pancreatitis diagnosed.

PREGNANCY
Only use low-dose booster to increase the effect of other protease inhibitors.

HEPATIC IMPAIRMENT
Avoid in decompensated liver disease; in severe impairment without decompensation, use “booster” doses with caution (avoid treatment doses).

DIRECTIONS FOR ADMINISTRATION
Bitter taste of oral solution can be masked by mixing with chocolate milk; do not mix with water, measuring cup must be dry.

PATIENT AND CARER ADVICE
Patients or carers should be given advice on how to administer ritonavir oral solution.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
CAUTIONARY AND ADVISORY LABELS 21, 25
> Norvir (AbbVie Ltd)
Ritonavir 100 mg Norvir 100mg tablets | 30 tablet [Fest] £19.44

Oral solution
CAUTIONARY AND ADVISORY LABELS 21
EXCIPIENTS: May contain Alcohol, propylene glycol
> Norvir (AbbVie Ltd)
Ritonavir 80 mg per 1 ml Norvir 80mg/ml oral solution (sugar-free) | 450 ml [Fest] £403.20

Saqinavir

INDICATIONS AND DOSE
HIV infection in combination with other antiretrovirals in patients previously treated with antiretroviral therapy—
with low-dose saquinavir
BY MOUTH
> Adult: 1 g every 12 hours
HIV infection in combination with other antiretrovirals in patients not previously treated with antiretroviral therapy—
with low-dose saquinavir
BY MOUTH
> Adult: 500 mg every 12 hours for 7 days, then increased to 1 g every 12 hours

CONTRA-INDICATIONS
Bradycardia · congenital QT prolongation · electrolyte disturbances · heart failure with reduced left ventricular ejection fraction · history of symptomatic arrhythmias · predisposition to cardiac arrhythmias

INTERACTIONS → Appendix 1 (saquinavir).
Caution with concomitant use of garlic (avoid garlic capsules—reduces plasma-saquinavir concentration). Contra-indicated if concomitant use of drugs that prolong QT or PR interval. Contra-indicated if concomitant use of drugs that increase plasma-saquinavir concentration (avoid unless no alternative treatment available).

SIDE-EFFECTS
> Common or very common Alopecia · changes in libido · dry mouth · dyspnoea · increased appetite · peripheral neuropathy
> Uncommon Convulsions · mucosal ulceration · renal impairment · visual impairment

HEPATIC IMPAIRMENT
Manufacturer advises caution in moderate impairment; avoid in decompensated liver disease.

RENAL IMPAIRMENT
Use with caution if eGFR less than 30 mL/minute/1.73 m².

MONITORING REQUIREMENTS
Monitor ECG before starting treatment (do not initiate treatment if QT interval over 450 milliseconds); if baseline QT interval less than 450 milliseconds, monitor ECG during treatment (particularly 10 days after starting treatment in patients not previously treated with antiretroviral therapy)—discontinue if QT interval increases over 480 milliseconds, if QT interval more than 20 milliseconds above baseline, if prolongation of PR interval, or if arrhythmias occur.

PATIENT AND CARER ADVICE
Arrhythmias Patients should be told how to recognise signs of arrhythmia and advised to seek medical attention if symptoms such as palpitation or syncope develop.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
6.7 Influenza

Oxeltevivir below and zanamivir p. 573 are most effective for the treatment of influenza if started within a few hours of the onset of symptoms; they are licensed for use within 48 hours of the first symptoms. In otherwise healthy individuals they reduce the duration of symptoms by about 1–1.5 days. Oxeltevivir or zanamivir can reduce the risk of complications from influenza in the elderly and in patients with chronic disease.

Oxeltevivir and zanamivir are licensed for post-exposure prophylaxis of influenza when influenza is circulating in the community. Oxeltevivir should be given within 48 hours of exposure to influenza while zanamivir should be given within 36 hours of exposure to influenza. However, in patients with severe influenza or in those who are immunocompromised, antivirals may still be effective after this time if viral shedding continues [unlicensed use]. Oxeltevivir and zanamivir are also licensed for use in exceptional circumstances (e.g. when vaccination does not cover the infecting strain) to prevent influenza in an epidemic.

There is evidence that some strains of influenza A virus have reduced susceptibility to osextamivir, but may retain susceptibility to zanamivir. Resistance to osextamivir may be greater in severely immunocompromised patients.

Osextamivir and zanamivir are also licensed for use in exceptional circumstances (e.g. when vaccination does not cover the infecting strain) to prevent influenza in an epidemic.

Information on pandemic influenza, avian influenza, and swine influenza may be found at www.gov.uk/phe.

Immunisation against influenza is recommended for persons at high risk, and to reduce transmission of infection.

Osextamivir in children under 1 year of age

Data on the use of osextamivir in children under 1 year of age is limited. Furthermore, osextamivir may be ineffective in neonates because they may not be able to metabolise osextamivir to its active form. However, osextamivir can be used (under specialist supervision) for the treatment or post-exposure prophylaxis of influenza in children under 1 year of age. The Department of Health has advised (May 2009) that during a pandemic, treatment with osextamivir can be overseen by healthcare professionals experienced in assessing children.

NEUROMINIDASE INHIBITORS

Oseltamivir

Caution

PRECAUTIONS

Caution with concomitant use of drugs that increase risk of bleeding.

SIDE-EFFECTS

Dehydration

FREQUENCY NOT KNOWN

Anorexia, dyspnoea, influenza-like symptoms, peripheral neuropathy, photosensitivity, renal impairment.

SIDE-EFFECTS, FURTHER INFORMATION

Hepatotoxicity. Potentially life-threatening hepatotoxicity reported. Discontinue if signs or symptoms of hepatitis develop or if liver-function abnormality develops (consult product literature).

PREGNANCY

Manufacturer advises use only if potential benefit outweighs risk—toxicity in animal studies.

HEPATIC IMPAIRMENT

Manufacturer advises caution in mild impairment; avoid in moderate or severe impairment—no information available.

MONITORING REQUIREMENTS

Monitor liver function before treatment then every 2 weeks for 1 month, then every 3 months.

PRESCRIBING AND DISPENSING INFORMATION

Flavours of oral liquid formulations may include toffee and mint.

PATIENT AND CARER ADVICE

Patients or carers should be told to observe the oral solution for crystallisation; the bottle should be replaced if more than a thin layer of crystals form (doses should continue to be taken at the normal time until the bottle is replaced).

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Capable

CAUTIONARY AND ADVISORY LABELS 5, 21

More than that of the capsules; the oral solution is not interchangeable with the capsules on a milligram-for-milligram basis.

DIFFERENCE AND CONVERSION

Tipranavir

INDICATIONS AND DOSE

HIV infection resistant to other protease inhibitors, in combination with other antiretroviral drugs in patients previously treated with antiretrovirals (with low-dose ritonavir).

BY MOUTH USING CAPSULES

Adult: 500 mg twice daily

Dose equivalence and conversion

The bioavailability of tipranavir oral solution is higher than that of the capsules; the oral solution is not interchangeable with the capsules on a milligram-for-milligram basis.

CAUTIONARY AND ADVISORY LABELS

5, 21

CAUTIONARY AND ADVISORY LABELS 5, 21

Capsule containing the same drug.

There can be variation in the licensing of different medicines containing the same drug.
Infection

- Child 1-12 years (body-weight 10-15 kg): 30 mg once daily for 10 days for post-exposure prophylaxis; for up to 6 weeks during an epidemic
- Child 1-12 years (body-weight 15-23 kg): 45 mg once daily for 10 days for post-exposure prophylaxis; for up to 6 weeks during an epidemic
- Child 1-12 years (body-weight 23-40 kg): 60 mg once daily for 10 days for post-exposure prophylaxis; for up to 6 weeks during an epidemic
- Child 1-12 years: 75 mg once daily for 10 days for post-exposure prophylaxis; for up to 6 weeks during an epidemic
- Adult: 75 mg once daily for 10 days for post-exposure prophylaxis; for up to 6 weeks during an epidemic

Treatment of influenza

BY MOUTH
- Child 1-2 months: 2.5 mg/kg twice daily for 5 days
- Child 3-11 months: 3 mg/kg twice daily for 5 days
- Child 1-12 years (body-weight 10-15 kg): 30 mg twice daily for 5 days
- Child 1-12 years (body-weight 15-23 kg): 45 mg twice daily for 5 days
- Child 1-12 years (body-weight 23-40 kg): 60 mg twice daily for 5 days
- Child 1-12 years (body-weight 40 kg and above): 75 mg twice daily for 5 days
- Child 13-17 years: 75 mg twice daily for 5 days
- Adult: 75 mg twice daily for 5 days

UNLICENSED USE
- Not licensed for use in children under 1 year of age unless there is a pandemic.

SIDE-EFFECTS
- Common or very common: Abdominal pain; dyspepsia; headache; nausea; vomiting
- Uncommon: Altered consciousness (usually in children and adolescents); arrhythmias; convulsions; eczema; rash
- Rare: Gastro-intestinal bleeding; hepatitis; neuropsychiatric disorders (usually in children and adolescents); Stevens-Johnson syndrome; thrombocytopenia; toxic epidermal necrolysis; visual disturbances

PREGNANCY
- Although safety data are limited, oseltamivir can be used in women who are pregnant when the potential benefit outweighs the risk (e.g. during a pandemic). Use only if potential benefit outweighs risk (e.g. during a pandemic).

BREAST FEEDING
- Although safety data are limited, oseltamivir can be used in women who are breast-feeding when the potential benefit outweighs the risk (e.g. during a pandemic). Oseltamivir is the preferred drug in women who are breast-feeding. Amount probably too small to be harmful; use only if potential benefit outweighs risk (e.g. during a pandemic).

RENAL IMPAIRMENT
- In adults For treatment, use 30 mg twice daily if eGFR 30–60 mL/minute/1.73 m² (30 mg once daily if eGFR 10–30 mL/minute/1.73 m²). For prevention, use 30 mg once daily if eGFR 30–60 mL/minute/1.73 m² (30 mg every 48 hours if eGFR 10–30 mL/minute/1.73 m²). Avoid for treatment and prevention if eGFR less than 10 mL/minute/1.73 m².
- In children For treatment, use 40% of normal dose twice daily if estimated glomerular filtration rate 30–60 mL/minute/1.73 m² (40% of normal dose once daily if estimated glomerular filtration rate 10–30 mL/minute/1.73 m²). For prevention, use 40% of normal dose once daily if estimated glomerular filtration rate 30–60 mL/minute/1.73 m² (40% of normal dose every 48 hours if estimated glomerular filtration rate 10–30 mL/minute/1.73 m²). Avoid for treatment and prevention if estimated glomerular filtration rate less than 10 mL/minute/1.73 m².

DIRECTIONS FOR ADMINISTRATION
- If suspension not available, capsules can be opened and the contents mixed with a small amount of sweetened food, such as sugar water or chocolate syrup, just before administration.

PRESCRIBING AND DISPENSING INFORMATION
- Flavours of oral liquid formulations may include tutti-frutti.

PATIENT AND CARER ADVICE
- Medicines for Children leaflet: Oseltamivir for influenza (flu) www.medicinesforchildren.org.uk/oseltamivir-for-influenza

NATIONAL FUNDING/ACCESS DECISIONS
- Oseltamivir, zanamivir, and amantadine for prophylaxis of influenza (September 2008) [NICE TA158]
- The drugs described here are not a substitute for vaccination, which remains the most effective way of preventing illness from influenza.
- Amantadine is not recommended for prophylaxis of influenza.
- Oseltamivir is not recommended for seasonal prophylaxis against influenza.
- When influenza is circulating in the community, either oseltamivir or zanamivir is recommended (in accordance with UK licensing) for post-exposure prophylaxis in at-risk patients who are not effectively protected by influenza vaccine, and who have been in close contact with someone suffering from influenza-like illness in the same household or residential setting. Oseltamivir should be given within 48 hours of exposure to influenza while zanamivir should be given within 36 hours of exposure to influenza. National surveillance schemes, including those run by Public Health England, should be used to indicate when influenza is circulating in the community.
- During local outbreaks of influenza-like illness, when there is a high level of certainty that influenza is present, either oseltamivir or zanamivir may be used for post-exposure prophylaxis in at-risk patients (regardless of influenza vaccination) living in long-term residential or nursing homes. At risk patients include those aged over 65 years or those who have one or more of the following conditions:
  - chronic respiratory disease (including asthma and chronic obstructive pulmonary disease);
  - chronic heart disease;
  - chronic renal disease;
  - chronic liver disease;
  - chronic neurological disease;
  - immunosuppression;
  - diabetes mellitus.
- The Department of Health in England has advised (November 2010 and April 2011) that ‘at risk patients’ also includes patients under 65 years of age who are at risk of developing medical complications from influenza (treatment only) or women who are pregnant. This guidance does not cover the circumstances of a pandemic, an impending pandemic, or a widespread epidemic of a new strain of influenza to which there is little or no immunity in the community. www.nice.org.uk/TA158
- Oseltamivir, zanamivir, and amantadine for prophylaxis of influenza (February 2009) [NICE TA168]
- The drugs described here are not a substitute for vaccination, which remains the most effective way of preventing illness from influenza.
- Amantadine is not recommended for prophylaxis of influenza.
When influenza is circulating in the community, either oseltamivir or zanamivir is recommended (in accordance with UK licensing) for the treatment of influenza in at-risk patients who can start treatment within 48 hours of the onset of symptoms. National surveillance schemes, including those run by Public Health England, should be used to indicate when influenza is circulating in the community.

During local outbreaks of influenza-like illness, when there is a high level of certainty that influenza is present, either oseltamivir or zanamivir may be used for treatment at-risk patients living in long-term residential or nursing homes. At risk patients include those aged over 65 years or those who have one or more of the following conditions:
- chronic respiratory disease (including asthma and chronic obstructive pulmonary disease);
- chronic heart disease;
- chronic renal disease;
- chronic liver disease;
- chronic neurological disease;
- immunosuppression;
- diabetes mellitus.

The Department of Health in England has advised (November 2010 and April 2011) that ‘at risk patients’ also includes patients under 65 years of age who are at risk of developing medical complications from influenza (treatment only) or women who are pregnant. This guidance does not cover the circumstances of a pandemic, an impending pandemic, or a widespread epidemic of a new strain of influenza to which there is little or no immunity in the community. www.nice.org.uk/TA168

NHS restrictions Except for the treatment and prophylaxis of influenza as indicated in the NICE guidance; endorse prescription ‘SLS’.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension.

Capsule
- Tamiflu (Roche Products Ltd)
  - Oseltamivir (as Oseltamivir phosphate) 30 mg Tamiflu 30mg capsules | 10 capsule (PO) £7.71
  - Oseltamivir (as Oseltamivir phosphate) 45 mg Tamiflu 45mg capsules | 10 capsule (PO) £15.41
  - Oseltamivir (as Oseltamivir phosphate) 75 mg Tamiflu 75mg capsules | 10 capsule (PO) £15.41

Oral suspension
- Tamiflu (Roche Products Ltd)
  - Oseltamivir (as Oseltamivir phosphate) 6 mg per 1 ml Tamiflu 6mg/ml oral suspension (sugar-free) | 65 ml (PO) £10.27

Oral solution
- Tamiflu (Roche Products Ltd)
  - Oseltamivir (as Oseltamivir phosphate) 15 mg per 1 ml Oseltamivir 15mg/ml oral solution sugar free (sugar-free) | 20 ml (PO) £10.00

Zanamivir
- DRUG ACTION Reduces replication of influenza A and B viruses by inhibiting viral neuraminidase.

INDICATIONS AND DOSE
Post-exposure prophylaxis of influenza
- Child 5-17 years: 10 mg once daily for up to 10 days
- Adult: 10 mg once daily for up to 10 days

Prevention of influenza during an epidemic
- Child 5-17 years: 10 mg once daily for up to 28 days
- Adult: 10 mg once daily for up to 28 days

TREATMENT OF INFLUENZA
- Child 5-17 years: 10 mg twice daily for 5 days (for up to 10 days if resistance to oseltamivir suspected)
- Adult: 10 mg twice daily for 5 days (for up to 10 days if resistance to oseltamivir suspected)

UNLICENSED USE Use of zanamivir for up to 10 days if resistance to oseltamivir suspected is an unlicensed duration.

CAUTIONS
- Asthma, chronic pulmonary disease
- Uncontrolled chronic illness

CAUTIONS, FURTHER INFORMATION
- Asthma and chronic pulmonary disease Risk of bronchospasm - short-acting bronchodilator should be available. Avoid in severe asthma unless close monitoring possible and appropriate facilities available to treat bronchospasm.

SIDE-EFFECTS
- Common or very common Rash
- Uncommon Angioedema, bronchospasm, dyspnoea, urticaria

RARE Neupyschiatric disorders (in children). Neupyschiatric disorders (especially in children and adolescents) (in adults) - Stevens-Johnson syndrome - toxic epidermal necrolysis

PREGNANCY Although safety data are limited, zanamivir can be used in women who are pregnant when the potential benefit outweighs the risk (e.g. during a pandemic). Use only if potential benefit outweighs risk (e.g. during a pandemic). Breastfeeding Although safety data are limited, zanamivir can be used in women who are breast-feeding when the potential benefit outweighs the risk (e.g. during a pandemic). Amount probably too small to be harmful; use only if potential benefit outweighs risk (e.g. during a pandemic).

DIRECTIONS FOR ADMINISTRATION Other inhaled drugs should be administered before zanamivir.

PRESCRIBING AND DISPENSING INFORMATION Except for the treatment and prophylaxis of influenza as indicated in the NICE guidance; endorse prescription ‘SLS’.

NATIONAL FUNDING/ACCESS DECISIONS
NICE technology appraisals (TAs)
- Oseltamivir, zanamivir, and amantadine for prophylaxis of influenza (September 2008) [NICE TA158], see p. 572
- Oseltamivir, zanamivir, and amantadine for treatment of influenza (February 2009) [NICE TA168], see p. 572

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Inhalation powder
- Relenza (GlxosSmithKline UK Ltd)
  - Zanamivir 5 mg Relenza 5mg inhalation powder blisters with Diskhaler 20 blister (PO) £16.36
Chapter 6
Endocrine system

1 Antidiuretic hormone disorders

Posterior pituitary hormones and antagonists

Posterior pituitary hormones

Diabetes insipidus

Vasopressin p. 576 (antidiuretic hormone, ADH) is used in the treatment of pituitary ('cranial') diabetes insipidus as is its analogue desmopressin. Dosage is tailored to produce a slight diuresis every 24 hours to avoid water intoxication. Treatment may be required for a limited period only in diabetes insipidus following trauma or pituitary surgery.

Desmopressin is more potent and has a longer duration of action than vasopressin; unlike vasopressin it has no vasoconstrictor effect. It is given by mouth or intranasally for maintenance therapy, and by injection in the postoperative period or in unconscious patients. Desmopressin is also used in the differential diagnosis of diabetes insipidus. Following a dose intramuscularly or intranasally, restoration of the ability to concentrate urine after water deprivation confirms a diagnosis of cranial diabetes insipidus. Failure to respond occurs in nephrogenic diabetes insipidus.

In nephrogenic and partial pituitary diabetes insipidus benefit may be gained from the paradoxical antidiuretic effect of thiazides.

Carbamazepine p. 387 is sometimes useful in partial pituitary diabetes insipidus [unlicensed]; it may act by sensitising the renal tubules to the action of remaining endogenous vasopressin.

Other uses

Desmopressin is also used to boost factor VIII concentration in mild to moderate haemophilia and in von Willebrand's disease; it is also used to test fibrinolytic response. Desmopressin may also have a role in nocturnal enuresis.

Vasopressin infusion is used to control variceal bleeding in portal hypertension, prior to more definitive treatment and with variable results. Terlipressin acetate p. 77, a derivative of vasopressin with reportedly less pressor and antidiuretic activity, is used similarly.

Oxytocin p. 705, another posterior pituitary hormone, is indicated in obstetrics.

Antidiuretic hormone antagonists

Demeclocycline hydrochloride p. 496 can be used in the treatment of hyponatraemia resulting from inappropriate secretion of antidiuretic hormone, if fluid restriction alone does not restore sodium concentration or is not tolerable. Demeclocycline hydrochloride is thought to act by directly blocking the renal tubular effect of antidiuretic hormone.

Tolvaptan p. 577 is a vasopressin V2-receptor antagonist licensed for the treatment of hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion; treatment duration with tolvaptan is determined by the underlying disease and its treatment. Rapid correction of hyponatraemia during tolvaptan therapy can cause osmotic demyelination, leading to serious neurological events; close monitoring of serum sodium concentration and fluid balance is essential.

1.1 Diabetes insipidus

Drugs used for Diabetes insipidus not listed below; Chlortalidone, p. 204

VASOPRESSIN AND ANALOGUES

Desmopressin

Drug action

Desmopressin is an analogue of vasopressin.
**INDICATIONS AND DOSE**

**Diabetes insipidus, diagnosis (water deprivation test)**

BY INTRANASAL ADMINISTRATION
- Adult: 20 micrograms, limit fluid intake to 500 mL from 1 hour before to 8 hours after administration

BY INTRAMUSCULAR INJECTION OR BY SUBCUTANEOUS INJECTION
- Adult: 2 micrograms for 1 dose, limit fluid intake to 500 mL from 1 hour before to 8 hours after administration

**Diabetes insipidus, treatment**

BY MOUTH
- Child 1 month-1 year: Initially 10 micrograms 2–3 times a day, adjusted according to response; usual dose 30–150 micrograms daily
- Child 2–11 years: Initially 50 micrograms 2–3 times a day, adjusted according to response; usual dose 100–800 micrograms daily
- Child 12-17 years: Initially 100 micrograms 2–3 times a day, adjusted according to response; usual dose 0.2–1.2 mg daily
- Adult: Initially 60 micrograms 3 times a day, maintenance 100–200 micrograms 3 times a day; usual dose 0.2–1.2 mg daily

BY SUBLINGUAL ADMINISTRATION
- Child 2-17 years: Initially 60 micrograms 3 times a day, adjusted according to response; usual dose 40–240 micrograms 3 times a day
- Adult: Initially 60 micrograms 3 times a day, adjusted according to response; usual dose 40–240 micrograms 3 times a day

BY INTRANASAL ADMINISTRATION
- Child 1 month-1 year: Initially 2.5–5 micrograms 1–2 times a day, adjusted according to response
- Child 2-11 years: Initially 5–20 micrograms 1–2 times a day, adjusted according to response
- Child 12-17 years: Initially 10–20 micrograms 1–2 times a day, adjusted according to response
- Adult: 10–40 micrograms daily in 1–2 divided doses

BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION
- Adult: 1–4 micrograms daily

**Primary nocturnal enuresis**

BY MOUTH
- Child 5-17 years: 200 micrograms once daily, only increased to 400 micrograms if lower dose not effective; withdraw for at least 1 week for reassessment after 3 months, dose to be taken at bedtime, limit fluid intake from 1 hour before to 8 hours after administration
- Adult 18-65 years: 200 micrograms once daily, only increased to 400 micrograms if lower dose not effective; withdraw for at least 1 week for reassessment after 3 months, dose to be taken at bedtime, limit fluid intake from 1 hour before to 8 hours after administration

BY SUBLINGUAL ADMINISTRATION
- Child 5-17 years: 120 micrograms once daily, increased if necessary to 240 micrograms once daily, dose to be taken at bedtime, limit fluid intake from 1 hour before to 8 hours after administration, dose to be increased only if lower dose not effective, reassess after 3 months by withdrawing treatment for at least 1 week
- Adult 18-65 years: 120 micrograms once daily, increased if necessary to 240 micrograms once daily, dose to be taken at bedtime, limit fluid intake from 1 hour before to 8 hours after administration, dose to be increased only if lower dose not effective, reassess after 3 months by withdrawing treatment for at least 1 week

**Postoperative polyuria or polydipsia**

BY MOUTH
- Adult: Dose to be adjusted according to urine osmolality

Polyuria or polydipsia after hypophysectomy

BY SUBLINGUAL ADMINISTRATION
- Adult: Dose to be adjusted according to urine osmolality

**Nocturia associated with multiple sclerosis (when other treatments have failed)**

BY INTRANASAL ADMINISTRATION
- Adult 18-65 years: 10–20 micrograms once daily, to be taken at bedtime, dose not to be repeated within 24 hours, limit fluid intake from 1 hour before to 8 hours after administration

Renal function testing

BY INTRANASAL ADMINISTRATION
- Adult: 40 micrograms, empty bladder at time of administration and limit fluid intake to 500 mL from 1 hour before until 8 hours after administration to avoid fluid overload

BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION
- Adult: 2 micrograms, empty bladder at time of administration and restrict fluid intake to 500 mL from 1 hour before until 8 hours after administration to avoid fluid overload

**Mild to moderate haemophilia and von Willebrand’s disease**

BY INTRANASAL ADMINISTRATION
- Adult: 300 micrograms every 12 hours if required, one 150 microgram spray into each nostril, 30 minutes before surgery or when bleeding, dose may alternatively be repeated at intervals of at least 3 days, if self-administered

BY INTRAVENOUS INFUSION OR BY SUBCUTANEOUS INJECTION
- Adult: 300 nanograms/kg for 1 dose, to be administered immediately before surgery or after trauma; may be repeated at intervals of 12 hours if no tachycardia

**Fibrinolytic response testing**

BY INTRANASAL ADMINISTRATION
- Adult: 300 micrograms, blood to be sampled after 1 hour for fibrinolytic activity, one 150 microgram spray to be administered into each nostril

BY SUBCUTANEOUS INJECTION OR BY INTRAVENOUS INJECTION
- Adult: 300 nanograms/kg for 1 dose, blood to be sampled after 20 minutes for fibrinolytic activity

**Lumbar-puncture-associated headache**

BY INTRANASAL ADMINISTRATION OR BY SUBCUTANEOUS INJECTION
- Adult: (consult product literature)

- **CONTRA-INDICATIONS** Cardiac insufficiency - conditions treated with diuretics - polydipsia in alcohol dependence - psychogenic polydipsia

- **CAUTIONS**

**GENERAL CAUTIONS**
- Asthma - avoid fluid overload - cardiovascular disease (not indicated for nocturnal enuresis or nocturia) - conditions which might be aggravated by water retention - cystic fibrosis - elderly (avoid for nocturnal enuresis and nocturia in those over 65 years) epilepsy - heart failure - hypertension (not indicated for nocturnal enuresis or nocturia) - migraine - nocturia — limit fluid intake to minimum from 1 hour before dose until 8 hours afterwards - nocturnal enuresis — limit fluid intake to minimum from 1 hour before dose until 8 hours afterwards

**SPECIFIC CAUTIONS**
- With intranasal use should not be given intranasally for nocturnal enuresis due to an increased incidence of side-effects
### Desmopressin

**Endocrine system**

#### PRESCRIBING AND DISPENSING INFORMATION

**DIRECTIONS FOR ADMINISTRATION**

- **With intranasal use**
- **Rhinitis**
- **SIDE-EFFECTS, FURTHER INFORMATION**
- **Hypotensive convulsions**
  - The risk of hypotensive convulsions can be minimised by keeping to the recommended starting doses and by avoiding concomitant use of drugs which increase secretion of vasopressin (e.g. tricyclic antidepressants).
- **PREGNANCY**
  - Small oxytocic effect in third trimester; increased risk of pre-eclampsia.
- **BREAST FEEDING**
  - Amount too small to be harmful.
- **RENAL IMPAIRMENT**
  - Use with caution; antidiuretic effect may be reduced.
- **MONITORING REQUIREMENTS**
  - In nocturia, periodic blood pressure and weight checks are needed to monitor for fluid overload.
- **DIRECTIONS FOR ADMINISTRATION**
  - BDVAP® and Desmotabs® tablets may be crushed. BDVAP® intranasal solution may be diluted with Sodium Chloride 0.9% to a concentration of 10 micrograms/mL.
  - In adults For intravenous infusion (BDVAP®, Octim®), give intermittently in Sodium chloride 0.9%; dilute with 50 mL and give over 20 minutes.
- **PRESCRIBING AND DISPENSING INFORMATION**
  - Oral, intranasal, intravenous, subcutaneous and intramuscular doses are expressed as desmopressin acetate; sublingual doses are expressed as desmopressin base.
- **CHILDREN**
  - Children requiring an intranasal dose of less than 10 micrograms should be given BDVAP® intranasal solution.
- **PATIENT AND CARER ADVICE**
  - Medicines for Children leaflet: Desmopressin for bedwetting www.medicinesforchildren.org.uk/ desmopressin-bedwetting-0
- **Hypotensive convulsions**
  - Patients being treated for primary nocturnal enuresis should be warned to avoid fluid overload (including during swimming) and to stop taking desmopressin during an episode of vomiting or diarrhoea (until fluid balance normal).

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, spray, oral solution, capsule, nasal drops.

- **Tablet**
  - DESMOPRESSIN (Non-proprietary)
    - Desmopressin acetate 100 microgram BDVAP 100 microgram tablets | 90 tablet (BDP) £61.43 DT price = £61.43
    - Desmopressin acetate 200 microgram BDVAP 0.2mg tablets | 90 tablet (BDP) £88.23
    - Desmotabs Ferring Pharmaceuticals Ltd
    - Desmopressin acetate 200 microgram Desmotabs 0.2mg tablets | 30 tablet (BDP) £35.23 DT price = £35.23
  - **Desmotabs**
    - Desmopressin acetate 200 microgram Desmotabs 0.2mg tablets | 30 tablet (BDP) £35.23 DT price = £35.23
  - **Oral solution**
    - DESMOPRESSIN (Non-proprietary)
      - Desmopressin (as Desmopressin acetate) 360 microgram per 1 ml Desmopressin 360micrograms/ml oral solution | 15 ml (BDP) £30.00

### Oral lyophilisate

#### CAUTIONARY AND ADVISORY LABELS

- **DESMPRESSIN (Non-proprietary)**
  - Desmopressin (as Desmopressin acetate) 60 microgram (BDVAP Melt oral lyophilisates sugar-free) | 100 tablet (BDP) £50.53
  - Desmopressin (as Desmopressin acetate) 120 microgram Desmopressin 120microgram oral lyophilisates sugar-free (sugar-free) | 30 tablet (BDP) no price available
  - Desmopressin (as Desmopressin acetate) 240 microgram Desmopressin 240microgram oral lyophilisates sugar-free | 100 tablet (BDP) £101.07
  - Desmopressin (as Desmopressin acetate) 240 microgram Desmopressin 240 microgram oral lyophilisates sugar-free | 30 tablet (BDP) £30.34
  - Desmopressin (as Desmopressin acetate) 240 microgram Desmopressin 240 microgram oral lyophilisates sugar-free | 100 tablet (BDP) £101.07
  - Desmopressin (as Desmopressin acetate) 240 microgram Desmopressin 240 microgram oral lyophilisates sugar-free | 30 tablet (BDP) £60.68

#### Solution for Injection

- **DESMPRESSIN (Non-proprietary)**
  - Desmopressin acetate 4 microgram per 1 mL BDVAP 4micrograms/mL solution for injection ampoules | 10 ampoule (BDP) £13.16
  - Octim (Ferring Pharmaceuticals Ltd)
  - Desmopressin acetate 15 microgram per 1 mL Octim 15 micrograms/mL solution for injection ampoules | 10 ampoule (BDP) £192.20
  - **Spray**
    - DESMOPRESSIN (Non-proprietary)
      - Desmopressin acetate 10 microgram per 1 dose Desmopressin 10 micrograms/dose nasal spray | 60 dose (BDP) £23.04 DT price = £8.18
      - Desmopressin acetate 2.5 microgram per 1 dose Desmopressin 2.5 micrograms/dose nasal spray | 50 dose no price available
  - **Desmospray**
    - Desmospray (Ferring Pharmaceuticals Ltd)
    - Desmopressin acetate 150 microgram per 1 dose Octim 150 micrograms/dose nasal spray | 25 dose (BDP) £576.60

### Vasopressin

#### INDICATIONS AND DOSE

- **Pituitary diabetes insipidus**
  - BY INTRAMUSCULAR INJECTION OR BY SUBCUTANEOUS INJECTION
    - Adult: 5–20 units every 4 hours
  - **Initial control of oesophageal variceal bleeding**
    - BY INTRAVENOUS INFUSION
      - Adult: 20 units, dose to be administered over 15 minutes

- **CONTRA-INDICATIONS**
  - Chronic nephritis (until reasonable blood nitrogen concentrations attained) - vascular disease (especially disease of coronary arteries) unless extreme caution
- **CAUTIONS**
  - Asthma - avoid fluid overload - conditions which might be aggravated by water retention - epilepsy - heart failure - hypertension - migraine
- **SIDE-EFFECTS**
  - Rare Gangrene
  - Frequency not known Abdominal cramps - anaphylaxis - anginal attacks - belching - constriction of coronary arteries - desire to defaecate - fluid retention - headache - hypersensitivity reactions - myocardial ischaemia - nausea - pallor - peripheral ischaemia - sweating - tremor - vertigo - vomiting
- **PREGNANCY**
  - Oxytocic effect in third trimester.
1.2 Syndrome of inappropriate antidiuretic hormone secretion

Drugs used for Syndrome of inappropriate antidiuretic hormone secretion not listed below; Demeclocycline hydrochloride, p. 496

SELECTIVE VASOPRESSIN V2-RECEPTOR ANTAGONISTS

Tolvaptan

- **DRUG ACTION** Tolvaptan is a vasopressin V2-receptor antagonist.

**INDICATIONS AND DOSE**

Treatment of hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion

BY MOUTH

- Adult: 15 mg once daily, increased if necessary up to 60 mg daily treatment duration is determined by the underlying disease and its treatment

**CONTRA-INDICATIONS** Anuria · hypernatraemia · hypovolaemic hyponatraemia · impaired perception of thirst · volume depletion

**CAUTIONS** Alcoholism (increased risk of demyelination syndrome if rapid correction of hyponatraemia) · diabetes mellitus · ensure adequate fluid intake · hypoxia (increased risk of demyelination syndrome if rapid correction of hyponatraemia) · malnutrition (increased risk of demyelination syndrome if rapid correction of hyponatraemia) · pseudohyponatraemia associated with diabetes mellitus (exclude before treatment)

**INTERACTIONS** → Appendix 1 (tolvaptan). Avoid concomitant drugs that increase serum-sodium concentration.

**SIDE-EFFECTS**

- Common or very common Constipation · decreased appetite · dehydration · dry mouth · ecchymosis · fever · hyperglycaemia · hyperkalaemia · increased blood creatinine · malaise · nausea · neurological disturbance (following rapid correction of hyponatraemia) · postural hypotension · pruritus · thirst · urinary frequency

- Uncommon Renal impairment · taste disturbance

- Frequency not known Dizziness · hepatic impairment (discontinue) · hypernatraemia · hyperuricaemia · hypoglycaemia · syncope

**SIDE-EFFECTS, FURTHER INFORMATION**

**Hepatic impairment** Discontinue and perform liver-function tests promptly if symptoms of hepatic impairment (anorexia, nausea, vomiting, fatigue, abdominal pain, jaundice, dark urine, pruritus).

- **PREGNANCY** Avoid—toxicity in animal studies.

- **BREAST FEEDING** Avoid—present in milk in animal studies.

- **RENAL IMPAIRMENT** Use with caution in severe impairment—no information available.

- **HEPATIC IMPAIRMENT** Use with caution in severe impairment.

- **MONITORING REQUIREMENTS**

  - Monitor for dehydration in patients who are fluid-restricted.
  - Monitor serum-sodium concentration and fluid balance no later than 6 hours after initiating treatment and every 6 hours during the first 1–2 days of treatment and until dose stabilised. Discontinue if rapid rise in serum-sodium concentration (greater than 12 mmol/litre in 24 hours or 18 mmol/litre in 48 hours).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Table**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage</th>
<th>Unit</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samsca 15 mg</td>
<td>496</td>
<td>£746.80</td>
<td></td>
</tr>
<tr>
<td>Tolvaptan 30 mg</td>
<td>581</td>
<td>£746.80</td>
<td></td>
</tr>
</tbody>
</table>

2 Corticosteroid responsive conditions

Corticosteroids, general use

Dosages of corticosteroids vary widely in different diseases and in different patients. If the use of a corticosteroid can save or prolong life, as in exfoliative dermatitis, pemphigus, acute leukaemia or acute transplant rejection, high doses may need to be given, because the complications of therapy are likely to be less serious than the effects of the disease itself.

When long-term corticosteroid therapy is used in some chronic diseases, the adverse effects of treatment may become greater than the disabilities caused by the disease. To minimise side-effects the maintenance dose should be kept as low as possible.

When potentially less harmful measures are ineffective corticosteroids are used topically for the treatment of inflammatory conditions of the skin. Corticosteroids should be avoided or used only under specialist supervision in psoriasis.

Corticosteroids are used both topically (by rectum) and systemically (by mouth or intravenously) in the management of ulcerative colitis and Crohn’s disease. They are also included in locally applied creams for haemorrhoids.

Use can be made of the mineralocorticoid activity of fludrocortisone acetate p. 582 to treat postural hypotension in autonomic neuropathy.

High-dose corticosteroids should be avoided for the management of septic shock. However, there is evidence that administration of lower doses of hydrocortisone p. 583 and fludrocortisone acetate is of benefit in adrenocortical insufficiency resulting from septic shock.

Dexamethasone p. 581 and betamethasone p. 581 have little if any mineralocorticoid action and their long duration of action makes them particularly suitable for suppressing corticotropin secretion in congenital adrenal hyperplasia where the dose should be tailored to clinical response and
by measurement of adrenal androgens and
17-hydroxyprogesterone. In common with all
glucocorticoids their suppressive action on the
hypothalamic-pituitary-adrenal axis is greatest and most
prolonged when they are given at night. In most individuals
a single dose of dexamethasone at night, is sufficient to
inhibit corticotropin secretion for 24 hours. This is the basis of
the ‘overnight dexamethasone suppression test’ for
diagnosing Cushing’s syndrome.

Betamethasone and dexamethasone are also appropriate
for conditions where water retention would be a
disadvantage.

A corticosteroid may be used in the management of raised
intracranial pressure or cerebral oedema that occurs as a
result of malignancy (see Prescribing in palliative care
p. 20); high doses of betamethasone or dexamethasone
are generally used. However, a corticosteroid should not be
used for the management of head injury or stroke because it
is unlikely to be of benefit and may even be harmful.

In acute hypersensitivity reactions, such as angioedema of
the upper respiratory tract and anaphylaxis, corticosteroids
are indicated as an adjunct to emergency treatment with
adrenaline/epinephrine p. 196. In such cases hydrocortisone
(as sodium succinate) by intravenous injection may be
required.

Corticosteroids are preferably used by inhalation in
the management of asthma but systemic therapy in association
with bronchodilators is required for the emergency
treatment of severe acute asthma.

Corticosteroids may also be useful in conditions such as
autoimmune hepatitis, rheumatoid arthritis and sarcoidosis;
they may also lead to remissions of acquired haemolytic
anaemia, and some cases of the nephrotic syndrome
(particularly in children) and thrombocytopenic purpura.

Corticosteroids can improve the prognosis of serious
conditions such as systemic lupus erythematosus, temporal
arteritis, and polyarteritis nodosa; the effects of the disease
process may be suppressed and symptoms relieved, but the
underlying condition is not cured, although it may
ultimately remit. It is usual to begin therapy in these
conditions at fairly high dose, and then to reduce the dose
to the lowest commensurate with disease control.

For other references to the use of corticosteroids see:
Prescribing in Palliative Care, immunosuppression,
rheumatic diseases, eye, otitis externa allergic rhinitis, and
aphthous ulcers.

Side-effects

Overdosage or prolonged use can exaggerate some of the
normal physiological actions of corticosteroids leading to
mineralocorticoid and glucocorticoid side-effects.

Mineralocorticoid side effects

- Hypertension
- Sodium retention
- Water retention
- Potassium loss
- Calcium loss

Mineralocorticoid side effects are most marked with
fludrocortisone, but are significant with hydrocortisone,
corticosterone, and tetracortisone. Mineralocorticoid actions
are negligible with the high potency glucocorticoids,
betamethasone and dexamethasone, and occur only slightly
with methylprednisolone, prednisolone, and triamcinolone.

Glucocorticoid side effects

- Diabetes
- Osteoporosis, which is a danger, particularly in
  the elderly, as it can result in osteoporotic fractures for
  example of the hip or vertebrae;
- In addition high doses are associated with avascular
  necrosis of the femoral head;

Managing side-effects

Side-effects can be minimised by using lowest effective dose
for minimum period possible. The suppressive action of a
corticosteroid on cortisol secretion is least when it is given
as a single dose in the morning. In an attempt to reduce
pituitary-adrenal suppression further, the usual dose for two
days can sometimes be taken as a single dose on alternate
days; alternate-day administration has not been very
successful in the management of asthma. Pituitary-adrenal
suppression can also be reduced by means of intermittent
therapy with short courses. In some conditions it may be
possible to reduce the dose of corticosteroid by adding a
small dose of an immunosuppressive drug.

Whenever possible local treatment with creams, intra-
articular injections, inhalations, eye-drops, or enemas
should be used in preference to systemic treatment.

Inhaled corticosteroids have considerably fewer systemic
effects than oral corticosteroids, but adverse effects
including adrenal suppression have been reported. Use of
other corticosteroid therapy (including topical) or
concurrent use of drugs which inhibit corticosteroid
metabolism should be taken into account when assessing
systemic risk. In children, growth restriction associated with
systemic corticosteroid therapy does not seem to occur with
recommended doses of inhaled therapy; although initial
growth velocity may be reduced, there appears to be no
effect on achieving normal adult height. Large-volume
spacer devices should be used for administering inhaled
corticosteroids in children under 15 years; they are also
useful in older children and adults, particularly if high doses
are required. Spacer devices increase airway deposition and
reduce oropharyngeal deposition.

Corticosteroids, replacement
therapy

The adrenal cortex normally secretes hydrocortisone p. 583
(cortisol) which has glucocorticoid activity and weak
mineralocorticoid activity. It also secretes the
mineralocorticoid aldosterone.

In deficiency states, physiological replacement is best
achieved with a combination of hydrocortisone and the
mineralocorticoid fludrocortisone acetate p. 582;
hydrocortisone alone does not usually provide sufficient
mineralocorticoid activity for complete replacement.

In Addison’s disease or following adrenalectomy,
hydrocortisone by mouth is usually required. This is given
in 2 doses, the larger in the morning and the smaller in the
evening, mimicking the normal diurnal rhythm of cortisol
secretion. The optimum daily dose is determined on the
basis of clinical response. Glucocorticoid therapy is
supplemented by fludrocortisone acetate.

In acute adrenocortical insufficiency, hydrocortisone is
given intravenously (preferably as sodium succinate) every 6
to 8 hours in sodium chloride p. 953 intravenous infusion
0.9%.

In hypopituitarism, glucocorticoids should be given as in
adrenocortical insufficiency, but since production of
aldosterone is also regulated by the renin-angiotensin
system a mineralocorticoid is not usually required.

Additional replacement therapy with levothyroxine sodium
p. 665 and sex hormones should be given as indicated by
the pattern of hormone deficiency.
Glucocorticoid therapy

In comparing the relative potencies of corticosteroids in terms of their anti-inflammatory (glucocorticoid) effects it should be borne in mind that high glucocorticoid activity in itself is of no advantage unless it is accompanied by relatively low mineralocorticoid activity (see Disadvantages of Corticosteroids). The mineralocorticoid activity of hydrocortisone acetate p. 582 is so high that its anti-inflammatory activity is of no clinical relevance.

Equivalent anti-inflammatory doses of corticosteroids

This table takes no account of mineralocorticoid effects, nor does it take account of variations in duration of action

<table>
<thead>
<tr>
<th>Prednisolone 5 mg</th>
<th>Betamethasone 750 micrograms</th>
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<tbody>
<tr>
<td>Deflazacort 6 mg</td>
<td>Dexamethasone 750 micrograms</td>
</tr>
<tr>
<td>Hydrocortisone 20 mg</td>
<td>Methylprednisolone 4 mg</td>
</tr>
<tr>
<td>Prednisone 5 mg</td>
<td>Triamcinolone 4 mg</td>
</tr>
</tbody>
</table>

The relatively high mineralocorticoid activity of hydrocortisone p. 583, and the resulting fluid retention, makes it unsuitable for disease suppression on a long-term basis. However, hydrocortisone can be used for adrenal replacement therapy. Hydrocortisone is used on a short-term basis by intravenous injection for the emergency management of some conditions. The relatively moderate anti-inflammatory potency of hydrocortisone also makes it a useful topical corticosteroid for the management of inflammatory skin conditions because side-effects (both topical and systemic) are less marked.

Prednisolone p. 585 and prednisone p. 586 have predominantly glucocorticoid activity. Prednisolone is the corticosteroid most commonly used by mouth for long-term disease suppression.

Betamethasone p. 581 and dexamethasone p. 581 have very high glucocorticoid activity in conjunction with insignificant mineralocorticoid activity. This makes them particularly suitable for high-dose therapy in conditions where fluid retention would be a disadvantage.

Betamethasone and dexamethasone also have a long duration of action and this, coupled with their lack of mineralocorticoid action makes them particularly suitable for conditions which require suppression of corticotropin (corticotrophin) secretion (e.g. congenital adrenal hyperplasia).

Some esters of betamethasone and of beclometasone dipropionate p. 38 (beclometasone) exert a considerably more marked topical effect (e.g. on the skin or the lungs) than when given by mouth; use is made of this to obtain topical effects whilst minimising systemic side-effects (e.g. for skin applications and asthma inhalations).

Deflazacort p. 581 has a high glucocorticoid activity; it is derived from prednisolone.

Corticosteroids (systemic)

• CONTRA-INDICATIONS Avoid live virus vaccines in those receiving immunosuppressive doses (serum antibody response diminished) - systemic infection (unless specific therapy given)

CONTRA-INDICATIONS, FURTHER INFORMATION

For further information on contra-indications associated with intra-articular, intradermal and intral esional preparations, consult product literature.

• CAUTIONS Congestive heart failure · diabetes mellitus (including a family history of) · diverticulitis · epilepsy · glaucoma (including a family history of or susceptibility to) · history of steroid myopathy · history of tuberculosis or X-ray changes (frequent monitoring required) · hypertension · hypothyroidism · infection (particularly untreated) · myasthenia gravis · ocular herpes simplex (risk of corneal perforation) · osteoporosis (post-menopausal women and the elderly at special risk) · peptic ulcer · psychiatric reactions · reactivation of dormant virus · recent myocardial infarction (rupture reported) · severe affective disorders (particularly if history of steroid-induced psychosis) · should not be used long-term · thromboembolic disorders · ulcerative colitis

CAUTIONS, FURTHER INFORMATION

For further information on cautions associated with intra-articular, intradermal and intral esional preparations, consult product literature.

• INTERACTIONS → Appendix 1 (corticosteroids).

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

Abdominal distension · acute pancreatitis · aggravation of epilepsy · aggravation of schizophrenia · amenorrhoea · bruising · candidiasis · congestive heart failure · corneal thinning · Cushing’s syndrome (with moon face, striae and acne) · dysepsia · ecchymoses · exacerbation of ophthalmic fungal disease · exacerbation of ophthalmic viral disease · exophthalmos · facial erythema · glaucoma · headache · hiccups · hirsutism · hypercholesterolaemia · hyperglycaemia · hypothyroidism · hyperlipidaemia · impaired healing · increased appetite · increased intraocular pressure · increased susceptibility to and severity of infection · insomnia · leucocytosis · long bone fractures · malaise · menstrual irregularities · muscle weakness · myocardial rupture following recent myocardial infarction · nausea · negative calcium balance · negative nitrogen balance · oesophageal ulceration · papilloedema · petechiae · posterior subcapsular cataracts · potassium loss · psychological dependence · reactivation of dormant tuberculosis · scleral thinning · skin atrophy · sodium retention · telangiectasia · tendon rupture · thromboembolism · urticaria · vertebral fractures · vertigo · weight gain

SPECIFIC SIDE-EFFECTS

• With intra-articular use Flushing · may affect the hyaline cartilage

SIDE-EFFECTS, FURTHER INFORMATION

For further information on side-effects associated with intra-articular, intradermal and intral esional preparations, consult product literature.

Side effects can be managed by choice of route and duration of course. For further detail see Corticosteroids, general use p. 577

Adrenal suppression During prolonged therapy with corticosteroids, particularly with systemic use, adrenal atrophy develops and can persist for years after stopping. Abrupt withdrawal after a prolonged period can lead to acute adrenal insufficiency, hypotension, or death. To compensate for a diminished adrenocortical response caused by prolonged corticosteroid treatment, any significant intercurrent illness, trauma, or surgical procedure requires a temporary increase in corticosteroid dose, or if already stopped, a temporary reintroduction of corticosteroid treatment. To avoid a precipitous fall in blood pressure during anaesthesia or in the immediate postoperative period, anaesthetists must know whether a patient is taking or has been taking a corticosteroid. A
Corticosteroid responsive conditions

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suitable regimen for corticosteroid replacement, in patients who have taken more than 10 mg prednisolone daily (or equivalent) within 3 months of surgery, is:

- Minor surgery under general anaesthesia—usual oral corticosteroid dose on the morning of surgery or hydrocortisone (usually the sodium succinate) intravenously at induction; the usual oral corticosteroid dose is recommenced after surgery.
- Moderate or major surgery—usual oral corticosteroid dose on the morning of surgery and hydrocortisone intravenously at induction, followed by hydrocortisone 3 times a day by intravenous injection for 24 hours after moderate surgery or for 48–72 hours after major surgery; the usual pre-operative oral corticosteroid dose is recommenced on stopping hydrocortisone injections. Patients on long-term corticosteroid treatment should carry a steroid treatment card which gives guidance on minimising risk and provides details of prescriber, drug, dosage and duration of treatment.

**Infections** Prolonged courses of corticosteroids increase susceptibility to infections and severity of infections; clinical presentation of infections may also be atypical. Serious infections e.g. *septicaemia* and *tuberculosis* may reach an advanced stage before being recognised, and *amoebiasis* or *strongyloidiasis* may be activated or exacerbated (exclude before initiating a corticosteroid in those at risk or with suggestive symptoms). Fungal or viral *ocular infections* may also be exacerbated. *Chickenpox* Unless they have had chickenpox, patients receiving oral or parenteral corticosteroids for purposes other than replacement should be regarded as being at *risk of severe chickenpox* (see Steroid Treatment Card). Manifestations of fulminant illness include pneumonia, hepatitis and disseminated intravascular coagulation; rash is not necessarily a prominent feature. Passive immunisation with varicella–zoster immunoglobulin is needed for exposed non–immune patients receiving systemic corticosteroids or for those who have used them within the previous 3 months. Confirmed chickenpox warrants specialist care and urgent treatment. Corticosteroids should not be stopped and dosage may need to be increased. Topical, inhaled or rectal corticosteroids are less likely to be associated with an increased risk of severe chickenpox. *Measles* Patients taking corticosteroids should be advised to take particular care to avoid exposure to measles and to seek immediate medical advice if exposure occurs. Prophylaxis with intramuscular normal immunoglobulin may be needed. *Psychiatric reactions* Systemic corticosteroids, particularly in high doses, are linked to psychiatric reactions including euphoria, nightmares, insomnia, irritability, mood lability, suicidal thoughts, psychotic reactions, and behavioural disturbances. A serious paranoid state or depression with risk of suicide can be induced, particularly in patients with a history of mental disorder. These reactions frequently subside on reducing the dose or discontinuing the corticosteroid but they may also require specific management. Patients should be advised to seek medical advice if psychiatric symptoms (especially depression and suicidal thoughts) occur and they should also be alert to the rare possibility of such reactions during withdrawal of corticosteroid treatment. Systemic corticosteroids should be prescribed with care in those predisposed to psychiatric reactions, including those who have previously suffered corticosteroid-induced psychosis, or who have a personal or family history of psychiatric disorders.

**Pregnancy** The benefit of treatment with corticosteroids during pregnancy outweighs the risk. Corticosteroid cover is required during labour. Following a review of the data on the safety of systemic corticosteroids used in pregnancy and breast-feeding the CSM (May 1998) concluded that corticosteroids vary in their ability to cross the placenta but there is no convincing evidence that systemic corticosteroids increase the incidence of congenital abnormalities such as cleft palate or lip. When administration is prolonged or repeated during pregnancy, systemic corticosteroids increase the risk of intra-uterine growth restriction; there is no evidence of intra-uterine growth restriction following short-term treatment (e.g. prophylactic treatment for neonatal respiratory distress syndrome). Any adrenal suppression in the neonate following prenatal exposure usually resolves spontaneously after birth and is rarely clinically important. Pregnant women with fluid retention should be monitored closely when given systemic corticosteroids.

- **Breast feeding** The benefit of treatment with corticosteroids during breast-feeding outweighs the risk.
- **Hepatic impairment** The plasma–drug concentration may be increased (particularly on systemic use). Oral and parenteral use should be undertaken with caution.
- **Renal impairment** Use by oral and injectable routes should be undertaken with caution.
- **Effect on laboratory tests** Suppression of skin test reactions.
- **Treatment cessation** Abrupt withdrawal after a prolonged period can lead to acute adrenal insufficiency, hypotension or death. Withdrawal can also be associated with fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and weight loss. The magnitude and speed of dose reduction in corticosteroid withdrawal should be determined on a case–by–case basis, taking into consideration the underlying condition that is being treated, and individual patient factors such as the likelihood of relapse and the duration of corticosteroid treatment. *Gradual* withdrawal of systemic corticosteroids should be considered in those whose disease is unlikely to relapse and have:
  - received more than 40 mg prednisolone (or equivalent) daily for more than 1 week;
  - been given repeat doses in the evening;
  - received more than 3 weeks’ treatment;
  - recently received repeated courses (particularly if taken for longer than 3 weeks);
  - taken a short course within 1 year of stopping long-term therapy;
  - other possible causes of adrenal suppression. Systemic corticosteroids may be stopped abruptly in those whose disease is unlikely to relapse and who have received treatment for 3 weeks or less and who are not included in the patient groups described above. During corticosteroid withdrawal the dose may be reduced rapidly down to physiological doses (equivalent to prednisolone 7.5 mg daily) and then reduced more slowly. Assessment of the disease may be needed during withdrawal to ensure that relapse does not occur.

- **Patient and carer advice** Advice for patients. Patients on long-term corticosteroid treatment should carry a Steroid Treatment Card which gives guidance on minimising risk and provides details of prescriber, drug, dosage and duration of treatment. A patient information leaflet should be supplied to every patient when a systemic corticosteroid is prescribed. Patients should especially be advised of the following:
  - **Immunosuppression** Prolonged courses of corticosteroids can increase susceptibility to infection and serious infections can go unrecognised. Unless already immune, patients are at risk of severe *chickenpox* and should avoid close contact with people who have chickenpox or shingles. Similarly,
Betamethasone

**INDICATIONS AND DOSE**

**Suppression of inflammatory and allergic disorders**

- **Congenital adrenal hyperplasia**
  - Adult: Usual dose 0.5–5 mg daily
  - By intramuscular injection or by slow intravenous injection or by intravenous infusion
  - Adult: 4–20 mg, repeated up to 4 times in 24 hours

**PREGNANCY**

Readily crosses the placenta. Transient effect on fetal movements and heart rate.

**DIRECTIONS FOR ADMINISTRATION**

For intravenous infusion (as sodium phosphate) (Betnesol®), give continuously or intermittently or via drip tubing in Glucose 5% or Sodium chloride 0.9%.

**PATIENT AND CARER ADVICE**

- With oral use: Patient counselling is advised for betamethasone soluble tablets (steroid card).

**MEDICINAL FORMS**

- Soluble tablet

  CAUTIONARY AND ADVISORY LABELS 10, 13, 21

  **Betamethasone (Non-proprietary)**
  Betamethasone (as Betamethasone sodium phosphate) 500 microgram
  Betamethasone 500 microgram tablets, sugar free, 100 tablet [Pack] £29.85 DT price + £29.70

**Solution for injection**

- **CAUTIONARY AND ADVISORY LABELS**
  - Betnesol (Focus Pharmaceuticals Ltd)
  Betamethasone (as Betamethasone sodium phosphate) 4 mg per 1 ml

**Deflazacort**

**INDICATIONS AND DOSE**

**Suppression of inflammatory and allergic disorders**

- **BY MOUTH**
  - Adult: Maintenance 3–18 mg daily

**Suppression of inflammatory and allergic disorders (acute disorders)**

- **BY MOUTH**
  - Adult: Initially up to 120 mg daily

**Inflammatory and allergic disorders**

- **BY MOUTH**
  - Child 1 month–11 years: Maintenance 0.25–1.5 mg/kg once daily or on alternate days; increased if necessary up to 2.4 mg/kg daily (max. per dose 120 mg), in emergency situations
  - Child 12–17 years: Initially 3–18 mg once daily or on alternate days; increased if necessary up to 2.4 mg/kg daily (max. per dose 120 mg), in emergency situations

**RENAL IMPAIRMENT**

Use with caution.

**PATIENT AND CARER ADVICE**

Patient counselling is advised for deflazacort tablets (steroid card).

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet

  **Tablet**

  CAUTIONARY AND ADVISORY LABELS 5, 10

  - **Calcort** (Sanofi)
    Deflazacort 6 mg Calcort 6mg tablets | 60 tablet [Pack] £15.82

Dexamethasone

**INDICATIONS AND DOSE**

**Diagnosis of Cushing's disease**

- **Congenital adrenal hyperplasia**
  - Adult: 0.5–10 mg daily
  - By intramuscular injection or by slow intravenous injection or by intravenous infusion
  - Adult: 0.4–20 mg

**Overnight dexamethasone supression test**

- **BY MOUTH**
  - Adult: 1 mg for 1 dose, to be given at night

**Suppression of inflammatory and allergic disorders**

- **BY MOUTH**
  - Adult: 0.5–10 mg daily

**Mild croup**

- **BY MOUTH**
  - Child: 150 micrograms/kg for 1 dose
  - Adult: 150 micrograms/kg for 1 dose

**Severe croup (or mild croup that might cause complications)**

- **INITIALLY BY MOUTH**
  - Child: Initially 150 micrograms/kg for 1 dose, to be given before transfer to hospital, then (by mouth or by intravenous injection) 150 micrograms/kg, then (by mouth or by intravenous injection) 150 micrograms/kg after 12 hours if required

continued →
**INDICATIONS AND DOSE**

**Fludrocortisone acetate**

**Mineralocorticoid replacement in adrenocortical insufficiency**

*By mouth*

- Adult: 50–300 micrograms daily

*Adrenocortical insufficiency resulting from septic shock (in combination with hydrocortisone)*

*By mouth*

- Adult: 50 micrograms daily

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**Corticosteroid responsive conditions**

- **DIRECTIONS FOR ADMINISTRATION**
  - With oral use in children: For administration *by mouth* tablets may be dispersed in water or injection solution given by mouth.
  - With intravenous use in children: For *intravenous infusion* dilute with Glucose 5% or Sodium Chloride 0.9%; give over 15–20 minutes.
  - With intravenous use in adults: For *intravenous infusion* (Dexamethasone, Hospira) give continuously or intermittently or via drip tubing in Glucose 5% or Sodium Chloride 0.9%.

**Prescribing and dispensing information**

Dexamethasone 3.8 mg/mL injection has replaced Dexamethasone 4 mg/mL injection.

**Patient and carer advice**

Medicines for Children leaflet: Dexamethasone for croup [www.medicinesforchildren.org.uk/dexamethasone-croup-0]

With systemic use: Patient counselling is advised for dexamethasone tablet, oral solution and injection (steroid card).

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, capsule,

**Tablet**

CAUTIONARY AND ADVISORY LABELS 10, 21

- **Dexamethasone (non-proprietary)**
  - Dexamethasone 500 microgram tablets
  - 28 tablet [P] £6.42 DT price = £5.83
  - 30 tablet [P] no price available
  - Dexamethasone 2 mg Dexamethasone 2mg tablets
  - 50 tablet [P] £5.50 DT price = £5.46
  - 100 tablet [P] £10.00
  - 500 tablet [P] no price available

**Oral solution**

CAUTIONARY AND ADVISORY LABELS 10, 21

- **Dexamethasone (non-proprietary)**
  - Dexamethasone (as Dexamethasone sodium phosphate) 400 microgram per 1 ml
  - Dexamethasone 2mg/5ml oral solution sugar free (sugar-free) | 150 ml [P] £4.12 DT price = £4.02
  - Dexamethasone (as Dexamethasone sodium phosphate) 2 mg per 1 ml
  - Dexamethasone 1mg/5ml oral solution sugar free (sugar-free) | 50 ml [P] £2.00
  - 150 ml [P] £10.00 DT price = £9.65
  - Dexamethasone (as Dexamethasone sodium phosphate) 4 mg per 1 ml
  - Dexamethasone 20mg/5ml oral solution sugar free (sugar-free) | 50 ml [P] £4.95
  - Brands may include Dexsol, Martapan

**Solution for injection**

CAUTIONARY AND ADVISORY LABELS 10

- **Dexamethasone (non-proprietary)**
  - Dexamethasone (as Dexamethasone sodium phosphate) 3.3 mg per 1 ml
  - Dexamethasone 6.6mg/2ml solution for injection vials | 5 vial [P] £24.00
  - Dexamethasone 6.6mg/2ml solution for injection ampoules | 5 ampoule [P] £11.00
  - Dexamethasone 3.3mg/1ml solution for injection ampoules | 5 ampoule [P] £12.00
  - 10 ampoule [P] £16.00
  - Dexamethasone (as Dexamethasone sodium phosphate) 3.8 mg per 1 ml
  - Dexamethasone 3.8mg/1ml solution for injection vials | 10 vial [P] £19.99

**Fludrocortisone acetate**

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**Unlicensed use** Consult product literature; not licensed for use in bacterial meningitis.

**Side-effects**

- With intravenous use: Perineal irritation may follow intravenous administration of the phosphate ester

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**Cerebral oedema associated with malignancy**

With intravenous use

- Adult: 8.3 mg every 6 hours for 4 days

Local inflammation of joints (with dexamethasone as sodium phosphate)

- Adult: Initially 8–16 mg, then (by intramuscular injection or by intravenous injection) 5 mg every 6 hours until adequate response achieved then taper-off gradually

Cerebral oedema associated with malignancy (with dexamethasone as sodium phosphate 3.3 mg/mL injection)

Initially by intravenous injection

- Adult: Initially 8.3 mg, then (by intramuscular injection) 3.3 mg every 6 hours as required for 2–4 days, subsequently, reduce dose gradually and stop over 5–7 days

Local inflammation of joints (with dexamethasone as sodium phosphate 3.3 mg/mL injection)

- By intra-articular injection
  - Adult: 0.3–3 mg, dose given according to size, where appropriate may be repeated at intervals of 3–21 days

Local inflammation of soft tissues (with dexamethasone as sodium phosphate 3.3 mg/mL injection)

- By local infiltration
  - Adult: 1.7–5 mg, dose given according to size, where appropriate may be repeated at intervals of 3–21 days

Symptom control of anorexia (in palliative care)

- Adult: 2–4 mg daily

Obstruction due to tumour (dysphagia in palliative care)

- Adult: 8 mg daily

Bronchospasm or partial obstruction (dyspnoea in palliative care)

- Adult: 4–8 mg daily

Nausea and vomiting (adjunct in palliative care)

- By mouth
  - Adult: 8–16 mg daily

Headaches due to raised intracranial pressure (in palliative care)

- Adult: 16 mg daily for 4–5 days, then reduced to 4–6 mg daily, reduce dose if possible. To be given before 6pm to reduce the risk of insomnia

Pain due to nerve compression (in palliative care)

- Adult: 8 mg daily

---

**Sodium Chloride**

Brands may include Dexsol, Martapan.
Hydrocortisone

**INDICATIONS AND DOSE**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Route</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyrotoxic crisis (thyroid storm)</td>
<td>INTRAVENOUS INJECTION</td>
<td>Adult: 100 mg every 6 hours, to be administered as sodium succinate</td>
</tr>
<tr>
<td>Adrenocortical insufficiency in Addison's disease or following adrenalectomy</td>
<td>MOUTH USING IMMEDIATE-RELEASE MEDICINES</td>
<td>Adult: 20–30 mg daily in 2 divided doses, the larger dose to be given in the morning and the smaller in the evening, mimicking the normal diurnal rhythm of cortisol secretion, the optimum daily dose is determined on the basis of clinical response</td>
</tr>
<tr>
<td>Replacement in adrenocortical insufficiency</td>
<td>MOUTH USING MODIFIED-RELEASE MEDICINES</td>
<td>Adult: 20–30 mg once daily, adjusted according to response, dose to be taken in the morning</td>
</tr>
<tr>
<td>Adrenocortical insufficiency resulting from septic shock</td>
<td>INTRAVENOUS INJECTION</td>
<td>Adult: 50 mg every 6 hours, given in combination with fludrocortisone</td>
</tr>
</tbody>
</table>

**SPECIFIC SIDE-EFFECTS**

- Acute hypersensitivity reactions such as angioedema of the upper respiratory tract and anaphylaxis (adjunct to adrenaline) followed by 25–50 mg 3 times a day for 24 hours after moderate surgery and for 48–72 hours after major surgery
- Severe inflammatory bowel disease followed by 25–50 mg 3–4 times a day or when required
- Ulcerative colitis | PROCTISI PROCTOSIGMOIDITIS | BY RECTUM USING RECTAL FOAM | Adult: Initially 1 metered application 1–2 times a day for 2–3 weeks, then reduced to 1 metered application once daily on alternate days, to be inserted into the rectum |
- Acute hypersensitivity reactions | ANGIOEDEMA | BY INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INJECTION | Child 1–5 months: Initially 25 mg 3 times a day, adjusted according to response |
- Severe acute asthma | LIFE-THREATENING ACUTE ASTHMA | BY INTRAVENOUS INJECTION | Child 1–5 years: 4 mg/kg every 6 hours (max. per dose 100 mg), alternatively 25 mg every 6 hours until conversion to oral prednisolone is possible, dose given, preferably, as sodium succinate |
- Hydrocortisone acetate 100 microgram (SoluCortef®) or Efcortesol® lower than immediate release tablets—monitor clinical response.

**CONTRA-INDICATIONS**

- With rectal use: Bowel perforation · extensive fistulas · intestinal obstruction · recent intestinal anastomoses

**SAFETY AND ECONOMICS**

- With intravenous use in children: For intravenous administration, dilute with Glucose 5% or Sodium Chloride 0.9%. For intermittent infusion give over 20–30 minutes.
- With intravenous use in adults: For intravenous infusion (SoluCortef® or Efcortesol®), give continuously or

**Hydrocortisone**

**INDICATIONS AND DOSE**

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**CONTRA-INDICATIONS**

- With rectal use: Bowel perforation · extensive fistulas · intestinal obstruction · recent intestinal anastomoses

**SAFETY AND ECONOMICS**

- With intravenous use in children: For intravenous administration, dilute with Glucose 5% or Sodium Chloride 0.9%. For intermittent infusion give over 20–30 minutes.
- With intravenous use in adults: For intravenous infusion (SoluCortef® or Efcortesol®), give continuously or
intermittently or via drip tubing in Glucose 5% or Sodium chloride 0.9%.

- **PATIENT AND CARER ADVICE** Patient counselling is advised for hydrocortisone tablets and injections (steroid card).

- **LESS SUITABLE FOR PRESCRIBING** Hydrocortisone as the sodium phosphate is less suitable for prescribing as paraesthesia and pain (particularly in the perineal region) may follow intravenous injection. Efcortesol® is less suitable for prescribing.

- **EXCEPTIONS TO LEGAL CATEGORY**
  - With intramuscular use or intravenous use. Prescription only medicine restriction does not apply where administration is for saving life in emergency.

### MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: suppository, oral suspension, oral solution, capsule, liquid

#### Table

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>10, 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYDROCORTISONE (Non-proprietary)</td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone 10 mg</td>
<td>Hydrocortisone 10mg tablets</td>
</tr>
<tr>
<td>30 tablet (£)</td>
<td>£87.00 DT price = £65.78</td>
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<tr>
<td>Hydrocortisone 20 mg</td>
<td>Hydrocortisone 20mg tablets</td>
</tr>
<tr>
<td>30 tablet (£)</td>
<td>£102.75 DT price = £88.75</td>
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#### Modified-release tablet

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>10, 22, 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plenadren (ViroPharma Ltd)</td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone 5 mg</td>
<td>Plenadren 5mg modified-release tablets</td>
</tr>
<tr>
<td>50 tablet (£)</td>
<td>£242.50</td>
</tr>
<tr>
<td>Hydrocortisone 20 mg</td>
<td>Plenadren 20mg modified-release tablets</td>
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<tr>
<td>50 tablet (£)</td>
<td>£400.00</td>
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### Solution for injection

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efcortesol (AMCo)</td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone (as Hydrocortisone sodium phosphate) 100 mg per 1 ml</td>
<td>Efcortesol 100mg/1ml solution for injection ampoules</td>
</tr>
<tr>
<td>5 ampoule (£)</td>
<td>£5.38</td>
</tr>
<tr>
<td>Efcortesol 500mg/5ml solution for injection ampoules</td>
<td>5 ampoule (£)</td>
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</tbody>
</table>

#### Powder for solution for injection

<table>
<thead>
<tr>
<th>Solu-Cortef (Pfizer Ltd)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone (as Hydrocortisone sodium succinate) 100 mg</td>
<td>Solu-Cortef 100mg powder for solution for injection vials</td>
</tr>
<tr>
<td>10 vial (£)</td>
<td>£9.17</td>
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</table>

### Powder and solvent for solution for injection

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solu-Cortef (Pfizer Ltd)</td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone (as Hydrocortisone sodium succinate) 100 mg</td>
<td>Solu-Cortef 100mg powder and solvent for solution for injection vials</td>
</tr>
<tr>
<td>1 vial (£)</td>
<td>£1.16 DT price = £1.16</td>
</tr>
</tbody>
</table>

### Suspension for injection

<table>
<thead>
<tr>
<th>Hydrocortistab (AMCo)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone acetate 25 mg per 1 ml</td>
<td>Hydrocortistab 25mg/1ml suspension for injection ampoules</td>
</tr>
<tr>
<td>10 ampoule (£)</td>
<td>£68.72 DT price = £68.72</td>
</tr>
</tbody>
</table>

#### Foam

| EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), hydroxybenzoates (parabens), propylene glycol |        |
| Colifoam (Meda Pharmaceuticals Ltd) |        |
| Hydrocortisone acetate 100 mg per 1 gram | Colifoam 10% aerosol |
| 14 dose (£) | £9.33 DT price = £9.33 |

### Methylprednisolone

#### INDICATIONS AND DOSE

- Suppression of inflammatory and allergic disorders
- Cerebral oedema associated with malignancy
  - **BY MOUTH**
    - Adult: Usual dose 2–40 mg daily
  - BY INTRAMUSCULAR INJECTION OR BY SLOW INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION
    - Adult: Initially 10–500 mg

#### Treatment of graft rejection reactions

- **BY INTRAVENOUS INFUSION**
  - Adult: Up to 1 g daily for up to 3 days

- **DEPO-MEDRONE®**
  - Local inflammation of joints and soft tissues
  - **BY INTRA-ARTICULAR INJECTION**
    - Adult: 4–80 mg, select dose according to size; where appropriate dose may be repeated at intervals of 7–35 days, for details consult product literature

- Suppression of inflammatory and allergic disorders
  - **BY DEEP INTRAMUSCULAR INJECTION**
    - Adult: 40–120 mg, then 40–120 mg after 2–3 weeks if required, to be injected into the gluteal muscle

#### CAUTIONS

- With intravenous use Rapid intravenous administration of large doses associated with cardiovascular collapse

#### DIRECTIONS FOR ADMINISTRATION

For intravenous infusion (as sodium succinate) (Solu-Medrone®), give continuously or intermittently or via drip tubing in Glucose 5% or Sodium chloride 0.9%. Reconstitute initially with water for injections; doses up to 250 mg should be given over at least 5 minutes, high doses over at least 30 minutes.

- **PATIENT AND CARER ADVICE** Patient counselling is advised for methylprednisolone tablets and injections (steroid card).

#### MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

#### Tablet

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>10, 21</th>
</tr>
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<tbody>
<tr>
<td>Medrone (Pfizer Ltd)</td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone 2 mg</td>
<td>Medrone 2mg tablets</td>
</tr>
<tr>
<td>30 tablet (£)</td>
<td>£3.88</td>
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<tr>
<td>Methylprednisolone 4 mg</td>
<td>Medrone 4mg tablets</td>
</tr>
<tr>
<td>30 tablet (£)</td>
<td>£6.19</td>
</tr>
<tr>
<td>Methylprednisolone 16 mg</td>
<td>Medrone 16mg tablets</td>
</tr>
<tr>
<td>30 tablet (£)</td>
<td>£17.17</td>
</tr>
<tr>
<td>Methylprednisolone 100 mg</td>
<td>Medrone 100mg tablets</td>
</tr>
<tr>
<td>20 tablet (£)</td>
<td>£48.32</td>
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</table>

### Powder and solvent for solution for injection

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Medrone (Pfizer Ltd)</td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone (as Methylprednisolone sodium succinate) 500 mg</td>
<td>Methylprednisolone sodium succinate 500mg powder and solvent for solution for injection vials</td>
</tr>
<tr>
<td>1 vial (£)</td>
<td>£9.60</td>
</tr>
<tr>
<td>Methylprednisolone (as Methylprednisolone sodium succinate)</td>
<td>Methylprednisolone sodium succinate 1g powder and solvent for solution for injection vials</td>
</tr>
<tr>
<td>1 vial (£)</td>
<td>£17.30</td>
</tr>
<tr>
<td>Solu-Medrone (Pfizer Ltd)</td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone (as Methylprednisolone sodium succinate) 40 mg</td>
<td>Solu-Medrone 40mg powder and solvent for solution for injection vials</td>
</tr>
<tr>
<td>1 vial (£)</td>
<td>£1.58</td>
</tr>
<tr>
<td>Methylprednisolone (as Methylprednisolone sodium succinate) 125 mg</td>
<td>Solu-Medrone 125mg powder and solvent for solution for injection vials</td>
</tr>
<tr>
<td>1 vial (£)</td>
<td>£4.75</td>
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<tr>
<td>Methylprednisolone (as Methylprednisolone sodium succinate)</td>
<td>Methylprednisolone sodium succinate 500 mg Solu-Medrone 500mg powder and solvent for solution for injection vials</td>
</tr>
<tr>
<td>1 vial (£)</td>
<td>£17.30</td>
</tr>
<tr>
<td>Methylprednisolone (as Methylprednisolone sodium succinate)</td>
<td>Solu-Medrone 1g powder and solvent for solution for injection vials</td>
</tr>
<tr>
<td>1 vial (£)</td>
<td>£32.86</td>
</tr>
</tbody>
</table>
**Prednisolone**

**INDICATIONS AND DOSE**

Exacerbation of chronic obstructive pulmonary disease (if increased breathlessness interferes with daily activities)

**BY MOUTH**
- Adult: 30 mg daily for 7–14 days

Severe cough (before transfer to hospital) | Mild cough that might cause complications (before transfer to hospital)

**BY MOUTH**
- Child: 1–2 mg/kg

Mild to moderate acute asthma (when oral corticosteroid taken for more than a few days) | Severe or life-threatening acute asthma (when oral corticosteroid taken for more than a few days)

**BY MOUTH**
- Child 1 month–11 years: 2 mg/kg once daily (max. per dose 60 mg) for up to 3 days, longer if necessary

Mild to moderate acute asthma | Severe or life-threatening acute asthma

**BY MOUTH**
- Child 1 month–11 years: 1–2 mg/kg once daily (max. per dose 40 mg) for up to 3 days, longer if necessary

- Child 12–17 years: 40–50 mg daily for at least 5 days

- Adults: 40–50 mg daily for at least 5 days

Suppression of inflammatory and allergic disorders

**BY MOUTH**
- Adult: Initially 10–20 mg daily, dose preferably taken in the morning after breakfast, can often be reduced within a few days but may need to be continued for several weeks or months; maintenance 2.5–15 mg daily, higher doses may be needed; cushingoid side-effects increasingly likely with doses above 7.5 mg daily

**BY INTRAMUSCULAR INJECTION**
- Adult: 25–100 mg 1–2 times a week, as prednisolone acetate

Suppression of inflammatory and allergic disorders (initial dose in severe disease)

**BY MOUTH**
- Adult: Initially up to 60 mg daily, dose preferably taken in the morning after breakfast, can often be reduced within a few days but may need to be continued for several weeks or months

Idiopathic thrombocytopenic purpura

**BY MOUTH**
- Adult: 1 mg/kg daily, gradually reduce dose over several weeks

Ulcerative colitis | Crohn's disease

**BY MOUTH**
- Adult: Initially 20–40 mg daily until remission occurs, followed by reducing doses, up to 60 mg daily, may be used in some cases, doses preferably taken in the morning after breakfast

**Distal ulcerative colitis**

**BY RECTUM USING RECTAL FOAM**
- Adult: 1 metered application 1–2 times a day for 2 weeks, continued for further 2 weeks if good response, to be inserted into the rectum, 1 metered application contains 20 mg prednisolone

**Rectal complications of Crohn's disease**

**BY RECTUM USING SUPPOSITORIES**
- Adult: 5 mg twice daily, to be inserted in to the rectum morning and night, after a bowel movement

**Rectal and rectosigmoidal ulcerative colitis | Rectal and rectosigmoidal Crohn's disease**

**BY RECTUM USING ENEMA**
- Adult: 20 mg daily for 2–4 weeks, continued if response good, to be used at bedtime

**Proctitis**

**BY RECTUM USING RECTAL FOAM**
- Adult: 1 metered application 1–2 times a day for 2 weeks, continued for further 2 weeks if good response, to be inserted into the rectum, 1 metered application contains 20 mg prednisolone

**Rectal and proctitis using suppositories**
- Adult: 5 mg twice daily, to be inserted in to the rectum morning and night, after a bowel movement

**Neuritic pain or weakness heralding rapid onset of permanent nerve damage (during reversal reactions multibacillary leprosy)**

**BY MOUTH**
- Adult: Initially 40–60 mg daily, dose to be instituted at once

**Generalised myasthenia gravis (when given on alternate days)**

**INITIALLY BY MOUTH**
- Adult: Initially 10 mg once daily on alternate days, then increased in steps of 10 mg once daily on alternate days, increased to 1–1.5 mg/kg once daily on alternate days (max. per dose 100 mg)

**Generalised myasthenia gravis in ventilated patients (when given on alternate days)**

**BY MOUTH**
- Adult: Initially 1.5 mg/kg once daily on alternate days (max. per dose 100 mg)

**Generalised myasthenia gravis (when giving daily)**

**BY MOUTH**
- Adult: Initially 5 mg daily, increased in steps of 5 mg daily. maintenance 60–80 mg daily, alternatively maintenance 0.75–1 mg/kg daily, ventilated patients may be started on 1.5 mg/kg (max. 100 mg) on alternate days

**Ocular myasthenia**

**BY MOUTH**
- Adult: Usual dose 10–40 mg daily on alternate days, reduce to minimum effective dose

**Reduction in rate of joint destruction in moderate to severe rheumatoid arthritis of less than 2 years’ duration**

**BY MOUTH**
- Adult: 7.5 mg daily

**Polymyalgia rheumatica**

**BY MOUTH**
- Adult: 10–15 mg daily until remission of disease activity; maintenance 7.5–10 mg daily, reduce gradually to maintenance dose. Many patients require treatment for at least 2 years and in some patients it may be necessary to continue long term low-dose corticosteroid treatment

**Giant cell (temporal) arteritis**

**BY MOUTH**
- Adult: 40–60 mg daily until remission of disease activity, the higher dose being used if visual symptoms occur; maintenance 7.5–10 mg daily, reduce gradually to maintenance dose. Many patients require treatment for at least 2 years and in continued →
Corticosteroid responsive conditions

Endocrine system

PATIENT AND CARER ADVICE
With systemic use
▶ BREAST FEEDING
With systemic use
▶ PREGNANCY
With rectal use
CAUTIONS
▶ CONTRA-INDICATIONS
With rectal use
Bowel perforation - extensive fistulas - intestinal obstruction - recent intestinal anastomoses
▶ CAUTIONS
With rectal use
Systemic absorption may occur with rectal preparations
With systemic use
Duchenne’s muscular dystrophy (possible transient rhabdomyolysis and myoglobinuria following strenuous physical activity)
▶ PREGNANCY
As it crosses the placenta 88% of prednisolone is inactivated.
With systemic use
Pregnant women with fluid retention should be monitored closely.
▶ BREAST FEEDING
Prednisolone appears in small amounts in breast milk but maternal doses of up to 40 mg daily are unlikely to cause systemic effects in the infant.
With systemic use
Infant should be monitored for adrenal suppression if mother is taking a dose higher than 40 mg.
▶ PATIENT AND CARER ADVICE
Medicines for Children leaflet: Prednisolone for asthma www. medicinesforchildren.org.uk/prednisolone-for-asthma and Prednisolone (oral) for nephrotic syndrome www. medicinesforchildren.org.uk/prednisolone-oral-for-nephrotic-syndrome
Patient counselling is advised for prednisolone tablets (steroid card).

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, enema

Tablet
CAUTIONARY AND ADVISORY LABELS 10, 21
▶ PREDNISOLONE (Non-proprietary)
Prednisolone 1 mg Prednisolone 1mg tablets | 28 tablet PNX £4.00 DT price = £1.08 | 100 tablet PNX no price available
Prednisolone 5 mg Prednisolone 5mg tablets | 28 tablet PNX £11.00 DT price = £1.29 | 100 tablet PNX no price available
Prednisolone 25 mg Prednisolone 25mg tablets | 56 tablet PNX £75.00 DT price = £50.00
▶ Brands may include Pevanti
Soluble tablet
CAUTIONARY AND ADVISORY LABELS 10, 13, 21
▶ PREDNISOLONE (Non-proprietary)
Prednisolone (as Prednisolone sodium phosphate) 5 mg Prednisolone 5mg soluble tablets | 30 tablet PNX £53.48 DT price = £53.48
Gastro-resistant tablet
CAUTIONARY AND ADVISORY LABELS 5, 10, 25
▶ PREDNISOLONE (Non-proprietary)
Prednisolone 2.5 mg Prednisolone 2.5mg gastro-resistant tablets | 28 tablet PNX £15.45 DT price = £1.59 | 30 tablet PNX £3.36 | 100 tablet PNX £13.41
Prednisolone 5 mg Prednisolone 5mg gastro-resistant tablets | 28 tablet PNX £13.50 DT price = £1.65 | 30 tablet PNX £6.29 | 100 tablet PNX £13.54
▶ Deltacortril Enteric (Alliance Pharmaceuticals Ltd)
Prednisolone 2.5 mg Deltacortril 2.5mg gastro-resistant tablets | 30 tablet PNX £1.16
Prednisolone 5 mg Deltacortril 5mg gastro-resistant tablets | 30 tablet PNX £1.19
▶ Brands may include Dicort.
Oral solution
▶ PREDNISOLONE (Non-proprietary)
Prednisolone 1 mg per 1 ml Prednisolone 5mg/5ml oral solution unit dose | 10 unit dose PNX £1.41
Suspension for injection
▶ Deltastab (AMCo)
Prednisolone acetate 25 mg per 1 ml Deltastab 25mg/1ml suspension for injection ampoule | 10 ampoule PNX £68.72
Foam
▶ PREDNISOLONE (Non-proprietary)
Prednisolone (as Prednisolone sodium metasulfobenzoate) 20 mg per 1 application Prednisolone 20mg/application foam enema | 14 dose PNX £68.00 DT price = £68.00
Suppository
▶ PREDNISOLONE (Non-proprietary)
Prednisolone (as Prednisolone sodium phosphate) 5 mg Prednisolone sodium phosphate 5mg suppositories | 10 suppository PNX £7.50 DT price = £7.36
Enema
▶ Predisol (Focus Pharmaceuticals Ltd)
Prednisolone sodium phosphate 200 microgram per 1 ml Predisol 20mg/100ml retention enema | 7 enema PNX £7.50 DT price = £7.50

Prednisone

INDICATIONS AND DOSE
Moderate to severe rheumatoid arthritis
BY MOUTH USING MODIFIED-RELEASE MEDICINES
▶ Adults: 10–20 mg daily, adjusted according to response, dose to be take at bedtime
▶ HEPATIC IMPAIRMENT
Monitor patient closely in hepatic impairment.
▶ PATIENT AND CARER ADVICE
Patient counselling is advised for prednisone tablets (steroid card).

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Modified-release tablet
CAUTIONARY AND ADVISORY LABELS 10, 21, 25
▶ Lodotra (Napp Pharmaceuticals Ltd)
Prednisone 1 mg Lodotra 1mg modified-release tablets | 30 tablet PNX £26.70
Prednisone 2 mg Lodotra 2mg modified-release tablets | 30 tablet PNX £26.70 | 100 tablet PNX £89.00
Prednisone 5 mg Lodotra 5mg modified-release tablets | 30 tablet PNX £26.70 | 100 tablet PNX £89.00
Triamcinolone acetonide

**INDICATIONS AND DOSE**

Suppression of inflammatory and allergic disorders

**BY DEEP INTRAMUSCULAR INJECTION**

- Adult: 40 mg (max. per dose 100 mg), repeated if necessary, dose given for depot effect, to be administered into gluteal muscle; repeated at intervals according to patient’s response

**KENALOG® VIALS**

Local inflammation of joints and soft tissues

**BY INTRA-ARTICULAR INJECTION**

- Adult: 5–40 mg (max. per dose 80 mg), for further details consult product literature, select dose according to size. For doses below 5 mg use Adcortyl® Intra-articular/Intradermal injection, where appropriate dose may be repeated when relapse occurs.

**ADCORTYL® INTRA-ARTICULAR/INTRADERMAL**

Local inflammation of joints and soft tissues

**BY INTRA-ARTICULAR INJECTION**

- Adult: 2.5–15 mg, adjusted according to size (for larger doses use Kenalog®). Where appropriate dose may be repeated when relapse occurs, for details consult product literature.

**BY INTRADERMAL INJECTION**

- Adult: 2–3 mg, max. 5 mg at any one site (total max. 30 mg). Where appropriate may be repeated at intervals of 1–2 weeks, for details consult product literature.

**CAUTIONS**

- With intramuscular use High dosage (may cause proximal myopathy), avoid in chronic therapy

**PATIENT AND CARER ADVICE**

Patient counselling is advised for triamcinolone acetonide injection (steroid card).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**

CAUTIONARY AND ADVISORY LABELS 10 EXCipients: May contain Benzyl alcohol

- Adcortyl Intra-articular / Intradermal (Bristol-Myers Squibb Pharmaceuticals Ltd)
- Triamcinolone acetonide 10 mg per 1 ml Adcortyl Intra-articular / Intradermal 50mg/5ml suspension for injection vials | 1 vial £3.63
- Adcortyl Intra-articular / Intradermal 10mg/1ml suspension for injection ampoules | 5 ampoule £4.47 DT price = £4.47
- Kenalog (Bristol-Myers Squibb Pharmaceuticals Ltd)
- Triamcinolone acetonide 40 mg per 1 ml Kenalog Intra-articular / Intramuscular 40mg/1ml suspension for injection vials | 5 vial £7.45 DT price = £7.45

2.1 Cushing’s syndrome and disease

**Cushing’s Syndrome**

Most types of Cushing’s syndrome are treated surgically, that which occasionally accompanies carcinoma of the bronchus is not usually amenable to surgery. Metyrapone p. 588 has been found helpful in controlling the symptoms of the disease; it is also used in other forms of Cushing’s syndrome to prepare the patient for surgery.
Endocrine system

Metyrapone

**DRUG ACTION** Metyrapone is a competitive inhibitor of 11β-hydroxylation in the adrenal cortex; the resulting inhibition of cortisol (and to a lesser extent aldosterone) production leads to an increase in ACTH production which, in turn, leads to increased synthesis and release of cortisol precursors. Metyrapone may be used as a test of anterior pituitary function.

**INDICATIONS AND DOSE**

**Differential diagnosis of ACTH-dependent Cushing’s syndrome (specialist supervision in hospital)**

**BY MOUTH**

- Adult: 750 mg every 4 hours for 6 doses

**MONITORING REQUIREMENTS**

**HEPATIC IMPAIRMENT**

Consult product literature; if liver enzymes are raised to 2 times the normal upper limit, discontinue dose if liver enzymes increase less than 3 times the normal upper limit.

**PREGNANCY**

Manufacturer advises avoid—teratogenic in animal studies.

**CONCEPTION AND CONTRACEPTION**

Effective contraception must be used in women of child-bearing potential.

**BREAST FEEDING**

Manufacturer advises avoid—present in breast milk.

**MONITORING REQUIREMENTS**

Monitor ECG before and one week after initiation, and then as clinically indicated thereafter.

Adrenal insufficiency Monitor adrenal function within one week of initiation, then regularly thereafter. When cortisol levels are normalised or close to target and effective dose established, monitor every 3–6 months as there is a risk of autoimmune disease development or exacerbation after normalisation of cortisol levels. If symptoms suggestive of adrenal insufficiency such as fatigue, anorexia, nausea, vomiting, hypotension, hyponatraemia, hyperkalaemia, and/or hypoglycaemia occur, measure cortisol levels and discontinue treatment temporarily (can be resumed thereafter at lower dose) or reduce dose and if necessary, initiate corticosteroid substitution.

Hepatotoxicity Monitor liver function before initiation of treatment, then weekly for 1 month after initiation, then monthly for 6 months—more frequently if dose adjusted or abnormal liver function detected. Reduce dose if liver enzymes increase less than 3 times the normal upper limit—consult product literature; if liver enzymes are raised to 3 times or greater the normal upper limit, discontinue treatment permanently.

**PATIENT AND CARER ADVICE** Dizziness and somnolence may affect the performance of skilled tasks (e.g. driving). Patients or their carers should be told how to recognise signs of liver disorder, and advised to discontinue treatment and seek prompt medical attention if symptoms such as anorexia, nausea, vomiting, fatigue, jaundice, abdominal pain, or dark urine develop. Patients or their carers should also be told how to recognise signs of adrenal insufficiency.

**SIDE-EFFECTS**

- Headache
- Hypotension
- Nausea
- Sedation
- Vomiting
- Hypothyroidism (delayed response)
- Hypopituitarism (risk of precipitating acute adrenal failure) (with glucocorticoid replacement therapy)
- Hypertension (long-term administration)
- Hypothyroidism (delayed response)

**INTERACTIONS**

- **Frequency not known**
  - Dizziness
  - Headache
  - Hypotension
  - Nausea
  - Sedation
  - Vomiting

**CONTRA-INDICATIONS**

- **Adrenocortical insufficiency**
- **Hypothyroidism**
- **Hypopituitarism**
- **Hypertension**
- **Hepatic failure**
- **Hepatic failure (with glucocorticoid replacement therapy)**
- **Hepatic impairment**
- **BREAST FEEDING** Avoid—no information available.
- **HEPATIC IMPAIRMENT** Use with caution in hepatic impairment (delayed response).
- **PATIENT AND CARER ADVICE** Drowsiness may affect the performance of skilled tasks (e.g. driving).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

- **CAUTIONARY AND ADVISORY LABELS. 21**
  - **Ketoconazole**
    - **Non-proprietary**
    - **Ketoconazole**
    - **200 mg**
    - **60 tablet**
    - **£480.00**

**11ß-HYDROXYLASE INHIBITORS**

Metyrapone

**DRUG ACTION** Metyrapone is a competitive inhibitor of 11ß-hydroxylation in the adrenal cortex; the resulting inhibition of cortisol (and to a lesser extent aldosterone) production leads to an increase in ACTH production which, in turn, leads to increased synthesis and release of cortisol precursors. Metyrapone may be used as a test of anterior pituitary function.

**INDICATIONS AND DOSE**

**Differential diagnosis of ACTH-dependent Cushing’s syndrome (specialist supervision in hospital)**

**BY MOUTH**

- Adult: Usual dose 0.25–6 g daily, dose to be tailored to cortisol production, dose is either low, and tailored to cortisol production, or high, in which case corticosterone replacement therapy is also needed

**Resistant oedema due to increased aldosterone secretion in cirrhosis, nephrotic syndrome, and congestive heart failure (with glucocorticoid replacement therapy)**

**Specialist supervision in hospital**

**BY MOUTH**

- Adult: 3g daily in divided doses

**CONTRA-INDICATIONS**

- **Adrenocortical insufficiency**
- **Hypothyroidism**
- **Hypopituitarism**
- **Hypertension**
- **Hepatic failure**
- **Hepatic failure (with glucocorticoid replacement therapy)**

**CAUTIONS**

- **Avoid in Acute porphyrias**
- **Non-proprietary**
- **Ketoconazole 200 mg**
- **£363.66**

3 **Diabetes mellitus and hypoglycaemia**

3.1 **Diabetes mellitus**

**Diabetes**

Diabetes mellitus occurs because of a lack of insulin or resistance to its action. It is diagnosed by measuring fasting or random blood-glucose concentration (and occasionally by oral glucose tolerance test). Although there are many subtypes, the two principal classes of diabetes are type 1 diabetes and type 2 diabetes.

**Type 1 diabetes**, (formerly referred to as insulin-dependent diabetes mellitus (IDDM)), occurs as a result of a deficiency of insulin following autoimmune destruction of pancreatic beta cells. Patients with type 1 diabetes require administration of insulin.

**Type 2 diabetes**, (formerly referred to as non-insulin-dependent diabetes (NIDDM)), is due to reduced secretion of insulin or to peripheral resistance to the action of insulin or to a combination of both. Although patients may be controlled on diet alone, many also require oral antidiabetic
drugs or insulin (or both) to maintain satisfactory control. In overweight individuals, type 2 diabetes may be prevented by losing weight and increasing physical activity; use of the anti-obesity drug orlistat p. 78 may be considered in obese patients.

Treatment of diabetes

Treatment of all forms of diabetes should be aimed at alleviating symptoms and minimising the risk of long-term complications; tight control of diabetes is essential.

Diabetes is a strong risk factor for cardiovascular disease. Other risk factors for cardiovascular disease such as smoking, hypertension, obesity, and hyperlipidaemia should be addressed. Cardiovascular risk in patients with diabetes can be further reduced by the use of an ACE inhibitor, low-dose aspirin p. 104 and a lipid-regulating drug.

Prevention of diabetic complications

Optimal glycaemic control in both type 1 diabetes and type 2 diabetes reduces, in the long term, the risk of microvascular complications including retinopathy, development of proteinuria and to some extent neuropathy. However, a temporary deterioration in established diabetic retinopathy may occur when normalising blood-glucose concentration. ACE inhibitors and angiotensin-II receptor antagonists may also have a role in the management of diabetic nephropathy.

A measure of the total glycosylated (or glycated) haemoglobin (HbA₁c) or a specific fraction (HbA₁cₙ) provides a good indication of glycaemic control over the previous 2–3 months. Overall it is ideal to aim for an HbA₁c (glycosylated haemoglobin) concentration of 48–59 mmol/mol or less (reference range 20–42 mmol/mol) but this cannot always be achieved and for those using insulin there is a significantly increased risk of disabling hypoglycaemia; in those at risk of arterial disease, the aim should be to maintain the HbA₁c concentration at 48 mmol/mol or less. HbA₁c should be measured every 3–6 months.

Measurement of HbA₁c

HbA₁c values are expressed in mmol of glycosylated haemoglobin per mol of haemoglobin (mmol/mol), a standardised unit specific for HbA₁c created by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). HbA₁c values were previously aligned to the assay used in the Diabetes Control and Complications Trial (DCCT) and expressed as a percentage.

<table>
<thead>
<tr>
<th>Equivalent values IFCC-HbA₁c (mmol/mol)</th>
<th>DCCT-HbA₁c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td>6.0</td>
</tr>
<tr>
<td>48</td>
<td>6.5</td>
</tr>
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<td>53</td>
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<td>64</td>
<td>8.0</td>
</tr>
<tr>
<td>75</td>
<td>9.0</td>
</tr>
</tbody>
</table>

Laboratory measurement of serum-fructosamine concentration is technically simpler and cheaper than the measurement of HbA₁c, and can be used to assess control over short periods of time, particularly when HbA₁c monitoring is invalid (e.g. disturbed erythrocyte turnover or abnormal haemoglobin type).

Tight control of blood pressure in hypertensive patients with type 2 diabetes reduces mortality and protects visual acuity (by reducing considerably the risks of maculopathy and retinal photocoagulation).

Driving

Drivers with diabetes may be required to notify the Driver and Vehicle Licensing Agency (DVLA) of their condition depending on their treatment, the type of licence, and whether they have diabetic complications. Detailed guidance on eligibility to drive, and precautions required, is available from the DVLA (www.gov.uk/government/publications/at-a-glance).

Drivers need to be particularly careful to avoid hypoglycaemia and should be warned of the problems. Drivers treated with insulin should normally check their blood-glucose concentration before driving and, on long journeys, at 2-hour intervals as specified by DVLA guidance; depending on the type of licence, monitoring may also be necessary for drivers taking oral antidiabetic drugs which carry a risk of hypoglycaemia (e.g. sulfonylureas, nateglinide p. 607, repaglinide p. 608). Drivers treated with insulin should ensure that a supply of sugar is always available in the vehicle and they should avoid driving if their meal is delayed. If hypoglycaemia occurs, or warning signs develop, the driver should:

- stop the vehicle in a safe place;
- switch off the ignition and move from the driver’s seat;
- eat or drink a suitable source of sugar;
- wait until 45 minutes after blood glucose has returned to normal, before continuing journey.

Diabetic nephropathy

Regular review of diabetic patients should include an annual test for urinary protein (using Albustix®) and serum creatinine measurement. If the urinary protein test is negative, the urine should be tested for microalbuminuria (the earliest sign of nephropathy). If reagent strip tests (Microtest II® or Microbunimeter®) are used and prove positive, the result should be confirmed by laboratory analysis of a urine sample. Provided there are no contra-indications, all diabetic patients with nephropathy causing proteinuria or with established microalbuminuria (at least 3 positive tests) should be treated with an ACE inhibitor or an angiotensin-II receptor antagonist even if the blood pressure is normal; in any case, to minimise the risk of renal deterioration, blood pressure should be carefully controlled. Patients with diabetic nephropathy are particularly susceptible to developing hyperkalaemia and should not be given an ACE inhibitor together with an angiotensin-II receptor antagonist.

ACE inhibitors can potentiate the hypoglycaemic effect of insulin and oral antidiabetic drugs; this effect is more likely during the first weeks of combined treatment and in patients with renal impairment. See also treatment of hypertension in diabetes.

Diabetic neuropathy

Optimal diabetic control is beneficial for the management of painful neuropathy in patients with type 1 diabetes. Paracetamol p. 354 or a non-steroidal anti-inflammatory drug such as ibuprofen p. 927 may relieve mild to moderate pain.

Duloxetine p. 288 is effective for the treatment of painful diabetic neuropathy; amitriptyline hydrochloride p. 292 [unlicensed use] can be used if duloxetine is ineffective or unsuitable. Nortriptyline p. 298 [unlicensed use] may be better tolerated than amitriptyline hydrochloride. If treatment with amitriptyline hydrochloride or duloxetine is inadequate, treatment with pregabalin p. 400 should be tried. Combination therapy of duloxetine or amitriptyline hydrochloride with pregabalin can be used if monotherapy at the maximum tolerated dose does not control symptoms. Neuropathic pain may respond to opioid analgesics. There is evidence of efficacy for tramadol hydrochloride p. 373, morphine p. 367, and oxycodone hydrochloride p. 369; however treatment with morphine or oxycodone hydrochloride should be initiated only under specialist supervision. Tramadol hydrochloride can be prescribed while the patient is waiting for assessment by a specialist if other treatments have been unsuccessful.
Diabetic ketoacidosis, management


- To restore circulating volume if systolic blood pressure is below 90 mmHg (adjusted for age, sex, and medication as appropriate), give 500 ml sodium chloride 0.9% by intravenous infusion over 10–15 minutes; repeat if blood pressure remains below 90 mmHg and seek senior medical advice.
- When blood pressure is over 90 mmHg, sodium chloride 0.5% should be given by intravenous infusion at a rate that replaces deficit and provides maintenance; see guideline or suggested regimen.
- Include potassium chloride in the fluids unless anuria is suspected; adjust according to plasma-potassium concentration (measure at 60 minutes, 2 hours, and 2 hourly thereafter; measure hourly if outside the normal range).
- Start an intravenous insulin infusion: soluble insulin should be diluted (and mixed thoroughly) with sodium chloride 0.5% intravenous infusion to a concentration of 1 unit/mL; infuse at a fixed rate of 0.1 units/kg/hour.
- Established subcutaneous therapy with long-acting insulin analogues (insulin detemir or insulin glargine) should be continued during treatment of diabetic ketoacidosis.
- Monitor blood-ketone and blood-glucose concentrations hourly and adjust the insulin infusion rate accordingly. Blood-ketone concentration should fall by at least 0.5 mmol/litre/hour and blood-glucose concentration should fall by at least 3 mmol/litre/hour.
- Once blood-glucose concentration falls below 14 mmol/litre, glucose 10% should be given by intravenous infusion (into a large vein through a large-gauge needle) at a rate of 125 mL/hour, in addition to the sodium chloride 0.9% infusion.
- Continue insulin infusion until blood-ketone concentration is below 0.3 mmol/litre, blood pH is above 7.3 and the patient is able to eat and drink; ideally give subcutaneous fast-acting insulin and a meal, and stop the insulin infusion 1 hour later.

The management of hyperosmolar hyperglycaemic state or hyperosmolar hyperglycaemic nonketotic coma is similar to that of diabetic ketoacidosis, although lower rates of insulin infusion are usually necessary and slower rehydration may be required.

Insulins and anti-diabetic drugs

Insulins

Insulin plays a key role in the regulation of carbohydrate, fat, and protein metabolism. It is a polypeptide hormone of complex structure. There are differences in the amino-acid sequence of animal insulins, human insulins and the human insulin analogues. Insulin may be extracted from pork pancreas and purified by crystallisation; it may also be extracted from beef pancreas, but beef insulins are now rarely used. Human sequence insulin may be produced semisynthetically by enzymatic modification of porcine insulin (emp) or biosynthetically by recombinant DNA technology using bacteria (crb, pbh) or yeast (pyr).

All insulin preparations are to a greater or lesser extent immunogenic in man but immunological resistance to insulin action is uncommon. Preparations of human sequence insulin should theoretically be less immunogenic, but no real advantage has been shown in trials.

Insulin is inactivated by gastro-intestinal enzymes, and must therefore be given by injection; the subcutaneous route is ideal in most circumstances. Insulin is usually injected into the upper arms, thighs, buttocks, or abdomen; absorption from a limb site may be increased if the limb is used in strenuous exercise after the injection. Generally subcutaneous insulin injections cause few problems; lipodystrophy may occur but can be minimised by using different injection sites in rotation. Local allergic reactions are rare.

Insulin is needed by all patients with ketoacidosis, and it is likely to be needed by most patients with:

- rapid onset of symptoms;
- substantial loss of weight;
- weakness;
- ketonuria;
- a first-degree relative who has type 1 diabetes.

Insulin is also needed for type 2 diabetes when other methods have failed to achieve good control, and temporarily in the presence of intercurrent illness or peri-operatively. Pregnant women with type 2 diabetes may be treated with insulin when diet alone fails. Antidiabetic drugs have a role in the management of diabetes in pregnancy.

Safe and Effective Use of Insulin in Hospitalised Patients (March 2010)


Management of diabetes with insulin

The aim of treatment is to achieve the best possible control of blood-glucose concentration without making the patient obsessional and to avoid disabling hypoglycaemia; close co-operation is needed between the patient and the medical team because good control reduces the risk of complications.

Insulin preparations can be divided into 3 types:

- those of short duration which have a relatively rapid onset of action, namely soluble insulin and the rapid-
acting insulin analogues, insulin aspart p. 604, insulin glulisine p. 605, and insulin lispro p. 606;
• those with an intermediate action, e.g. isophane insulin p. 607; and
• those whose action is slower in onset and lasts for long periods, e.g. protamine zinc insulin p. 607, insulin detemir p. 605, and insulin glargine p. 605.

The duration of action of a particular type of insulin varies considerably from one patient to another, and needs to be assessed individually.

Mixtures of insulin preparations may be required and appropriate combinations have to be determined for the individual patient. Treatment should be started with a short-acting insulin (e.g. soluble insulin) or a rapid-acting insulin analogue (e.g. insulin aspart) given before meals with intermediate-acting or long-acting insulin once or twice daily. Alternatively, for those who have difficulty with, or prefer not to use, multiple injection regimens, a mixture of premixed short-acting insulin or rapid-acting insulin analogue with an intermediate-acting or long-acting insulin (most commonly in a proportion of 30% soluble insulin and 70% isophane insulin) can be given once or twice daily. The dose of short-acting or rapid-acting insulin (or the proportion of the short-acting soluble insulin component in premixed insulin) can be increased in those with excessive postprandial hyperglycaemia. The dose of insulin is increased gradually according to the patient’s individual requirements, taking care to avoid troublesome hypoglycaemic reactions.

Insulin requirements may be increased by infection, stress, accidental or surgical trauma, and during puberty. Requirements may be decreased in those with certain endocrine disorders (e.g. Addison’s disease, hyperpituitarism), or in coeliac disease.

Examples of recommended insulin regimens
• Multiple injection regimen: short-acting insulin or rapid-acting insulin analogue, before meals. With intermediate-acting or long-acting insulin, once or twice daily;
• Short-acting insulin or rapid-acting insulin analogue mixed with intermediate-acting or long-acting insulin, once or twice daily (before meals);
• Intermediate-acting or long-acting insulin, once or twice daily. With or without short-acting insulin or rapid-acting insulin before meals;
• Continuous subcutaneous insulin infusion.

Hypoglycaemia
Loss of warning of hypoglycaemia among insulin-treated patients can be a serious hazard, especially for drivers and those in dangerous occupations. Very tight control of diabetes lowers the blood-glucose concentration needed to trigger hypoglycaemic symptoms; an increase in the frequency of hypoglycaemic episodes may reduce the warning symptoms experienced by the patient. Beta-blockers can also blunt hypoglycaemic awareness (and also delay recovery).

To restore the warning signs, episodes of hypoglycaemia must be minimised; this involves appropriate adjustment of insulin type, dose and frequency together with suitable timing and quantity of meals and snacks.

Some patients have reported loss of hypoglycaemia warning after transfer to human insulin. Clinical studies do not confirm that human insulin decreases hypoglycaemia awareness. If a patient believes that human insulin is responsible for the loss of warning it is reasonable to revert to animal insulin and essential to educate the patient about avoiding hypoglycaemia. Great care should be taken to specify whether a human or an animal preparation is required.

Few patients are now treated with beef insulins; when undertaking conversion from beef to human insulin, the total dose should be reduced by about 10% with careful monitoring for the first few days. When changing between pork and human-sequence insulins, a dose change is not usually needed, but careful monitoring is still advised.

Diabetes and surgery
Perioperative control of blood-glucose concentrations in patients with type 1 diabetes is achieved via an adjustable, continuous, intravenous infusion of insulin. Detailed local protocols should be available to all healthcare professionals involved in the treatment of these patients; in general, the following steps should be followed:
• give an injection of the patient’s usual insulin on the night before the operation;
• early on the day of the operation, start an intravenous infusion of glucose containing potassium chloride (provided that the patient is not hyperkalaemic) and infuse at a constant rate appropriate to the patient’s fluid requirements (usually 125 mL per hour); make up a solution of soluble insulin in sodium chloride 0.9% and infuse intravenously using a syringe pump piggy-backed to the intravenous infusion. Glucose and potassium infusions, and insulin infusions should be made up according to locally agreed protocols;
• the rate of the insulin infusion should be adjusted according to blood-glucose concentration (frequent monitoring necessary) in line with locally agreed protocols. Other factors affecting the rate of infusion include the patient’s volume depletion, cardiac function, and age.

Protocols should include specific instructions on how to manage resistant cases (such as patients who are in shock or severely ill or those receiving corticosteroids or sympathomimetics) and those with hypoglycaemia.

If a syringe pump is not available, soluble insulin should be added to the intravenous infusion of glucose and potassium chloride (provided the patient is not hyperkalaemic), and the infusion run at the rate appropriate to the patient’s fluid requirements (usually 125 mL per hour) with the insulin dose adjusted according to blood-glucose concentration in line with locally agreed protocols.

Once the patient starts to eat and drink, give subcutaneous insulin before breakfast and stop intravenous insulin 30 minutes later; the dose may need to be 10–20% more than usual if the patient is still in bed or unwell. If the patient was not previously receiving insulin, an appropriate initial dose is 20–40 units daily in four divided doses using soluble insulin before meals and intermediate-acting insulin at bedtime and the dose adjusted from day to day. Patients with hypoglycaemia often relapse after conversion back to subcutaneous insulin calling for one of the following approaches:
• additional doses of soluble insulin at any of the four injection times (before meals or bedtime) or
• temporary addition of intravenous insulin infusion (while continuing the subcutaneous regimen) until blood-glucose concentration is satisfactory or
• complete reversion to the intravenous regimen (especially if the patient is unwell).

Short-acting insulins
Soluble insulin is a short-acting form of insulin. For maintenance regimens it is usual to inject it 15 to 30 minutes before meals. Soluble insulin is the most appropriate form of insulin for use in diabetic emergencies e.g. diabetic ketoacidosis (see Diabetic ketoacidosis, management p. 590) and at the time of surgery. It can be given intravenously and intramuscularly, as well as subcutaneously.

When injected subcutaneously, soluble insulin has a rapid onset of action (30 to 60 minutes), a peak action between 2 and 4 hours, and a duration of action of up to 8 hours. When injected intravenously, soluble insulin has a very short half-life of only about 5 minutes and its effect disappears within 30 minutes.
The rapid-acting human insulin analogues, insulin aspart, insulin glulisine, and insulin lispro have a faster onset and shorter duration of action than soluble insulin; as a result, compared to soluble insulin, fasting and preprandial blood-glucose concentrations are a little higher, postprandial blood-glucose concentration is a little lower, and hypoglycaemia occurs slightly less frequently. Subcutaneous injection of insulin analogues may be convenient for those who wish to inject shortly before or, when necessary, shortly after a meal. They can also help those susceptible to hypoglycaemia before lunch and those who eat late in the evening and are prone to nocturnal hypoglycaemia. They can also be administered by subcutaneous infusion. Insulin aspart and insulin lispro can be administered intravenously and can be used as alternatives to soluble insulin for diabetic emergencies and at the time of surgery.

**Intermediate- and long-acting insulins**

When given by subcutaneous injection, intermediate- and long-acting insulins have an onset of action of approximately 1–2 hours, a maximal effect at 4–12 hours, and a duration of 16–42 hours. Some are given twice daily in conjunction with short-acting (soluble) insulin, and others are given once daily, particularly in elderly patients. Soluble insulin can be mixed with intermediate and long-acting insulins (except insulin detemir, insulin glargine, and insulin degludec) in the syringe, essentially retaining the properties of the two components, although there may be some blunting of the initial effect of the soluble insulin component (especially on mixing with protamine zinc insulin).

Isophane insulin is a suspension of insulin with protamine; it is of particular value for initiation of twice-daily insulin regimens. Patients usually mix isophane with soluble insulin but ready-mixed preparations may be appropriate (biphasic isophane insulin, biphasic insulin aspart, or biphasic insulin lispro).

Insulin zinc suspension (30% amorphous, 70% crystalline) has a more prolonged duration of action.

Protamine zinc insulin is usually given once daily with short-acting (soluble) insulin. It has the drawback of binding with the soluble insulin when mixed in the same syringe and is now rarely used.

Insulin glargine and insulin detemir are both long-acting human insulin analogues with a prolonged duration of action; insulin glargine is given once daily and insulin detemir is given once or twice daily. NICE (December 2002) has recommended that insulin glargine should be available as an option for patients with type 1 diabetes.

NICE (May 2009) has recommended that, if insulin is required in patients with type 2 diabetes, insulin detemir or insulin glargine may be considered for those:

- who require assistance with injecting insulin or
- whose lifestyle is significantly restricted by recurrent symptomatic hypoglycaemia or
- who would otherwise need twice–daily basal insulin injections in combination with oral antidiabetic drugs or
- who cannot use the device needed to inject isophane insulin.

Insulin detemir is also licensed as add-on therapy in patients receiving treatment with lixisenatide.

Insulin degludec is a long-acting human insulin analogue for once daily subcutaneous administration.

**Hypodermic equipment**

Patients should be advised on the safe disposal of lancets, single-use syringes, and needles. Suitable arrangements for the safe disposal of contaminated waste must be made before these products are prescribed for patients who are carriers of infectious diseases.

**Lancets, syringes, and accessories** are listed under Hypodermic Equipment in Part IXA of the Drug Tariff (Part III of the Northern Ireland Drug Tariff, Part 3 of the Scottish Drug Tariff). The drug Tariffs can be accessed online at:
- National Health Service Drug Tariff for England and Wales: [www.ppa.org.uk/pfa/edt_intro.htm](http://www.ppa.org.uk/pfa/edt_intro.htm)

**Antidiabetic drugs**

Oral antidiabetic drugs are used for the treatment of type 2 diabetes mellitus. They should be prescribed only if the patient fails to respond adequately to at least 3 months’ restriction of energy and carbohydrate intake and an increase in physical activity. They should be used to augment the effect of diet and exercise, and not to replace them.

For patients not adequately controlled by diet and oral hypoglycaemic drugs, insulin may be added to the treatment regimen or substituted for oral therapy. When insulin is added to oral therapy, it is generally given at bedtime as isophane or long-acting insulin, and when insulin replaces an oral regimen it may be given as twice-daily injections of a biphasic insulin (or isophane insulin p. 607 mixed with soluble insulin), or a multiple injection regimen. Weight gain and hypoglycaemia may be complications of insulin therapy but weight gain may be reduced if the insulin is given in combination with metformin hydrochloride p. 594.

**Pregnancy and breast-feeding**

During pregnancy, women with *pre-existing diabetes* can be treated with metformin hydrochloride [unlicensed use], either alone or in combination with insulin. Metformin hydrochloride can be continued, or glibenclamide p. 611 resumed, during breast-feeding for those with pre-existing diabetes. Women with *gestational diabetes* may be treated, with or without concomitant insulin, with glibenclamide from 11 weeks gestation (after organogenesis) [unlicensed use] or with metformin [unlicensed use]. Women with gestational diabetes should discontinue hypoglycaemic treatment after giving birth.

**Sulfonylureas**

The sulfonylureas act mainly by augmenting insulin secretion and consequently are effective only when some residual pancreatic beta-cell activity is present; during long-term administration they also have an extrapancreatic action. All may cause hypoglycaemia but this is uncommon and usually indicates excessive dosage. Sulfonylurea-induced hypoglycaemia may persist for many hours and must always be treated in hospital.

Sulfonylureas are considered for patients who are not overweight, or in whom metformin hydrochloride is contraindicated or not tolerated. Several sulfonylureas are available and choice is determined by side-effects and the duration of action as well as the patient’s age and renal function. Glibenclamide, a long-acting sulfonylurea, is associated with a greater risk of hypoglycaemia; for this reason it should be avoided in the elderly, and shorter-acting alternatives, such as gliclazide p. 611 or tolbutamide p. 613, should be used instead.

When the combination of strict diet and sulfonylurea treatment fails, other options include:

- combining with metformin;
- combining with pioglitazone;
- combining with alogliptin, linagliptin, saxagliptin, sitagliptin, or vildagliptin;
- combining with canagliflozin, dapagliflozin or empagliflozin;
- combining with exenatide, lixisenatide, or liraglutide;
- combining with acarbose, which may have a small beneficial effect, but flatulence can be a problem;

- Empagliflozin, dapagliflozin, and empagliflozin are not recommended for use in pregnancy.

- For patients with type 1 diabetes who are not using a pump, insulin replacement regimens are being evaluated (one of which is a 3 1/2-hour basal bolus regimen).

- For patients who are not adequately controlled by diet and oral hypoglycaemic drugs, insulin may be added to the treatment regimen or substituted for oral therapy. When insulin is added to oral therapy, it is generally given at bedtime as isophane or long-acting insulin, and when insulin replaces an oral regimen it may be given as twice-daily injections of a biphasic insulin (or isophane insulin p. 607 mixed with soluble insulin), or a multiple injection regimen. Weight gain and hypoglycaemia may be complications of insulin therapy but weight gain may be reduced if the insulin is given in combination with metformin hydrochloride p. 594.

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- combining with bedtime isophane insulin but weight gain and hypoglycaemia can occur.
- Insulin therapy should be instituted temporarily during intercurrent illness (such as myocardial infarction, coma, infection, and trauma). Sulfonylureas should be omitted on the morning of surgery; insulin is required because of the ensuing hyperglycaemia in these circumstances.

**Biguanides**

Metformin hydrochloride, the only available biguanide, has a different mode of action from the sulfonylureas, and is not interchangeable with them.

Metformin hydrochloride is the drug of first choice in overweight patients in whom strict dieting has failed to control diabetes, if appropriate it may also be considered as an option in patients who are not overweight. It is also used when diabetes is inadequately controlled with sulfonylurea treatment. When the combination of strict diet and metformin hydrochloride treatment fails, other options include:

- combining with a sulfonylurea;
- combining with pioglitazone;
- combining with repaglinide or nateglinide;
- combining with alogliptin, linagliptin, saxagliptin, sitagliptin, or vildagliptin;
- combining with canagliflozin, dapagliflozin or empagliflozin;
- combining with exenatide, liraglutide, or lixisenatide;
- combining with acarbose, which may have a small beneficial effect, but flatulence can be a problem;
- combining with insulin but weight gain and hypoglycaemia can be problems (weight gain minimised if insulin given at night).

Insulin treatment is almost always required in medical and surgical emergencies; insulin should also be substituted before elective surgery (omit metformin hydrochloride on the morning of surgery and give insulin if required).

Hypoglycaemia does not usually occur with metformin hydrochloride; other advantages are the lower incidence of weight gain and lower plasma-insulin concentration. It does not exert a hypoglycaemic action in non-diabetic subjects unless given in overdose.

Metformin hydrochloride is used for the symptomatic management of polycystic ovary syndrome [unlicensed indication]; however, treatment should be initiated by a specialist. Metformin hydrochloride improves insulin sensitivity, may aid weight reduction, helps to normalise menstrual cycle (increasing the rate of spontaneous ovulation), and may improve hirsutism.

**Other antidiabetic drugs**

Use of acarbose p. 594 is usually reserved for when other oral hypoglycaemics are not tolerated or are contra-indicated. Postprandial hyperglycaemia in type 1 diabetes can be reduced by acarbose, but it has been little used for this purpose. Flatulence deters some from using acarbose although this side-effect tends to decrease with time.

Nateglinide p. 607 and repaglinide p. 608 stimulate insulin secretion. Both drugs have a rapid onset of action and short duration of activity, and should be administered shortly before each main meal. Repaglinide may be given as monotherapy for patients who are not overweight or for those in whom metformin hydrochloride is contra-indicated or not tolerated, or it may be given in combination with metformin hydrochloride. Nateglinide is licensed only for use with metformin hydrochloride.

Pioglitazone p. 613 can be used alone or in combination with metformin hydrochloride or with a sulfonylurea (if metformin hydrochloride inappropriate), or with both; the combination of pioglitazone plus metformin hydrochloride is preferred to pioglitazone plus sulfonylurea, particularly for obese patients. Inadequate response to a combination of metformin hydrochloride and sulfonylurea may indicate failing insulin release; the introduction of pioglitazone has a limited role in these circumstances and the initiation of insulin is often more appropriate. Pioglitazone is also licensed in combination with insulin, in patients who have not achieved adequate glycaemic control with insulin alone, when metformin hydrochloride is inappropriate. Blood-glucose control may deteriorate temporarily when pioglitazone is substituted for an oral antidiabetic drug that is being used in combination with another. Long-term benefits of pioglitazone have not yet been demonstrated. NICE (May 2009) has recommended that, when glycaemic control is inadequate with existing treatment, pioglitazone can be added to:

- a sulfonylurea, if metformin hydrochloride is contra-indicated or not tolerated;
- metformin, if risks of hypoglycaemia with sulfonylurea are unacceptable or a sulfonylurea is contraindicated or not tolerated;
- a combination of metformin hydrochloride and a sulfonylurea, if insulin is unacceptable because of lifestyle or other personal issues, or because the patient is obese.

NICE has recommended that treatment with pioglitazone is continued only if HbA1c concentration is reduced by at least 0.5 percentage points within 6 months of starting treatment.

Linagliptin p. 596 is licensed for use in type 2 diabetes as monotherapy (if metformin hydrochloride inappropriate), or in combination with metformin hydrochloride (when treatment with metformin hydrochloride alone fails to achieve adequate glycaemic control), or both metformin hydrochloride and a sulfonylurea (when dual therapy with these drugs fails to achieve adequate glycaemic control). Linagliptin may also be used in combination with insulin (with or without metformin hydrochloride p. 594) when a stable dose of insulin has not provided adequate glycaemic control.

Saxagliptin p. 597 and vildagliptin p. 598 are licensed for use in type 2 diabetes as monotherapy (if metformin hydrochloride inappropriate), or in combination with metformin hydrochloride or a sulfonylurea (if metformin hydrochloride inappropriate), or pioglitazone (when treatment with either metformin hydrochloride or a sulfonylurea or pioglitazone fails to achieve adequate glycaemic control), and also in combination with both metformin hydrochloride and a sulfonylurea (when dual therapy with these drugs fails to achieve adequate glycaemic control). The combination of either saxagliptin or vildagliptin, and insulin (with or without metformin hydrochloride) is also licensed for use when a stable dose of insulin has not provided adequate glycaemic control.

Alogliptin p. 596 is also licensed for use as triple therapy in combination with metformin hydrochloride and either pioglitazone or insulin.

NICE (May 2009) has recommended that, when glycaemic control is inadequate with existing treatment:

- sitagliptin or vildagliptin (instead of a sulfonylurea) can be added to metformin, if there is a significant risk of hypoglycaemia or if a sulfonylurea is contraindicated or not tolerated;
- sitagliptin or vildagliptin can be added to a sulfonylurea, if metformin is contra-indicated or not tolerated;
- sitagliptin can be added to both metformin and a sulfonylurea, if insulin is unacceptable because of lifestyle or other personal issues, or because the patient is obese.

NICE has recommended that treatment with sitagliptin or vildagliptin is continued only if HbA1c concentration is reduced by at least 0.5 percentage points within 6 months of starting treatment.

Treatment with exenatide p. 599, liraglutide p. 600, and lixisenatide p. 601 is associated with the prevention of
weight gain and possible promotion of weight loss which can be beneficial in overweight patients. They are given by subcutaneous injection for the treatment of type 2 diabetes mellitus.

Exenatide is licensed in combination with metformin hydrochloride or a sulfonylurea, or both, or with either metformin hydrochloride and pioglitazone, or both, with metformin hydrochloride and pioglitazone, in patients who have not achieved adequate glycaemic control with these drugs alone or in combination; standard-release exenatide is also licensed in combination with basal insulin alone or with metformin hydrochloride or pioglitazone (or both).

NICE (May 2009) has recommended that, when glycaemic control is inadequate with metformin hydrochloride and sulfonylurea treatment, the addition of standard-release exenatide may be considered if the patient has:
- a body mass index of 35 kg/m² or over and is of European descent (with appropriate adjustment for other ethnic groups) and weight-related psychological or medical problems or
- a body mass index less than 35 kg/m², and insulin would be unacceptable for occupational reasons or weight loss would benefit other significant obesity-related comorbidities.

NICE has recommended that treatment with standard release exenatide is continued only if HbA1c concentration is reduced by at least 1 percentage point and a weight loss of at least 3% is achieved within 6 months of starting treatment.

Liraglutide is licensed for the treatment of type 2 diabetes mellitus in combination with metformin hydrochloride or a sulfonylurea, or both, in patients who have not achieved adequate glycaemic control with these drugs alone or in combination. Liraglutide is also licensed for use in combination with basal insulin or both metformin hydrochloride and pioglitazone when dual therapy with these drugs fails to achieve adequate glycaemic control. Lixisenatide is licensed for the treatment of type 2 diabetes mellitus in combination with oral antidiabetic drugs (e.g. metformin hydrochloride, pioglitazone, or a sulfonylurea) or basal insulin, or both, when adequate glycaemic control has not been achieved with these drugs; lixisenatide should not be used in combination with both basal insulin and a sulfonylurea because of an increased risk of hypoglycaemia. Canagliflozin p. 608 and dapagliflozin p. 609, and empagliflozin p. 610 are licensed for use in type 2 diabetes as monotherapy (if metformin hydrochloride inappropriate), or in combination with insulin or other antidiabetic drugs (if existing treatment fails to achieve adequate glycaemic control). Dapagliflozin is not recommended in combination with pioglitazone.

ALPHA GLUCOSIDASE INHIBITORS

Acarbose

- **DRUG ACTION** Acarbose, an inhibitor of intestinal alpha glucosidases, delays the digestion and absorption of starch and sucrose; it has a small but significant effect in lowering blood glucose.

**INDICATIONS AND DOSE**

Diabetes mellitus inadequately controlled by diet or by diet with oral antidiabetic drugs

**BY MOUTH**

- Adult: Initially 50 mg daily, then increased to 50 mg 3 times a day for 6–8 weeks, then increased if necessary to 100 mg 3 times a day (max. per dose 200 mg 3 times a day)

- CONTRA-INDICATIONS Hernia · inflammatory bowel disease · predisposition to partial intestinal obstruction · previous abdominal surgery
- **CAUTIONS** May enhance hypoglycaemic effects of insulin and sulfonylureas (hypoglycaemic episodes may be treated with oral glucose but not with sucrose)
- **INTERACTIONS** → Appendix 1 (antidiabetics).
- **SIDE-EFFECTS**
  - Common or very common Abdominal distention and pain · diarrhoea (may need to reduce dose or withdraw) · flatulence · soft stools
  - Rare Abnormal liver function tests · nausea · skin reactions
  - Very rare Hepatitis · ileus · jaundice · oedema

**SIDE-EFFECTS, FURTHER INFORMATION**

Antacids Antacids unlikely to be beneficial for treating side effects.

- **PREGNANCY** Avoid.
- **BREAST FEEDING** Avoid.
- **HEPATIC IMPAIRMENT** Avoid.
- **RENAL IMPAIRMENT** Avoid if eGFR less than 25 ml/minute/1.73 m².
- **MONITORING REQUIREMENTS** Monitor liver function.
- **DIRECTIONS FOR ADMINISTRATION** Tablets should be chewed with first mouthful of food or swallowed whole with a little liquid immediately before food.

**PATIENT AND CARER ADVICE** Antacids unlikely to be beneficial for treating side-effects. To counteract possible hypoglycaemia, patients receiving insulin or a sulfonylurea as well as acarbose need to carry glucose (not sucrose — acarbose interferes with sucrose absorption). Patients should be given advice on how to administer acarbose tablets.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **ACARBOSE (Non-proprietary)**
  - Acarbose 50 mg Acarbose 50 mg tablets | 90 tablet [POD] £9.65 DT price = £9.65
  - Acarbose 100 mg Acarbose 100 mg tablets | 90 tablet [POD] £16.42 DT price = £16.42
- **Glucobay (Bayer Plc)**
  - Acarbose 50 mg Glucobay 50 mg tablets | 90 tablet [POD] £7.35 DT price = £7.35
  - Acarbose 100 mg Glucobay 100 mg tablets | 90 tablet [POD] £13.50 DT price = £13.50

**BIGUANIDES**

Metformin hydrochloride

- **DRUG ACTION** Metformin exerts its effect mainly by decreasing gluconeogenesis and by increasing peripheral utilisation of glucose; since it acts only in the presence of endogenous insulin it is effective only if there are some residual functioning pancreatic islet cells.

**INDICATIONS AND DOSE**

Diabetes mellitus

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

- Adult: Initially 500 mg once daily for at least 1 week, dose to be taken with breakfast, then 500 mg twice daily for at least 1 week, dose to be taken with breakfast and evening meal, then 500 mg 3 times a day, dose to be taken with breakfast, lunch and evening meal; maximum 2 g per day

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

- Adult: Initially 500 mg once daily, then increased if necessary up to 2 g once daily, dose increased
RENAL IMPAIRMENT

NATIONAL FUNDING/ACCESS DECISIONS

Frequency not known
Common or very common

CAUTIONS

CONTRA-INDICATIONS
Ketoacidosis - use of general anaesthesia (suspend metformin on the morning of surgery and restart when renal function returns to baseline)

CONTRA-INDICATIONS, FURTHER INFORMATION

Iodine-containing X-ray contrast media

Glucophage

Glucophage SR

Canagliflozin, p. 596; canagliflozin, p. 609; dapagliflozin, p. 610; linagliptin, p. 597; pioglitazone, p. 614; saxagliptin, p. 597; sitagliptin, p. 598; vildagliptin, p. 599

Endocrine system

Diabetes mellitus 595

45 mL/minute/1.73 m² and to avoid if eGFR less than 30 mL/minute/1.73 m².

MONITORING REQUIREMENTS
Determine renal function before treatment and at least annually (at least twice a year in patients with additional risk factors for renal impairment, or if deterioration suspected).

PRESCRIBING AND DISPENSING INFORMATION
Patients taking up to 2 g daily of the standard-release metformin may start with the same daily dose of metformin modified release; not suitable if dose of standard-release tablets more than 2 g daily.

MEDITICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, capsule

Tablet

CAUTIONARY AND ADVISORY LABELS 21
METFORMIN HYDROCHLORIDE (Non-proprietary)

Metformin hydrochloride 500 mg Metformin 500mg tablets | 28 tablet (P) £1.55 DT price = £1.47 | 56 tablet (P) £4.41 | 500 tablet (P) £26.25

Metformin hydrochloride 850 mg Metformin 850mg tablets | 56 tablet (P) £2.48 DT price = £1.86 | 60 tablet (P) price = £10.12

Glucophage (Merck Serono Ltd)

Metformin hydrochloride 500 mg Glucophage 500mg tablets | 84 tablet (P) £2.88

Metformin hydrochloride 850 mg Glucophage 850mg tablets | 56 tablet (P) £3.20 DT price = £1.86

Modified-release tablet

CAUTIONARY AND ADVISORY LABELS 21, 25
METFORMIN HYDROCHLORIDE (Non-proprietary)

Metformin hydrochloride 500 mg Metformin 500mg modified-release tablets | 28 tablet (P) £7.89 | 56 tablet (P) £18.25 DT price = £5.32

Metformin hydrochloride 1 gram Metformin 1g modified-release tablets | 28 tablet (P) £4.26 | 56 tablet (P) £8.52 DT price = £8.52

Glucophage SR (Merck Serono Ltd)

Metformin hydrochloride 500 mg Glucophage SR 500mg tablets | 28 tablet (P) £2.66 | 56 tablet (P) £5.32 DT price = £5.32

Metformin hydrochloride 750 mg Glucophage SR 750mg tablets | 28 tablet (P) £3.20 | 56 tablet (P) £6.40 DT price = £6.40

Metformin hydrochloride 1 gram Glucophage SR 1000mg tablets | 28 tablet (P) £4.26 | 56 tablet (P) £8.52 DT price = £8.52

Brands may include Bolamyn SR; Diagemet XL; Glucient SR; Metabet SR; Sukkarto SR

Oral solution

CAUTIONARY AND ADVISORY LABELS 21
METFORMIN HYDROCHLORIDE (Non-proprietary)

Metformin hydrochloride 100 mg per 1 ml Metformin 500mg/5ml oral solution sugar free (sugar-free) | 100 ml (P) £47.52 (sugar-free) | 150 ml (P) £69.80 DT price = £63.80

Powder

METFORMIN HYDROCHLORIDE (Non-proprietary)

Metformin hydrochloride 1 gram Metformin 1g oral powder sachets sugar free (sugar-free) | 30 sachet (P) price = £32.00

Also available in combination with alogliptin, p. 596; canagliflozin, p. 609; dapagliflozin, p. 610; linagliptin, p. 597; pioglitazone, p. 614; saxagliptin, p. 597; sitagliptin, p. 598; vildagliptin, p. 599

Gradually, every 10–15 days, dose to be taken with evening meal, alternatively increased to 1 g twice daily, dose to be taken with meals, alternative dose only to be used if control not achieved with once daily dose regimen. If control still not achieved then change to standard release tablets

Polycystic ovary syndrome

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

Adult: Initially 500 mg once daily for 1 week, dose to be taken with breakfast, then 500 mg twice daily for 1 week, dose to be taken with breakfast and evening meal, then 1.5–1.7 g daily in 2–3 divided doses

UNLICENSED USE
Doses in the BNF may differ from those in the product literature. Not licensed for polycystic ovary syndrome.

CONTRA-INDICATIONS
Ketoacidosis - use of general anaesthesia (suspend metformin on the morning of surgery and restart when renal function returns to baseline)

CONTRA-INDICATIONS, FURTHER INFORMATION

Iodine-containing X-ray contrast media

Intravenous administration of iodinated contrast agents can cause renal failure, which can increase the risk of lactic acidosis with metformin. Suspend metformin prior to the test; restart no earlier than 48 hours after the test if renal function has returned to baseline.

CAUTIONS
Can provoke lactic acidosis

INTERACTIONS
Appendix 1 (antidiabetics).

SIDE-EFFECTS
Common or very common
Abdominal pain - anorexia - diarrhoea (usually transient) - nausea - taste disturbance - vomiting

Rare
Decreased vitamin-B₁₂ absorption - erythema - lactic acidosis (withdraw treatment) - pruritus - urticaria

FREQUENCY NOT KNOWN
Hepatitis

GASTRO-INTESTINAL EFFECTS
Gastro-intestinal side-effects are initially common with metformin, and may persist in some patients, particularly when very high doses are given. A slow increase in dose may improve tolerability.

PREGNANCY
Can be used in pregnancy for both pre-existing and gestational diabetes. Women with gestational diabetes should discontinue treatment after giving birth.

BREAST FEEDING
May be used during breast-feeding in women with pre-existing diabetes.

NATIONAL FUNDING/ACCESS DECISIONS
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (September 2009) that Glucophage® SR is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus in adult patients who are intolerant of standard-release metformin, and in whom the prolonged-release tablet allows the use of a dose of metformin not previously tolerated, or in patients for whom a once daily preparation offers a clinically significant benefit.

HEPATIC IMPAIRMENT
Withdraw if tissue hypoxia likely.

RENAL IMPAIRMENT
Use with caution in renal impairment - increased risk of lactic acidosis.

Lactic acidosis
Withdraw or interrupt treatment in those at risk of tissue hypoxia or sudden deterioration in renal function, such as those with dehydration, severe infection, shock, sepsis, acute heart failure, respiratory failure or hepatic impairment, or those who have recently had a myocardial infarction.

NICE (clinical guideline 87 (May 2009): Type 2 diabetes: The management of type 2 diabetes) recommends that the dose should be reviewed if eGFR less than

BNF 70
Dipeptidylpeptidase-4 inhibitors (glitins)

Alogliptin

**Drug action** Inhibits dipeptidylpeptidase-4 to increase insulin secretion and lower glucagon secretion.

**Indications and dose**
Type 2 diabetes as dual therapy in combination with either metformin, pioglitazone, a sulfonylurea, or insulin (when treatment with these drugs alone fails to achieve adequate glycaemic control), or as triple therapy in combination with metformin and either pioglitazone or insulin.

**By mouth**
- Adult: 25 mg once daily

Dose adjustments due to interactions
Dose of concomitant sulfonylurea or insulin may need to be reduced. Caution with use in combination with both metformin and pioglitazone—risk of hypoglycaemia (dose of metformin or pioglitazone may need to be reduced).

**Contra-indications** Ketoacidosis

**CAUTIONS** History of pancreatitis—not recommended in moderate to severe heart failure (limited experience).

**Interactions** → Appendix 1 (antidiabetics).

**Side-effects**
- Common or very common Abdominal pain, gastro-oesophageal reflux, headache, nasopharyngitis, pruritis, rash, upper respiratory tract infection
- Frequency not known Angioedema, hepatic impairment, pancreatitis, Stevens-Johnson syndrome, urticaria

**Side-effects, further information**
Pancreatitis Discontinue if symptoms of acute pancreatitis (persistent, severe abdominal pain).

**Allergy and cross-sensitivity** Contraindicated if history of serious hypersensitivity to dipeptidylpeptidase-4 inhibitors.

**Pregnancy** Manufacturer advises avoid—no information available.

**Breastfeeding** Avoid—present in milk in animal studies.

**Hepatic impairment** Manufacturer advises avoid in severe impairment—no information available.

**Renal impairment** Reduce dose to 12.5 mg once daily if eGFR 30–50 mL/minute/1.73 m². Reduce dose to 6.25 mg once daily if eGFR less than 30 mL/minute/1.73 m². Use with caution if eGFR less than 30 mL/minute/1.73 m².

**Monitoring requirements** Determine renal function before treatment and periodically thereafter.

**Medicinal forms**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- Vipdomet (Takeda UK Ltd) ▼
  - Alogliptin (as Alogliptin benzoate) 6.25 mg Vipdomet 6.25mg tablets | 28 tablet £26.60
  - Alogliptin (as Alogliptin benzoate) 12.5 mg Vipdomet 12.5mg tablets | 28 tablet £26.60
  - Alogliptin (as Alogliptin benzoate) 25 mg Vipdomet 25mg tablets | 28 tablet £26.60

Alogliptin with metformin

The properties listed below are those particular to the combination only. For the properties of the components please consider, alogliptin above, metformin hydrochloride p. 594.

**Indications and dose**
Type 2 diabetes mellitus not controlled by metformin alone or by metformin in combination with either pioglitazone or insulin.

**By mouth**
- Adult: 1 tablet twice daily, based on patient’s current metformin dose

**Interactions** Dose of concomitant sulfonylurea or insulin may need to be reduced. Caution with use in combination with both metformin and pioglitazone—risk of hypoglycaemia (dose of metformin or pioglitazone may need to be reduced).

**Medicinal forms**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- Vipdomet (Takeda UK Ltd) ▼
  - Alogliptin (as Alogliptin benzoate) 12.5 mg, Metformin hydrochloride 1 gram Vipdomet 12.5mg/1000mg tablets | 56 tablet £26.60

Linagliptin

**Drug action** Inhibits dipeptidylpeptidase-4 to increase insulin secretion and lower glucagon secretion.

**Indications and dose**
Type 2 diabetes mellitus as monotherapy (if metformin inappropriate), or in combination with metformin (when treatment with metformin alone fails to achieve adequate glycaemic control), or both metformin and a sulfonylurea (when dual therapy with these drugs fails to achieve adequate glycaemic control). Type 2 diabetes mellitus in combination with insulin (with or without metformin) when a stable dose of insulin has not provided adequate glycaemic control.

**By mouth**
- Adult: 5 mg once daily

Dose adjustments due to interactions
Dose of concomitant sulfonylurea or insulin may need to be reduced.

**Interactions** → Appendix 1 (antidiabetics).

**Side-effects**
- Uncommon Cough, nasopharyngitis
- Frequency not known Pancreatitis

**Side-effects, further information**
Pancreatitis Discontinue if symptoms of acute pancreatitis (persistent, severe abdominal pain).

**Pregnancy** Avoid—no information available.

**Breastfeeding** Avoid—present in milk in animal studies.

**National funding/access decisions**
Scottish medicines consortium (SMC) decisions
The Scottish medicines consortium has advised that linagliptin (Trajenta®) is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus as monotherapy when both metformin and a sulfonylurea are inappropriate (January 2013), and in combination with metformin when addition of a sulfonylurea is inappropriate (December 2011).

**Medicinal forms**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- Trajenta (Boehringer Ingelheim Ltd) ▼
  - Linagliptin 5 mg Trajenta 5mg tablets | 28 tablet £33.26
Linagliptin with metformin

The properties listed below are those particular to the combination only. For the properties of the components please consider, linagliptin p. 596, metformin hydrochloride p. 594.

INDICATIONS AND DOSE
Type 2 diabetes mellitus not controlled by metformin alone or by metformin in combination with either a sulfonylurea or insulin

BY MOUTH
> Adult: 1 tablet twice daily, based on patient’s current metformin dose

INTERACTIONS Dose of concomitant sulfonylurea or insulin may need to be reduced.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 21
> Jentadueto (Boehringer Ingelheim Ltd)

Linagliptin 2.5 mg, Metformin hydrochloride 850 mg Jentadueto
2.5mg/850mg tablets | 56 tablet pack £33.26
Linagliptin 2.5 mg, Metformin hydrochloride 1000 mg Jentadueto 2.5mg/1000mg tablets | 56 tablet pack £33.26

Saxagliptin

DRUG ACTION Inhibits dipeptidylpeptidase-4 to increase insulin secretion and lower glucagon secretion.

INDICATIONS AND DOSE
Type 2 diabetes mellitus as monotherapy (if metformin inappropriate), or in combination with metformin or a sulfonylurea (if metformin inappropriate), or pioglitazone (when treatment with either metformin or a sulfonylurea or pioglitazone fails to achieve adequate glycaemic control), and also in combination with both metformin and a sulfonylurea (when dual therapy with these drugs fails to achieve adequate glycaemic control) | Type 2 diabetes mellitus in combination with insulin (with or without metformin) when a stable dose of insulin has not provided adequate glycaemic control

BY MOUTH
> Adult: 5 mg once daily

Dose adjustments due to interactions Dose of concomitant sulfonylurea or insulin may need to be reduced.

CAUTIONS Elderly

INTERACTIONS → Appendix 1 (antidiabetics).

SIDE-EFFECTS
> Common or very common Dizziness · dyspepsia · fatigue · gastritis · gastroenteritis · headache · hypoglycaemia · myalgia · nasopharyngitis · peripheral oedema · sinusitis · upper respiratory tract infection · urinary tract infection · vomiting
> Uncommon Anaphylaxis · arthralgia · dyslipidaemia · erectile dysfunction · hypersensitivity reactions · hypertriglyceridaemia · pancreatitis
> Frequency not known Rash

SIDE-EFFECTS, FURTHER INFORMATION
pancreatitis Discontinue if symptoms of acute pancreatitis (persistent, severe abdominal pain).

ALLERGY AND CROSS-SENSITIVITY Contraindicated if patient has a history of serious hypersensitivity to dipeptidylpeptidase-4 inhibitors.

PREGNANCY Avoid unless essential—toxicity in animal studies.

Metformin with saxagliptin

The properties listed below are those particular to the combination only. For the properties of the components please consider, metformin hydrochloride p. 594, saxagliptin above.

INDICATIONS AND DOSE
Type 2 diabetes mellitus not controlled by metformin alone or by metformin in combination with either a sulfonylurea or insulin

BY MOUTH
> Adult: 1 tablet twice daily, based on patient’s current metformin dose

INTERACTIONS Dose of concomitant sulfonylurea or insulin may need to be reduced.

NATIONAL FUNDING/ACCESS DECISIONS
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised that saxagliptin (Onglyza®) is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes patients unable to achieve adequate glycaemic control with metformin and a sulfonylurea, as an alternative to existing dipeptidyl peptidase-4 inhibitors, when treatment with metformin and a sulfonylurea is inadequate (November 2013).

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
> Onglyza (AstraZeneca UK Ltd)
Saxagliptin (as Saxagliptin hydrochloride) 2.5 mg Onglyza 2.5mg tablets | 28 tablet pack £31.60 OT price = £31.60
Saxagliptin (as Saxagliptin hydrochloride) 5 mg Onglyza 5mg tablets | 28 tablet pack £31.60 OT price = £31.60

Diabetes mellitus 597

BREAST FEEDING Avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT Use with caution in moderate impairment. Avoid in severe impairment.

RENAL IMPAIRMENT Reduce dose to 2.5 mg once daily in moderate to severe impairment. Use with caution in severe impairment.

MONITORING REQUIREMENTS Determine renal function before treatment and periodically thereafter.

NATIONAL FUNDING/ACCESS DECISIONS
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised that Komboglyze® is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus in patients unable to achieve adequate glycaemic control with metformin alone and when the addition of a sulfonylurea is inappropriate.
Sitagliptin

- **DRUG ACTION** Inhibits dipeptidylpeptidase-4 to increase insulin secretion and lower glucagon secretion.

**INDICATIONS AND DOSE**
Type 2 diabetes mellitus as monotherapy (if metformin inappropriate), or in combination with both metformin and a sulfonylurea (if metformin inappropriate), or pioglitazone (when treatment with either metformin or a sulfonylurea or pioglitazone fails to achieve adequate glycaemic control), and also in combination with both metformin and a sulfonylurea (when dual therapy with these drugs fails to achieve adequate glycaemic control) | Type 2 diabetes mellitus in combination with both metformin and pioglitazone when dual therapy with these drugs fails to achieve adequate glycaemic control, and may also be used in combination with insulin (with or without metformin) when a stable dose of insulin has not provided adequate glycaemic control

**BY MOUTH**
- **Adult:** 100 mg once daily
- **Dose adjustments due to interactions**
  - Dose of concomitant sulfonylurea or insulin may need to be reduced.

**CONTRA-INDICATIONS** KETOACIDOSIS

**INTERACTIONS** → Appendix 1 (antidiabetics).

**SIDE-EFFECTS**
- **Common or very common** Gastro-intestinal disturbances - nasopharyngitis - pain - peripheral oedema - upper respiratory tract infection
- **Uncommon** Anorexia - dizziness - drowsiness - dry mouth - headache - hypoglycaemia - osteoarthritis
- **Frequency not known** Cutaneous vasculitis - pancreatitis - rash - Stevens-Johnson syndrome

**SIDE-EFFECTS, FURTHER INFORMATION**
Pancreatitis Discontinue if symptoms of acute pancreatitis (persistent, severe abdominal pain).

**PREGNANCY** Avoid — toxicity in animal studies.

**BREAST FEEDING** Avoid — present in milk in animal studies.

**RENAI IMPAIRMENT** Reduce dose to 50 mg once daily if eGFR 30–50 mL/minute/1.73 m². Reduce dose to 25 mg once daily if eGFR less than 30 mL/minute/1.73 m².

**NATIONAL FUNDING/ACCESS DECISIONS**
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (July 2008) that Janumet® is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus when the addition of a sulfonylurea to metformin is not appropriate; it is also accepted for use in NHS Scotland in combination with a sulfonylurea in patients inadequately controlled on maximum tolerated doses of metformin and a sulfonylurea.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Januvia** (Merck Sharp & Dohme Ltd) 25 mg Januvia 25mg tablets | 28 tablet | £3.26 07 price = £3.26
- **Sitagliptin (as Sitagliptin phosphate) 50 mg** Januvia 50mg tablets | 28 tablet | £3.26 07 price = £3.26
- **Sitagliptin (as Sitagliptin phosphate) 100 mg** Januvia 100mg tablets | 28 tablet | £3.26 07 price = £3.26

Vildagliptin

- **DRUG ACTION** Inhibits dipeptidylpeptidase-4 to increase insulin secretion and lower glucagon secretion.

**INDICATIONS AND DOSE**
Type 2 diabetes mellitus not controlled by metformin alone or by metformin in combination with either a sulfonylurea or pioglitazone or insulin

**BY MOUTH**
- **Adult:** 1 tablet twice daily

**INTERACTIONS** Dose of concomitant sulfonylurea or insulin may need to be reduced.

**NATIONAL FUNDING/ACCESS DECISIONS**
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (July 2008) that Janumet® is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus when the addition of a sulfonylurea to metformin is not appropriate; it is also accepted for use in NHS Scotland in combination with a sulfonylurea in patients inadequately controlled on maximum tolerated doses of metformin and a sulfonylurea.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Januvia** (Merck Sharp & Dohme Ltd) 25 mg Januvia 25mg tablets | 28 tablet | £3.26 07 price = £3.26
- **Vildagliptin hydrochloride 1 gram, Sitagliptin (as Sitagliptin phosphate) 50 mg** Janumet 50mg/1000mg tablets | 56 tablet [Pres] £33.26 07 price = £33.26

Metformin with sitagliptin

The properties listed below are those particular to the combination only. For the properties of the components please consider, metformin hydrochloride p. 594, sitagliptin above.
Metformin with vildagliptin

The properties listed below are those particular to the combination only. For the properties of the components please consider, metformin hydrochloride p. 594, vildagliptin p. 598.

INDICATIONS AND DOSE
Type 2 diabetes mellitus not controlled by metformin alone or by metformin in combination with either a sulfonylurea or insulin

INTERACTIONS
Dose of concomitant sulfonylurea or insulin may need to be reduced.

NATIONAL FUNDING/ACCESS DECISIONS
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium (SMC) Decisions (June 2008) that Eucreas® is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus in patients unable to achieve adequate glycaemic control with metformin alone or those already treated with vildagliptin and metformin as separate tablets.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS

EUCREAS (Novartis Pharmaceuticals UK Ltd)
Metformin hydrochloride 850 mg, Vildagliptin 50 mg
50mg/850mg tablets  | 60 tablet (PSN) £33.98 DT price = £33.98
Metformin hydrochloride 1 gram, Vildagliptin 50 mg
50mg/1000mg tablets  | 60 tablet (PSN) £33.98 DT price = £33.98

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

Exenatide

DRUG ACTION
Binds to, and activates, the GLP-1 (glucagon-like-peptide-1) receptor to increase insulin secretion, suppresses glucagon secretion, and slows gastric emptying.

INDICATIONS AND DOSE
Type 2 diabetes mellitus in combination with metformin or a sulfonylurea, or both, or with pioglitazone, or with both metformin and pioglitazone, in patients who have not achieved adequate glycaemic control with these drugs alone or in combination

BY SUBCUTANEOUS INJECTION USING IMMEDIATE-RELEASE MEDICINES
Adult: Initially 5 micrograms twice daily for at least 1 month, then increased if necessary up to 10 micrograms twice daily, dose to be taken within 1 hour before 2 main meals (at least 6 hours apart) by subcutaneous injection using modified-release medicines
Adult: 2 mg once weekly

BY SUBCUTANEOUS INJECTION USING MODIFIED-RELEASE MEDICINES
Adult: Initially 5 micrograms twice daily for at least 1 month, then increased if necessary up to 10 micrograms twice daily, dose to be taken within 1 hour before 2 main meals (at least 6 hours apart)
Dose adjustments due to interactions
Dose of concomitant sulfonylurea may need to be reduced.

PHARMACOKINETICS
Effect of modified-release exenatide injection (Bydureon®) may persist for 10 weeks after discontinuation.

CONTRA-INDICATIONS
Ketoacidosis · severe gastrointestinal disease

CAUTIONS
Elderly · may cause weight loss greater than 1.5 kg weekly · pancreatitis

INTERACTIONS
Appendix 1 (antidiabetics), Other drugs administered orally may need to be taken at least 1 hour before or 4 hours after exenatide injection, or taken with a meal when exenatide is not administered, to minimise possible interference with absorption.

SIDE-EFFECTS
Common or very common · Abdominal pain and distension · agitation · antibody formation · asthma · decreased appetite · diarrhoea · dizziness · dyspepsia · gastro-intestinal disturbances · gastro-oesophageal reflux disease · headache · hypoglycaemia · increased sweating · injection-site reactions · nausea · vomiting · weight loss
Uncommon · Pancreatitis
Rare · Alopecia
Very rare · Anaphylactic reactions
Frequency not known · Angioedema · constipation · dehydration · drowsiness · eructation · flatulence · pruritus · rash · renal impairment · taste disturbance · urticaria
Endocrine system

Exenatide modified-release for the treatment of type 2 diabetes mellitus (February 2012) NICE TA248

Modified-release exenatide in triple therapy regimens (in combination with metformin and a sulfonylurea, or metformin and a thiazolidinedione) is recommended for treatment of type 2 diabetes mellitus in combination with metformin or pioglitazone as a third-line pre-insulin treatment option. Some oral medications should be taken at least 30 minutes before or 2 hours after exenatide injection—consult product literature for details.

NICE technology appraisals (TAs)

Exenatide modified-release for the treatment of type 2 diabetes mellitus (February 2012) NICE TA248

Modified-release exenatide in triple therapy regimens (in combination with metformin or a sulfonylurea, or metformin and a thiazolidinedione) is recommended for treatment of type 2 diabetes mellitus with these drugs alone or in combination with metformin and a thiazolidinedione when basal insulin or both metformin and pioglitazone when dual therapy with these drugs fails to achieve adequate glycaemic control. Treatment with modified-release exenatide in a triple therapy regimen should be continued only if HbA1c concentration is reduced by at least 1 percentage point and a weight loss of at least 3% is achieved within 6 months of starting treatment.

Modified-release exenatide in dual therapy regimens (in combination with metformin or a sulfonylurea) is recommended only if:
- treatment with metformin or a sulphonylurea is contraindicated or not tolerated, and
- treatment with a thiazolidinedione and dipeptidylpeptidase-4 inhibitors is contra-indicated or not tolerated.

Modified-release exenatide in a dual therapy regimen should be continued only if HbA1c concentration is reduced by at least 1 percentage point within 6 months of starting treatment. www.nice.org.uk/TA248

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (June 2007) that standard-release exenatide (Byetta®) is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes in combination with metformin or sulfonylurea (or both), as an alternative to treatment with insulin in patients where treatment with metformin or sulfonylurea (or both) at maximally tolerated doses has been inadequate, and treatment with insulin would be the next option.

Byetta (AstraZeneca UK Ltd) Exenatide 250 microgram per 1 ml Byetta 10micrograms/0.04ml solution for injection 2.4ml pre-filled disposable devices | 1 pre-filled disposable injection (P) £68.24 DT price = £68.24

Byetta 5micrograms/0.2ml solution for injection 1.2ml pre-filled disposable devices | 1 pre-filled disposable injection (P) £68.24 DT price = £68.24

Bydureon (AstraZeneca UK Ltd) Exenatide 2 mg Bydureon 2mg powder and solvent for suspension for injection vials | 4 vial (P) £73.36

Bydureon 2mg powder and solvent for suspension for injection pre-filled pen | 4 pre-filled disposable injection (P) £73.36

Liraglutide

Drug action

Binds to, and activates, the GLP-1 (glucagon-like peptide-1) receptor to increase insulin secretion, suppresses glucagon secretion, and slows gastric emptying.

Indications and dose

Type 2 diabetes mellitus in combination with metformin or a sulfonylurea, or both, in patients who have not achieved adequate glycaemic control with these drugs alone or in combination | Type 2 diabetes mellitus in combination with basal insulin or both metformin and pioglitazone when dual therapy with these drugs fails to achieve adequate glycaemic control.

By subcutaneous injection

Adult: Initially 0.6 mg once daily for at least 1 week, then increased to 1.2 mg once daily for at least 1 week, then increased if necessary up to 1.8 mg once daily.

Dose adjustments due to interactions

Dose of concomitant insulin or sulfonylurea may need to be reduced.

Contra-indications

Diabetic gastroparesis - inflammatory bowel disease - ketoacidosis - moderate to severe congestive heart failure—no information available

Caution

Asymptomatic left ventricular dysfunction - history of pancreatitis - mild congestive heart failure—limited experience - thyroid disease

Interactions

Appendix 1 (antidiabetics).

Side-effects

Common or very common Abdominal pain and distension - bronchitis - constipation - decreased appetite - diarrhoea - dizziness - dyspepsia - flatulence - gastritis - gastrointestinal disturbances - gastro-oesophageal reflux disease - headache - hypoglycaemia - injection site reactions - malaise - nasopharyngitis - nausea - tachycardia - vomiting

Uncommon Acute renal failure - dehydration - renal impairment
Lixisenatide

**DRUG ACTION**  Binds to, and activates, the GLP-1 (glucagon-like peptide-1) receptor to increase insulin secretion, suppresses glucagon secretion, and slows gastric emptying.

**SIDE-EFFECTS, FURTHER INFORMATION**

<table>
<thead>
<tr>
<th>Common or very common</th>
<th>Acute pancreatitis</th>
<th>Discontinue if symptoms of acute pancreatitis (persistent, severe abdominal pain).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PREGNANCY</strong></td>
<td>Avoid—toxicity in animal studies.</td>
<td></td>
</tr>
<tr>
<td><strong>BREAST FEEDING</strong></td>
<td>Avoid—no information available.</td>
<td></td>
</tr>
<tr>
<td><strong>HEPATIC IMPAIRMENT</strong></td>
<td>Avoid—limited experience.</td>
<td></td>
</tr>
<tr>
<td><strong>RENAL IMPAIRMENT</strong></td>
<td>Avoid if eGFR less than 30 mL/minute/1.73 m².</td>
<td></td>
</tr>
<tr>
<td><strong>PATIENT AND CARER ADVICE</strong></td>
<td>Patients or carers should be given advice on how to administer lixisenatide injection. Acute pancreatitis Patients should be told how to recognise signs and symptoms of acute pancreatitis and advised to seek immediate medical attention if symptoms such as persistent, severe abdominal pain develop.</td>
<td></td>
</tr>
<tr>
<td><strong>NATIONAL FUNDING/ACCESS DECISIONS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NICE technology appraisals (TAs)</strong></td>
<td>Liraglutide for the treatment of type 2 diabetes mellitus (October 2010) NICE TA203</td>
<td></td>
</tr>
<tr>
<td>Liraglutide in triple therapy regimens (in combination with metformin and a sulfonylurea, or metformin and a thiazolidinedione) is recommended for the treatment of type 2 diabetes, only when glycaemic control is inadequate, and the patient has;</td>
<td></td>
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</tr>
<tr>
<td>a body mass index of 35 kg/m² or over and is of European descent (with appropriate adjustment for other ethnic groups) and weight-related psychological or medical problems, or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a body mass index of less than 35 kg/m², and insulin would be unacceptable for occupational reasons or weight loss would benefit other significant obesity-related comorbidities.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment with lixisenatide in a triple therapy regimen should be continued only if HbA₁c concentration is reduced by at least 1 percentage point and a weight loss of at least 3% is achieved within 6 months of starting treatment. Liraglutide in dual therapy regimens (in combination with metformin or a sulfonylurea) is recommended only if:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment with metformin or a sulfonylurea is contraindicated or not tolerated, and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment with thiazolidinediones and dipeptidylpeptidase-4 inhibitors is contra-indicated or not tolerated. Liraglutide, in combination with metformin or a sulfonylurea should be continued only if HbA₁c concentration is reduced by at least 1 percentage point within 6 months of starting treatment. Liraglutide 1.8 mg daily is not recommended.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MEDICINAL FORMS**

- Liraglutide 6 mg per 1 ml Liraglutide 6mg/ml solution for injection 3ml pre-filled disposable devices | 2 pre-filled disposable injection | no price available | 3 pre-filled disposable injection | no price available |
- Victoza (Novo Nordisk Ltd) Liraglutide 6 mg per 1 ml Victoza 6mg/ml solution for injection 3ml pre-filled pen | 2 pre-filled disposable injection | £78.48 | 3 pre-filled disposable injection | £117.72 |

**Lixisenatide**

**DRUG ACTION**  Binds to, and activates, the GLP-1 (glucagon-like peptide-1) receptor to increase insulin secretion, suppresses glucagon secretion, and slows gastric emptying.

**INDICATIONS AND DOSE**

Type 2 diabetes mellitus in combination with oral antidiabetic drugs (e.g. metformin, pioglitazone, or a sulfonylurea) or basal insulin, or both, when adequate glycaemic control has not been achieved with these drugs by subcutaneous injection.

- Adult: Initially 10 micrograms once daily for 14 days, then increased to 20 micrograms once daily, dose to be taken within 1 hour before the first meal of the day or the evening meal.

**Dose adjustments due to interactions**

Dose of concomitant sulfonylurea or insulin may need to be reduced.

**CONTRA-INDICATIONS**  Ketoacidosis · severe gastro-intestinal disease

**INTERACTIONS**  Appendix (antidiabetics).

Other drugs administered orally may need to be taken at least 1 hour before or 4 hours after lixisenatide injection, or taken with a meal when lixisenatide is not administered, to minimise possible interference with absorption.

**SIDE-EFFECTS**

- Diarrhoea · dizziness · drowsiness · dyspepsia · headache · hypoglycaemia · injection-site reactions · nausea · palpitation · vomiting

- Tachycardia · urticaria

**SIDE-EFFECTS, FURTHER INFORMATION**

**RENAL IMPAIRMENT**  Use with caution if eGFR 30–50 mL/minute/1.73 m². Avoid if eGFR less than 30 mL/minute/1.73 m²—no information available.

**PATIENT AND CARER ADVICE**

Missed doses If a dose is missed, inject within 1 hour before the next meal—do not administer after a meal. Some oral medications should be taken at least 1 hour before or 4 hours after lixisenatide injection—consult product literature for details.

**NATIONAL FUNDING/ACCESS DECISIONS**

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (August 2013) that lixisenatide (*Lyxumia®*) is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes in combination with oral antidiabetic drugs or basal insulin (or both), when adequate glycaemic control has not been achieved with these drugs; use is restricted to patients in whom a GLP-1 agonist is appropriate, as an alternative to an existing GLP-1 agonist (exenatide or lixisenatide).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

**LIRAGLUTIDE (Non-proprietary)**

- Liraglutide 6 mg per 1 ml Liraglutide 6mg/ml solution for injection 3ml pre-filled disposable devices | 2 pre-filled disposable injection | no price available | 3 pre-filled disposable injection | no price available |
- Victoza (Novo Nordisk Ltd) Liraglutide 6 mg per 1 ml Victoza 6mg/ml solution for injection 3ml pre-filled pen | 2 pre-filled disposable injection | £78.48 | 3 pre-filled disposable injection | £117.72 |

**Lixisenatide 50 microgram per 1 ml**

- Lyxumia 10micrograms/0.2ml solution for injection 3ml pre-filled pen | 1 pre-filled disposable injection | £27.07 |

**Lixisenatide 100 microgram per 1 ml**

- Lyxumia 20micrograms/0.2ml solution for injection 3ml pre-filled pen | 1 pre-filled disposable injection | no price available | 2 pre-filled disposable injection | £54.14 |

**Very rare** Acute pancreatitis

**Frequency not known** Goitre · increased blood calcitonin · thyroid neoplasm
INSULINS

**Insulins**

- **SIDE-EFFECTS**
  - **Common or very common** Fat hypertrophy at injection site · local reactions at injection site · transient oedema
  - **Rare** Hypersensitivity reactions · rash · urticaria
  - **Overdose** Overdose causes hypoglycaemia.

- **PREGNANCY** During pregnancy, insulin requirements may alter and doses should be assessed frequently by an experienced diabetes physician. The dose of insulin generally needs to be increased in the second and third trimesters of pregnancy.

- **BREAST FEEDING** During breast-feeding, insulin requirements may alter and doses should be assessed frequently by an experienced diabetes physician.

- **HEPATIC IMPAIRMENT** Insulin requirements may be decreased in patients with hepatic impairment.

- **RENAL IMPAIRMENT** Insulin requirements may decrease in patients with renal impairment and therefore dose reduction may be necessary. The compensatory response to hypoglycaemia is impaired in renal impairment.

- **MONITORING REQUIREMENTS**
  - Many patients now monitor their own blood-glucose concentrations; all carers and children need to be trained to do this.
  - Since blood-glucose concentration varies substantially throughout the day, ‘normoglycaemia’ cannot always be achieved throughout a 24-hour period without causing damaging hypoglycaemia.
  - It is therefore best to recommend that patients should maintain a blood-glucose concentration of between 4 and 9 mmol/litre for most of the time (4–7 mmol/litre before meals and less than 9 mmol/litre after meals).
  - While accepting that occasionally, for brief periods, the blood-glucose concentration will be above these values; strenuous efforts should be made to prevent it from falling below 4 mmol/litre. Patients using multiple injection regimens should understand how to adjust their insulin dose according to their carbohydrate intake. With fixed-dose insulin regimens, the carbohydrate intake needs to be regulated, and should be distributed throughout the day to match the insulin regimen. The injection site should
  - **DIRECTIONS FOR ADMINISTRATION** Insulin is generally given by subcutaneous injection; the injection site should be rotated to prevent lipodystrophy. Injection devices (‘pens’), which hold the insulin in a cartridge and meter the required dose, are convenient to use. Insulin syringes (for use with needles) are required for insulins not available in cartridge form, but are less popular with children and carers. For intensive insulin regimens multiple subcutaneous injections (3 or more times daily) are usually recommended.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Units The word ‘unit’ should not be abbreviated. Show container to patient or carer and confirm the expected version is dispensed.

- **PATIENT AND CARER ADVICE** Drivers need to be particularly careful to avoid hypoglycaemia and should be warned of the problems.

Insulin Passport Insulin Passports and patient information booklets should be offered to patients receiving insulin. The Insulin Passport provides a record of the patient’s current insulin preparations and contains a section for emergency information. The patient information booklet provides advice on the safe use of insulin. They are available for purchase from:

- 3M Security Print and Systems Limited
- Gorse Street, Chadderton
- Oldham OL9 9QH
- 0845 610 1112

GP practices can obtain supplies through their Local Area Team stores.

- NHS Trusts can order supplies from www.nhsforms.co.uk or by emailing nhsforms@mmm.com. Further information is available at www.npsa.nhs.uk.

Hypoglycaemia Hypoglycaemia is a potential problem with insulin therapy. All patients must be carefully instructed on how to avoid it; this involves appropriate adjustment of insulin type, dose and frequency together with suitable timing and quantity of meals and snacks.

Biphasic insulin aspart

(Intermediate-acting insulin)

**INDICATIONS AND DOSE**

**Diabetes mellitus**

- **BY SUBCUTANEOUS INJECTION**
  - **Child**: Administer dose up to 10 minutes before or soon after a meal, according to requirements
  - **Adult**: Administer dose up to 10 minutes before or soon after a meal, according to requirements

- **INTERACTIONS** → Appendix 1 (antidiabetics).

- **SIDE-EFFECTS** Protamine may cause allergic reactions.

- **PRESCRIBING AND DISPENSING INFORMATION** Check product container—the proportions of the two components should be checked carefully (the order in which the proportions are stated may not be the same in other countries).

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**

- NovoMix 30 FlexPen (Novo Nordisk Ltd) Insulin aspart 30 unit per 1 ml, Insulin aspart (as insulin aspart protamine) 70 unit per 1 ml NovoMix 30 FlexPen 100units/ml suspension for injection 3ml pre-filled pen | 5 pre-filled disposable injection (£59) £29.89
- NovoMix 30 Penfill (Novo Nordisk Ltd) Insulin aspart 30 unit per 1 ml, Insulin aspart (as Insulin aspart protamine) 70 unit per 1 ml NovoMix 30 Penfill 100units/ml suspension for injection 3ml cartridges | 5 cartridge (£59) £28.79

Biphasic insulin lispro

(Intermediate-acting insulin)

**INDICATIONS AND DOSE**

**Diabetes mellitus**

- **BY SUBCUTANEOUS INJECTION**
  - **Child**: Administer up to 15 minutes before or soon after a meal, according to requirements
  - **Adult**: Administer up to 15 minutes before or soon after a meal, according to requirements

- **CAUTIONS** Children under 12 years (use only if benefit likely compared to soluble insulin)

- **INTERACTIONS** → Appendix 1 (antidiabetics).

- **SIDE-EFFECTS** Protamine may cause allergic reactions.

- **PRESCRIBING AND DISPENSING INFORMATION** Check product container—the proportions of the two components should be checked carefully (the order in
which the proportions are stated may not be the same in other countries).

- **MEDICINAL FORMS**
  
  There can be variation in the licensing of different medicines containing the same drug.

  **Suspension for injection**
  
  - **Humalog Mix25** (Eli Lilly and Company Ltd)
    
    Insulin lispro 25 unit per 1 ml, Insulin lispro (as Insulin lispro protamine) 75 unit per 1 ml, Humalog Mix25 100 units/ml suspension for injection 10 ml vials | 5 vials (PFS) £16.61
  
  - **Humalog Mix25 KwikPen** (Eli Lilly and Company Ltd)
    
    Insulin lispro 25 unit per 1 ml, Insulin lispro (as Insulin lispro protamine) 75 unit per 1 ml, Humalog Mix25 KwikPen 100 units/ml suspension for injection 3 ml pre-filled pen | 5 pre-filled disposable injection (PFS) £29.46
  
  - **Humalog Mix50** (Eli Lilly and Company Ltd)
    
    Insulin lispro 50 unit per 1 ml, Insulin lispro (as Insulin lispro protamine) 50 unit per 1 ml, Humalog Mix50 100 units/ml suspension for injection 3 ml cartridges | 5 cartridge (PFS) £29.46
  
  - **Humalog Mix50 KwikPen** (Eli Lilly and Company Ltd)
    
    Insulin lispro 50 unit per 1 ml, Insulin lispro (as Insulin lispro protamine) 50 unit per 1 ml, Humalog Mix50 KwikPen 100 units/ml suspension for injection 3 ml pre-filled pen | 5 pre-filled disposable injection (PFS) £30.98

  **Biphasic isophane insulin**

  *(Biphasic Isophane Insulin Injection–intermediate acting)*

  **INDICATIONS AND DOSE**

  **Diabetes mellitus**

  - **BY SUBCUTANEOUS INJECTION**
    
    - **Child:** According to requirements
    - **Adult:** According to requirements

  - **INTERACTIONS** → Appendix 1 (antidiabetics).
  
  - **SIDE-EFFECTS**

    Protamine may cause allergic reactions.

  - **PRESCRIBING AND DISPENSING INFORMATION**

    A sterile buffered suspension of either porcine or human insulin complexed with protamine sulfate (or another suitable protamine) in a solution of insulin of the same species. Check product container—the proportions of the two components should be checked carefully (the order in which the proportions are stated may not be the same in other countries).

  - **MEDICINAL FORMS**

    There can be variation in the licensing of different medicines containing the same drug.

  **Suspension for injection**

  - **Humulin M3** (Eli Lilly and Company Ltd)
    
    Insulin human (as Insulin isophane human) 70 unit per 1 ml, Insulin human (as insulin soluble human) 30 unit per 1 ml, Humulin M3 100 units/ml suspension for injection 3 ml cartridges | 5 cartridge (PFS) £19.08
  
  - **Humulin M3 KwikPen** (Eli Lilly and Company Ltd)
    
    Insulin human (as Insulin isophane human) 70 unit per 1 ml, Insulin human (as insulin soluble human) 30 unit per 1 ml, Humulin M3 KwikPen 100 units/ml suspension for injection 3 ml pre-filled pen | 5 pre-filled disposable injection (PFS) £21.70
  
  - **Hypurin Porcine 30/70 Mix** (Wockhardt UK Ltd)
    
    Insulin porcine (as Insulin isophane porcine) 70 unit per 1 ml, Insulin porcine (as insulin soluble porcine) 30 unit per 1 ml, Hypurin Porcine 30/70 Mix 100 units/ml suspension for injection 3 ml cartridges | 5 cartridge (PFS) £37.80
  
  - **Insunan Comb 15** (Sanofi)
    
    Insulin human (as Insulin isophane human) 85 unit per 1 ml, Insulin human (as insulin soluble human) 15 unit per 1 ml, Insunan Comb 15 100 units/ml suspension for injection 3 ml cartridges | 5 cartridge (PFS) £17.50
  
  - **Insunan Comb 25** (Sanofi)
    
    Insulin human (as insulin isophane human) 75 unit per 1 ml, Insulin human (as insulin soluble human) 25 unit per 1 ml, Insunan Comb 25 100 units/ml suspension for injection 5 ml vials | 1 vial (PFS) £5.61

**Diabetes mellitus**

- **BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION**

- **BY INTRAVENOUS INJECTION**

- **Adult:** According to requirements

  **Diabetic ketoacidosis | Diabetes during surgery**

- **Adult:** (consult local protocol)

**INTERACTIONS**

- Appendix 1 (antidiabetics).

**DIRECTIONS FOR ADMINISTRATION**

Short-acting injectable insulins can be given by continuous subcutaneous infusion using a portable infusion pump. This device delivers a continuous basal insulin infusion and patient-activated bolus doses at meal times. This technique can be useful for patients who suffer recurrent hypoglycaemia or marked morning rise in blood-glucose concentration despite optimised multiple-injection regimens. Patients on subcutaneous insulin infusion must be highly motivated, able to monitor their blood-glucose concentration, and have expert training, advice and supervision from an experienced healthcare team. Some insulin preparations are not recommended for use in subcutaneous insulin infusion pumps—may precipitate in catheter or needle—consult product literature.

For intravenous infusion give continuously in Sodium chloride 0.9%. Adsorbed to some extent by plastic infusion set; ensure insulin is not injected into ‘dead space’ of injection port of the infusion bag.

- **PRESCRIBING AND DISPENSING INFORMATION**

  A sterile solution of insulin (i.e. bovine or porcine) or of human insulin; pH 6.6–8.0.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (type 1) (July 2008) NICE TA151

Continuous subcutaneous insulin infusion is recommended as an option in adults and children over 12 years with type 1 diabetes:

- who suffer repeated or unpredictable hypoglycaemia, whilst attempting to achieve optimal glycaemic control with multiple-injection regimens, or

- whose glycaemic control remains inadequate (HbA1c over 8.5% [69 mmol/mol]) despite optimised multiple-injection regimens (including the use of long-acting insulin analogues where appropriate).

Continuous subcutaneous insulin infusion is also recommended as an option for children under 12 years with type 1 diabetes for whom multiple-injection regimens are considered impractical or inappropriate. Children on insulin pumps should undergo a trial of

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**Insulin (Insulin Injection; Neutral Insulin; Soluble Insulin)**

**INDICATIONS AND DOSE**

**Diabetes mellitus**

- **BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION**

- **BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION**

- **Adult:** According to requirements

- **Diabetic ketoacidosis | Diabetes during surgery**

- **Adult:** (consult local protocol)
multiple-injection therapy between the ages of 12 and 18 years. www.nice.org.uk/TA151

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

**Solution for injection**

- **Actrapid (Novo Nordisk Ltd)**
  - Insulin human (as insulin soluble human) 100 unit per 1 ml
  - Insulin human (as insulin soluble human) 100 unit per 1 ml
  - Hypurin Bovine Neutral (Wockhardt UK Ltd)
  - Insulin porcine (as insulin soluble porcine) 100 unit per 1 ml
  - Insulin human (as insulin soluble human) 100 unit per 1 ml
  - Hypurin Bovine Neutral (Wockhardt UK Ltd)
  - Insulin porcine (as insulin soluble porcine) 100 unit per 1 ml
  - Insulin human (as insulin soluble human) 100 unit per 1 ml

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (type 1) (July 2008) NICE TA151

Continuous subcutaneous insulin infusion is recommended as an option in adults and children over 12 years with type 1 diabetes:

- who suffer repeated or unpredictable hypoglycaemia, whilst attempting to achieve optimal glycaemic control with multiple-injection regimens, or
- whose glycaemic control remains inadequate (HbA1c over 8.5% [69 mmol/mol]) despite optimised multiple-injection regimens (including the use of long-acting insulin analogues where appropriate).

Continuous subcutaneous insulin infusion is also recommended as an option for children under 12 years with type 1 diabetes for whom multiple-injection regimens are considered impractical or inappropriate.

Children on insulin pumps should undergo a trial of multiple-injection therapy between the ages of 12 and 18 years. www.nice.org.uk/TA151

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **NovoRapid (Novo Nordisk Ltd)**
  - Insulin aspart 100 unit per 1 ml
  - Insulin aspart 100 unit per 1 ml
  - Insulin aspart 100 unit per 1 ml
  - Insulin aspart 100 unit per 1 ml
  - Insulin aspart 100 unit per 1 ml

**INDICATIONS AND DOSE**

**Diabetes mellitus**

**BY SUBCUTANEOUS INJECTION**

- Adult: Administer immediately before meals or when necessary shortly after meals, according to requirements

**BY SUBCUTANEOUS INFUSION OR BY INTRAVENOUS INFUSION OR BY INTRAVENOUS INJECTION**

- Child 2-17 years: According to requirements
- Adult: According to requirements

**INTERACTIONS** → Appendix 1 (antidiabetics).

**PREGNANCY** Not known to be harmful—may be used during pregnancy.

**BREAST FEEDING** Not known to be harmful—may be used during lactation.

**DIRECTIONS FOR ADMINISTRATION** Short-acting injectable insulins can be given by continuous subcutaneous infusion using a portable infusion pump. This device delivers a continuous basal insulin infusion and patient-activated bolus doses at meal times. This technique can be useful for patients who suffer recurrent hypoglycaemia or marked morning rise in blood-glucose concentration despite optimised multiple-injection regimens. Patients on subcutaneous insulin infusion must be highly motivated, able to monitor their blood-glucose concentration, and have expert training, advice and supervision from an experienced healthcare team.

- In adults For intravenous infusion, give continuously in Glucose 5% or Sodium chloride 0.9%; dilute to 0.05-1 unit/ml with infusion fluid; adsorbed to some extent by plastics of infusion set.
- In children For intravenous infusion, dilute to a concentration of 0.05–1 unit/ml with Glucose 5% or Sodium Chloride 0.9% and mix thoroughly; insulin may be adsorbed by plastics, flush giving set with 5 mL of infusion fluid containing insulin.

**Prescribing and dispensing information** Insulin degludec (Tresiba®) is available in strengths of 100 units/ml (allows 1-unit dose adjustment) and 200 units/ml (allows 2-unit dose adjustment)—ensure correct strength prescribed.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Tresiba FlexTouch (Novo Nordisk Ltd)**
  - Insulin human (as Insulin degludec) 100 unit per 1 ml
  - Insulin human (as Insulin degludec) 100 unit per 1 ml
  - Insulin human (as Insulin degludec) 100 unit per 1 ml

**INDICATIONS AND DOSE**

**Diabetes mellitus**

**BY SUBCUTANEOUS INJECTION**

- Adult: Dose to be given according to requirements

**INTERACTIONS** → Appendix 1 (antidiabetics).

**PREGNANCY** Evidence of the safety of long-acting insulin analogues in pregnancy is limited, therefore isophane insulin is recommended where longer-acting insulins are needed; insulin detemir may also be considered.

**Prescribing and dispensing information** Insulin degludec (Tresiba®) is available in strengths of 100 units/ml (allows 1-unit dose adjustment) and 200 units/ml (allows 2-unit dose adjustment)—ensure correct strength prescribed.
Insulin degludec with liraglutide

The properties listed below are those particular to the combination only. For the properties of the components please consider, insulin degludec p. 604, liraglutide p. 600.

INDICATIONS AND DOSE
As add-on to oral antidiabetics in type 2 diabetes mellitus not controlled by oral antidiabetics alone or by oral antidiabetics in combination with basal insulin

BY SUBCUTANEOUS INJECTION

- **Adult:** Initially 10 dose-steps once daily, adjusted according to response; maximum 50 dose-steps per day

When transferring from basal insulin in type 2 diabetes mellitus not controlled by oral antidiabetics alone or by oral antidiabetics in combination with basal insulin

BY SUBCUTANEOUS INJECTION

- **Adult:** Initially 16 dose-steps once daily, adjusted according to response; maximum 50 dose-steps per day

INTERACTIONS
- Dose of concomitant sulfonylurea may need to be reduced.

PATIENT AND CARER ADVICE
- Counselling advised on administration. Show container to patient and confirm that patient is expecting the version dispensed.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

- Xultophy (Novo Nordisk Ltd)

Insulin human (as insulin degludec) 100 unit per 1 ml, liraglutide 3.6 mg per 1 ml Xultophy 100units/ml / 3.6mg/ml solution for injection 3ml pre-filled pen | 5 pre-filled disposable injection | £159.22

Insulin degludec with liraglutide

(Recombinant human insulin analogue—long acting)

INDICATIONS AND DOSE
Diabetes mellitus

BY SUBCUTANEOUS INJECTION

- **Child 2-17 years:** According to requirements
- **Adult:** According to requirements

INTERACTIONS
- Appendix 1 (antidiabetics).

PREGNANCY
- Evidence of the safety of long-acting insulin analogues in pregnancy is limited, therefore isophane insulin is recommended where longer-acting insulins are needed; insulin detemir may also be considered.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

- Levemir FlexPen (Novo Nordisk Ltd)

Insulin human (as insulin detemir) 100 unit per 1 ml Levemir FlexPen 100units/ml solution for injection 3ml pre-filled pen | 5 pre-filled disposable injection | £42.00

Insulin detemir

(Recombinant human insulin analogue—long acting)

INDICATIONS AND DOSE
Diabetes mellitus

BY SUBCUTANEOUS INJECTION

- **Child 6-17 years:** Administrator immediately before meals or when necessary shortly after meals, according to requirements
- **Adult:** Administrator immediately before meals or when necessary shortly after meals, according to requirements

INTERACTIONS
- Appendix 1 (antidiabetics).

DIRECTIONS FOR ADMINISTRATION
- Short-acting injectable insulins can be given by continuous subcutaneous infusion using a portable infusion pump. This device
Endocrine system

Diabetes mellitus and hypoglycaemia

Delivers a continuous basal insulin infusion and patient-activated bolus doses at meal times. This technique can be useful for patients who suffer recurrent hypoglycaemia or marked morning rise in blood-glucose concentration despite optimised multiple-injection regimens. Patients on subcutaneous insulin infusion must be highly motivated, able to monitor their blood-glucose concentration, and have expert training, advice and supervision from an experienced healthcare team.

In adults For intravenous infusion (Apidra®), give continuously in Sodium chloride 0.9%; dilute to 1 unit/mL with infusion fluid; use a co-extruded polyelefin/polyamide plastic infusion bag with a dedicated infusion line.

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (type 1) (July 2008) NICE TAI51

Continuous subcutaneous insulin infusion is recommended as an option in adults and children over 12 years with type 1 diabetes:
- who suffer repeated or unpredictable hypoglycaemia, whilst attempting to achieve optimal glycaemic control with multiple-injection regimens,
- whose glycaemic control remains inadequate (HbA1c over 8.5% [65 mmol/mol]) despite optimised multiple-injection regimens (including the use of long-acting insulin analogues where appropriate).

Continuous subcutaneous insulin infusion is also recommended as an option for children under 12 years with type 1 diabetes for whom multiple-injection regimens are considered impractical or inappropriate.

In adults For intravenous infusion give continuously in Glucose 5% or Sodium chloride 0.9%. Adsorbed to some extent by plastics of infusion set.

In children For intravenous infusion, dilute to a concentration of 0.1–1 unit/mL with Glucose 5% or Sodium Chloride 0.9% and mix thoroughly; insulin may be adsorbed by plastics, flush giving set with 5 mL of infusion fluid containing insulin.

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (October 2008) that Apidra® is accepted for restricted use within NHS Scotland for the treatment of adults and children over 6 years with diabetes mellitus in whom the use of a short-acting insulin analogue is appropriate.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

- Apidra (Sanofi)
  - Insulin lispro 100 unit per 1 mL Apidra 100units/mL solution for injection 10ml vials | vial | £16.00
  - Apidra 100units/mL solution for injection 3ml cartridges | 5 cartridge | £28.30
- Apidra SoloStar (Sanofi)
  - Insulin lispro 100 unit per 1 mL Apidra 100units/mL solution for injection 3ml pre-filled SoloStar pen | 5 pre-filled disposable injection | £28.30

Insulin lispro

(Recombinant human insulin analogue)

INDICATIONS AND DOSE

Diabetes mellitus

BY SUBCUTANEOUS INJECTION
- Child 2-17 years: Administer shortly before meals or when necessary shortly after meals, according to requirements
- Adult: Administer shortly before meals or when necessary shortly after meals, according to requirements

BY SUBCUTANEOUS INFUSION OR BY INTRAVENOUS INFUSION OR BY INTRAVENOUS INJECTION
- Child 2-17 years: According to requirements

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (type 1) (July 2008) NICE TAI51

Continuous subcutaneous insulin infusion is recommended as an option in adults and children over 12 years with type 1 diabetes:
- who suffer repeated or unpredictable hypoglycaemia, whilst attempting to achieve optimal glycaemic control with multiple-injection regimens,
- whose glycaemic control remains inadequate (HbA1c over 8.5% [65 mmol/mol]) despite optimised multiple-injection regimens (including the use of long-acting insulin analogues where appropriate).

Continuous subcutaneous insulin infusion is also recommended as an option for children under 12 years with type 1 diabetes for whom multiple-injection regimens are considered impractical or inappropriate.

Children on insulin pumps should undergo a trial of multiple-injection therapy between the ages of 12 and 18 years. www.nice.org.uk/TA151

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (October 2008) that Apidra® is accepted for restricted use within NHS Scotland for the treatment of adults and children over 6 years with diabetes mellitus in whom the use of a short-acting insulin analogue is appropriate.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

- Humalog (Eli Lilly and Company Ltd)
  - Insulin lispro 100 unit per 1 mL Humalog 100units/mL solution for injection 10ml vials | vial | £16.01
  - Humalog 100units/mL solution for injection 3ml cartridges | 5 cartridge | £28.31
- Humalog KwikPen (Eli Lilly and Company Ltd)
  - Insulin lispro 100 unit per 1 mL Humalog KwikPen 100units/mL solution for injection 3ml pre-filled pen | 5 pre-filled disposable injection | £58.92
### Insulin zinc suspension

**Indications and Dose**

**Diabetes mellitus**

- **By subcutaneous injection**
  - Child: According to requirements
  - Adult: According to requirements

**Interactions** → Appendix 1 (antidiabetics).

**Pregnancy**

Evidence of the safety of long-acting insulin analogues in pregnancy is limited, therefore isophane insulin below is recommended where longer-acting insulins are needed; insulin detemir p. 605 may also be considered.

**Prescribing and Dispensing Information**

A sterile neutral suspension of bovine and/or porcine insulin or of human insulin in the form of a complex obtained by the addition of a suitable zinc salt; consists of rhombohedral crystals (10–40 microns) and of particles of no uniform shape (not exceeding 2 microns).

**Medicinal Forms**

There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**

- **Humulin Bovine Lente (Wockhardt UK Ltd)**
  - Insulin bovine (as insulin zinc suspension mixed bovine) 100 unit per 1 ml
  - **Hypurin Bovine Lente 100 units/ml suspension for injection 10 ml vials** | 1 vial £27.72

### Isophane insulin

**Indications and Dose**

**Diabetes mellitus**

- **By subcutaneous injection**
  - Child: According to requirements
  - Adult: According to requirements

**Interactions** → Appendix 1 (antidiabetics).

**Side-effects**

Protamine may cause allergic reactions

**Pregnancy**

Recommended where longer-acting insulins are needed.

**Prescribing and Dispensing Information**

A sterile suspension of bovine or porcine insulin or of human insulin in the form of a complex obtained by the addition of protamine sulphate or another suitable protamine.

**Medicinal Forms**

There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**

- **Humulin I (Eli Lilly and Company Ltd)**
  - Insulin human (as insulin isophane human) 100 unit per 1 ml
  - **Humulin I 100 units/ml suspension for injection 10 ml vials** | 1 vial £15.68
  - **Humulin I 100 units/ml suspension for injection 3 ml cartridges** | 5 cartridge £19.08
- **Humulin I KwikPen (Eli Lilly and Company Ltd)**
  - **Humulin I 100 units/ml suspension for injection 3 ml pre-filled pen** | 5 pre-filled disposable injection £21.70
- **Humyrion Bovine Isophane (Wockhardt UK Ltd)**
  - Insulin bovine (as insulin isophane bovine) 100 unit per 1 ml
  - **Humyrion Bovine Isophane 100 units/ml suspension for injection 10 ml vials** | 1 vial £27.72
  - **Humyrion Bovine Isophane 100 units/ml suspension for injection 3 ml cartridges** | 5 cartridge £41.58

### Protamine zinc insulin

**Indications and Dose**

**Diabetes mellitus**

- **By subcutaneous injection**
  - Child: According to requirements
  - Adult: According to requirements

**Interactions** → Appendix 1 (antidiabetics).

**Side-effects**

Protamine may cause allergic reactions

**Pregnancy**

Evidence of the safety of long-acting insulin analogues in pregnancy is limited, therefore isophane insulin above is recommended where longer-acting insulins are needed; insulin detemir p. 605 may also be considered.

**Prescribing and Dispensing Information**

A sterile suspension of insulin in the form of a complex obtained by the addition of a suitable protamine and zinc chloride; this preparation was included in BP 1980 but is not included in BP 1988.

**Medicinal Forms**

There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**

- **Hypurin Bovine Protamine Zinc (Wockhardt UK Ltd)**
  - Insulin bovine (as insulin protamine zinc bovine) 100 unit per 1 ml
  - **Hypurin Bovine Protamine Zinc 100 units/ml suspension for injection 10 ml vials** | 1 vial £27.72

### Meglitinides

Nateglinide

**Drug Action**

Nateglinide stimulates insulin secretion.

**Indications and Dose**

**Type 2 diabetes mellitus in combination with metformin when metformin alone inadequate**

**By mouth**

- **Adult:** Initially 60 mg 3 times a day (max. per dose 180 mg), adjusted according to response, to be taken within 30 minutes before main meals

**Contra-indications**

Ketoacidosis
CAUTIONS Debilitated patients - elderly - malnourished patients

CAUTIONS, FURTHER INFORMATION
Substitute insulin during intercurrent illness (such as myocardial infarction, coma, infection, and trauma) and during surgery (omit nateglinide on morning of surgery and recommence when eating and drinking normally).

INTERACTIONS → Appendix 1 (antidiabetics).

SIDE-EFFECTS Hypersensitivity reactions - hypoglycaemia - pruritus - rashes - urticaria

PREGNANCY Avoid - toxicity in animal studies.

BREAST FEEDING Avoid - present in milk in animal studies.

HEPATIC IMPAIRMENT Caution in moderate hepatic impairment. Avoid in severe impairment - no information available.

PATIENT AND CARER ADVICE Drivers need to be particularly careful to avoid hypoglycaemia and should be warned of the problems.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
- **Starlix** (Novartis Pharmaceuticals UK Ltd)
  - Nateglinide 60 mg Starlix 60mg tablets | 84 tablet £22.71 DT price = £22.71
  - Nateglinide 120 mg Starlix 120mg tablets | 84 tablet £25.88 DT price = £25.88
  - Nateglinide 180 mg Starlix 180mg tablets | 84 tablet £25.88 DT price = £25.88

Repaglinide

DRUG ACTION Repaglinide stimulates insulin secretion.

INDICATIONS AND DOSE
Type 2 diabetes mellitus (as monotherapy or in combination with metformin when metformin alone inadequate)

BY MOUTH
- Adult 18-74 years: Initially 500 micrograms (max. per dose 4 mg), adjusted according to response, dose to be taken within 30 minutes before main meals and adjusted at intervals of 1–2 weeks; maximum 16 mg per day
- Adult 75 years and over: Not recommended

Type 2 diabetes mellitus (as monotherapy or in combination with metformin when metformin alone inadequate), if transferring from another oral hypoglycaemic drug

BY MOUTH
- Adult 18-74 years: Initially 1 mg (max. per dose 4 mg), adjusted according to response, dose to be taken within 30 minutes before main meals and adjusted at intervals of 1–2 weeks; maximum 16 mg per day
- Adult 75 years and over: Not recommended

CONTRA-INDICATIONS Ketoacidosis

CAUTIONS Debilitated patients - malnourished patients

CAUTIONS, FURTHER INFORMATION
Substitute insulin during intercurrent illness (such as myocardial infarction, coma, infection, and trauma) and during surgery (omit repaglinide on morning of surgery and recommence when eating and drinking normally).

INTERACTIONS → Appendix 1 (antidiabetics).

SIDE-EFFECTS
- Common or very common Abdominal pain - constipation - diarrhoea - nausea - vomiting
- Rare Hypersensitivity reactions - hypoglycaemia - pruritus - rashes - urticaria - vasculitis - visual disturbances

PREGNANCY Avoid.

MEDICINE FORMS

Tablet
- **REPAGLINIDE (Non-proprietary)**
  - Repaglinide 500 microgram tablet | 30 tablet £3.92 | 90 tablet £11.76 DT price = £9.03
  - Repaglinide 1 mg tablet | 30 tablet £3.92 | 90 tablet £11.76 DT price = £10.69
  - Repaglinide 2 mg tablet | 30 tablet £5.89
  - Prandin (Novo Nordisk Ltd)
    - Repaglinide 500 microgram Prandin 0.5mg tablet | 30 tablet £3.92 | 90 tablet £11.76 DT price = £9.03
    - Repaglinide 1 mg Prandin 1mg tablet | 30 tablet £3.92 | 90 tablet £11.76 DT price = £10.69
    - Repaglinide 2 mg Prandin 2mg tablet | 90 tablet £11.76 DT price = £5.89
  - Brands may include Englyd

SODIUM GLUCOSE CO-TRANSPORTER 2 INHIBITORS

Canagliflozin

DRUG ACTION Reversibly inhibits sodium-glucose co-transporter 2 (SGLT2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion.

INDICATIONS AND DOSE
Type 2 diabetes mellitus as monotherapy if metformin inappropriate | Type 2 diabetes mellitus in combination with insulin or other antidiabetic drugs (if existing treatment fails to achieve adequate glycaemic control)

BY MOUTH
- Adult: 100 mg once daily; increased if tolerated to 300 mg once daily if required, dose to be taken preferably before breakfast

Dose adjustments due to interactions
Dose of concomitant insulin or drugs that stimulate insulin secretion may need to be reduced.

CONTRA-INDICATIONS Ketoacidosis

CAUTIONS Cardiovascular disease (risk of hypotension) - elderly (risk of hypotension) - elevated haematocrit - history of hypotension

FURTHER INFORMATION
Volume depletion Correct hypovolaemia before starting treatment.

INTERACTIONS → Appendix 1 (antidiabetics).

SIDE-EFFECTS
- Common or very common Constipation - dyslipidaemia - genital infection - hypoglycaemia (in combination with insulin or sulfonylurea) - nausea - polyuria - raised haematocrit - thirst - urinary frequency - urinary-tract infection
- Uncommon Dehydration - dizziness - hypovolaemia - postural hypotension - raised serum creatinine - raised serum urea - rash - syncope

VOLUME DEPLETION
Volume depletion Consider interrupting treatment if volume depletion occurs.

PREGNANCY Avoid — toxicity in animal studies.
**Diabetes mellitus 609**

**Indications and dose**

Type 2 diabetes mellitus not controlled by metformin alone or by metformin in combination with insulin or other antidiabetic drugs

**By mouth**

- Adult: 1 tablet twice daily, dose based on patient’s current metformin dose, daily dose of metformin should not exceed 2 g

Dose adjustments due to interactions

Dose of concomitant insulin or drugs that stimulate insulin secretion may need to be reduced.

**Renal impairment** Avoid if eGFR less than 60 mL/minute/1.73 m².

**National funding/access decisions**

**Scottish medicines consortium (SMC) decisions**

The Scottish Medicines Consortium (SMC) has advised (December 2014) that Vokanamet® is accepted for restricted use within NHS Scotland in patients with type 2 diabetes mellitus for whom a combination of canagliflozin and metformin is an appropriate choice of therapy.

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS 21**
  - **Vokanamet** (Janssen-Cilag Ltd) ▼
    - Canagliflozin (as Canagliflozin hemihydrate) 50 mg, Metformin hydrochloride 850 mg Vokanamet 50mg/850mg tablets | 60 tablet | £39.20 DT price = £39.20
    - Canagliflozin (as Canagliflozin hemihydrate) 50 mg, Metformin hydrochloride 1 gram Vokanamet 50mg/1000mg tablets | 60 tablet | £39.20 DT price = £39.20

**Dapagliflozin**

**Drug action** Reversibly inhibits sodium-glucose co-transporter 2 (SGLT2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion.

**Indications and dose**

Type 2 diabetes mellitus as monotherapy if metformin inappropriate

**Type 2 diabetes mellitus in combination with insulin or other antidiabetic drugs (if existing treatment fails to achieve adequate glycaemic control)**

**By mouth**

- Adult 18-74 years: 10 mg once daily
- Adult 75 years and over: Initiation not recommended

Dose adjustments due to interactions

Dose of concomitant insulin or drugs that stimulate insulin secretion may need to be reduced.

**Contra-indications**

Ketoacidosis

**Caution** Cardiovascular disease (risk of hypotension) - elderly (risk of hypotension) - electrolyte disturbances - hypotension - raised haematocrit

**Caution, further information**

Volume depletion Correct hypovolaemia before starting treatment.

**Interactions**

- Appendix 1 (antidiabetics).

**Side-effects**

- **Common or very common** Back pain - constipation - dyslipidaemia - dysuria - genital infection - hypoglycaemia (in combination with insulin or sulphonylurea) - polyuria - sweating - thirst - urinary-tract infection
- **Uncommon** Dehydration - dizziness - hypotension - hypovolaemia - nausea - nocturia - raised serum creatinine - raised serum urea - rash

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**Canagliflozin with metformin**

The properties listed below are those particular to the combination only. For the properties of the components please consider, canagliflozin p. 608, metformin hydrochloride p. 594.

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**Breast feeding** Avoid—present in milk in animal studies.

**Hepatic impairment** Manufacturer advises avoid in severe impairment—no information available.

**Renal impairment** Reduce dose to 100 mg once daily if eGFR falls persistently below 60 mL/minute/1.73 m² and existing canagliflozin treatment tolerated. Avoid initiation if eGFR less than 60 mL/minute/1.73 m². Avoid if eGFR less than 45 mL/minute/1.73 m². Monitor renal function at least twice a year in moderate impairment.

**Monitoring requirements** Determine renal function before treatment and at least annually thereafter, and before initiation of concomitant drugs that reduce renal function and periodically thereafter.

**Patient and carer advice** Patients or carers should be advised to report symptoms of volume depletion including postural hypotension and dizziness.

**National funding/access decisions**

**NICE technology appraisals (TAs)**

- Canagliflozin in combination therapy for treating type 2 diabetes (June 2014) NICE TA315
  - Canagliflozin in a dual therapy regimen in combination with metformin is recommended for the treatment of type 2 diabetes, only if a sulfonylurea is contra-indicated or not tolerated or the patient has a significant risk of hypoglycaemia.
  - Canagliflozin in a triple therapy regimen is an option for the treatment of type 2 diabetes in combination with metformin and a sulfonylurea or metformin and a thiazolidinedione.
  - Canagliflozin in combination with insulin (alone or with other antidiabetic drugs) is an option for the treatment of type 2 diabetes.
  - Patients currently receiving canagliflozin in a dual or triple therapy regimen that is not recommended according to the above criteria should have the option to continue treatment until they and their clinician consider it appropriate to stop. www.nice.org.uk/TA315

**Scottish medicines consortium (SMC) decisions**

The Scottish Medicines Consortium has advised (May 2014) that canagliflozin (Invokana®) is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes in combination with metformin as dual therapy, or in combination with metformin and standard of care as triple therapy, or in combination with insulin and standard of care.

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Canagliflozin (Non-proprietary)**
  - Canagliflozin (as Canagliflozin hemihydrate) 100 mg Canagliflozin 100mg tablets | 30 tablet | £39.20
  - Canagliflozin (as Canagliflozin hemihydrate) 300 mg Canagliflozin 300mg tablets | 30 tablet | £49.99

**Canagliflozin with metformin**

The properties listed below are those particular to the combination only. For the properties of the components please consider, canagliflozin p. 608, metformin hydrochloride p. 594.
Dapagliflozin with metformin

The properties listed below are those particular to the combination only. For the properties of the components please consider, dapagliflozin p. 609, metformin hydrochloride p. 594.

**INDICATIONS AND DOSE**

Type 2 diabetes mellitus not controlled by metformin alone or by metformin in combination with insulin or other antidiabetic drugs

**BY MOUTH**
- **Adult 18-74 years:** 1 tablet twice daily, based on patient’s current metformin dose
- **Adult 75 years and over:** Initiation not recommended

**INTERACTIONS**
- Dose of concomitant insulin or drugs that stimulate insulin secretion may need to be reduced.

**HEPATIC IMPAIRMENT**
- Avoid.

**SIDE-EFFECTS, FURTHER INFORMATION**

**Volume depletion** Consider interrupting treatment if volume depletion occurs.

**PREGNANCY**
- Avoid—toxicity in animal studies.

**BREAST FEEDING**
- Avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**
- Initial dose 5 mg daily in severe impairment, increased according to response.

**RENAL IMPAIRMENT**
- Avoid if eGFR less than 60 mL/minute/1.73 m² (ineffective).

**MONITORING REQUIREMENTS**
- Determine renal function before treatment and at least annually thereafter.

**NATIONAL FUNDING/ACCESS DECISIONS**

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (July 2014) that dapagliflozin plus metformin (Xigduo®) is accepted for restricted use within NHS Scotland in patients for whom a combination of dapagliflozin and metformin is an appropriate choice of therapy i.e when metformin alone does not provide adequate glycemic control and a sulfonylurea is inappropriate, or in combination with insulin, when insulin and metformin does not provide adequate control, or in combination with a sulphonylurea, when a sulfonylurea and metformin does not provide adequate control.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Dapagliflozin 5 mg, Metformin hydrochloride 850 mg Tablet £36.59 DT price = £36.59
- Dapagliflozin 5 mg, Metformin hydrochloride 1 gram Tablet £36.59 DT price = £36.59

**Empagliflozin**

**DRUG ACTION**

Reversibly inhibits sodium-glucose co-transporter 2 (SGLT2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion.

**INDICATIONS AND DOSE**

Type II diabetes as monotherapy (if metformin inappropriate) | Type II diabetes in combination with insulin or other antidiabetic drugs (if existing treatment fails to achieve adequate glycaemic control)

**BY MOUTH**
- **Adult 18-84 years:** 10 mg once daily, increased to 25 mg once daily if necessary and if tolerated
- **Adult 85 years and over:** Initiation not recommended

Dose adjustments due to interactions

Dose of concomitant insulin or drugs that stimulate insulin secretion may need to be reduced.

**CONTRA-INDICATIONS**

Diabetic ketoacidosis

**CAUTIONS**

Cardiovascular disease (increased risk of volume depletion) - complicated urinary tract infections—consider temporarily interrupting treatment - concomitant antihypertensive therapy (increased risk of volume depletion) - elderly patients aged over 75 years (increased risk of volume depletion) - heart failure - history of hypotension (increased risk of volume depletion) - patients at increased risk of volume depletion - predisposition to fluid disturbances e.g. gastro-intestinal illness, concomitant use of diuretics (increased risk of volume depletion)

**CAUTIONS, FURTHER INFORMATION**

**Volume depletion** Correct hypovolaemia before starting treatment. Consider interrupting treatment if volume depletion occurs.

**INTERACTIONS**

Appendix 1 (antidiabetics).

**SIDE-EFFECTS**

- **Common or very common** Genital infection - hypoglycaemia (in combination with insulin or sulfonylurea) - polyuria - pruritus - urinary tract infection
- **Uncommon** Dysuria - volume depletion

**PREGNANCY**

Manufacturer advises avoid—toxicity in animal studies.

**BREAST FEEDING**

Manufacturer advises avoid—present in milk in animal studies.
SULFONYLUREAS

**Sulfonylureas**

**DRUG ACTION** The sulfonylureas act mainly by augmenting insulin secretion and consequently are effective only when some residual pancreatic beta-cell activity is present; during long-term administration they also have an extrapancreatic action.

**CONTRA-INDICATIONS** Presence of ketoacidosis

**CAUTIONS** Can encourage weight gain (should be prescribed only if poor control and symptoms persist despite adequate attempts at dieting) • elderly • G6PD deficiency

**SIDE-EFFECTS**

- **Uncommon** Hypoglycaemia
- **Rare** Agranulocytosis • aplastic anaemia • Blood disorders • cholestatic jaundice • haemolytic anaemia • hepatic failure • hepatitis • leucopenia • pancytopenia • thrombocytopenia
- **Frequency not known** Allergic skin reactions (usually in the first 6–8 weeks of therapy) • constipation • diarrhoea • disturbance in liver function • erythema multiforme (usually in the first 6–8 weeks of therapy) • exfoliative dermatitis (usually in the first 6–8 weeks of therapy) • fever (usually in the first 6–8 weeks of therapy) • gastro-intestinal disturbances • Hypersensitivity reactions (usually in the first 6–8 weeks of therapy) • jaundice (usually in the first 6–8 weeks of therapy) • leucopenia –8 weeks of therapy)

**SIDE-EFFECTS, FURTHER INFORMATION**

- **Hypoglycaemia** This is uncommon and usually indicates excessive dosage. Sulfonylurea-induced hypoglycaemia may persist for many hours and must always be treated in hospital.

- **HEPATIC IMPAIRMENT** Sulfonylureas should be avoided or a reduced dose should be used in severe hepatic impairment, because there is an increased risk of hypoglycaemia. Jaundice may occur.

- **RENAL IMPAIRMENT** Sulfonylures should be used with care in those with mild to moderate renal impairment, because of the hazard of hypoglycaemia. Care is required to use the lowest dose that adequately controls blood glucose. Avoid where possible in severe renal impairment.

**PATIENT AND CARER ADVICE** Drivers need to be particularly careful to avoid hypoglycaemia and should be warned of the problems. The risk of hypoglycaemia associated with sulfonylureas should be discussed with the patient, especially when concomitant glucose-lowering drugs are prescribed.

**Glibenclamide**

**INDICATIONS AND DOSE**

**Type 2 diabetes mellitus**

**BY MOUTH**

- **Adult** Initially 5 mg daily, adjusted according to response, dose to be taken with or immediately after breakfast; maximum 15 mg per day


**CONTRA-INDICATIONS** Avoid where possible in Acute porphyrias p. 864

**INTERACTIONS** → Appendix 1 (antidiabetics).

**PREGNANCY** The use of sulfonylureas in pregnancy should generally be avoided because of the risk of neonatal hypoglycaemia; however, glibenclamide can be used during the second and third trimesters of pregnancy in women with gestational diabetes.

**BREAST FEEDING** Glibenclamide can be used during breast-feeding in women with pre-existing diabetes.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Glibenclamide 2.5 mg** Glibenclamide 2.5 mg tablets | 28 tablet (POS) £19.99 09 DT price = £11.09
- **Glibenclamide 5 mg** Glibenclamide 5 mg tablets | 28 tablet (POS) £36.59 09 DT price = £22.22

**BNF 70**

**Diabetes mellitus 611**

- **HEPATIC IMPAIRMENT** Manufacturer advises avoid in severe impairment—no information available.
- **RENAL IMPAIRMENT** Reduce dose to 10 mg once daily if eGFR falls persistently below 60 mL/minute/1.73 m². Avoid initiation if eGFR below 60 mL/minute/1.73 m². Avoid if eGFR is persistently below 45 mL/minute/1.73 m².
- **MONITORING REQUIREMENTS** Determine renal function before treatment and before initiation of concomitant drugs that may reduce renal function, then at least annually thereafter.
- **NATIONAL FUNDING/ACCESS DECISIONS**

  **NICE technology appraisals (TAs)**

  - **Empagliflozin in combination therapy for treating type 2 diabetes (March 2015) NICE TA336**
  - **Jardiance in dual therapy regimen in combination with metformin is an option for the treatment of type 2 diabetes, only if:**
    - a sulfonylurea is contraindicated or not tolerated, or
    - the patient is at significant risk of hypoglycaemia or its consequences.
  - **Empagliflozin in a triple therapy regimen is an option for the treatment of type 2 diabetes in combination with:**
    - metformin and a sulfonylurea or
    - metformin and a thiazolidinedione.
  - **Empagliflozin in combination with insulin with or without other antidiabetic drugs is an option for the treatment of type 2 diabetes. Patients currently receiving empagliflozin whose disease does not meet the above criteria should have the option to continue treatment until they and their clinician consider it appropriate to stop. www.nice.org.uk/TA336**

**SULFONYLUREAS**

**GLIBENCLAMIDE (Non-proprietary)**

- **Tablet**
  - **Glibenclamide 2.5 mg** Glibenclamide 2.5 mg tablets | 28 tablet (POS) £15.48 09 DT price = £9.22
  - **Glibenclamide 5 mg** Glibenclamide 5 mg tablets | 28 tablet (POS) £19.99 09 DT price = £11.09

**Gliclazide**

**INDICATIONS AND DOSE**

**Type 2 diabetes mellitus**

- **INITIALLY BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
  - **Adult**
    - Initially 40–80 mg daily, adjusted according to response, by mouth increased if necessary up to 160 mg once daily, dose to be taken with breakfast, doses higher than 160 mg to be given in divided doses; maximum 320 mg per day

**Drivers need to be particularly careful to avoid hypoglycaemia and should be warned of the problems. The risk of hypoglycaemia associated with sulfonylureas should be discussed with the patient, especially when concomitant glucose-lowering drugs are prescribed.**
PREGNANCY

Avoid where possible in Acute porphyrias p. 864
INTERACTIONS

Avoid if the patient has both renal and hepatic impairment.

RENAL IMPAIRMENT

If necessary, gliclazide which is principally metabolised in the liver, can be used in renal impairment but careful monitoring of blood-glucose concentration is essential.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

Tablet

Gliclazide 40 mg Glacepak 40 capsule [30 tablet ] £3.36 DT price = £3.30
Gliclazide 80 mg Glacepak 80 capsule [30 tablet ] £7.74 DT price = £7.70
Diamicron (Servier Laboratories Ltd) Gliclazide 80 mg Diamicron 800mg tablets [60 tablet ] £4.38
Brands may include Zicron

Modified-release tablet

CAUTIONARY AND ADVISORY LABELS 25
Gliclazide 30 mg Glacepak 30 capsule [28 tablet ] £4.00 DT price = £3.96 | 56 tablet [POS] £8.00
Diamicron MR (Servier Laboratories Ltd) Gliclazide 30 mg Diamicron 30mg MR tablets [28 tablet ] £2.81 DT price = £2.76 | 56 tablet [POS] £5.62
Brands may include Dacardis MR; Laaglyda MR; Nazdoor MR; Vanju; Ziclaseg

Glimepiride

INDICATIONS AND DOSE

Type 2 diabetes mellitus

BY MOUTH

Adult: Initially 1 mg daily, adjusted according to response, then increased in steps of 1 mg every 1–2 weeks, increased to 4 mg daily, dose to be taken shortly before or with first main meal, the daily dose may be increased further, in exceptional circumstances; maximum 6 mg per day

CAUTIONS

CAUTIONS, FURTHER INFORMATION

Porphyria Sulfonylureas should be avoided where possible in Acute porphyrias p. 864 but glimepiride is thought to be safe.

INTERACTIONS

Hyponatraemia

PREGNANCY

The use of sulfonylureas in pregnancy should generally be avoided because of the risk of neonatal hypoglycaemia.

BREAST FEEDING

Avoid—theoretical possibility of hypoglycaemia in the infant.
Tolbutamide

**INDICATIONS AND DOSE**

**Type 2 diabetes mellitus**

**BY MOUTH**

- Adult: 0.5–1.5 g daily in divided doses (max. per dose 2 g), dose to be taken with or immediately after meals, alternatively 0.5–1.5 g once daily (max. per dose 2 g), dose to be taken with or immediately after breakfast

**MEDICINAL FORMS**

- CONTRA-INDICATIONS Avoid where possible in Acute porphyrias p. 864
- INTERACTIONS Appendix 1 (antidiabetics).
- SIDE-EFFECTS Headache • tinnitus
- PREGNANCY The use of sulfonylureas in pregnancy should generally be avoided because of the risk of neonatal hypoglycaemia.
- BREAST FEEDING The use of sulfonylureas in breast-feeding should be avoided because there is a theoretical possibility of hypoglycaemia in the infant.
- RENAL IMPAIRMENT If necessary, the short-acting drug tolbutamide can be used in renal impairment but careful monitoring of blood-glucose concentration is essential.

**THIAZOLIDINEDIONES**

Pioglitazone

- **DRUG ACTION** The thiazolidinedione, pioglitazone, reduces peripheral insulin resistance, leading to a reduction of blood-glucose concentration.

**INDICATIONS AND DOSE**

**Type 2 diabetes mellitus, (alone or combined with metformin or a sulfonylurea, or with both, or with insulin)**

**BY MOUTH**

- Adult: Initially 15–30 mg once daily, adjusted according to response to 45 mg once daily, in elderly patients, initiate with lowest possible dose and increase gradually; review treatment after 3–6 months and regularly thereafter

Dose adjustments due to interactions

Dose of concomitant sulfonylurea or insulin may need to be reduced.

**Important safety information**

MHRA/CHM ADVICE: PIOGLITAZONE CARDIOVASCULAR SAFETY (DECEMBER 2007 AND JANUARY 2011)

Incidence of heart failure is increased when pioglitazone is combined with insulin especially in patients with predisposing factors e.g. previous myocardial infarction. Patients who take pioglitazone should be closely monitored for signs of heart failure; treatment should be discontinued if any deterioration in cardiac status occurs.

Pioglitazone should not be used in patients with heart failure or a history of heart failure.

PIOGLITAZONE: RISK OF BLADDER CANCER (JULY 2011)

The European Medicines Agency has advised that there is a small increased risk of bladder cancer associated with pioglitazone use. However, in patients who respond adequately to treatment, the benefits of pioglitazone continue to outweigh the risks. Pioglitazone should not be used in patients with active bladder cancer or a past history of bladder cancer, or in those who have uninvestigated macroscopic haematuria. Pioglitazone should be used with caution in elderly patients as the risk of bladder cancer increases with age.

Before initiating treatment with pioglitazone, patients should be assessed for risk factors of bladder cancer (including age, smoking status, exposure to certain occupational or chemotherapy agents, or previous radiation therapy to the pelvic region) and any macroscopic haematuria should be investigated. The safety and efficacy of pioglitazone should be reviewed after 3–6 months and pioglitazone should be stopped in patients who do not respond adequately to treatment.

Patients already receiving treatment with pioglitazone should be assessed for risk factors of bladder cancer and treatment should be reviewed after 3–6 months, as above.

Patients should be advised to report promptly any haematuria, dysuria, or urinary urgency during treatment.

**CONTRA-INDICATIONS** History of heart failure • previous or active bladder cancer • uninvestigated macroscopic haematuria

**CAUTIONS** Avoid in Acute porphyrias p. 864 • cardiovascular disease or in combination with insulin (risk of heart failure) • elderly (increased risk of heart failure, fractures, and bladder cancer) • increased risk of bone fractures, particularly in women • risk factors for bladder cancer

CAUTIONS, FURTHER INFORMATION

Substitute insulin during peri-operative period (omit pioglitazone on morning of surgery and recommence when eating and drinking normally).

**INTERACTIONS Appendix 1 (antidiabetics).**

**SIDE-EFFECTS**

- Common or very common Anaemia • arthralgia • dizziness • gastro-intestinal disturbances • haematuria • headache • hypoaesthesia • impotence • oedema • vertigo • visual disturbances • weight gain

- Uncommon Altered blood lipids • bladder cancer • fatigue • hypoglycaemia • insomnia • proteinuria • sweating

- Rare Liver dysfunction

SIDE-EFFECTS, FURTHER INFORMATION

Liver toxicity Rare reports of liver dysfunction; discontinue if jaundice occurs.

PREGNANCY Avoid—toxicity in animal studies.

BREAST FEEDING Avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT** Avoid.

**MONITORING REQUIREMENTS** Monitor liver function before treatment and periodically thereafter.

**PATIENT AND CARER ADVICE**

Liver toxicity Patients should be advised to seek immediate medical attention if symptoms such as nausea, vomiting, abdominal pain, fatigue and dark urine develop.

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium accepts use of pioglitazone (February 2007) with metformin and a sulfonylurea, for patients (especially if overweight) whose glycaemic control is inadequate despite the use of 2 oral hypoglycaemic drugs and who are unable or unwilling to take insulin; treatment should be initiated and monitored by an experienced diabetes physician.
614 Diabetes mellitus and hypoglycaemia

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**
- **Pioglitazone (Non-proprietary)**
  - Pioglitazone (as Pioglitazone hydrochloride) 15 mg Diabiam 15mg tablets | 28 tablet (PO) £26.00 DT price = £1.23
  - Pioglitazone 15mg tablets | 28 tablet (PO) £25.83 DT price = £1.23
  - Pioglitazone (as Pioglitazone hydrochloride) 30 mg Diabiam 30mg tablets | 28 tablet (PO) £36.00 DT price = £1.46
  - Pioglitazone 30mg tablets | 28 tablet (PO) £35.89 DT price = £1.46
  - Pioglitazone (as Pioglitazone hydrochloride) 45 mg Diabiam 45mg tablets | 28 tablet (PO) £40.00 DT price = £1.68
  - Pioglitazone 45mg tablets | 28 tablet (PO) £39.55 DT price = £1.68
  - Actos (Takeda UK Ltd) Pioglitazone (as Pioglitazone hydrochloride) 15 mg Actos 15mg tablets | 28 tablet (PO) £25.83 DT price = £1.23
  - Pioglitazone (as Pioglitazone hydrochloride) 30 mg Actos 30mg tablets | 28 tablet (PO) £35.89 DT price = £1.46
  - Pioglitazone (as Pioglitazone hydrochloride) 45 mg Actos 45mg tablets | 28 tablet (PO) £35.57 DT price = £1.68
  - Brands may include Glijpion

**Metformin with pioglitazone**
The properties listed below are those particular to the combination only. For the properties of the components please consider, metformin hydrochloride p. 594, pioglitazone p. 613.

**INDICATIONS AND DOSE**
Type 2 diabetes not controlled by metformin alone

BY MOUTH
- Adult: 1 tablet twice daily, titration with the individual components (pioglitazone and metformin) desirable before initiation

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Competact** (Takeda UK Ltd)
  - Metformin hydrochloride 850 mg, Pioglitazone (as Pioglitazone hydrochloride) 15 mg Competact 15mg tablets | 56 tablet (PO) £35.89 DT price = £0.68

3.2 Diabetes mellitus, diagnosis and monitoring

**Diabetes mellitus, diagnostic and monitoring devices**

**Urilalysis**
Reagent strips are available for measuring for glucose in the urine. Tests for ketones by patients are rarely required unless they become unwell—see Blood Monitoring. Microalbuminuria can be detected with *Micral-Test II®* but this should be followed by confirmation in the laboratory, since false positive results are common.

**Blood monitoring**
Blood glucose monitoring using a meter gives a direct measure of the glucose concentration at the time of the test and can detect hypoglycaemia as well as hyperglycaemia. Patients should be properly trained in the use of blood glucose monitoring systems and to take appropriate action on the results obtained. Inadequate understanding of the normal fluctuations in blood glucose can lead to confusion and inappropriate action.

Patients using multiple injection regimens should understand how to adjust their insulin dose according to their carbohydrate intake. With fixed-dose insulin regimens, the carbohydrate intake needs to be regulated, and should be distributed throughout the day to match the insulin regimen.

Self-monitoring of blood-glucose concentration is appropriate for patients with type 2 diabetes:
- who are treated with insulin;
- who are treated with oral hypoglycaemic drugs e.g. sulfonylureas, to provide information on hypoglycaemia;
- to monitor changes in blood-glucose concentration resulting from changes in lifestyle or medication, and during intercurrent illness;
- to ensure safe blood-glucose concentration during activities, including driving.

In the UK blood-glucose concentration is expressed in mmol/litre and Diabetes UK advises that these units should be used for self-monitoring of blood glucose. In other European countries units of mg/100 mL (or mg/dL) are commonly used.

It is advisable to check that the meter is pre-set in the correct units.

If the patient is unwell and diabetic ketoacidosis is suspected, blood ketones should be measured according to local guidelines. Patients and their carers should be trained in the use of blood ketone monitoring systems and to take appropriate action on the results obtained, including when to seek medical attention.

**Oral glucose tolerance test**
The oral glucose p. 852 tolerance test is used mainly for diagnosis of impaired glucose p. 852 tolerance; it is not recommended or necessary for routine diagnostic use when severe symptoms of hyperglycaemia are present. In patients who have less severe symptoms and blood glucose levels that do not establish or exclude diabetes (e.g. impaired fasting glycaemia), an oral glucose p. 852 tolerance test may be required. It is also used to establish the presence of gestational diabetes. The oral glucose p. 852 tolerance test generally involves giving anhydrous glucose p. 852 by mouth to the fasting patient, and measuring blood-glucose concentrations at intervals.

The appropriate amount of glucose p. 852 should be given with 200–300 mL fluid. Anhydrous glucose p. 852 may alternatively be given as 113 mL Polycal® with extra fluid to administer a total volume of 200–300 mL, or as Rapilose® OGTT oral solution.

**Blood monitoring test strips**

**BLOOD GLUCOSE TESTING STRIPS**
- **Diastix testing strips (Bayer Diagnostics Manufacturing Ltd)**
  - 50 strip | NHS indicative price = £2.89 | Drug Tariff (Part IXr)
- **Element testing strips (Neon Diagnostics Ltd)**
  - 36 strip | NHS indicative price = £3.69 | Drug Tariff (Part IXr)
- **FreeStyle Lite testing strips (Abbott Laboratories Ltd)**
  - 50 strip | NHS indicative price = £15.73 | Drug Tariff (Part IXr)
- **FreeStyle Optium testing strips (Abbott Laboratories Ltd)**
  - 50 strip | NHS indicative price = £15.64 | Drug Tariff (Part IXr)
- **FreeStyle testing strips (Abbott Laboratories Ltd)**
  - 50 strip | NHS indicative price = £15.74 | Drug Tariff (Part IXr)
- **GlucOGEN testing strips (Neon Diagnostics Ltd)**
  - 50 strip | NHS indicative price = £3.89 | Drug Tariff (Part IXr)
- **GlucoDock testing strips (Medisana Healthcare (UK) Ltd)**
  - 50 strip | NHS indicative price = £14.90 | Drug Tariff (Part IXr)
- **Glucolab testing strips (Neon Diagnostics Ltd)**
  - 50 strip | NHS indicative price = £3.89 | Drug Tariff (Part IXr)
- **Glucomon GM testing strips (A Menarini Diagnostics Ltd)**
  - 50 strip | NHS indicative price = £3.95 | Drug Tariff (Part IXr)
- **Glucomon LX Sensor testing strips (A Menarini Diagnostics Ltd)**
  - 50 strip | NHS indicative price = £15.52 | Drug Tariff (Part IXr)
### Meters and test strips

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<th>Meter (all <strong>®</strong>)</th>
<th>Type of monitoring</th>
<th>Compatible test strips</th>
<th>Test strip net price</th>
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### Diabetes mellitus, diagnosis and monitoring 617

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### Hypodermic insulin injection pens

#### HYPODERMIC INSULIN INJECTION PENS

- **AUTOOPEN®**
  - **AUTOOPEN® 24**
    - For use with Sanofi: Aventis 3-mL insulin cartridges, allowing 1-unit dosage adjustment, max. 21 units (single-unit version) or 2-unit dosage adjustment, max. 42 units (2-unit version).
    - **AUTOOPEN® CLASSIC**
      - For use with Lilly and Wockhardt 3-mL insulin cartridges, allowing 1-unit dosage adjustment, max. 21 units (single-unit version) or 2-unit dosage adjustment, max. 42 units (2-unit version).

- **CLIKSTAR®**
  - For use with Lantus®, Apidra®, and InsuLan® 3-mL insulin cartridges; allowing 1-unit dose adjustment, max. 143 units.

#### NEEDLE FREE INSULIN DELIVERY SYSTEMS

- **INSUJET®**
  - For use with any 10-mL vial or 3-mL cartridge of insulin, allowing 1-unit dosage adjustment, max. 40 units. Available as **starter set** (Insulet® device, nozzle cap, nozzle and piston, 1 x 10-mL adaptor, 1 x 3-mL adaptor, 1 cartridge cap removal key), **needle pack** (15 nozzles), **cartridge adaptor pack** (15 adaptors), or **vial adaptor pack** (15 adaptors).
    - Insulet 10mL vial adaptor pack (Spirit Healthcare Ltd)
    - 1 pack · NHS indicative price = £13.50 · Drug Tariff (Part IXa)
    - Insulet 3mL cartridge adaptor pack (Spirit Healthcare Ltd)
    - 1 pack · NHS indicative price = £21.70 · Drug Tariff (Part IXa)
    - Insulet needle pack (Spirit Healthcare Ltd)
    - 1 pack · NHS indicative price = £28.40 · Drug Tariff (Part IXa)
    - **Insulet starter set** (Spirit Healthcare Ltd)
    - 1 pack · NHS indicative price = £14.00 · Drug Tariff (Part IXa)
3.3 Hypoglycaemia

Hypoglycaemia

Treatment of hypoglycaemia

Initially glucose p. 852 10–20 g is given by mouth either in liquid form or as granulated sugar or sugar lumps. Approximately 10 g of glucose is available from non-diet versions of Lucozade® Energy Original 55 mL, Coca-Cola® 100 mL, Ribena® Blackcurrant 19 mL (to be diluted), 2 teaspoons of sugar, and also from 3 sugar lumps. Proprietary products of quick-acting carbohydrate (e.g. GlucoGel®, Dextrogel®, GSF-Syrup®, Rapilose® gel) are available on prescription for the patient to keep to hand in case of hypoglycaemia. If necessary this may be repeated in 10–15 minutes. After initial treatment, a snack providing sustained availability of carbohydrate (e.g. a sandwich, fruit, milk, or biscuits) or the next meal, if it is due, can prevent blood-glucose concentration from falling again.

Hypoglycaemia which causes unconsciousness is an emergency. Glucagon, a polypeptide hormone produced by the alpha cells of the islets of Langerhans, increases plasma-glucose concentration by mobilising glycogen stored in the liver. In hypoglycaemia, if sugar cannot be given by mouth, glucagon can be given by injection.

Carbohydrates should be given as soon as possible to restore liver glycogen; glucagon is not appropriate for chronic hypoglycaemia. Glucagon may be issued to close relatives of insulin-treated patients for emergency use in hypoglycaemic attacks. It is often advisable to prescribe on an ‘if necessary’ basis to hospitalised insulin-treated patients, so that it may be given rapidly by the nurses during an hypoglycaemic emergency. If not effective in 10 minutes intravenous glucose should be given.

Alternatively, glucose intravenous infusion 20% may be given intravenously into a large vein through a large-gauge needle; care is required since this concentration is irritant especially if extravasation occurs. Glucose intravenous infusion 10% may also be used but larger volumes are needed. Glucose intravenous infusion 50% is not recommended because of the higher risk of extravasation injury and because administration is difficult. Close monitoring is necessary in the case of an overdose with a long-acting insulin because further administration of glucose may be required. Patients whose hypoglycaemia is caused by an oral antidiabetic drug should be transferred to hospital because the hypoglycaemic effects of these drugs may persist for many hours.

See also emergency management of hypoglycaemia in dental practice for further advice.

Chronic hypoglycaemia

Diazboxide p. 619, administered by mouth, is useful in the management of patients with chronic hypoglycaemia from excess endogenous insulin secretion, either from an islet cell tumour or islet cell hyperplasia. It has no place in the management of acute hypoglycaemia.

GLYCOGENOLYTIC HORMONES

Glucagon

INDICATIONS AND DOSE

Insulin-induced hypoglycaemia

BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION

Child 1 month–1 year: 500 micrograms

Child 2–17 years (body-weight up to 25 kg): 500 micrograms, if no response within 10 minutes intravenous glucose must be given.

Child 2–17 years (body-weight 25 kg and above): 1 mg, if no response within 10 minutes intravenous glucose must be given.

Adult: 1 mg, if no response within 10 minutes intravenous glucose must be given.

Beta-blocker poisoning (cardiogenic shock unresponsive to atropine)

INITIALLY BY INTRAVENOUS INJECTION

Child: 50–150 micrograms/kg (max. per dose 10 mg), to be administered in glucose 5% (with precautions to protect the airway in case of vomiting), followed by (by intravenous infusion) 50 micrograms/kg/hour.

Adult: 2–10 mg, to be administered in glucose 5% (with precautions to protect the airway in case of vomiting), followed by (by intravenous infusion) 50 micrograms/kg/hour.

Dose equivalence and conversion

1 unit of glucagon = 1 mg of glucagon.

UNLICENSED USE

Dose and indication for cardiogenic shock unresponsive to atropine in beta-blocker overdose not licensed.

In children Unlicensed for growth hormone test and hyperinsulinism.

CONTRA-INDICATIONS

Phaeochromocytoma

CAUTIONS

Glucagonoma - ineffective in chronic hypoglycaemia, starvation, and adrenal insufficiency - insulinoma - when used in the diagnosis of growth hormone secretion, delayed hypoglycaemia may result — deaths reported (ensure a meal is eaten before discharge).

SIDE-EFFECTS

Rare Hypersensitivity reactions.
3.4 Hypoglycaemia, chronic

**THIAZIDES AND RELATED DIURETICS**

**Diazoxide**

**INDICATIONS AND DOSE**

**Chronic intractable hypoglycaemia**

**BY MOUTH**

- Adult: Initially 5 mg/kg daily in 2–3 divided doses, adjusted according to response; maintenance 3–8 mg/kg daily in 2–3 divided doses

**CAUTIONS**

- Aortic coarctation • aortic stenosis • arteriovenous shunt • heart failure • hyperuricaemia • impaired cardiac circulation • impaired cerebral circulation

**INTERACTIONS**

- Appendix 1 (diazoxide).

**SIDE-EFFECTS**

- abdominal pain • anaemia • anorexia (prolonged use) • bleeding • constipation • decreased libido • dermatitis • diarrhoea • diziness • dyspnoea • eosinophilia • extrapyramidal effects • galactorrhoea • headache • heart failure • hyperglycaemia • hyperosmolar non-ketotic coma • hypertrichosis • hyperuricaemia • (prolonged use) • hypotension • ileus • lacrimation • leucopenia • lichenoid eruption • musculoskeletal pain • nausea • pancreatitis • pruritus • pulmonary hypertension • raised serum creatinine • raised serum urea • reversible nephritic syndrome • sodium and fluid retention • taste disturbance • thrombocytopenia • tinnitus • transient catacacts • visual disturbances • vomiting

**PREGNANCY**

- Use only if essential; alopecia and hypertrichosis reported in neonates with prolonged use; may inhibit uterine activity during labour.

**BREAST FEEDING**

- Manufacturer advises avoid—no information available.

**RENAL IMPAIRMENT**

- Dose reduction may be required.

**MONITORING REQUIREMENTS**

- Monitor blood pressure.
- Monitor white cell and platelet count during prolonged use.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension, capsule.

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use in children

**Tablet**

- **Eudemine** (Focus Pharmaceuticals Ltd)
  - Diazoxide 50 mg  Eudemine 50mg tablets | 100 tablet £46.45

### 4 Disorders of bone metabolism

**Bone metabolism**

**Osteoporosis**

Osteoporosis occurs most commonly in postmenopausal women and in those taking long-term oral corticosteroids (glucocorticosteroids). Other risk factors for osteoporosis include low body weight, cigarette smoking, excess alcohol intake, lack of physical activity, family history of osteoporosis, and early menopause.

Those at risk of osteoporosis should maintain an adequate intake of calcium and vitamin D and any deficiency should be corrected by increasing dietary intake or taking supplements.

Elderly patients, especially those who are housebound or live in residential or nursing homes, are at increased risk of calcium and vitamin D deficiency and may benefit from supplements. Reversible secondary causes of osteoporosis such as hyperthyroidism, hyperparathyroidism, osteomalacia or hypogonadism should be excluded, in both men and women, before treatment for osteoporosis is initiated.

**Postmenopausal osteoporosis**

The bisphosphonates (alendronate and risedronate) are effective for preventing postmenopausal osteoporosis.

**Hormone replacement therapy** (HRT) is an option where other therapies are contra-indicated, cannot be tolerated, or if there is a lack of response. The CSM has advised that HRT should not be considered first-line therapy for long-term prevention of osteoporosis in women over 50 years of age. HRT is of most benefit for the prophylaxis of postmenopausal osteoporosis if started early in menopause and continued for up to 5 years, but bone loss resumes (possibly at an accelerated rate) on stopping HRT. Women of Afro-Caribbean origin appear to be less susceptible to osteoporosis than those who are white or of Asian origin.

Postmenopausal osteoporosis may be treated with a bisphosphonate. The bisphosphonates (such as alendronate and risedronate) decrease the risk of vertebral fracture; alendronate and risedronate have also been shown to reduce non-vertebral fractures. If bisphosphonates are unsuitable calcitriol p. 885 or strontium ranelate may be considered. Calcitonin (salmon)/salcatonin is no longer recommended for the treatment of postmenopausal osteoporosis as the benefits are outweighed by the risk of malignancy associated with long-term use. Calcitonin (salmon)/salcatonin (unlicensed indication) has been used for pain relief for up to 3 months after a vertebral fracture when other analgesics were ineffective, but the benefits of treatment should be balanced against the risks.

**Parathyroid hormone, and teriparatide** have been introduced for the treatment of postmenopausal osteoporosis.

Raloxifene hydrochloride p. 659 is licensed for the prophylaxis and treatment of vertebral fractures in postmenopausal women.

**Corticosteroid-induced osteoporosis**

To reduce the risk of osteoporosis doses of oral corticosteroids should be as low as possible and courses of treatment as short as possible. The risk of osteoporosis may be related to cumulative dose of corticosteroids; even
intermittent courses can therefore increase the risk. The greatest rate of bone loss occurs during the first 6–12 months of corticosteroid use and so early steps to prevent the development of osteoporosis are important. Long-term use of high-dose inhaled corticosteroids may also contribute to corticosteroid-induced osteoporosis. Patients taking (or who are likely to take) an oral corticosteroid for 3 months or longer should be assessed and where necessary given prophylactic treatment; those aged over 65 years are at greater risk. Patients taking oral corticosteroids who have sustained a low trauma fracture should receive treatment for osteoporosis. The therapeutic options for prophylaxis and treatment of corticosteroid-induced osteoporosis are the same:
- a bisphosphonate;
- calcitriol [unlicensed indication];
- hormone replacement (HRT in women, testosterone in men [unlicensed indication]).

Calcitonin and parathyroid hormone
Calcitonin is involved with parathyroid hormone in the regulation of bone turnover and hence in the maintenance of calcium balance and homoeostasis. Calcitonin (salmon)/salcatonin (synthetic or recombinant salmon calcitonin) is used to lower the plasma-calcium concentration in patients with hypercalcaemia associated with malignancy.

Calcitonin (salmon)/salcatonin is also licensed for treatment of Paget’s disease of bone when other treatments are ineffective or inappropriate; it is also licensed for the prevention of acute bone loss due to sudden immobility. Calcitonin (salmon)/salcatonin is no longer recommended for the prevention or treatment of postmenopausal osteoporosis because the benefits are outweighed by the risk of malignancy associated with long-term use.

Recombinant parathyroid hormone is used for the treatment of postmenopausal osteoporosis. Teriparatide p. 629 (a recombinant fragment of parathyroid hormone) is used for the treatment of postmenopausal osteoporosis, osteoporosis in men at increased risk of fracture, and corticosteroid-induced osteoporosis.

Cinacalcet p. 855 is licensed for the treatment of hypercalcaemia in parathyroid carcinoma.

Bisphosphonates
Bisphosphonates have an important role in the prophylaxis and treatment of osteoporosis and corticosteroid-induced osteoporosis; alendronate p. 621 or risedronate sodium p. 624 are considered the drugs of choice for these conditions. Bisphosphonates are also used in the treatment of Paget’s disease, hypercalcaemia of malignancy, and in bone metastases in breast cancer.

Strontium ranelate
Strontium ranelate treatment has been associated with an increased risk of serious cardiovascular disease, including myocardial infarction, and the risk should be assessed before treatment and regularly during treatment. Strontium ranelate should be initiated only by specialists for the treatment of severe osteoporosis in postmenopausal women or men at high risk of fracture for whom other treatments are contra-indicated or not tolerated.

See also calcium, phosphorus, vitamin D and oestrogens in postmenopausal osteoporosis.

Drugs used for Disorders of bone metabolism not listed below; Calcitriol, p. 885

ANABOLIC STEROIDS

**Nandrolone**

**INDICATIONS AND DOSE**

Osteoporosis in postmenopausal women (but not recommended)

**BY DEEP INTRAMUSCULAR INJECTION**

- Adult: 50 mg every 3 weeks.

**CONTRA-INDICATIONS**

Acute porphyrias p. 864 - male breast cancer - prostate cancer

**CAUTIONS**

Cardiac impairment - diabetes mellitus - epilepsy - hypertension - migraine - skeletal metastases (risk of hypercalcaemia)

**INTERACTIONS**

→ Appendix 1 (anabolic steroids).

**SIDE-EFFECTS**

Abnormal liver-function tests (with high doses) - acne - amenorrhoea - inhibition of spermatogenesis - liver tumours (with prolonged treatment with anabolic steroids) - premature epiphyseal closure - sodium retention with oedema - virilisation (with high doses including voice changes—sometimes irreversible)

**HEPATIC IMPAIRMENT**

Use in severe hepatic impairment only if benefit outweighs risk.

**RENAL IMPAIRMENT**

Use with caution—may cause sodium and water retention.

**MONITORING REQUIREMENTS**

Monitor skeletal maturation in young patients.

**LESS SUITABLE FOR PRESCRIBING**

Nandrolone injection is less suitable for prescribing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

**EXCIPIENTS:** May contain Arachis (peanut) oil, benzyl alcohol

- Deca-Durabolin (Aspen Pharma Trading Ltd)

  Nandrolone decanoate 50 mg per 1 ml Deca-Durabolin 50mg/1ml solution for injection ampoules | 1 ampoule £3.17 Schedule 4 (CD Anab)

**BISPHOSPHONATES**

**Bisphosphonates**

**DRUG ACTION**

Bisphosphonates are adsorbed onto hydroxyapatite crystals in bone, slowing both their rate of growth and dissolution, and therefore reducing the rate of bone turnover.

**Important safety information**

MHRA/CHM ADVICE: BISPHOSPHONATES: ATYPICAL FEMORAL FRACTURES (JUNE 2011)

Atypical femoral fractures have been reported rarely with bisphosphonate treatment, mainly in patients receiving long-term treatment for osteoporosis. The need to continue bisphosphonate treatment for osteoporosis should be re-evaluated periodically based on an assessment of the benefits and risks of treatment for individual patients, particularly after 5 or more years of use.

Patients should be advised to report any thigh, hip, or groin pain during treatment with a bisphosphonate. Discontinuation of bisphosphonate treatment in patients suspected to have an atypical femoral fracture should be considered after an assessment of the benefits and risks of continued treatment.

BISPHOSPHONATES: OSTEONECROSIS OF THE JAW

The risk of osteonecrosis of the jaw is substantially greater for patients receiving intravenous
Alendronic acid (Alendronate)

INDICATIONS AND DOSE
Treatment of postmenopausal osteoporosis
BY MOUTH
Adult: 10 mg daily, alternatively 70 mg once weekly.

Treatment of osteoporosis in men
BY MOUTH
Adult: 10 mg daily.
Prevention and treatment of corticosteroid-induced osteoporosis in postmenopausal women not receiving hormone replacement therapy
BY MOUTH
Adult: 10 mg daily.

CONTRA-INDICATIONS
Abnormalities of oesophagus - hypocalcaemia - other factors which delay emptying (e.g. stricture or achalasia)

CAUTIONS
Active gastro-intestinal bleeding - atypical femoral fractures - duodenitis - dysphagia - exclude other causes of osteoporosis - gastritis - history (within 1 year) of ulcers - surgery of the upper gastro-intestinal tract - symptomatic oesophageal disease - ulcers - upper gastrointestinal disorders

INTERACTIONS
Appendix 1 (bisphosphonates).

SIDE-EFFECTS
Common or very common Abdominal distension - abdominal pain - alopecia - asthenia - constipation - diarrhoea - dizziness - dyspepsia - flatulence - headache - joint swelling - musculoskeletal pain - oesophageal reactions - peripheral oedema - pruritus - regurgitation - vertigo
Uncommon Dysgeusia - episceratitis - erythema - gastritis - malaise (on initiation) - melena - myalgia (on initiation) - nausea - rash - scleritis - uveitis - vomiting
Rare Atypical femoral fractures with long-term use - fever (on initiation) - hypocalcaemia - osteonecrosis of the jaw - photosensitivity - severe skin reactions - Stevens-Johnson syndrome - toxic epidermal necrolysis

SIDE-EFFECTS, FURTHER INFORMATION
Oesophageal reactions Severe oesophageal reactions (oesophagitis, oesophageal ulcers, oesophageal stricture and oesophageal erosions) have been reported; patients should be advised to stop taking the tablets and to seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, new or worsening heartburn, pain on swallowing or retrosternal pain.

PREGNANCY
Avoid.

BREAST FEEDING
Manufacturer advises avoid—no information available.

RENAL IMPAIRMENT
Avoid if eGFR less than 35 mL/minute/1.73 m².

MONITORING REQUIREMENTS
Correct disturbances of calcium and mineral metabolism (e.g. vitamin-D deficiency, hypocalcaemia) before starting treatment.

DIRECTIONS FOR ADMINISTRATION
Tablets should be swallowed whole and oral solution should be swallowed as a single 100 mL dose. Doses should be taken with plenty of water while sitting or standing, on an empty stomach at least 30 minutes before breakfast (or another oral medicine); patient should stand or sit upright for at least 30 minutes after administration.

PATIENT AND CARER ADVICE
Patients or their carers should be given advice on how to administer alendronic acid tablets and oral solution.

Oesophageal reactions Patients (or their carers) should be advised to stop taking alendronic acid and to seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, new or worsening heartburn, pain on swallowing or retrosternal pain.

NATIONAL FUNDING/ACCESS DECISIONS
NICE technology appraisals (TAs)
- Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (October 2008) NICE TA160

Alendronate is recommended as a treatment option for the primary prevention of osteoporotic fractures in the following susceptible postmenopausal women:
- Women over 70 years who have an independent risk factor for fracture (parental history of hip fracture, alcohol intake of 4 or more units per day, or rheumatoid arthritis) or an indicator of low bone mineral density (body mass index under 22 kg/m², ankylosing spondylitis, Crohn’s disease, prolonged immobility, untreated premature menopause, or rheumatoid arthritis) and confirmed osteoporosis.
- Women aged 65–69 years who have an independent risk factor for fracture and confirmed osteoporosis.
- Women under 65 years who have an independent risk factor for fracture and at least one additional indicator of low bone mineral density and confirmed osteoporosis. www.nice.org.uk/TA160
- Alendronate, etidronate, risedronate, raloxifene, strontium ranelate, and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (October 2008) NICE TA161

This guideline recommends treatment options for the secondary prevention of osteoporotic fractures in postmenopausal women with confirmed osteoporosis who have also sustained a clinically apparent osteoporotic fracture.

Alendronate is recommended as a treatment option for the secondary prevention of osteoporotic fractures in susceptible postmenopausal women. www.nice.org.uk/TA161
Alendronic acid with calcitriol

The properties listed below are those particular to the combination only. For the properties of the components please consider, alendronic acid p. 621, calcitriol p. 886.

INDICATIONS AND DOSE
Treatment of postmenopausal osteoporosis in women at risk of vitamin D deficiency
BY MOUTH
Adult: 1 tablet once weekly.

DIRECTIONS FOR ADMINISTRATION
Tablets should be swallowed whole with plenty of water while sitting or standing; to be taken on an empty stomach at least 30 minutes before breakfast (or another oral medicine); patient should stand or sit upright for at least 30 minutes after taking tablet.

PATIENT AND CARER ADVICE
Patients or carers should be given advice on how to administer alendronic acid with calcitriol tablets.

MEDIINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Table

<table>
<thead>
<tr>
<th>MEDICINAL FORMS</th>
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<tbody>
<tr>
<td>There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution</td>
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<th>TABLET</th>
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<tbody>
<tr>
<td>ALENDRONIC ACID (Non-proprietary)</td>
</tr>
<tr>
<td>Alendronic acid (as Alendronate sodium) 10 mg Alendronic acid 10mg tablets</td>
</tr>
<tr>
<td>Alendronic acid (as Alendronate sodium) 70 mg Alendronic acid 70mg tablets</td>
</tr>
<tr>
<td>Fosamax (Merck Sharp &amp; Dohme Ltd)</td>
</tr>
<tr>
<td>Alendronic acid (as Alendronate sodium) 10 mg Fosamax 10mg tablets</td>
</tr>
<tr>
<td>Alendronic acid (as Alendronate sodium) 70 mg Fosamax Once Weekly 70mg tablets</td>
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</tbody>
</table>

Alendronic acid 700 microgram per 1 ml Alendronic acid 70mg/100ml oral solution unit dose sugar free (sugar-free) | 4 unit dose £22.80 DT price = £22.80 |

Ibandronic acid

INDICATIONS AND DOSE
Reduction in bone damage in bone metastases in breast cancer
INITIALLY BY MOUTH
Adult: 50 mg daily, alternatively (by intravenous infusion) 6 mg every 3–4 weeks

Hypercalcaemia of malignancy
BY INTRAVENOUS INFUSION
Adult: 2–4 mg as a single infusion, dose to be adjusted according to serum calcium concentration

Treatment of postmenopausal osteoporosis
INITIALLY BY MOUTH
Adult: 150 mg once a month, alternatively (by intravenous injection) 3 mg every 3 months, to be administered over 15–30 seconds.

CONTRA-INDICATIONS
GENERAL CONTRA-INDICATIONS:
Hypocalcaemia

SPECIFIC CONTRA-INDICATIONS:
With oral use Abnormalities of the oesophagus - other factors which delay emptying (e.g. stricture or achalasia)

CAUTIONS
Atypical femoral fractures - cardiac disease (avoid fluid overload)

INTERACTIONS
 Appendix 1 (bisphosphonates).

SIDE-EFFECTS
GENERAL SIDE-EFFECTS
Common or very common
Abdominal pain, asthenia, bone pain, chill, diarrhoea, dyspepsia, fever, gastritis, headache, hypocalcaemia, hypophosphataemia, influenza-like symptoms, muscle pain, nausea, pharyngitis, rash, vomiting

Rare Anaemia, angioedema, atypical femoral fractures, bronchospasm, hypersensitivity reactions, injection-site reactions, pruritus, urticaria

Very rare Osteonecrosis of the jaw

SPECIFIC SIDE-EFFECTS
Common or very common
With oral use Severe oesophageal reactions (discontinue)

PREGNANCY
Avoid.

BRST FEEDING
Avoid—present in milk in animal studies.

RENO IMPAIRMENT
With intravenous use When used for bone metastases, if eGFR 30–50 mL/minute/1.73 m² reduce dose to 4 mg and infuse over 1 hour; if eGFR less than 30 mL/minute/1.73 m² reduce dose to 2 mg and infuse over 1 hour.

With oral use When used for bone metastases, if eGFR 30–50 mL/minute/1.73 m² reduce dose to 50 mg on alternative days; if eGFR less than 30 mL/minute/1.73 m² reduce dose to 50 mg once weekly. When used for postmenopausal osteoporosis, avoid if eGFR less than 30 mL/minute/1.73 m².

MONITORING REQUIREMENTS
Monitor renal function and serum calcium, phosphate and magnesium.

DIRECTIONS FOR ADMINISTRATION
Tablets should be swallowed whole with plenty of water while sitting or standing; to be taken on an empty stomach at least 30 minutes before breakfast (or another oral medicine); patient should stand or sit upright for at least 30 minutes after taking tablet.

PATIENT AND CARER ADVICE
Patients or carers should be given advice on how to administer ibandronic acid tablets.

MEDIINAL FORMS
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<tr>
<td>Ibandronic acid (as Ibandronic sodium monohydrate) 50 mg Ibandronic acid 50mg tablets</td>
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<tr>
<td>Ibandronic acid (as Ibandronic sodium monohydrate) 150 mg Ibandronic acid 150mg tablets</td>
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</table>
Pamidronate disodium
(Formerly called aminohydroxypropylidenediphosphonate disodium (APD))

**INDICATIONS AND DOSE**

**Hypercalcaemia of malignancy**
- Adult: 15–60 mg, to be given (via cannula in a relatively large vein) as a single infusion or in divided doses over 2–4 days, dose adjusted according to serum calcium concentration; maximum 90 mg per course

**Osteolytic lesions and bone pain in bone metastases associated with breast cancer or multiple myeloma**
- Adult: 90 mg every 4 weeks, to be administered via cannula in a relatively large vein, dose may alternatively be administered every 3 weeks, to coincide with chemotherapy in breast cancer

**Paget’s disease of bone**
- Adult: 30 mg every 1 week for a 6 week course (total dose 180 mg), alternatively initially 30 mg once weekly for 1 week, then increased to 60 mg every 2 weeks (max. per dose 60 mg) for a 6 week course (total dose 210 mg), to be administered via cannula in a relatively large vein, course may be repeated every 6 months; maximum 360 mg per course

**SIDE-EFFECTS**

**Rare**

**Frequency not known**
- Atrial fibrillation - injection-site reactions - reactivation of herpes simplex - reactivation of herpes zoster

**SIDE-EFFECTS, FURTHER INFORMATION**

**Calcium and vitamin D supplements**
Oral supplements are advised to minimise potential risk of hypocalcaemia for those with mainly lytic bone metastases or multiple myeloma at risk of calcium or vitamin D deficiency (e.g. through malabsorption or lack of exposure to sunlight) and in those with Paget’s disease.

**PREGNANCY** Avoid—toxicity in animal studies.

**BREAST FEEDING** Avoid.

**HEPATIC IMPAIRMENT** Caution in severe hepatic impairment—no information available.

**RENAL IMPAIRMENT** Max. infusion rate 20 mg/hour. Avoid if eGFR less than 30 mL/minute/1.73 m², except in life-threatening hypercalcaemia if benefit outweighs risk. If renal function deteriorates in patients with bone metastases, withhold dose until serum creatinine returns to within 10% of baseline value.

**MONITORING REQUIREMENTS**
- Monitor serum electrolytes, calcium and phosphate—possibility of convulsions due to electrolyte changes.
- Assess renal function before each dose.

**DIRECTIONS FOR ADMINISTRATION**
- With intravenous use For slow intravenous infusion (Aredia®, Pamidronate disodium, Hospira, Medac, Wockhardt), give intermittently in Glucose 5% or Sodium chloride 0.9%; give at a rate not exceeding 1 mg/minute; not to be given with infusion fluids containing calcium. For Aredia® reconstitute initially with water for injections (15 mg in 5 mL, 30 mg or 90 mg in 10 mL), then dilute with infusion fluid to a concentration of not more than 90 mg in 250 mL. For Pamidronate disodium (Wockhardt), dilute with infusion fluid to a concentration of not more than 60 mg in 250 mL or for Pamidronate disodium (Medac, Hospira) dilute with infusion fluid to a concentration of not more than 90 mg in 250 mL.

**PATIENT AND CARER ADVICE** Patients should be warned against performing skilled tasks (e.g. cycling, driving or operating machinery) immediately after treatment (somnolence or dizziness can occur).

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- Pamidronate disodium 3 mg per 1 ml Pamidronate disodium 15mg/5ml solution for infusion vials | 1 vial (Roche) £27.50 (Hospital only) | 5 vial (Roche) £149.15 Pamidronate disodium 30mg/10ml solution for infusion vials | 1 vial (Roche) £35.00 (Hospital only) | 1 vial (Roche) £59.66 Pamidronate disodium 60mg/20ml solution for infusion vials | 1 vial (Roche) £110.00 (Hospital only) Pamidronate disodium 90mg/30ml solution for infusion vials | 1 vial (Roche) £165.00 (Hospital only)

- Pamidronate disodium 6 mg per 1 ml Pamidronate disodium 60mg/10ml solution for infusion vials | 1 vial (Roche) £115.25

- Pamidronate disodium 9 mg per 1 ml Pamidronate disodium 90mg/10ml solution for infusion vials | 1 vial (Roche) £170.45

- Pamidronate disodium 15 mg per 1 ml Pamidronate disodium 60mg/4ml solution for infusion ampoules | 1 ampoule (Roche) £113.32

- Pamidronate disodium 15mg/1ml solution for infusion ampoules | 4 ampoule (Roche) £113.32

- Pamidronate disodium 90mg/6ml solution
**INDICATIONS AND DOSE**

Paget’s disease of bone

**BY MOUTH**

- **Adult:** 30 mg daily for 2 months, course may be repeated if necessary after at least 2 months

**Treatment of postmenopausal osteoporosis to reduce risk of vertebral or hip fractures**

**BY MOUTH**

- **Adult:** 5 mg daily, alternatively 35 mg once weekly.

**Prevention of osteoporosis (including corticosteroid-induced osteoporosis) in postmenopausal women**

**BY MOUTH**

- **Adult:** 5 mg daily.

**Treatment of osteoporosis in men at high risk of fractures**

**BY MOUTH**

- **Adult:** 35 mg once weekly.

---

**CONTRA-INDICATIONS**

- Hypocalcaemia

**CAUTIONS**

- Atypical femoral fractures · oesophageal abnormalities · other factors which delay transit or emptying (e.g. stricture or achalasia)

**INTERACTIONS**

- **Common or very common** · Abdominal pain · constipation · diarrhoea · dyspepsia · headache · musculoskeletal pain · nausea

- **Uncommon** · Duodenitis · dysphagia · gastritis · oesophageal ulcer · oesophagitis · uveitis

- **Rare** · Atypical femoral fractures · glossoitis · oesophageal stricture

- **Frequency not known** · Cutaneous vasculitis · gastro-duodenal ulceration · hair loss · hepatic disorders · osteonecrosis of the jaw · Stevens-Johnson syndrome · toxic epidermal necrolysis

**PREGNANCY**

- Avoid.

**BREAST FEEDING**

- Avoid.

**RENAL IMPAIRMENT**

- Avoid if eGFR less than 30 mL/minute/1.73 m².

**MONITORING REQUIREMENTS**

- Correct hypocalcaemia before starting.

- Correct other disturbances of bone and mineral metabolism (e.g. vitamin D deficiency) at onset of treatment.

**DIRECTIONS FOR ADMINISTRATION**

- Swallow tablets whole with full glass of water; on rising, take on an empty stomach at least 30 minutes before first food or drink of the day or, if taking at any other time of the day, avoid food and drink for at least 2 hours before or after risedronate (particularly avoid calcium-containing products e.g. milk; also avoid iron and mineral supplements and antacids); stand or sit upright for at least 30 minutes; do not take tablets at bedtime or before rising.

**PATIENT AND CARER ADVICE**

- Patients or carers should be given advice on how to administer risedronate sodium tablets.

- Oesophageal reactions. Patients should be advised to stop taking the tablets and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain, or heartburn.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (October 2008) NICE TA160

Risedronate is recommended as an alternative for women:

- in whom alendronate is contra-indicated or not tolerated and

- who comply with particular combinations of bone mineral density measurement, age, and independent risk factors for fracture, as indicated in the full NICE guidance. www.nice.org.uk/TA160

- Alendronate, etidronate, risedronate, raloxifene, strontium ranelate, and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (October 2008) NICE TA161

This guideline recommends treatment options for the secondary prevention of osteoporotic fractures in postmenopausal women with confirmed osteoporosis who have also sustained a clinically apparent osteoporotic fracture.

Risedronate is recommended as an alternative for women:

- in whom alendronate is contra-indicated or not tolerated and

- who comply with particular combinations of bone mineral density measurement, age, and independent risk factors for fracture (parental history of hip fracture, alcohol intake of 4 or more units per day, or rheumatoid arthritis, as indicated in the full NICE guidance. www.nice.org.uk/TA161

**MEDICINAL FORMS**

There may be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

**Tablet**

- **RISEDRONATE SODIUM (Non-proprietary)**

  - Risedronate sodium 5 mg
  - Risedronate sodium 30 mg
  - Risedronate sodium 35 mg

- **Actonel** (Warner Chilcott UK Ltd)

  - Risedronate sodium 5 mg

**Risedronate with calcium carbonate and colecalciferol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, calcium carbonate p. 856, colecalciferol p. 886, risedronate sodium above.
## Sodium clodronate

### INDICATIONS AND DOSE

**Osteolytic lesions, hypercalcaemia and bone pain associated with skeletal metastases in patients with breast cancer or multiple myeloma**

**BY MOUTH**
- **Adult:** 1.6 g daily in 1–2 divided doses, then increased if necessary up to 3.2 g daily in 2 divided doses

**LORON 520®**

**Osteolytic lesions, hypercalcaemia and bone pain associated with skeletal metastases in patients with breast cancer or multiple myeloma**

**BY MOUTH**
- **Adult:** Initially 2 tablets daily in 1–2 divided doses, increased if necessary up to 4 tablets daily

### DIRECTIONS FOR ADMINISTRATION

- Tablets should be swallowed whole with plenty of water while sitting or standing; to be taken on an empty stomach at least 30 minutes before breakfast (or another oral medicine); patient should stand or sit upright for at least 30 minutes after taking tablet. Granules should be stirred into a glass of water and after dissolution complete taken immediately.

### PATIENT AND CARER ADVICE

- Patients or carers should be given advice on how to administer sodium clodronate with colecalciferol and risedronate tablets and granules.

### MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug.

#### Granules
- **Actonel Combi** (Warner Chilcott UK Ltd)
- Actonel Combi 35 mg tablets and 1000 mg/880 unit effervescent granules sachets | 4 week supply (DST) £19.12

#### Tablets

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Brand Name</th>
<th>Unit</th>
<th>Dose</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium clodronate 400 mg</td>
<td>Bonefos</td>
<td>60 cap</td>
<td>£83.83</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>£43.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium clodronate 800 mg</td>
<td>Bonefos</td>
<td>40 cap</td>
<td>£139.83</td>
<td></td>
</tr>
</tbody>
</table>

### SIDE-EFFECTS

- Common or very common: Bronchospasm, diarrhoea, nausea, skin reactions, vomiting
- Rare: Atypical femoral fractures
- Very rare: Osteonecrosis of the jaw
- Frequency not known: Renal impairment, uveitis

### CONTRA-INDICATIONS

- Acute gastro-intestinal inflammatory conditions

### CAUTIONS

- Atypical femoral fractures: maintain adequate fluid intake during treatment

### INTERACTIONS

- Appendix 1 (bisphosphonates).

### PRECAUTIONS

- **PREGNANCY**: Avoid.
- **BREAST FEEDING**: Manufacturer advises avoid — no information available.

### RENAL IMPAIRMENT

- Max. initial dose 1200 mg daily if eGFR 30–50 mL/minute/1.73 m². Use half normal dose if eGFR 10–30 mL/minute/1.73 m². Avoid if eGFR less than 10 mL/minute/1.73 m².

### MONITORING REQUIREMENTS

- Monitor renal function, serum calcium and serum phosphate before and during treatment.

### DIRECTIONS FOR ADMINISTRATION

- Avoid food for 2 hours before and 1 hour after treatment, particularly calcium-containing products e.g. milk; also avoid iron and mineral supplements and antacids; maintain adequate fluid intake.

### PATIENT AND CARER ADVICE

- Patients or carers should be given advice on how to administered sodium clodronate with coleccalciferol and risedronate tablets and granules.

### MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug.

#### Tablet

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Dose</th>
<th>Price</th>
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</thead>
<tbody>
<tr>
<td>Sodium clodronate 800 mg</td>
<td>60 tab</td>
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</tbody>
</table>

#### Capsule

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Dose</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium clodronate 400 mg</td>
<td>120 cap</td>
<td>£139.83</td>
</tr>
</tbody>
</table>

### Disorders of bone metabolism 625

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## Zoledronic acid

### INDICATIONS AND DOSE

**ZOMETA® INFUSION**

**Reduction of bone damage in advanced malignancies involving bone**

**BY INTRAVENOUS INFUSION**
- **Adult:** 4 mg every 3–4 weeks, to be administered over at least 15 minutes, calcium 500 mg daily and vitamin D 400 units daily should also be taken

**Hypercalcaemia of malignancy**

**BY INTRAVENOUS INFUSION**
- **Adult:** 4 mg for 1 dose, to be administered over at least 15 minutes

**ACLASTA®**

**Treatment of Paget’s disease of bone**

**BY INTRAVENOUS INFUSION**
- **Adult:** 5 mg 1 times yearly, to be administered over at least 15 minutes, at least 500 mg elemental calcium twice daily (with vitamin D) for at least 10 days is recommended following infusion

**Treatment of postmenopausal osteoporosis and osteoporosis in men (including corticosteroid-induced osteoporosis)**

**BY INTRAVENOUS INFUSION**
- **Adult:** 5 mg 1 times yearly, to be administered over at least 15 minutes, in patients with a recent low-trauma hip fracture, the dose should be given 2 or more weeks following hip fracture repair; before first infusion give 50000–125000 units of vitamin D

### CAUTIONS

- Atypical femoral fractures, cardiac disease (avoid fluid overload) concomitant medicines that affect renal function

### INTERACTIONS

- Appendix 1 (bisphosphonates).

### SIDE-EFFECTS

- Common or very common: Anaemia, arthralgia, atrial fibrillation, bone pain, conjunctivitis, dizziness, fever, gastro-intestinal disturbances, headache.
Disorders of bone metabolism

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

- **Infusion**
  - **Zoledronic Acid (Non-proprietary)**
    - Zoledronic acid (as Zoledronic acid monohydrate) 40 microgram per 1 ml
    - Zoledronic acid 4mg/100ml infusion bags [1 bag PMP £174.14 (Hospital only)]
    - Zoledronic acid 4mg/100ml infusion bottles [1 bottle PMP £150.00]
    - Zoledronic acid (as Zoledronic acid monohydrate) 50 microgram per 1 ml
    - Zoledronic acid 5mg/100ml infusion bags [1 bag PMP £217.68]
    - Aclasta (Novartis Pharmaceuticals UK Ltd)
      - Zoledronic acid (as Zoledronic acid monohydrate) 50 microgram per 1 ml
      - Aclasta 5mg/100ml infusion bottles [1 bottle PMP £253.38]
    - Zometa (Novartis Pharmaceuticals UK Ltd)
      - Zoledronic acid (as Zoledronic acid monohydrate) 40 microgram per 1 ml
      - Zometa 4mg/100ml infusion bottles [1 bottle PMP £174.14]
    - Brands may include Zerlinda

- **Solution for infusion**
  - **Zoledronic Acid (Non-proprietary)**
    - Zoledronic acid (as Zoledronic acid monohydrate) 40 microgram per 1 ml
    - Zoledronic acid 4mg/100ml solution for infusion vials [1 vial PMP £147.30–£174.14]
    - Zoledronic acid (as Zoledronic acid monohydrate) 50 microgram per 1 ml
    - Zoledronic acid 5mg/100ml solution for infusion vials [1 vial PMP £215.37–£266.72]
    - Zoledronic acid (as Zoledronic acid monohydrate) 800 microgram per 1 ml
      - Zoledronic acid 4mg/ml concentrate for solution for infusion vials [1 vial PMP £174.14 (Hospital only)]
      - Zoledronic acid 4mg/ml solution for infusion vials [1 vial PMP £150.00]
    - Zometa (Novartis Pharmaceuticals UK Ltd)
      - Zoledronic acid (as Zoledronic acid monohydrate) 800 microgram per 1 ml
      - Zometa 4mg/ml solution for infusion vials [1 vial PMP £174.14]

- **Bone Formation Stimulants**

  - **Strontium Ranelate**
    - **Drug Action**
      - Stimulates bone formation and reduces bone resorption.
    - **Indications and Dose**
      - Treatment of severe osteoporosis in postmenopausal women or men at high risk of fracture for whom other treatments are contra-indicated or not tolerated (initiated under specialist supervision)
    - **POM**
    - - Adult: 2 g once daily, dose to be taken in water, preferably at bedtime
    - **Contra-Indications**
      - Cerebrovascular disease - current or previous venous thromboembolic event - ischaemic heart disease - peripheral arterial disease - temporary or prolonged immobilisation - uncontrolled hypertension
    - **Caution**
      - Predisposition to cardiovascular disease—assess risk before and every 6–12 months during treatment
    - **Interactions**
      - Appendix 1 (strontium ranelate).
    - **Side-Effects**
      - Common or very common: Dermatitis - diarrhoea - eczema - headache - myocardial infarction - nausea - venous thromboembolism
      - Very rare: Angioedema - hypersensitivity reactions - urticaria - urticarial rash
      - Frequency not known: Abdominal pain - alopeedia - bone marrow suppression - constipation - dyspepsia - flatulence - gastro-oesophageal reflux - peripheral oedema - stomatitis - vomiting
SIDE-EFFECTS, FURTHER INFORMATION
Severe allergic reactions Severe allergic reactions, including drug rash with eosinophilia and systemic symptoms (DRESS), have been reported in patients taking strontium ranelate. DRESS starts with rash, fever, swollen glands, and increased white cell count, and it can affect the liver, kidneys and lungs; DRESS can also be fatal. Treatment with strontium ranelate should not be restarted.
- **RENAL IMPAIRMENT** Avoid if eGFR less than 30 mL/minute/1.73 m².
- **EFFECT ON LABORATORY TESTS** Interferes with colorimetric measurements of calcium in blood and urine.
- **DIRECTIONS FOR ADMINISTRATION** Avoid food for 2 hours before and after taking granules, particularly calcium-containing products e.g. milk; also preferably avoid concomitant antacids containing aluminium and magnesium hydroxides for 2 hours after taking granules.
- **PATIENT AND CARER ADVICE** Severe allergic reactions Patients should be advised to stop taking strontium ranelate and consult their doctor immediately if skin rash develops. Patients or carers should be given advice on how to administer strontium ranelate granules.
- **NATIONAL FUNDING/ACCESS DECISIONS**

### NICE technology appraisals (TAs)

- Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (October 2008) NICE TA160

**Strontium ranelate** is recommended as an alternative for women:
- in whom alendronate and risedronate are contra-indicated or not tolerated and
- who comply with particular combinations of bone mineral density measurement, age, and independent risk factors for fracture, as indicated in the full NICE guidance. [www.nice.org.uk/TA160](http://www.nice.org.uk/TA160)

- Alendronate, etidronate, risedronate, raloxifene, strontium ranelate, and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (October 2008) NICE TA161

This guideline recommends treatment options for the secondary prevention of osteoporotic fractures in postmenopausal women with confirmed osteoporosis who have also sustained a clinically apparent osteoporotic fracture.

**Strontium ranelate** is recommended as an alternative for women:
- in whom alendronate and risedronate are contra-indicated or not tolerated and
- who comply with particular combinations of bone mineral density measurement, age, and independent risk factors for fracture, as indicated in the full NICE guidance. [www.nice.org.uk/TA161](http://www.nice.org.uk/TA161)

### MEDICINAL FORMS

**Granules**

| CAUTIONARY AND ADVISORY LABELS 5, 13 |
| EXCipients: May contain Aspartame |

- **Protelos** (Servier Laboratories Ltd)
- **Strontium ranelate 2 gram** Protelos 2g granules sachets (sugar-free) | 28 sachet pack £27.08 DT price = £27.08

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**CALCITONINS**

### Calcitonin salmon

**Calcitonin (salmon)** (Salcaltonin)

#### INDICATIONS AND DOSE

**Hypercalcaemia of malignancy**

- **BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION**
  - Adult: 100 units per day, adjusted according to response

- **BY INTRAVENOUS INFUSION**
  - Adult: Up to 10 units/kg, in severe or emergency cases, to be administered by slow intravenous infusion over at least 6 hours

**Paget’s disease of bone**

- **BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION**
  - Adult: Initially 100 units daily in 1–2 divided doses, then reduced to 50 units daily at the start of mobilisation, usual duration of treatment is 2 weeks; maximum 4 weeks

#### CONTRA-INDICATIONS

- Hypocalcaemia

#### CAUTIONS

- Heart failure - history of allergy (skin test advised) - risk of malignancy—avoid prolonged use (use lowest effective dose for shortest possible time)

#### SIDE-EFFECTS

- Common or very common Abdominal pain - diarrhoea - dizziness - fatigue - flushing - headache - malignancy (with long-term use) - muscularkeletal pain - nausea - taste disturbances - vomiting
- Uncommon Cough - hypersensitivity reactions - hypertension - injection-site reactions - oedema - polyuria - pruritus - rash - visual disturbances
- Frequency not known Tremor

#### PREGNANCY

- Avoid unless potential benefit outweighs risk (toxicity in animal studies).

#### BREAST FEEDING

- Avoid; inhibits lactation in animals.

#### RENAL IMPAIRMENT

- Use with caution.

#### DIRECTIONS FOR ADMINISTRATION

For intravenous infusion (Miacalcic®), give intermittently in Sodium chloride 0.9%. Diluted solution given without delay. Dilute in 500 mL give over at least 6 hours; glass or hard plastic containers should not be used; some loss of potency on dilution and administration.

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Miacalcic** (Novartis Pharmaceuticals UK Ltd)
  - Calcitonin (salmon) 50 unit per 1 mL Miacalcic 50units/1ml solution for injection ampoules | 5 ampoule pack £11.10
  - Calcitonin (salmon) 100 unit per 1 mL Miacalcic 100units/1ml solution for injection ampoules | 5 ampoule pack £34.21
  - Calcitonin (salmon) 200 unit per 1 mL Miacalcic 400units/2ml multidose solution for injection vials | 1 vial pack £24.60
DENOSUMAB

**Drug action** Denosumab is a human monoclonal antibody that inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption.

**Indications and dose**

**XGEVA®**

Prevention of skeletal related events in patients with bone metastases from solid tumours

**By subcutaneous injection**

- **Adult:** 120 mg every 4 weeks, supplementation of at least Calcium 500 mg and vitamin D 400 units daily should also be taken unless hypercalcaemia is present

Treatment of giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity in adults and skeletally mature adolescent

**By subcutaneous injection**

- **Adult:** 120 mg every 4 weeks, give additional dose on days 8 and 15 of the first month of treatment only, supplementation of at least Calcium 500 mg and vitamin D 400 units daily should also be taken unless hypercalcaemia is present

**PROLIA®**

Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures | Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures

**By subcutaneous injection**

- **Adult:** 60 mg every 6 months, supplement with calcium and vitamin D

**Important safety information**

**MHRA/CHM advice: Denosumab: atypical femoral fractures (February 2013)**

Atypical femoral fractures have been reported rarely in patients receiving denosumab for the long-term treatment (2.5 or more years) of postmenopausal osteoporosis. Patients should be advised to report any new or unusual thigh, hip, or groin pain during treatment with denosumab. Discontinuation of denosumab in patients suspected to have an atypical femoral fracture should be considered after an assessment of the benefits and risks of continued treatment.

**MHRA/CHM advice: Denosumab: minimising the risk of osteonecrosis of the jaw; monitoring for hypocalcaemia—updated recommendations (September 2014)**

Denosumab is associated with a risk of osteonecrosis of the jaw (ONJ) and with a risk of hypocalcaemia.

**Osteonecrosis of the jaw**

Osteonecrosis of the jaw is a well-known and common side-effect in patients receiving denosumab 120 mg for cancer. Risk factors include smoking, old age, poor oral hygiene, invasive dental procedures (including tooth extractions, dental implants, oral surgery), comorbidity (including dental disease, anaemia, coagulopathy, infection), advanced cancer, previous treatment with bisphosphonates, and concomitant treatments (including chemotherapy, anti-angiogenic biologics, corticosteroids, and radiotherapy to head and neck). The following precautions are now recommended to reduce the risk of ONJ:

- Denosumab 120 mg (cancer indication)
- A dental examination and appropriate preventative dentistry before starting treatment are now recommended for all patients

**Contra-indications** Hypocalcaemia

**Caution** Atypical femoral fractures • hypocalcaemia • osteonecrosis of the jaw—consider temporary interruption of treatment if occurs

**Side-effects**

- **Common or very common** Abdominal discomfort • cataracts • constipation • diarrhoea • dysphonia • eczema • hypocalcaemia (fatal cases reported) • hypophosphataemia • musculoskeletal pain • osteonecrosis of the jaw • pain in extremity • rash • sciatica • sweating • upper respiratory tract infection • urinary tract infection

- **Uncommon** Cellulitis (seek prompt medical attention) • diverticulitis • ear infection • skin infections (seek prompt medical attention)

- **Rare** Atypical femoral fractures • osteonecrosis of the jaw

**Conception and contraception** Ensure effective contraception in women of child-bearing potential, during treatment and for at least 5 months after stopping treatment.

**Pregnancy** Avoid—toxicity in animal studies; risk of toxicity increases with each trimester—advise women who become pregnant during treatment to enrol in the manufacturer’s Pregnancy Surveillance Programme (consult product literature).

**Breast feeding** Avoid (if women do decide to breast-feed during treatment, they should enrol in the manufacturer’s Lactation Surveillance Programme—consult product literature.)

- Do not start denosumab in patients with a dental or jaw condition requiring surgery, or in patients who have not recovered following oral surgery

Denosumab 60 mg (osteoporosis indication)

- Check for ONJ risk factors before starting treatment. A dental examination and appropriate preventative dentistry are now recommended for patients with risk factors

All patients should be informed to maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain, or swelling to a doctor and dentist.

**Hypocalcaemia**

Denosumab is associated with a risk of hypocalcaemia. This risk increases with the degree of renal impairment. Hypocalcaemia usually occurs in the first weeks of denosumab treatment, but it can also occur later in treatment.

Plasma-calcium concentration monitoring is recommended for denosumab 120 mg (cancer indication):

- before the first dose
- within two weeks after the initial dose
- if suspected symptoms of hypocalcaemia occur
- consider monitoring more frequently in patients with risk factors for hypocalcaemia (e.g. severe renal impairment, creatinine clearance less than 30 mL/minute)

Plasma-calcium concentration monitoring is recommended for denosumab 60 mg (osteoporosis indication):

- before each dose
- within two weeks after the initial dose in patients with risk factors for hypocalcaemia (e.g. severe renal impairment, creatinine clearance less than 30 mL/minute)
- if suspected symptoms of hypocalcaemia occur

All patients should be advised to report symptoms of hypocalcaemia to their doctor (e.g. muscle spasms, twitches, cramps, numbness or tingling in the fingers, toes, or around the mouth).

- Avoid (if women do decide to breast-feed during treatment)

- Pregnancy surveillance programme

- Lactation surveillance programme
PATIENT AND CARER ADVICE

RENAL IMPAIRMENT
Increased risk of hypocalcaemia if eGFR less than 30 mL/minute/1.73 m².

MONITORING REQUIREMENTS
Correct hypocalcaemia and vitamin D deficiency before starting. Monitor plasma-calcium concentration during therapy.

PATIENT AND CARER ADVICE
Atypical femoral fractures. Patients should be advised to report any new or unusual thigh, hip, or groin pain during treatment with denosumab.

Osteonecrosis of the jaw. All patients should be informed to maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain, or swelling to a doctor. Hypocalcaemia. All patients should be advised to report symptoms of hypocalcaemia to their doctor (e.g., muscle spasms, twitches, cramps, numbness or tingling in the fingers, toes, or around the mouth).

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)
• Denosumab for the prevention of osteoporotic fractures in postmenopausal women (October 2010) NICE TA204

Denosumab is recommended as a treatment option for the primary prevention of osteoporotic fragility fractures in postmenopausal women at increased risk of fractures:
- who are unable to comply with the special instructions for administering alendronate and risedronate, or have an intolerance of, or a contra-indication to, those treatments and
- who comply with particular combinations of bone mineral density measurement, age, and independent risk factors for fracture, as indicated in the full NICE guidance.

Denosumab is recommended as a treatment option for the secondary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fractures who are unable to comply with the special instructions for administering alendronate and risedronate, or have an intolerance of, or a contra-indication to, those treatments. www.nice.org.uk/TA204

• Denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours (October 2012) NICE TA265

Denosumab is recommended for the prevention of skeletal-related events in adults with bone metastases from breast cancer and from solid tumours other than prostate if:
- bisphosphonates would otherwise be prescribed, and
- the manufacturer provides denosumab with the discount agreed in the patient access scheme.

Denosumab is not recommended for preventing skeletal-related events in adults with bone metastases from prostate cancer.

Patients with bone metastases from solid tumours currently receiving denosumab whose disease does not meet the above criteria can continue treatment until they and their clinician consider it appropriate to stop. www.nice.org.uk/TA265

PROLIA®

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (November 2010) that denosumab (Prolia®) is accepted for restricted use within NHS Scotland for the treatment of osteoporosis in postmenopausal women at increased risk of fractures who have a bone mineral density T-score <-2.5 and ≥-4.0 and for whom bisphosphonates are unsuitable.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
• Prolia (Amgen Ltd) Denosumab 60 mg per 1 ml Prolia 60mg/1ml solution for injection pre-filled disposable injection pen £183.00
• Xgeva (Amgen Ltd) Denosumab 70 mg per 1 ml Xgeva 120mg/1.7ml solution for injection £109.86

PARATHYROID HORMONES AND ANALOGUES

Parathyroid hormone
(Human recombinant parathyroid hormone)

INDICATIONS AND DOSE
Treatment of osteoporosis in postmenopausal women at high risk of fractures (to reduce the risk of vertebral fractures)

BY SUBCUTANEOUS INJECTION
• Adult: 100 micrograms daily for maximum duration of treatment 24 months

CONTRA-INDICATIONS
Hyperparathyroidism - metabolic bone disease - Paget’s disease - pre-existing hyperparathyroidism - previous radiation therapy to skeleton - unexplained raised levels of alkaline phosphatase

CAUTIONS
Active urolithiasis - previous urolithiasis

INTERACTIONS
Use with caution with concomitant cardiac glycosides.

SIDE-EFFECTS
• Common or very common Asthenia - back pain - constipation - diarrhoea - dizziness - dyspepsia - fatigue - headache - hypercalcaemia - injection-site reactions - muscle cramp - nausea - pain in extremities - palpitation - transient hypercalcaemia - vomiting

• Uncommon Abdominal pain - altered sense of smell - anorexia - hyperuricaemia - influenza - taste disturbance

PREGNANCY
Avoid.

BREAST FEEDING
Avoid.

HEPATIC IMPAIRMENT
Avoid.

RENAL IMPAIRMENT
Avoid if eGFR less than 30 mL/minute/1.73 m².

MONITORING REQUIREMENTS
Monitor serum or urinary calcium concentration at 1, 3 and 6 months after initiation of treatment (consult product literature for guidance if serum-calcium concentration raised).

PRESCRIBING AND DISPENSING INFORMATION
Preotact® cartriges are for use with Preotact® pen device.

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium, has advised (February 2007) that parathyroid hormone (Preotact®) should be initiated by specialists experienced in the treatment of osteoporosis.

MEDICINAL FORMS
Medicines not identified.

Teriparatide

INDICATIONS AND DOSE
Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures | Treatment of corticosteroid-induced osteoporosis

BY SUBCUTANEOUS INJECTION
• Adult: 20 micrograms daily for maximum duration of treatment 24 months (course not to be repeated)

CONTRA-INDICATIONS
Bone metastases - hyperparathyroidism - metabolic bone diseases - Paget’s disease - hyperparathyroidism - previous radiation therapy to skeleton - unexplained raised levels of alkaline phosphatase

CAUTIONS
Active urolithiasis - previous urolithiasis

INTERACTIONS
Use with caution with concomitant cardiac glycosides.

SIDE-EFFECTS
• Common or very common Asthenia - back pain - constipation - diarrhoea - dizziness - dyspepsia - fatigue - headache - hypercalcaemia - injection-site reactions - muscle cramp - nausea - pain in extremities - palpitation - transient hypercalcaemia - vomiting

• Uncommon Abdominal pain - altered sense of smell - anorexia - hyperuricaemia - influenza - taste disturbance

PREGNANCY
Avoid.

BREAST FEEDING
Avoid.

HEPATIC IMPAIRMENT
Avoid.

RENAL IMPAIRMENT
Avoid if eGFR less than 30 mL/minute/1.73 m².

MONITORING REQUIREMENTS
Monitor serum or urinary calcium concentration at 1, 3 and 6 months after initiation of treatment (consult product literature for guidance if serum-calcium concentration raised).

PRESCRIBING AND DISPENSING INFORMATION
Preotact® cartriges are for use with Preotact® pen device.

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium, has advised (February 2007) that parathyroid hormone (Preotact®) should be initiated by specialists experienced in the treatment of osteoporosis.
Dopamine-responsive conditions

DOPAMINE RECEPTOR AGONISTS

**Bromocriptine**

Bromocriptine is used for the treatment of galactorrhoea, and for the treatment of prolactinomas (when it reduces both plasma prolactin concentration and tumour size). Bromocriptine also inhibits the release of growth hormone and is sometimes used in the treatment of acromegaly, but somatostatin analogues (such as octreotide p. 789) are more effective.

Cabergoline p. 334 has similar side-effects to bromocriptine, however patients intolerant of bromocriptine may be able to tolerate cabergoline (and vice versa).

Quinagolide has actions and uses similar to those of ergot-derived dopamine agonists, but its side-effects differ slightly.

**Suppression of lactation**

Although bromocriptine and cabergoline are licensed to suppress lactation, they are not recommended for routine suppression (or for the relief of symptoms of postpartum pain and engorgement) that can be adequately treated with simple analgesics and breast support. If a dopamine-receptor agonist is required, cabergoline is preferred. Quinagolide is not licensed for the suppression of lactation.

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**Quinagolide**

**INDICATIONS AND DOSE**

Hyperprolactinaemia

**BY MOUTH**

- Adult: Initially 25 micrograms once daily for 3 days, dose to be taken at bedtime, increased in steps of 25 micrograms every 3 days; usual dose 75–150 micrograms daily, for doses higher than 300 micrograms daily increase in steps of 75–150 micrograms at intervals of not less than 4 weeks

**SIDE-EFFECTS, FURTHER INFORMATION**

Hyperprolactinaemic patients, the source of the hyperprolactinaemia should be established (i.e. exclude pituitary tumour before treatment).

- **INTERACTIONS**  ➔ Appendix 1 (quinagolide).
- **SIDE-EFFECTS**
  - **Unlicensed Use** Not licensed for the suppression of lactation.
  - **CAUTIONS** Acute porphyrias p. 864 · history of psychotic illness · history of serious mental disorders

Hyperprolactinaemic patients. In hyperprolactinaemic patients, the source of the hyperprolactinaemia should be established (i.e. exclude pituitary tumour before treatment).

- **INTERACTIONS**  ➔ Appendix 1 (quinagolide).
- **SIDE-EFFECTS**
  - **Unlicensed Use** Not licensed for the suppression of lactation.
  - **CAUTIONS** Acute porphyrias p. 864 · history of psychotic illness · history of serious mental disorders

**CONCEPTION AND CONTRACEPTION**

Advise non-hormonal contraception if pregnancy not desired.

**PREGNANCY**

Discontinue when pregnancy confirmed unless medical reason for continuing (specialist advice needed).

**BREAST FEEDING**

Suppresses lactation.

**HEPATIC IMPAIRMENT**

Avoid—no information available.

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**Dopamine-receptor agonists**

Bromocriptine p. 333 is used for the treatment of galactorrhoea, and for the treatment of prolactinomas (when it reduces both plasma prolactin concentration and tumour size). Bromocriptine also inhibits the release of...
6 Gonadotrophin responsive conditions

Gonadotrophins

Drugs affecting gonadotrophins

Danazol p. 636 is licensed for the treatment of endometriosis and for the relief of severe pain and tenderness in benign fibrocystic breast disease where other measures have proved unsatisfactory. It may also be effective in the long-term management of hereditary angioedema [unlicensed indication].

Cetrorelix p. 636 and ganirelix p. 636 are luteinising hormone releasing hormone antagonists, which inhibit the release of gonadotrophins (luteinising hormone and follicle stimulating hormone). They are used in the treatment of infertility by assisted reproductive techniques.

Gonadorelin analogues

Gonadorelin analogues are used in the treatment of endometriosis, precocious puberty, infertility, male hyposexuality with severe sexual deviation, anaemia due to uterine fibroids (together with iron supplementation), breast cancer, prostate cancer and before intra-uterine surgery. Use of leuprorelin acetate p. 633 and triptorelin p. 635 for 3 to 4 months before surgery reduces the uterine volume, fibroid size and associated bleeding. For women undergoing hysterectomy or myomectomy, a vaginal procedure is made more feasible following the use of a gonadorelin analogue.

Breast pain (mastalgia)

Once any serious underlying cause for breast pain has been ruled out, most women will respond to reassurance and reduction in dietary fat; withdrawal of an oral contraceptive or of hormone replacement therapy may help to resolve the pain.

Mild, non-cyclical breast pain is treated with simple analgesics; moderate to severe pain, cyclical pain or symptoms that persist for longer than 6 months may require specific drug treatment.

Danazol is licensed for the relief of severe pain and tenderness in benign fibrocystic breast disease which has not responded to other treatment.

Tamoxifen p. 791 may be a useful adjunct in the treatment of mastalgia [unlicensed indication] especially when symptoms can definitely be related to cyclic oestrogen production; it may be given on the days of the cycle when symptoms are predicted.

Treatment for breast pain should be reviewed after 6 months and continued if necessary. Symptoms recur in about 50% of women within 2 years of withdrawal of therapy but may be less severe.

GONADOTROPHIN-RELEASING HORMONE ANALOGUES

Buserelin

- **DRUG ACTION** Administration of gonadorelin analogues produces an initial phase of stimulation; continued administration is followed by down-regulation of gonadotrophin-releasing hormone receptors, thereby reducing the release of gonadotrophins (follicle stimulating hormone and luteinising hormone) which in turn leads to inhibition of androgen and oestrogen production.

INDICATIONS AND DOSE

**Endometriosis**

**BY INTRanasAL ADMINISTRATION**

- **Adult:** 300 micrograms 3 times a day maximum duration of treatment 6 months (do not repeat), to be started on days 1 or 2 of menstruation; administer one 150 microgram spray into each nostril

**Pituitary desensitisation before induction of ovulation by gonadotrophins for in vitro fertilisation (under expert supervision)**

**BY SUBCUTaneous INJECTION**

- **Adult:** 200–500 micrograms once daily, increased if necessary up to 500 micrograms twice daily, starting in early follicular phase (day 1) or, after exclusion of pregnancy, in midluteal phase (day 21) and continued until down-regulation achieved (usually 1–3 weeks) then maintained during gonadotrophin administration (stopping gonadotrophin and buserelin on administration of chorionic gonadotrophin at appropriate stage of follicular development)

**BY INTRanasAL ADMINISTRATION**

- **Adult:** 150–300 micrograms 4 times a day, (150 micrograms equivalent to one spray), to be administered during waking hours. Start in early follicular phase (day 1) or, after exclusion of pregnancy, in midluteal phase (day 21) and continued until down-regulation achieved (usually about 2–3 weeks) then maintained during gonadotrophin administration (stopping continued →
gonadotrophin and buserelin on administration of chorionic gonadotrophin at appropriate stage of follicular development

- **Advanced prostate cancer**
  - *Initially by subcutaneous injection*
    - Adult: 500 micrograms every 8 hours for 7 days, then (by intranasal administration) 200 micrograms 6 times a day, (a single 100 microgram spray to be administered into each nostril)

- **Contra-indications**
  - When used for endometriosis
  - Hormone dependent tumours - undiagnosed vaginal bleeding - use longer than 6 months (do not repeat)

- **Caution**
  - Depression - diabetes - hypertension - patients with metabolic bone disease (decrease in bone mineral density can occur) - polycystic ovarian disease

- **Side-effects**
  - General side-effects

  - Specific side-effects
    - With intranasal use
      - Altered sense of taste and smell - nasal irritation - nose bleeds

- **Drug action**
  - Administration of gonadorelin analogues produces an initial phase of stimulation; continued administration is followed by down-regulation of gonadotrophin-releasing hormone receptors, thereby reducing the release of gonadotrophins (follicle stimulating hormone and luteinising hormone) which in turn leads to inhibition of androgen and oestrogen production.

### Goserelin

- **Indications and dose**
  - ZOLADEX®
    - Locally advanced prostate cancer as an alternative to surgical castration / Adjuvant treatment to radiotherapy or radical prostatectomy in patients with high-risk localised or locally advanced prostate cancer / Neoadjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer / Metastatic prostate cancer / Advanced breast cancer / Oestrogen-receptor-positive early breast cancer
    - **By subcutaneous injection**
      - Adult: 3.6 mg every 28 days, to be administered into the anterior abdominal wall

  - Endometriosis
    - **By subcutaneous injection**
      - Adult: 3.6 mg every 28 days maximum duration of treatment 6 months (do not repeat), to be administered into the anterior abdominal wall

  - Endometrial thinning before intra-uterine surgery
    - **By subcutaneous injection**
      - Adult: 3.6 mg, dose may be repeated after 28 days if uterus is large or to allow flexible surgical timing, to be administered into the anterior abdominal wall

  - Before surgery in women who have anaemia due to uterine fibroids
    - **By subcutaneous injection**
      - Adult: 3.6 mg every 28 days maximum duration of treatment 3 months, to be given with supplementary iron, to be administered into the anterior abdominal wall

  - Pituitary desensitisation before induction of ovulation by gonadotrophins for in vitro fertilisation (after exclusion of pregnancy) (under expert supervision)
    - **By subcutaneous injection**
      - Adult: 3.6 mg, dose given to achieve pituitary down-regulation (usually 1–3 weeks) then gonadotrophin is administered (stopping gonadotrophin on
administration of chorionic gonadotrophin at appropriate stage of follicular development), to be administered into the anterior abdominal wall.

Zoladex LA®
Locally advanced prostate cancer as an alternative to surgical castration | Adjuvant treatment to radiotherapy or radical prostatectomy in patients with high-risk localised or locally advanced prostate cancer | Neoadjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer | Metastatic prostate cancer

BY SUBCUTANEOUS INJECTION
Adult: 10.8 mg every 12 weeks, to be administered into the anterior abdominal wall

Contra-Indications
Undiagnosed vaginal bleeding - use longer than 6 months in endometriosis (do not repeat)

Caution
Depression, diabetes, hypertension - patients with metabolic bone disease (decrease in bone mineral density can occur) - polycystic ovarian disease - risk of spinal cord compression in men - risk of ureteric obstruction in men

Side-effects
Rare
Hypercalcaemia (in women)
Frequency not known
Anaphylaxis, arthralgia, asthma, breast tenderness - changes in blood pressure - changes in breast size - changes in scalp and body hair - decrease in trabecular bone density - depression - dizziness - dyspareunia (when used for gynaecological conditions) - gastro-intestinal disturbances - gynaecomastia - headache - heart failure (when used for prostate or breast cancer) - hot flushes - hypersensitivity reactions - increased sweating - local reactions at injection site - loss of libido - menopausal-like symptoms - migraine - mood changes - musculoskeletal pain (when used for gynaecological conditions) - musculoskeletal weakness (when used for gynaecological conditions) - myalgia - myocardial infarction (when used for prostate or breast cancer) - oedema of the face and extremities (when used for gynaecological conditions) - oedema of the lower extremity (when used for gynaecological conditions) - oedema of the upper extremity (when used for gynaecological conditions) - palpitation (when used for gynaecological conditions) - paraesthesia - paraesthesia - pruritus - rash - sexual dysfunction - sleep disorders - urticaria - vaginal bleeding - vaginal dryness - visual disturbances - weight change - withdrawal bleeding

Tumour flare
During the initial stage (1–2 weeks) increased production of testosterone may be associated with progression of prostate cancer. In susceptible patients this tumour 'flare' may cause spinal cord compression, ureteric obstruction or increased bone pain. When such problems are anticipated, alternative treatments (e.g. orchidectomy) or concomitant use of an anti-androgen such as cyproterone acetate or flutamide are recommended; anti-androgen treatment should be started before the gonadorelin analogue.

Conception and Contraception
Non-hormonal, barrier methods of contraception should be used during entire treatment period. Pregnancy should be excluded before treatment, the first injection should be given during menstruation or shortly afterwards or use barrier contraception for 1 month beforehand.

Pregnancy
Avoid.

Breast Feeding
Avoid.

Monitoring Requirements
Men at risk of tumour 'flare' should be monitored closely during the first month of therapy for prostate cancer.

Directions for Administration
Rotate injection site to prevent atrophy and nodule formation.

Leuprolrel acetate

Drug action
Administration of gonadorelin analogues produces an initial phase of stimulation; continued administration is followed by down-regulation of gonadotrophin-releasing hormone receptors, thereby reducing the release of gonadotrophins (follicle stimulating hormone and luteinising hormone) which in turn leads to inhibition of androgen and oestrogen production.

Indications and Dose

Prostap 3 DCS®
Endometriosis
By Intramuscular Injection
Adult: Initially 11.25 mg for 1 dose, dose to be given as a single dose in first 5 days of menstrual cycle, then 11.25 mg every 3 months for maximum 6 months (course not to be repeated)

Locally advanced prostate cancer as an alternative to surgical castration | Adjuvant treatment to radiotherapy or radical prostatectomy in patients with high-risk localised or locally advanced prostate cancer | Metastatic prostate cancer

By Subcutaneous Injection
Adult: 11.25 mg every 3 months

Prostap SR DCS®
Endometriosis
By Subcutaneous Injection or by Intramuscular Injection
Adult: Initially 3.75 mg for 1 dose, dose to be given as a single dose in first 5 days of menstrual cycle, then 3.75 mg every 1 month for maximum 6 months (course not to be repeated)

Endometrial thickening before intra-uterine surgery
By Subcutaneous Injection or by Intramuscular Injection
Adult: Initially 3.75 mg for 1 dose, dose to be given as a single dose between day 3 and 5 of menstrual cycle, 5–6 weeks before surgery

Reduction of size of uterine fibroids and of associated bleeding before surgery
By Subcutaneous Injection or by Intramuscular Injection
Adult: Initially 3.75 mg every 1 month usually for 3–4 months (maximum 6 months)

Locally advanced prostate cancer as an alternative to surgical castration | Adjuvant treatment to radiotherapy or radical prostatectomy in patients with high-risk localised or locally advanced prostate cancer | Metastatic prostate cancer

By Subcutaneous Injection or by Intramuscular Injection
Adult: 3.75 mg every 1 month
Endocrine system

- **CONTRA-INDICATIONS** Undiagnosed vaginal bleeding - use longer than 6 months in the treatment of endometriosis (do not repeat)

- **CAUTIONS** Patients with metabolic bone disease (decrease in bone mineral density can occur)


- **SIDE-EFFECTS, FURTHER INFORMATION**
  - **When used for prostate cancer**
    - **Tumour flare** In prostate cancer, during the initial stage (1–2 weeks) increased production of testosterone may be associated with progression of prostate cancer. In susceptible patients this tumour 'flare' may cause spinal cord compression, ureteric obstruction or increased bone pain. When such problems are anticipated, alternative treatments (e.g. orchidectomy) or concomitant use of an anti-androgen such as cyproterone acetate or flutamide are recommended; anti-androgen treatment should be started before the gonadorelin analogue.
  - **CONCEPTION AND CONTRACEPTION** Non-hormonal, barrier methods of contraception should be used during entire treatment period. Pregnancy should be excluded before treatment, the first injection should be given during menstruation or shortly afterwards or use barrier contraception for 1 month beforehand.
  - **PREGNANCY** Avoid—teratogenic in animal studies.
  - **BREAST FEEDING** Avoid.
  - **MONITORING REQUIREMENTS**
    - Monitor liver function.
    - Men at risk of tumour 'flare' should be monitored closely during the first month of therapy.
  - **DIRECTIONS FOR ADMINISTRATION** Rotate injection site to prevent atrophy and nodule formation.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Powder and solvent for suspension for injection**
    - **Prostop 3 DCS (Takeda UK Ltd)**
      - Leuprorelin acetate 11.25 mg
      - Prostop 3 DCS 11.25mg powder and solvent for suspension for injection pre-filled syringes | 1 pre-filled disposable injection (PFS) £225.72 DT price = £225.72
    - **Prostop SR DCS (Takeda UK Ltd)**
      - Leuprorelin acetate 3.75 mg
      - Prostop SR DCS 3.75mg powder and solvent for suspension for injection pre-filled syringes | 1 pre-filled disposable injection (PFS) £75.24 DT price = £75.24

Nafarelin

- **DRUG ACTION** Administration of gonadorelin analogues produces an initial phase of stimulation; continued administration is followed by down-regulation of gonadotrophin-releasing hormone receptors, thereby reducing the release of gonadotrophins (follicle stimulating hormone and luteinising hormone) which in turn leads to inhibition of androgen and oestrogen production.

**INDICATIONS AND DOSE**

**Endometriosis**

- **BY INTRANASAL ADMINISTRATION**
  - Adult: 200 micrograms twice daily for maximum 6 months (do not repeat), one spray in one nostril in the morning, and one spray in the other nostril in the evening (starting on days 2–4 of menstruation).

**Pituitary desensitisation before induction of ovulation by gonadotrophins for in vitro fertilisation (under expert supervision)**

- **BY INTRANASAL ADMINISTRATION**
  - Adult: 400 micrograms twice daily, one spray in each nostril, to be started in early follicular phase (day 2) or, after exclusion of pregnancy, in midluteal phase (day 21) and continued until down regulation achieved (usually within 4 weeks) then maintained (usually for 8–12 days) during gonadotrophin administration (stopping gonadotrophin and nafarelin on administration of choric gonadotrophin at follicular maturity), discontinue if down-regulation not achieved within 12 weeks

**SIDE-EFFECTS, FURTHER INFORMATION**

**Menopausal-like symptoms** These effects can be reduced by hormone replacement (e.g. with an oestrogen and a progestogen or with tibolone).

- **CONCEPTION AND CONTRACEPTION** Non-hormonal, barrier methods of contraception should be used during entire treatment period. Pregnancy should be excluded before treatment, the first dose should be given during menstruation or shortly afterwards or use barrier contraception for 1 month beforehand.

- **PREGNANCY** Avoid.

- **BREAST FEEDING** Avoid.

- **DIRECTIONS FOR ADMINISTRATION** Avoid use of nasal decongestants before and for at least 30 minutes after treatment; repeat dose if sneezing occurs during or immediately after administration.

**PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer nafarelin nasal spray.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Spray**

**CAUTIONARY AND ADVISORY LABELS**

10. **Synarel (Pfizer Ltd)**

- Nafarelin (as Nafarelin acetate) 200 microgram per 1 dose
  - Synarel 200micrograms/dose nasal spray | 60 dose (PFS) £52.43
Triptorelin

**DRUG ACTION** Administration of gonadorelin analogues produces an initial phase of stimulation; continued administration is followed by down-regulation of gonadotrophin-releasing hormone receptors, thereby reducing the release of gonadotrophins (follicle stimulating hormone and luteinising hormone) which in turn leads to inhibition of androgen and oestrogen production.

**INDICATIONS AND DOSE**

**DECAPEPTYL<sup>®</sup> SR 3MG**

**Endometriosis**

- **BY INTRAMUSCULAR INJECTION**
  - Adult: 3 mg every 4 weeks maximum duration of 6 months (not to be repeated), to be started during first 5 days of menstrual cycle

**Reduction in size of fibroids**

- **BY INTRAMUSCULAR INJECTION**
  - Adult: 3 mg every 4 weeks for at least 3 months, maximum duration of treatment 6 months (not to be repeated), to be started during first 5 days of menstrual cycle

**Locally advanced non-metastatic prostate cancer as an alternative to surgical castration**

- **Metastatic prostate cancer**
  - **Adjuvant treatment to radiotherapy in high-risk localised or locally advanced prostate cancer**
  - **Neoadjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer**
  - **Adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression**

- **BY INTRAMUSCULAR INJECTION**
  - Adult: 3 mg every 4 weeks

**DECAPEPTYL<sup>®</sup> SR 11.25MG**

**Endometriosis**

- **BY INTRAMUSCULAR INJECTION**
  - Adult: 11.25 mg every 3 months for maximum 6 months (not to be repeated), to be started during first 5 days of menstrual cycle

**Locally advanced non-metastatic prostate cancer as an alternative to surgical castration**

- **Metastatic prostate cancer**
  - **Adjuvant treatment to radiotherapy in high-risk localised or locally advanced prostate cancer**
  - **Neoadjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer**
  - **Adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression**

- **BY INTRAMUSCULAR INJECTION**
  - Adult: 11.25 mg every 3 months

**DECAPEPTYL<sup>®</sup> SR 22.5MG**

**Locally advanced non-metastatic prostate cancer as an alternative to surgical castration**

- **Metastatic prostate cancer**
  - **Adjuvant treatment to radiotherapy in high-risk localised or locally advanced prostate cancer**
  - **Neoadjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer**
  - **Adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression**

- **BY INTRAMUSCULAR INJECTION**
  - Adult: 22.5 mg every 6 months

**SALVACYL<sup>®</sup>**

**Male hypersexuality with severe sexual deviation**

- **BY INTRAMUSCULAR INJECTION**
  - Adult: 11.25 mg every 12 weeks

**GONAPETYL DEPOT<sup>®</sup>**

**Endometriosis | Reduction in size of fibroids**

- **BY SUBCUTANEOUS INJECTION OR BY DEEP INTRAMUSCULAR INJECTION**
  - **Adult:** 3.75 mg every 4 weeks maximum duration of 6 months (not to be repeated), to be started during first 5 days of menstrual cycle

**Advanced prostate cancer**

- **BY SUBCUTANEOUS INJECTION OR BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 3.75 mg every 4 weeks

**CONTRA-INDICATIONS** In endometriosis do not use for longer than 6 months (do not repeat) - undiagnosed vaginal bleeding

**SALVACYL<sup>®</sup>** Severe osteoporosis

**CAUTIONS**

**GENERAL CAUTIONS**

Patients with metabolic bone disease (decrease in bone mineral density can occur)

**SPECIFIC CAUTIONS**

- **When used for prostate cancer** risk factors for osteoporosis - risk of spinal cord compression in men - risk of ureteric obstruction in men

**SALVACYL<sup>®</sup>** Increased risk of sensitivity to restored testosterone if treatment interrupted—consider administration of an antiandrogen before stopping treatment - transient increase in serum testosterone occurs on initiation—consider administration of an antiandrogen

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

- Anaphylaxis - arthralgia - asthenia - asthma - breast tenderness (males and females) - changes in blood pressure - changes in breast size - changes in scalp and body hair - depression - gastro-intestinal disturbances - headache - hot flushes - hypersensitivity reactions - increased sweating - local reactions at injection site - mood changes - ovarian cysts (may require withdrawal) - paraesthesia - pruritus - rash - urticaria - visual disturbances - weight changes

**SPECIFIC SIDE-EFFECTS**

- **When used for prostate cancer** Dizziness - dry mouth - hair loss - increased dysuria - myalgia - peripheral oedema - sexual dysfunction - sleep disorders

- **When used for reduction in size of uterine fibroids** Bleeding associated with fibroid degeneration - decrease in trabecular bone density - dyspareunia - loss of libido - menopausal-like symptoms - migraine - musculoskeletal pain - musculoskeletal weakness - oedema of the face and extremities - palpitation - vaginal dryness - withdrawal bleeding (may occur in the first month of treatment)

- **When used for endometriosis** Decrease in trabecular bone density - dyspareunia - loss of libido - menopausal-like symptoms - migraine - musculoskeletal pain - musculoskeletal weakness - oedema of the face and extremities - palpitation - vaginal dryness - withdrawal bleeding (may occur in the first month of treatment)

- **When used for endometriosis** Decrease in trabecular bone density - dyspareunia - loss of libido - menopausal-like symptoms - migraine - musculoskeletal pain - musculoskeletal weakness - oedema of the face and extremities - palpitation - vaginal dryness - withdrawal bleeding (may occur in the first month of treatment)

- **When used for gonadotrophin-dependent precocious puberty** Decrease in trabecular bone density - dyspareunia - loss of libido - menopausal-like symptoms - migraine - musculoskeletal pain - musculoskeletal weakness - oedema of the face and extremities - palpitation - vaginal dryness - withdrawal bleeding (may occur in the first month of treatment)
636 Gonadotrophin responsive conditions

ENDOCRINE SYSTEM

Cetrorelix

ANTAGONISTS

GONADOTROPHIN-RELEASING HORMONE ANTAGONISTS

Cetrorelix

INDICATIONS AND DOSE

Adjucent in the treatment of female infertility (initiated under specialist supervision)

BY SUBCUTANEOUS INJECTION

- Adult: 250 micrograms daily, dose to be injected preferably into the upper leg (rotate injection sites to prevent lipoatrophy), dose to be administered in the morning (or each afternoon) starting on day 5 or day 6 of ovarian stimulation with gonadotrophins, continue throughout administration of gonadotrophins including day of ovulation induction (if administering in afternoon, give last dose in afternoon before ovulation induction).

SIDE-EFFECTS

- Rare: Hypersensitivity reactions
- Pregnancy: Avoid in confirmed pregnancy.
- Breastfeeding: Avoid.
- Hepatic impairment: Avoid in moderate or severe hepatic impairment.
- Renal impairment: Avoid in moderate or severe renal impairment.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Ganirelix

INDICATIONS AND DOSE

Adjunct in the treatment of female infertility (under expert supervision)

BY SUBCUTANEOUS INJECTION

- Adult: 250 micrograms daily, dose to be injected preferably into the upper leg (rotate injection sites to prevent lipoatrophy), dose to be administered in the morning (or each afternoon) starting on day 5 or day 6 of ovarian stimulation with gonadotrophins, continue throughout administration of gonadotrophins including day of ovulation induction (if administering in afternoon, give last dose in afternoon before ovulation induction).

SIDE-EFFECTS

- Common or very common: Headache, injection site reactions, nausea
- Rare: Hypersensitivity reactions
- Pregnancy: Avoid in confirmed pregnancy.
- Breastfeeding: Avoid.
- Hepatic impairment: Avoid in moderate or severe liver impairment.
- Renal impairment: Avoid in moderate or severe renal impairment.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

6.1 Hereditary angioedema

GONADOTROPHIN-RELEASING HORMONE ANTAGONISTS

Danazol

- Drug action: Danazol inhibits pituitary gonadotrophins; it combines androgenic activity with antioestrogenic and antiprogestogenic activity.
7 Hypothalamic and anterior pituitary hormone related disorders

Hypothalamic and anterior pituitary hormones

Anterior pituitary hormones

Tetracosactide (tetracosacin), an analogue of corticotropin (ACTH), is used to test adrenocortical function; failure of the plasma cortisol concentration to rise after administration of tetracosactide indicates adrenocortical insufficiency.

Both corticotropin and tetracosactide were formerly used as alternatives to corticosteroids in conditions such as Crohn’s disease or rheumatoid arthritis; their value was limited by the variable and unpredictable therapeutic response and by the waning of their effect with time.

Gonadotrophins

Follicle-stimulating hormone (FSH) and luteinising hormone (LH) together, follicle-stimulating hormone alone (as in follitropin), or chorionic gonadotrophin p. 639, are used in the treatment of infertility in women with proven hypopituitarism or who have not responded to clomifene citrate p. 659, or in superovulation treatment for assisted conception (such as in vitro fertilisation).

The gonadotrophins are also occasionally used in the treatment of hypogonadotropic hypogonadism and associated oligosperma. There is no justification for their use in primary gonadal failure.

Chorionic gonadotrophin has also been used in delayed puberty in the male to stimulate endogenous testosterone production, but has little advantage over testosterone.

Growth hormone

Growth hormone is used to treat deficiency of the hormone in children and in adults. In children it is used in Prader-Willi syndrome, Turner syndrome, chronic renal insufficiency, short children considered small for gestational age at birth, and short stature homeobox-containing gene (SHOX) deficiency.

Growth hormone of human origin (hGH; somatotrophin) has been replaced by a growth hormone of human sequence, somatropin p. 642, produced using recombinant DNA technology.

Mecasermin, a human insulin-like growth factor-I (rhIGF-I), is licensed to treat growth failure in children and adolescents with severe primary insulin-like growth factor-I deficiency.

Hypothalamic hormones

Gonadorelin p. 639 when injected intravenously in normal subjects leads to a rapid rise in plasma concentrations of both luteinising hormone (LH) and follicle-stimulating

...
hormone (FSH). It has not proved to be very helpful, however, in distinguishing hypothalamic pituitary lesions. 

**7.1 Adrenocortical function testing**

**CORTICOTROPHINS**

**Tetracosactide**

(Tetracosactrin)

**INDICATIONS AND DOSE**

Diagnosis of adrenocortical insufficiency (diagnostic 30-minute test)
- By intravenous injection or by intramuscular injection
  - Adult: 250 micrograms for 1 dose

Diagnosis of adrenocortical insufficiency (diagnostic 5-hour test)
- By intramuscular injection using depot injection
  - Adult: 1 mg for 1 dose

Alternative to corticosteroids in conditions such as Crohn’s disease or rheumatoid arthritis (formerly used but value was limited by the variable and unpredictable therapeutic response and by the waning of effect with time)

Initially by intramuscular injection using depot injection
  - Adult: Initially 1 mg daily, alternatively (by intramuscular injection) initially 1 mg every 12 hours, (in acute cases), then (by intramuscular injection) reduced to 1 mg every 2–3 days, followed by (by intramuscular injection) 1 mg once weekly, alternatively (by intramuscular injection) 500 micrograms every 2–3 days

**SIDE-EFFECTS**


**ALLERGY AND CROSS-SENSITIVITY**

Contraindicated in patients with history of hypersensitivity to tetracosactide/corticotrophins or excipients.

**PREGNANCY**

Avoid (but may be used diagnostically if essential).

**BREAST FEEDING**

Avoid (but may be used diagnostically if essential).

**HEPATIC IMPAIRMENT**

An enhanced effect of tetracosactide therapy may occur in patients with cirrhosis of the liver. Use with caution in hepatic impairment. Monitor hepatic function closely during treatment.

**RENAL IMPAIRMENT**

Use with caution in patients with renal impairment.

**EFFECT ON LABORATORY TESTS**

May suppress skin test reactions. Post administration total plasma cortisol levels during 30-minute test for diagnosis of adrenocortical insufficiency might be misleading due to altered cortisol binding globulin levels in some special clinical situations including, patients on oral contraceptives, post-operative patients, critical illness, severe liver disease and nephrotic syndrome.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Synacthen (Questcor Operations Ltd)

  Tetracosactide acetate 250 microgram per 1 ml Synacthen 250micrograms/1ml solution for injection ampoules | 5 ampoule | £190.00

**Suspension for injection**

- Synacthen Depot (Questcor Operations Ltd)

  Tetracosactide acetate 1 mg per 1 ml Synacthen Depot 1mg/1ml suspension for injection ampoules | 10 ampoule | £41.83
7.2 Assessment of pituitary function

GONADOTROPIN-RELEASING HORMONE ANALOGUES

Gonadorelin
(Gonadotrophin-releasing hormone; GnRH; LH-RH)

**INDICATIONS AND DOSE**
Assessment of pituitary function
BY SUBCUTANEOUS INJECTION OR BY INTRAVENOUS INJECTION
▶ Adult: 100 micrograms for 1 dose

- **CAUTIONS** Pituitary adenoma
- **SIDE-EFFECTS** Abdominal pain, headache, hypersensitivity reaction on repeated administration of large doses, increased menstrual bleeding, irritation at injection site, nausea
- **PREGNANCY** Avoid.
- **BREAST FEEDING** Avoid.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  - **EXCIPIENTS:** May contain Benzyl alcohol
  - **GONADORELIN (Non-proprietary)**
    Gonadorelin (as Gonadorelin hydrochloride) 100 microgram: Gonadorelin 100microgram powder and solvent for solution for injection vials | 1 vial (PSt) £75.00 (Hospital only)

7.3 Gonadotrophin replacement therapy

GONADOTROPHINS

Chorionic gonadotrophin alfa
(Human chorionic gonadotrophin; HCG)

**INDICATIONS AND DOSE**
Treatment of infertility in women with proven hypopituitarism or who have not responded to clomifene | Supovulation treatment for assisted conception (such as in vitro fertilisation)
BY SUBCUTANEOUS INJECTION
▶ Adult: Adjusted according to response.

- **CONTRA-INDICATIONS** Androgen-dependent tumours
- **CAUTIONS** Asthma, cardiac impairment, epilepsy, migraine, prepubertal boys (risk of premature epiphyseal closure or precocious puberty)
- **SIDE-EFFECTS** Gynaecomastia, headache, local reactions, may aggravate ovarian hyperstimulation, mood changes, multiple pregnancy, oedema (particularly in males—reduce dose), tiredness
- **RENAL IMPAIRMENT** Use with caution.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  - **Powder and solvent for solution for injection**
    Chorionic gonadotrophin human 5000 unit Choragon 5,000 unit powder and solvent for solution for injection ampoules | 3 ampoules (PSt) £3.77 Schedule 4 (CD Anab)
    Pregnyl (Merck Sharp & Dohme Ltd) Chorionic gonadotrophin human 1,500 unit Pregnyl 1,500 unit powder and solvent for solution for injection ampoules | 1 ampoule (PSt) £1.12 Schedule 4 (CD Anab)
    Chorionic gonadotrophin human 5000 unit Pregnyl 5,000 unit powder and solvent for solution for injection ampoules | 1 ampoule (PSt) £3.15 Schedule 4 (CD Anab)

Corifollitropin alfa

**INDICATIONS AND DOSE**
Controlled ovarian stimulation in combination with a gonadotrophin-releasing hormone antagonist
BY SUBCUTANEOUS INJECTION
▶ Adult (body-weight up to 60 kg): 100 micrograms
▶ Adult (body-weight 60 kg and above): 150 micrograms

- **CONTRA-INDICATIONS** History of ovarian hyperstimulation syndrome, ovarian enlargement or cyst, polycystic ovarian syndrome, tumours of breast, tumours of hypopituitarism, tumours of ovaries, tumours of pituitary, tumours of uterus, vaginal bleeding of unknown cause
- **CAUTIONS** Acute porphyrias p. 864, risk factors for thromboembolism, risk of ovarian hyperstimulation syndrome

- **SIDE-EFFECTS**
  - Common or very common Breast pain, fatigue, headache, nausea, ovarian hyperstimulation, pelvic pain
**Hypothalamic and anterior pituitary hormone related disorders**

*Uncommon*  Abdominal distension and pain • constipation • diarrhoea • dizziness • ovarian torsion • vomiting
*Frequency not known*  Ectopic pregnancy • miscarriage • multiple pregnancies

**BREAST FEEDING**  Avoid.

**RENAL IMPAIRMENT**  Avoid.

**SIDE-EFFECTS**

**CONTRA-INDICATIONS**  Ovarian cysts (not caused by polycystic ovarian syndrome) • tumours of breast • tumours of hypothalamus • tumours of ovaries • tumours of pituitary • tumours of prostate • tumours of testes • tumours of uterus • vaginal bleeding of unknown cause

**CAUTIONS**  Acute porphyrias p. 864

**SIDE-EFFECTS**

**Common or very common**  Fever • gastro-intestinal disturbances • headache • hypersensitivity reactions • injection site reactions • joint pain • ovarian hyperstimulation

**Very rare**  Thromboembolism

**Frequency not known**  Acne • gynaecomastia • increased risk of miscarriage • increased risk of multiple pregnancy • weight gain

**PREGNANCY**  Avoid.

**BREAST FEEDING**  Avoid.

**PATIENT AND CARER ADVICE**  Patients planning to conceive should be warned that there is a risk of multiple pregnancy.

**MEDICINAL FORMS**  There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Elonva (Merck Sharp & Dohme Ltd)
- Corifollitropin alfa 200 microgram per 1 ml  Elonva 100micrograms/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (£94.00)
- Corifollitropin alfa 300 microgram per 1 ml  Elonva 150micrograms/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (£141.00)

**Indications and dose**

Infertility in women with proven hypopituitarism or who have not responded to clomifene | Superovulation treatment for assisted conception (such as in vitro fertilisation)

**BY SUBCUTANEOUS INJECTION**

- Adult: Adjusted according to response.

**Hypogonadotrophic hypogonadism**

**BY SUBCUTANEOUS INJECTION**

- Adult: (consult product literature).

**Contraindications**

Ovarian cysts (not caused by polycystic ovarian syndrome) • tumours of breast • tumours of hypothalamus • tumours of ovaries • tumours of pituitary • tumours of prostate • tumours of testes • tumours of uterus • vaginal bleeding of unknown cause

**Caution**

Acute porphyrias p. 864

**Side-effects**

**Common or very common**  Fever • gastro-intestinal disturbances • headache • hypersensitivity reactions • injection site reactions • joint pain • ovarian hyperstimulation

**Very rare**  Thromboembolism

**Frequency not known**  Acne • gynaecomastia • increased risk of miscarriage • increased risk of multiple pregnancy • weight gain

**Pregnancy**  Avoid.

**Breast feeding**  Avoid.

**Patient and carer advice**  Patients planning to conceive should be warned that there is a risk of multiple pregnancy.

**Medicinal forms**  There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Follitropin alfa 600 unit per 1 ml  Bemfola 225units/0.375ml solution for injection pre-filled pen | 1 pre-filled disposable injection (£94.00)
- Bemfola 300units/0.5ml solution for injection pre-filled pen | 1 pre-filled disposable injection (£141.00)
- Bemfola 450units/0.75ml solution for injection pre-filled pen | 1 pre-filled disposable injection (£194.00)

**Indications and dose**

Infertility in women with proven hypopituitarism or who have not responded to clomifene | Superovulation treatment for assisted conception (such as in vitro fertilisation)

**By subcutaneous injection**

- Adult: Adjusted according to response.

**Contraindications**

Ovarian cysts (not caused by polycystic ovarian syndrome) • tumours of breast • tumours of hypothalamus • tumours of ovaries • tumours of pituitary • tumours of prostate • tumours of testes • tumours of uterus • vaginal bleeding of unknown cause

**Caution**

Acute porphyrias p. 864

**Side-effects**

**Common or very common**  Fever • gastro-intestinal disturbances • headache • hypersensitivity reactions • injection site reactions • joint pain • ovarian hyperstimulation

**Very rare**  Thromboembolism

**Frequency not known**  Acne • gynaecomastia • increased risk of miscarriage • increased risk of multiple pregnancy • weight gain

**Pregnancy**  Avoid.
Lutropin alfa
(Recombinant human luteinising hormone)

INDICATIONS AND DOSE
Treatment of infertility in women with proven hypopituitarism or who have not responded to clomifene (in conjunction with follicle-stimulating hormone) Superovulation treatment for assisted conception (such as in vitro fertilisation) (in conjunction with follicle-stimulating hormone)
BY SUBCUTANEOUS INJECTION
Adult: Adjusted according to response.

CONTRA-INDICATIONS Mammary carcinoma - ovarian carcinoma - ovarian enlargement or cyst (unless caused by polycystic ovarian disease) - tumours of hypothalamus - tumours of pituitary - undiagnosed vaginal bleeding - uterine carcinoma
CAUTIONS Acute porphyrias p. 864

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Powder and solvent for solution for injection
- Luveris (Merck Serono Ltd)
- Lutropin alfa 75 unit Luveris 75unit powder and solvent for solution for injection vials | 1 vial £31.38

Also available in combination with follitropin alfa, p. 640

Menotrophin

INDICATIONS AND DOSE
Infertility in women with proven hypopituitarism or who have not responded to clomifene | Superovulation treatment for assisted conception (such as in vitro fertilisation)
BY SUBCUTANEOUS INJECTION OR BY DEEP INTRAMUSCULAR INJECTION
Adult: Adjusted according to response.

CONTRA-INDICATIONS Ovarian cysts (not caused by polycystic ovarian syndrome) - tumours of breast - tumours of hypothalamus - tumours of ovaries - tumours of pituitary - tumours of prostate - tumours of testes - tumours of uterus - vaginal bleeding of unknown cause
CAUTIONS Acute porphyrias p. 864
SIDE-EFFECTS Very rare Thromboembolism
Frequency not known Fever - gastro-intestinal disturbances - headache - hypersensitivity reactions - increased risk of miscarriage - increased risk of multiple

Urofollitropin

INDICATIONS AND DOSE
Infertility in women with proven hypopituitarism or who have not responded to clomifene | Superovulation treatment for assisted conception (such as in vitro fertilisation)
BY SUBCUTANEOUS INJECTION OR BY DEEP INTRAMUSCULAR INJECTION
Adult: Adjusted according to response.
7.4 Growth hormone disorders

GROWTH HORMONE RECEPTOR ANTAGONISTS

Pegvisomant

- **DRUG ACTION** Pegvisomant is a genetically modified analogue of human growth hormone and is a highly selective growth hormone receptor antagonist.

- **INDICATIONS AND DOSE**
  - Treatment of acromegaly in patients with inadequate response to surgery, radiation, or both, and to treatment with somatostatin analogues (initiated by a specialist) **BY SUBCUTANEOUS INJECTION**
  - Adult: Initially 80 mg for 1 dose, followed by 10 mg daily, then increased in steps of 5 mg daily, adjusted according to response; maximum 30 mg per day

- **CAUTIONS**
  - Diabetes mellitus (adjustment of antidiabetic therapy may be necessary) - liver disease

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Injection-site reactions: Rotate injection sites to avoid lipoatrophy.

- **CONCEPTION AND CONTRACEPTION** Possible increase in female fertility.

- **PREGNANCY** Avoid.

- **BREAST FEEDING** Avoid.

- **MONITORING REQUIREMENTS** Monitor liver enzymes every 4–6 weeks for 6 months or if symptoms of hepatitis develop.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  - **Powder and solvent for solution for injection**
    - Somavert (Pfizer Ltd)
      - Pegvisomant 10 mg Somavert 10 mg powder and solvent for solution for injection vials | 30 vial PSH £1.500.00
      - Pegvisomant 15 mg Somavert 15 mg powder and solvent for solution for injection vials | 30 vial PSH £2.250.00
      - Pegvisomant 20 mg Somavert 20 mg powder and solvent for solution for injection vials | 1 vial PSH £100.00 | 30 vial PSH £3.000.00

**HUMAN GROWTH HORMONES**

Somatropin

*(Recombinant Human Growth Hormone)*

- **INDICATIONS AND DOSE**
  - Gonadal dysgenesis (Turner syndrome)
    - **BY SUBCUTANEOUS INJECTION**
      - Adult: 1.4 mg/m² daily, alternatively 45–50 micrograms/kg daily
  - Deficiency of growth hormone
    - **BY SUBCUTANEOUS INJECTION**
      - Adult: Initially 150–300 micrograms daily, then increased if necessary up to 1 mg daily, dose to be increased gradually, use minimum effective dose (requirements may decrease with age)

- **Dose equivalence and conversion**
  - Dose formerly expressed in units; somatropin 1 mg equivalent to 3 units.

- **CONTRA-INDICATIONS** Evidence of tumour activity (complete antitumour therapy and ensure intracranial lesions inactive before starting) - not to be used after renal transplantation - not to be used for growth promotion in children with closed epiphyses (or near closure in Prader-Willi syndrome) - severe obesity in Prader-Willi syndrome - severe respiratory impairment in Prader-Willi syndrome

- **CAUTIONS**
  - Diabetes mellitus (adjustment of antidiabetic therapy may be necessary) - disorders of the epiphysis of the hip (monitor for limping) - history of malignant disease - hypothyroidism—manufacturers recommend periodic thyroid function tests but limited evidence of clinical value - initiation of treatment close to puberty not recommended in child born small for corrected gestational age - papilloma - relative deficiencies of other pituitary hormones - resolved intracranial hypertension (monitor closely) - Silver-Russell syndrome

- **INTERACTIONS**
  - Appendix 1 (somatropin).

- **SIDE-EFFECTS**
  - Antibody formation - arthralgia - benign intracranial hypertension - carpal tunnel syndrome - fluid retention (peripheral oedema) - headache - hyperglycaemia - hypoglycaemia - hypothyroidism - insulin resistance - leukaemia in children with growth hormone deficiency - myalgia - nausea - papilloedema - paraesthesia - reactions at injection site - visual problems - vomiting

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Papilloma - Funduscopic for papilloma recommended if severe or recurrent headache, visual problems, nausea and vomiting occur — if papilloma confirmed consider benign intracranial hypertension (rare cases reported).

- **PREGNANCY** Discontinue if pregnancy occurs — no information available.

- **BREAST FEEDING** No information available. Absorption from milk unlikely.

- **DIRECTIONS FOR ADMINISTRATION** Rotate subcutaneous injection sites to prevent lipoatrophy.
Genotropin®, Humatrope cartridges, Norditropin®, NutropinAq®, Omnitrope®, Saizen® and Zomacton® preparations

For use by subcutaneous injection.

**HUMATROPE® POWDER FOR RECONSTITUTION**

For use by subcutaneous or intramuscular injection.

- **PRESCRIBING AND DISPENSING INFORMATION** Medicinal products containing somatropin are not identical and although there should be no important differences in terms of safety and efficacy, when prescribing biological products it is good practice to use the brand name.

**GENOTROPIN® PREPARATIONS**

Cartridges are for use with Genotropin® Pen device (non-NHS but available free of charge from clinics).

**NORDITROPIN® PREPARATIONS**

Cartridges are for use with appropriate NordiPen® device (non-NHS but available free of charge from clinics). Multidose disposable prefilled pens for use with Novofine® or NovoTwist® needles.

**NUTROPINaq®**

For use with NutropinAq® Pen device (non-NHS but available free of charge from clinics).

**OMNITROPE®**

For use with Omnitrope Pen 5® and Omnitrope Pen 10® devices (non-NHS but available free of charge from clinics).

**SAIZEN® POWDER AND SOLVENT FOR SOLUTION FOR INJECTION**

For use with one.click® autoinjector device or cool.click® needle-free autoinjector device or easypod® autoinjector device (non-NHS but available free of charge from clinics).

**SAIZEN® SOLUTION FOR INJECTION**

For use with cool.click® needle-free autoinjector device or easypod® autoinjector device (non-NHS but available free of charge from clinics).

**ZOMACTON®**

4mg vial for use with ZomaJet 2® Vision needle-free device (non-NHS but available free of charge from clinics) or with needles and syringes. 10mg vial for use with ZomaJet Vision X® needle-free device (non-NHS but available free of charge from clinics) or with needles and syringes.

- **NATIONAL FUNDING/ACCESS DECISIONS**

NICE technology appraisals (TAs)

- Somatropin for the treatment of growth failure in children (May 2010) NICE TA188

Somatropin is recommended for children with growth failure who:

- have growth-hormone deficiency
- have Turner syndrome
- have Prader-Willi syndrome
- have chronic renal insufficiency

- are born small for gestational age with subsequent growth failure at 4 years of age or later
- have short stature homeobox-containing gene (SHOX) deficiency.

Treatment should be discontinued if growth velocity increases by less than 50% from baseline in the first year of treatment. [www.nice.org.uk/TA188](http://www.nice.org.uk/TA188)

- **MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

EXCIPIENTS: May contain Benzyl alcohol

- **Norditropin NordiFlex** (Novo Nordisk Ltd)
  - Somatropin (epr) 10 mg per 1 ml Norditropin NordiFlex
  - 15mg/1.5ml solution for injection pre-filled pen | 1 pre-filled disposable injection [PDF] £347.70 Schedule 4 (CD Anab)
- **Norditropin Simplexx** (Novo Nordisk Ltd)
  - Somatropin (epr) 3.3 mg per 1 ml Norditropin Simplexx
  - 5mg/1.5ml solution for injection cartridges | 1 cartridge [PDF] £106.35 Schedule 4 (CD Anab)
  - Somatropin (epr) 6.7 mg per 1 ml Norditropin Simplexx
  - 10mg/1.5ml solution for injection cartridges | 1 cartridge [PDF] £212.70 Schedule 4 (CD Anab)
- **Omnitrope** (Merck Serono Ltd)
  - Somatropin (epr) 10 mg per 1 ml Omnitrope Simplexx
  - 15mg/1.5ml solution for injection cartridges | 1 cartridge [PDF] £319.05 Schedule 4 (CD Anab)
- **Saizen** (Ipsen Ltd)
  - Somatropin (epr) 5 mg per 1 ml Saizen Aq10mg/2ml solution for injection cartridges | 1 cartridge [PDF] £203.00 Schedule 4 (CD Anab)
  - Somatropin (epr) 6.67 mg per 1 ml Saizen Aq
  - 10mg/1.5ml solution for injection cartridges | 1 cartridge [PDF] £609.00 Schedule 4 (CD Anab)
- **Omnitrope Pen** (Sandoz Ltd)
  - Somatropin (rbe) 3.33 mg per 1 ml Omnitrope Pen 5 mg/1.5ml solution for injection cartridges | 5 cartridge [PDF] £368.74 Schedule 4 (CD Anab)
  - Somatropin (rbe) 6.67 mg per 1 ml Omnitrope Pen 10
  - 10mg/1.5ml solution for injection cartridges | 5 cartridge [PDF] £737.49 Schedule 4 (CD Anab)
- **Omnitrope SurePal** (Sandoz Ltd)
  - Somatropin (rbe) 3.33 mg per 1 ml Omnitrope SurePal 5
  - 5mg/1.5ml solution for injection cartridges | 5 cartridge [PDF] £368.74 Schedule 4 (CD Anab)
  - Somatropin (rbe) 6.67 mg per 1 ml Omnitrope SurePal
  - 10mg/1.5ml solution for injection cartridges | 5 cartridge [PDF] £737.49 Schedule 4 (CD Anab)
  - Somatropin (rbe) 10 mg per 1 ml Omnitrope SurePal
  - 15mg/1.5ml solution for injection cartridges | 5 cartridge [PDF] £1,106.22 Schedule 4 (CD Anab)
- **Saizen** (Merck Serono Ltd)
  - Somatropin (rbe) 5.825 mg per 1 ml Saizen 6mg/1.3ml solution for injection cartridges | 1 cartridge [PDF] £139.08 Schedule 4 (CD Anab)
  - Somatropin (rbe) 8 mg per 1 ml Saizen 12mg/1.5ml solution for injection cartridges | 1 cartridge [PDF] £278.16 Schedule 4 (CD Anab)
  - Saizen 20mg/2.5ml solution for injection cartridges | 1 cartridge [PDF] £463.60 Schedule 4 (CD Anab)

Powder and solvent for solution for injection

EXCIPIENTS: May contain Benzyl alcohol

- **Genotropin** (Pfizer Ltd)
  - Somatropin (rbe) 5.3 mg Genotropin
  - 5.3mg powder and solvent for solution for injection cartridges | 1 cartridge [PDF] £92.15 Schedule 4 (CD Anab)
  - Somatropin (rbe) 12 mg Genotropin
  - 12mg powder and solvent for solution for injection cartridges | 1 cartridge [PDF] £208.65 Schedule 4 (CD Anab)
- **Genotropin GoQuick** (Pfizer Ltd)
  - Somatropin (rbe) 5.3 mg Genotropin GoQuick
  - 5.3mg powder and solvent for solution for injection pre-filled disposable devices | 1 pre-filled disposable injection [PDF] £92.15 Schedule 4 (CD Anab)
8 Sex hormone responsive conditions

Sex hormones

Oestrogens and HRT

Oestrogens are necessary for the development of female secondary sexual characteristics; they also stimulate myometrial hypertrophy with endometrial hyperplasia. In terms of oestrogenic activity natural oestrogens (estradiol p. 649 (estradiol)), estrone (estrone), and estriol p. 713 (estriol)) have a more appropriate profile for hormone replacement therapy (HRT) than synthetic oestrogens (ethinylestradiol p. 655 (ethinylestradiol) and mestranol). Tibolone p. 646 has oestrogenic, progestogenic and weak androgenic activity.

Oestrogen therapy is given cyclically or continuously for a number of gynaecological conditions. If long-term therapy is required in women with a uterus, a progestogen should normally be added to reduce the risk of cystic hyperplasia of the endometrium (or of endometriotic foci in women who have had a hysterectomy) and possible transformation to cancer.

Oestrogens are no longer used to suppress lactation because of their association with thromboembolism.

Hormone replacement therapy

Hormone replacement therapy (HRT) with small doses of an oestrogen (together with a progestogen in women with a uterus) is appropriate for alleviating menopausal symptoms such as vaginal atrophy or vasomotor instability. Oestrogen given systemically in the perimenopausal and postmenopausal period or tibolone given in the postmenopausal period also diminish postmenopausal osteoporosis but other drugs are preferred. Menopausal atrophic vaginitis may respond to a short course of a topical vaginal oestrogen preparation used for a few weeks and repeated if necessary.

Systemic therapy with an oestrogen or drugs with oestrogenic properties alleviates the symptoms of oestrogen deficiency such as vasomotor symptoms. Tibolone combines oestrogenic and progestogenic activity with weak androgenic activity; it is given continuously, without cyclical progestogen.

HRT may be used in women with early natural or surgical menopause (before age 45 years), since they are at high risk of osteoporosis. For early menopause, HRT can be given until the approximate age of natural menopause (i.e. until age 50 years). Alternatives to HRT should be considered if osteoporosis is the main concern.

Clonidine hydrochloride p. 137 may be used to reduce vasomotor symptoms in women who cannot take an oestrogen, but clonidine hydrochloride may cause unacceptable side-effects.

HRT increases the risk of venous thromboembolism, stroke, endometrial cancer (reduced by a progestogen), breast cancer, and ovarian cancer; there is an increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause. For details of these risks see HRT Risk table.

The minimum effective dose of HRT should be used for the shortest duration. Treatment should be reviewed at least annually and for osteoporosis alternative treatments considered. HRT does not prevent coronary heart disease or protect against a decline in cognitive function and it should not be prescribed for these purposes. Experience of treating women over 65 years with HRT is limited.

For the treatment of menopausal symptoms the benefits of short-term HRT outweigh the risks in the majority of women, especially in those aged under 60 years.

Risk of breast cancer

It is estimated that using all types of HRT, including tibolone, increases the risk of breast cancer within 1–2 years of initiating treatment. The increased risk is related to the duration of HRT use (but not to the age at which HRT is started) and this excess risk disappears within 5 years of stopping. Radiological detection of breast cancer can be made more difficult as mammographic density can increase with HRT use; tibolone has only a limited effect on mammographic density.

Risk of endometrial cancer

The increased risk of endometrial cancer depends on the dose and duration of oestrogen-only HRT. In women with a uterus, the addition of a progestogen cyclically (for at least 10 days per 28-day cycle) reduces the additional risk of endometrial cancer; this additional risk is eliminated if a
progestogen is given continuously. However, this should be weighed against the increased risk of breast cancer.

**Risk of ovarian cancer**
Long-term use of combined HRT or oestrogen-only HRT is associated with a small increased risk of ovarian cancer; this excess risk disappears within a few years of stopping.

**Risk of venous thromboembolism**
Women using combined or oestrogen-only HRT are at an increased risk of deep vein thrombosis and of pulmonary embolism especially in the first year of use. In women who have predisposing factors (such as a personal or family history of deep vein thrombosis or pulmonary embolism, severe varicose veins, obesity, trauma, or prolonged bed-rest) it is prudent to review the need for HRT, as in some cases the risks of HRT may exceed the benefits. Travel involving prolonged immobility further increases the risk of deep vein thrombosis.

**Risk of stroke**
Risk of stroke increases with age, therefore older women have a greater absolute risk of stroke. Combined HRT or oestrogen-only HRT slightly increases the risk of stroke. Tibolone increases the risk of stroke about 2.2 times from the first year of treatment.

**Risk of coronary heart disease**
HRT does not prevent coronary heart disease and should not be prescribed for this purpose. There is an increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause. Although very little information is available on the risk of coronary heart disease in younger women who start HRT close to the menopause, studies suggest a lower relative risk compared with older women.

**Choice**
The choice of HRT for an individual depends on an overall balance of indication, risk, and convenience. A woman with a uterus normally requires oestrogen with cyclical progestogen for the last 12 to 14 days of the cycle or a preparation which involves continuous administration of an oestrogen and a progestogen (or one which provides both oestrogenic and progestogenic activity in a single preparation). Continuous combined preparations or tibolone are not suitable for use in the perimenopause or within 12 months of the last menstrual period; women who use such preparations may bleed irregularly in the early stages of treatment—if bleeding continues endometrial abnormality should be ruled out and consideration given to changing to cyclical HRT.

An oestrogen alone is suitable for continuous use in women without a uterus. However, in endometriosis, endometrial foci may remain despite hysterectomy and the addition of a progestogen should be considered in these circumstances.

An oestrogen may be given by mouth or by transdermal administration, which avoids first-pass metabolism.

**Surgery**
Major surgery under general anaesthesia, including orthopaedic and vascular leg surgery, is a predisposing factor for venous thromboembolism and it may be prudent to stop HRT 4–6 weeks before surgery; it should be restarted only after full mobilisation. If HRT is continued or if discontinuation is not possible (e.g. in non-elective
surgery), prophylaxis with unfractionated or low molecular weight heparin and graduated compression hosiery is advised.

**Reasons to stop HRT**
Hormone replacement therapy should be stopped (pending investigation and treatment), if any of the following occur:
- sudden severe chest pain (even if not radiating to left arm);
- sudden breathlessness (or cough with blood-stained sputum);
- unexplained swelling or severe pain in calf of one leg;
- severe stomach pain;
- serious neurological effects including unusual severe, prolonged headache especially if first time or getting progressively worse or sudden partial or complete loss of vision or sudden disturbance of hearing or other perceptual disorders or dysphasia or bad fainting attack or collapse or first unexplained epileptic seizure or weakness, motor disturbances, very marked numbness suddenly affecting one side or one part of body;
- hepatitis, jaundice, liver enlargement;
- blood pressure above systolic 160 mmHg or diastolic 95 mmHg;
- prolonged immobility after surgery or leg injury;
- detection of a risk factor which contra-indicates treatment

**Ethinylestradiol**
Ethinylestradiol p. 655 (ethinylestradiol) is licensed for short-term treatment of symptoms of oestrogen deficiency, for osteoporosis prophylaxis if other drugs cannot be used and for the treatment of female hypogonadism and menstrual disorders. Ethinylestradiol is occasionally used under specialist supervision for the management of hereditary haemorrhagic telangiectasia (but evidence of benefit is limited). It is also used licensed for the palliative treatment of prostate cancer.

**Raloxifene**
Raloxifene hydrochloride p. 659 is licensed for the treatment and prevention of postmenopausal osteoporosis; unlike hormone replacement therapy, raloxifene hydrochloride does not reduce menopausal vasomotor symptoms.

Raloxifene hydrochloride may reduce the incidence of oestrogen-receptor-positive breast cancer but its role in established breast cancer is not yet clear. The manufacturer advises avoiding its use during treatment for breast cancer.

**Progestogens and progesterone receptor modulators**
There are two main groups of progestogen, progesterone and its analogues (dydrogesterone and medroxyprogesterone acetate p. 695) and testosterone analogues (norethisterone p. 656 and norgestrel). The newer progestogens (desogestrel p. 691, norgestimate, and gestodene) are all derivatives of norgestrel; levonorgestrel p. 692 is the active isomer of norgestrel and has twice its potency. Progestogen p. 658 and its analogues are less androgenic than the testosterone derivatives and neither progesterone nor dydrogesterone causes virilisation.

Where endometriosis requires drug treatment, it may respond to a progestogen, e.g. norethisterone, administered on a continuous basis. Danazol p. 626 and gonadorelin analogues are also available.

Although oral progestogens have been used widely for menorrhagia they are relatively ineffective compared with tranexamic acid p. 95 or, particularly where dysmenorrhoea is also a factor, mefenamic acid p. 932; the levonorgestrel-releasing intra-uterine system may be particularly useful for women also requiring contraception. Oral progestogens have also been used for severe dysmenorrhoea, but where contraception is also required in younger women the best choice is a combined oral contraceptive.

Progestogens have also been advocated for the alleviation of premenstrual symptoms, but no convincing physiological basis for such treatment has been shown.

Progestogens have been used for the prevention of miscarriage in women with a history of recurrent miscarriage but there is no evidence of benefit and they are **not** recommended for this purpose. In pregnant women with antiphospholipid antibody syndrome who have suffered recurrent miscarriage, administration of low-dose aspirin p. 104 and a prophylactic dose of a low molecular weight heparin may decrease the risk of fetal loss (use under specialist supervision only).

**Hormone replacement therapy**
In women with a uterus a progestogen needs to be added to long-term oestrogen therapy for hormone replacement, to prevent cystic hyperplasia of the endometrium and possible transformation to cancer; it can be added on a cyclical or a continuous basis. Combined packs incorporating suitable progestogen tablets are available.

**Oral contraception**
Desogestrel, gestodene, levonorgestrel, norethisterone, and norgestimate are used in combined oral contraceptives and in progestogen-only contraceptives.

**Cancer**
Progestogens also have a role in neoplastic disease.

**Progesterone receptor modulators**
Ulipristal acetate p. 691 is a progesterone receptor modulator with a partial progesterone antagonist effect. Ulipristal acetate is used in the pre-operative treatment of moderate to severe symptoms of uterine fibroids; it is also used as an hormonal emergency contraceptive.

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**8.1 Female sex hormone responsive conditions**

**Drugs used for Female sex hormones responsive conditions not listed below:**
- Medroxyprogesterone acetate, p. 695; Clonidine hydrochloride, p. 137

**NORETYNODREL DERIVATIVES**

**Tibolone**

**INDICATIONS AND DOSE**
Short-term treatment of symptoms of oestrogen deficiency (including women being treated with gonadotrophin releasing hormone analogues) | Osteoporosis prophylaxis in women at high risk of fractures when other prophylaxis contra-indicated or not tolerated
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**By Mouth**
- Adult: 2.5 mg daily

- **CONTRA-INDICATIONS**
  - Acute porphyrias p. 864 | active or recent arterial thromboembolic disease (e.g. angina or myocardial infarction) | active thrombophilebitis | Dubin-Johnson and Rotor syndrome (or monitor closely) | history of breast cancer | history of cardiovascular disease | history of cerebrovascular disease | history of recurrent venous thromboembolism (unless already on anticoagulant treatment) | history of thromboembolism | history of thrombophilebitis, hormone-dependent tumours | liver disease (where liver function tests have failed to return to normal) | oestrogen-dependent cancer | thrombophilic disorder | uninvestigated or undiagnosed
vaginal bleeding - untreated endometrial hyperplasia - venous thromboembolism

- **CAUTIONS** Acute porphyrias p. 864 - diabetes (increased risk of heart disease) - epilepsy - factors predisposing to thromboembolism - history of breast nodules - closely monitor breast status (risk of breast cancer) - history of endometrial hyperplasia - history of fibrocystic disease - closely monitor breast status (risk of breast cancer) - history of liver disease - hyperglycaemia - hypophyseal tumours - migraine (or migraine-like headaches) - presence of antithrombin antibodies (increased risk of thrombotic events) - prolonged exposure to unopposed oestrogens may increase risk of developing endometrial cancer - risk factors for oestrogen-dependent tumours (e.g. breast cancer in first-degree relative) - risk of stroke

**CAUTIONS, FURTHER INFORMATION**

**Other conditions** The product literature advises caution in other conditions including hypertension, renal disease, asthma, epilepsy, sickle-cell disease, melanoma, osteosclerosis, multiple sclerosis, and systemic lupus erythematosus (but care required if antiphospholipid antibodies present). Evidence for caution in these conditions is unsatisfactory and many women with these conditions may stand to benefit from HRT.

- **INTERACTIONS** → Appendix 1 (tibolone).

- **SIDE-EFFECTS**
  - **Common or very common** Abdominal pain - facial hair - leucorrhoea - vaginal bleeding - weight changes
  - **Rare** Amnesia
  - **Frequency not known** Arthralgia - breast cancer - depression - dizziness - gastro-intestinal disturbances - headache - increased risk of gall-bladder disease - migraine - myalgia - oedema - pruritus - rash - seborrhoeic dermatitis - symptoms of endometriosis may be exacerbated - uterine fibroids may increase in size - visual disturbances

**SIDE-EFFECTS, FURTHER INFORMATION**

**Vaginal bleeding** Investigate for endometrial cancer if bleeding continues beyond 6 months or after stopping treatment.

**Reasons to withdraw treatment** Withdraw treatment if signs of thromboembolic disease, abnormal liver function tests, or signs of cholestatic jaundice.

- **PREGNANCY** Avoid; toxicity in animal studies.

- **BREAST FEEDING** Avoid.

- **HEPATIC IMPAIRMENT** Avoid in acute liver disease or if history of liver disease and liver function tests not returned to normal.

- **RENAL IMPAIRMENT** Patients with renal impairment should be closely monitored (risk of fluid retention).

- **PRESCRIBING AND DISPENSING INFORMATION** Unsuitable for use in the premenopause (unless being treated with gonadotrophin-releasing hormone analogue) and as (or with) an oral contraceptive. Also unsuitable for use within 12 months of last menstrual period (may cause irregular bleeding). If transferring from cyclical HRT, start at end of regimen; if transferring from continuous-compounded HRT, start at any time.

- **MEDICINAL FORMS**

  **Tablet**
  - **TIBOLONE (Non-proprietary)**
    - Tibolone 2.5 mg Tablets: 28 tablet 
      - price = £10.36 DF Tier 1
  - **Livial (Merck Sharp & Dohme Ltd)**
    - Livial 2.5 mg Tablets: 28 tablet 
      - price = £10.36 DF Tier 1

**OESTROGENS**

**Conjugated oestrogens (equine)**

**INDICATIONS AND DOSE**

**PREMARIN® TABLETS**

- **Menopausal symptoms**
  - **BY MOUTH**
    - Adult: 0.3–1.25 mg daily continuously; with cyclical progestogen for 12–14 days of each cycle in women with a uterus

- **Osteoporosis prophylaxis**
  - **BY MOUTH**
    - Adult: 0.625–1.25 mg daily continuously; with cyclical progestogen for 12–14 days of each cycle in women with a uterus

- **CONTRA-INDICATIONS** Active arterial thromboembolic disease (e.g. angina or myocardial infarction) - active thrombophlebitis - Dubin-Johnson syndromes (or monitor closely) - history of breast cancer - history of recurrent venous thromboembolism (unless already on anticoagulant treatment) - liver disease (where liver function tests have failed to return to normal) - oestrogen-dependent cancer - recent arterial thromboembolic disease (e.g. angina or myocardial infarction) - Rotor syndromes (or monitor closely) - thrombophilic disorder - undiagnosed vaginal bleeding - untreated endometrial hyperplasia - venous thromboembolism

- **CAUTIONS** Acute porphyrias p. 864 - diabetes (increased risk of heart disease) - factors predisposing to thromboembolism - history of breast nodules (closely monitor breast status — risk of breast cancer) - history of endometrial hyperplasia - history of fibrocystic disease (closely monitor breast status — risk of breast cancer) - hypophyseal tumours - increased risk of gall-bladder disease reported - migraine - migraine-like headaches - presence of antithrombin antibodies (increased risk of thrombotic events) - risk factors for oestrogen-dependent tumours (e.g. breast cancer in first-degree relative) - risk of breast cancer

**CAUTIONS, FURTHER INFORMATION**

**Risk of breast cancer** It is estimated that using all types of HRT, including tibolone, increases the risk of breast cancer within 1–2 years of initiating treatment. The increased risk is related to the duration of HRT use (but not to the age at which HRT is started) and this excess risk disappears within 5 years of stopping. Radiological detection of breast cancer can be made more difficult as mammographic density can increase with HRT use.

**Risk of endometrial cancer** The increased risk of endometrial cancer depends on the dose and duration of oestrogen-only HRT. In women with a uterus, the addition of a progestogen cyclically (for at least 10 days per 28-day cycle) reduces the additional risk of endometrial cancer; this additional risk is eliminated if a progestogen is given continuously. However, this should be weighed against the increased risk of breast cancer.

**Risk of ovarian cancer** Long-term use of combined HRT or oestrogen-only HRT is associated with a small increased risk of ovarian cancer. This excess risk disappears within a few years of stopping.

**Risk of venous thromboembolism** Women using combined or oestrogen-only HRT are at an increased risk of deep vein thrombosis and of pulmonary embolism especially in the first year of use. In women who have predisposing factors (such as a personal or family history of deep vein thrombosis or pulmonary embolism, severe varicose veins, obesity, trauma, or prolonged bed-rest) it is
Endocrine system

PREGNANCY

l

SIDE-EFFECTS

INTERACTIONS

l

Necessary preclude the possibility of becoming pregnant.

l

Pregnancy

INTERACTIONS

l

Risk of stroke

Risk of coronary heart disease

Hormonal contraceptive measures (such as condoms) are necessary. Measurement of follicle-stimulating hormone can help to determine fertility, but high measurements alone (particularly in women aged under 50 years) do not necessarily preclude the possibility of becoming pregnant.

PREGNANCY

l

Breast feeding

Avoid until weaning or for 6 months after birth (adverse effects on lactation).

SIDE-EFFECTS

Abdominal bloating - abdominal cramps - altered blood lipids (may lead to pancreatitis, rashes and chloasma) - breast enlargement - breast tenderness - changes in libido - cholestatic jaundice - contact lenses may irritate - depression - dizziness - fluid retention - glucose intolerance - headache - headache (on vigorous exercise) - leg cramps (rule out venous thrombosis) - migraine - mood changes - nausea - premenstrual-like syndrome - prolonged exposure to unopposed oestrogens may increase risk of developing endometrial cancer - sodium retention - symptoms of endometriosis may be exacerbated - uterine fibroids may increase in size - vaginal candidiasis - vomiting - weight changes

SIDE-EFFECTS, FURTHER INFORMATION

Withdrawal bleeding

Cyclical HRT (where a progestogen is taken, usually in a single continuous combined HRT (where a combination of oestrogen and progestogen is taken, usually in a single 28-day treatment cycle) is to avoid bleeding, but irregular bleeding may occur during the early treatment stages (if it continues endometrial abnormality should be excluded and consideration given to cyclical HRT instead).

CONCEPTION AND CONTRACEPTION

HRT does not provide contraception and a woman is considered potentially fertile for 2 years after her last menstrual period if she is under 50 years, and for 1 year if she is over 50 years. A woman who is under 50 years and free of all risk factors for venous and arterial disease can use a low-oestrogen combined oral contraceptive pill to provide both relief of menopausal symptoms and contraception; it is recommended that the oral contraceptive be stopped at 50 years of age since there are more suitable alternatives. If any potentially fertile woman needs HRT, non-hormonal contraceptive measures (such as condoms) are necessary. Measurement of follicle-stimulating hormone can help to determine fertility, but high measurements alone (particularly in women aged under 50 years) do not necessarily preclude the possibility of becoming pregnant.

PREGNANCY

Not known to be harmful.

Breast feeding

Avoid until weaning or for 6 months after birth (adverse effects on lactation).

l

HEPATIC IMPAIRMENT

Avoid in active liver disease including disorders of hepatic excretion (e.g. Dubin-Johnson or Rotor syndromes), infective hepatitis (until liver function returns to normal), and liver tumours.

l

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

- CONJUGATED OESTROGENS (EQUINE) (Non-proprietary)
  - Conjugated oestrogens 625 microgram Conjugated oestrogens 625 microgram tablets | 42 tablet (Pfizer) no price available | 84 tablet (Pfizer) no price available DT price = £4.02
  - Conjugated oestrogens 1.25 mg Conjugated oestrogens 1.25 mg tablets | 84 tablet (Pfizer) no price available DT price = £3.58
  - Premarin (Pfizer Ltd)
    - Conjugated oestrogens 300 microgram Premarin 0.3 mg tablets | 84 tablet (Pfizer) £6.07 DT price = £6.07
    - Conjugated oestrogens 625 microgram Premarin 0.625 mg tablets | 84 tablet (Pfizer) £4.02 DT price = £4.02
    - Conjugated oestrogens 1.25 mg Premarin 1.25 mg tablets | 84 tablet (Pfizer) £3.58 DT price = £3.58

Conjugated oestrogens with medroxyprogesterone

The properties listed below are those particular to the combination only. For the properties of the components please consider, medroxyprogesterone acetate p. 695, conjugated oestrogens (equine) p. 647.

INDICATIONS AND DOSE

PREMIQUE®

Menopausal symptoms in women with a uterus | Osteoporosis prophylaxis in women with a uterus

BY MOUTH

Adult: 1 tablet daily continuously

PREMIQUE® LOW DOSE TABLETS

Menopausal symptoms in women with a uterus

BY MOUTH

Adult: 1 tablet daily continuously

INTERACTIONS

Appendix 1 (oestrogens, progestogens).

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

- Premique (Pfizer Ltd)
  - Conjugated oestrogens 625 microgram, Medroxyprogesterone acetate 5 mg Premique 0.625 mg/5 mg tablets | 84 tablet (Pfizer) £10.61 DT price = £10.61

Modified-release tablet

- Premique (Pfizer Ltd)
  - Conjugated oestrogens 300 microgram, Medroxyprogesterone acetate 1.5 mg Premique Low Dose 0.3 mg/1.5 mg modified-release tablets | 84 tablet (Pfizer) £6.52 DT price = £6.52

Conjugated oestrogens with norgestrel

The properties listed below are those particular to the combination only. For the properties of the components please consider, conjugated oestrogens (equine) p. 647.

INDICATIONS AND DOSE

PREMPAK C® 0.625

Menopausal symptoms in women with a uterus | Osteoporosis prophylaxis in women with a uterus

BY MOUTH

Adult: 1 tablet daily continuously, maroon tablet to taken and started on day 1 of menstruation (or at any time if cycles have ceased or are infrequent) and

Conjugated oestrogens with medroxyprogesterone

The properties listed below are those particular to the combination only. For the properties of the components please consider, medroxyprogesterone acetate p. 695, conjugated oestrogens (equine) p. 647.
1 tablet daily, brown tablet to be taken and started on days 17–28 of each 28-day treatment cycle, subsequent courses are repeated without interval

PREMPAK C® 1.25
Menopausal symptoms in women with a uterus (if symptoms not fully controlled with lower strength pack) | Osteoporosis prophylaxis in women with a uterus (if symptoms not fully controlled with lower strength pack)
BY MOUTH

Adult: 1 tablet daily continuously, (yellow tablet) to be taken and started on day 1 of menstruation (or at any time if cycles have ceased or are infrequent) and 1 tablet daily, (brown tablet) to be taken and started on days 17–28 of each 28-day treatment cycle, subsequent courses are repeated without interval

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
- Prempak-C (Pfizer Ltd)
  Prempak-C 1.25mg/0.15mg tablets | 120 tablet pack £4.40 DT price = £4.40
  Prempak-C 0.625mg/0.15mg tablets | 120 tablet pack £6.25 DT price = £6.25

Estradiol

INDICATIONS AND DOSE
BEDOL®
Menopausal symptoms | Osteoporosis prophylaxis
BY MOUTH

Adult: 2 mg daily, started on day 1–5 of menstruation (or at any time if cycles have ceased or are infrequent), to be taken with cyclical progesterone for 12–14 days of each cycle in women with a uterus

CLIMAVAL®
Menopausal symptoms (if patient has had a hysterectomy)
BY MOUTH

Adult: 1–2 mg daily

ELLESTE-SOLO® 1-MG
Menopausal symptoms
BY MOUTH

Adult: 1 mg daily, starting on day 1 of menstruation (or at any time if cycles have ceased or are infrequent), to be taken with cyclical progesterone for 12–14 days of each cycle in women with a uterus

ELLESTE-SOLO® 2-MG
Menopausal symptoms not controlled with lower strength | Osteoporosis prophylaxis
BY MOUTH

Adult: 2 mg daily, started on day 1 of menstruation (or at any time if cycles have ceased or are infrequent), to be given with cyclical progesterone for 12–14 days of each cycle in women with a uterus

PROGYNOVA®
Menopausal symptoms
BY MOUTH

Adult: 1–2 mg daily continuously, to be started on day 1 of menstruation (or at any time if cycles have ceased or are infrequent), to be taken with cyclical progesterone for 12–14 days of each cycle in women with a uterus

Osteoporosis prophylaxis
BY MOUTH

Adult: 2 mg daily continuously, to be taken with cyclical progesterone for 12–14 days of each cycle in women with a uterus

ZUMENON®
Menopausal symptoms
BY MOUTH

Adult: Initially 1 mg daily, to be started within 5 days of onset of menstruation (or any time if cycles have ceased or are infrequent), increased if necessary to 2 mg daily, to be taken with a cyclical progestogen for 12–14 days of each cycle in women with a uterus

Osteoporosis prophylaxis
BY MOUTH

Adult: 2 mg daily, to be taken with a cyclical progestogen for 12–14 days of each cycle in women with a uterus

ELLESTE SOLO® MX
Menopausal symptoms
BY TRANSDERMAL APPLICATION

Adult: Apply 1 patch twice weekly continuously, started within 5 days of onset of menstruation (or at any time if cycles have ceased or are infrequent), to be used with cyclical progesterone for 12–14 days of each cycle in women with a uterus, initiate therapy with MX 40, subsequently adjust according to response

Osteoporosis prophylaxis
BY TRANSDERMAL APPLICATION

Adult: Apply 1 patch twice weekly continuously, started within 5 days of onset of menstruation (or at any time if cycles have ceased or are infrequent), to be used with cyclical progesterone for 12–14 days of each cycle in women with a uterus, initiate therapy with MX 80, subsequently adjust according to response

ESTRADERM MX®
Menopausal symptoms
BY TRANSDERMAL APPLICATION

Adult: Apply 1 patch twice weekly continuously, started within 5 days of onset of menstruation (or at any time if cycles have ceased or are infrequent), to be used with cyclical progesterone for at least 12 days of each cycle in women with a uterus, initiate therapy with MX 50; subsequently adjust according to response

ESTRADOT®
Menopausal symptoms
BY TRANSDERMAL APPLICATION

Adult: Apply 1 patch twice weekly continuously, to be used with cyclical progesterone for 12–14 days of each cycle in women with a uterus, initiate therapy with 25 patch for 3 months; subsequently adjust according to response

Osteoporosis prophylaxis
BY TRANSDERMAL APPLICATION

Adult: Apply 1 patch twice weekly continuously, to be used with cyclical progesterone for 12–14 days of each cycle in women with a uterus, initiate therapy with 50 patch; subsequently adjust according to response

EVOREL®
Menopausal symptoms | Osteoporosis prophylaxis
BY TRANSDERMAL APPLICATION

Adult: Apply 1 patch twice weekly continuously, started within 5 days of onset of menstruation (or at any time if cycles have ceased or are infrequent), continued →
650  Sex hormone responsive conditions

FEMSEVEN®
Menopausal symptoms | Osteoporosis prophylaxis
BY TRANSDERMAL APPLICATION
- Adult: Apply 1 patch once weekly continuously, to be used with cyclical prostogesten for 12–14 days of each cycle in women with a uterus, to be applied over an area twice that of the template provided, starting within 5 days of menstruation (or anytime if cycles have ceased or are infrequent), to be used with cyclical prostogesten for at least 12 days of each cycle in women with a uterus

PROGYNOVA® TS
Menopausal symptoms | Osteoporosis prophylaxis
BY TRANSDERMAL APPLICATION
- Adult: Apply 1 patch once weekly continuously, to be applied over an area twice that of the template provided, starting within 5 days of menstruation (or anytime if cycles have ceased or are infrequent), to be used with cyclical prostogesten for at least 12 days of each cycle in women with a uterus

OESTROGEL®
Menopausal symptoms | TO THE SKIN
- Adult: Apply 1.5 mg once daily continuously, increased if necessary up to 3 mg after 1 month continuously, to be applied over an area twice that of the template provided, starting within 5 days of menstruation (or anytime if cycles have ceased or are infrequent), to be used with cyclical prostogesten for at least 12 days of each cycle in women with a uterus

Dose equivalence and conversion
2 measures is equivalent to estradiol 1.5 mg

SANDRENA®
Menopausal symptoms | TO THE SKIN
- Adult: Apply 1 mg once daily, to be applied over area 1–2 times size of hand; with cyclical prostogesten for 12–14 days of each cycle in women with a uterus, dose may be adjusted after 2–3 cycles to lowest effective dose; usual dose 0.5–1.5 mg daily

ESTRING®
Postmenopausal urogenital conditions (not suitable for vasomotor symptoms or osteoporosis prophylaxis)
BY VAGINA
- Adult: To be inserted into upper third of vagina and worn continuously; replace after 3 months; max. duration of continuous treatment 2 years

VAGIFEM®
Improve the vaginal epithelium in menopausal atrophic vaginitis
BY VAGINA
- Adult: 1 tablet daily for 2 weeks, then reduced to 1 tablet twice weekly

CONTRA-INDICATIONS
Active arterial thromboembolic disease (e.g. angina or myocardial infarction) - active thrombophlebitis - Dubin-Johnson syndrome (or monitor closely) - history of breast cancer - history of recurrent venous thromboembolism (unless already on anticoagulant treatment) - oestrogen-dependent cancer - recent arterial thromboembolic disease (e.g. angina or myocardial infarction) - Rotor syndrome (or monitor closely) - thrombophilic disorder - undiagnosed vaginal bleeding - untreated endometrial hyperplasia - venous thromboembolism

CAUTIONS
GENERAL CAUTIONS
Acute porphyrias p. 864 - diabetes (increased risk of heart disease) - history of breast nodules - closely monitor breast status (risk of breast cancer) - history of endometrial hyperplasia; factors predisposing to thromboembolism - history of fibrocystic disease - closely monitor breast status (risk of breast cancer) - hypophysial tumours - increased risk of gall-bladder disease - migraine (or migraine-like headaches) - presence of antiphospholipid antibodies (increased risk of thrombotic events) - prolonged exposure to unopposed oestrogens may increase risk of developing endometrial cancer - risk factors for oestrogen-dependent tumours (e.g. breast cancer in first-degree relative) - symptoms of endometriosis may be exacerbated - uterine fibroids may increase in size

SPECIFIC CAUTIONS
- With vaginal use Interrupt treatment periodically to assess need for continued treatment

CAUTIONS, FURTHER INFORMATION
Risk of breast cancer
It is estimated that using all types of HRT increases the risk of breast cancer in women by about 3% after 1–2 years of initiating treatment. The increased risk is related to the duration of HRT use (but not to the age at which HRT is started) and this excess risk disappears within 5 years of stopping. Radiological detection of breast cancer can be made more difficult as mammographic density can increase with HRT use.

Risk of endometrial cancer
The increased risk of endometrial cancer depends on the dose and duration of oestrogen-only HRT. In women with a uterus, the addition of a progestogen cyclically (for at least 10 days per 28-day cycle) reduces the additional risk of endometrial cancer; this additional risk is eliminated if a progestogen is given continuously. However, this should be weighed against the increased risk of breast cancer.

Risk of ovarian cancer
Long-term use of combined HRT or oestrogen-only HRT is associated with a small increased risk of ovarian cancer. This excess risk disappears within a few years of stopping.

Risk of venous thromboembolism
Women using combined or oestrogen-only HRT are at an increased risk of deep vein thrombosis and of pulmonary embolism especially in the first year of use. In women who have predisposing factors (such as a personal or family history of deep vein thrombosis or pulmonary embolism, severe varicose veins, obesity, trauma, or prolonged bed-rest) it is prudent to review the need for HRT, as in some cases the risks of HRT may exceed the benefits. Travel involving prolonged immobility further increases the risk of deep vein thrombosis.

Risk of stroke
Risk of stroke increases with age, therefore older women have a greater absolute risk of stroke. Combined HRT or oestrogen–only HRT slightly increases the risk of stroke.

Risk of coronary heart disease
HRT does not prevent coronary heart disease and should not be prescribed for this purpose. There is an increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause. Although very little...
HEPATIC IMPAIRMENT

PREGNANCY

With transdermal use

SIDE-EFFECTS

INTERACTIONS

APPENDIX (oestrogens).

PATTER AND CARER ADVICE

SPECIFIC SIDE-EFFECTS

WITH transdermal use

SIDE-EFFECTS, FURTHER INFORMATION

Withdrawal bleeding

Cyclical HRT (where a progestogen is taken for 12–14 days of each 28-day oestrogen treatment cycle) usually results in regular withdrawal bleeding towards the end of the progestogen. The aim of continuous combined HRT (where a combination of oestrogen and progestogen is taken, usually in a single tablet, throughout each 28-day treatment cycle) is to avoid bleeding, but irregular bleeding may occur during the early treatment stages (if it continues endometrial abnormality should be excluded and consideration given to cyclical HRT instead).

CONCEPTION AND CONTRACEPTION HRT does not provide contraception and a woman is considered potentially fertile for 2 years after her last menstrual period if she is under 50 years, and for 1 year if she is over 50 years. A woman who is under 50 years and free of all risk factors for venous and arterial disease can use a low-oestrogen combined oral contraceptive pill to provide both relief of menopausal symptoms and contraception; it is recommended that the oral contraceptive be stopped at 50 years of age since there are more suitable alternatives. If any potentially fertile woman needs HRT, non-hormonal contraceptive measures (such as condoms) are necessary. Measurement of follicle-stimulating hormone can help to determine fertility, but high measurements alone (particularly in women aged under 50 years) do not necessarily preclude the possibility of becoming pregnant.

VAGIFEM® No evidence of damage to latex condoms and vaginal tracts.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: implant

Tablet

Estradiol (Non-proprietary)

Estradiol 1 mg Estradiol 1mg tablets | 18 tablet (PVM) no price available | 42 tablet (PVM) no price available | 48 tablet (PVM) no price available

Estradiol valerate 1 mg Estradiol valerate 1mg tablets | 6 tablet (PVM) no price available | 11 tablet (PVM) no price available | 16 tablet (PVM) no price available | 48 tablet (PVM) no price available

Estradiol valerate 2 mg Estradiol valerate 2mg tablets | 11 tablet (PVM) no price available | 16 tablet (PVM) no price available | 48 tablet (PVM) no price available | 70 tablet (PVM) no price available

Estradiol valerate 3 mg Estradiol valerate 3mg tablets | 6 tablet (PVM) no price available

Estradiol 4 mg Estradiol 4mg tablets | 36 tablet (PVM) no price available

Bedol (ReSource Medical UK Ltd)

£2.94 | 84 tablet (PVM) £8.82

£2.94 | 84 tablet (PVM) £8.82

£5.06

£5.06

Eileste Solo (Meda Pharmaceuticals Ltd)

£5.06

£5.06

£7.30

£7.30

£6.89

£6.89

Zumenon (BGP Products Ltd)

£6.89

£6.89

Pessary

Vagifem (Novo Nordisk Ltd)

Estradiol 10 microgram Vagifem 10microgram vaginal tablets | 24 pessary (PVM) £16.72 DT price = £16.72

information is available on the risk of coronary heart disease in younger women who start HRT close to the menopause, studies suggest a lower relative risk compared with older women.

Other conditions The product literature advises caution in other conditions including hypertension, renal disease, asthma, epilepsy, sickle-cell disease, melanoma, otosclerosis, multiple sclerosis, and systemic lupus erythematosus (but care required if antiphospholipid antibodies present). Evidence for caution in these conditions is unsatisfactory and many women with these conditions may stand to benefit from HRT.

 Specialist advice is advised for estradiol gels (administration).

OESTROGEL® Apply gel to clean, dry, intact skin such as arms, shoulders or inner thighs and allow to dry for 1 minute. Wash hands after application. Not to be applied on or near breasts or on vulval region. Avoid skin contact with another person (particularly male) and avoid other skin products or washing the area for at least 1 hour after application.

SANDRENA® Apply gel to intact areas of skin such as lower trunk or thighs, using right and left sides on alternate days. Wash hands after application. Not to be applied on the breasts or face and avoid contact with eyes. Allow area of application to dry for 5 minutes and do not wash area for at least 1 hour.

Oestradiol 10 microgram

Estradiol 10 microgram Vagifem 10microgram vaginal tablets | 24 pessary (PVM) £16.72 DT price = £16.72
Vaginal delivery system

CAUTIONARY AND ADVISORY LABELS

- Estrin (Pfizer Ltd)
  Estradiol (as Estradiol hemihydrate) 75 microgram per 24 hour
  Estrin 75 microgram/24 hours vaginal delivery system
  1 device [PST] £1.42

Transdermal patch

- ESTRADIOL (Non-proprietary)
  Estradiol 25 microgram per 24 hour
  Estradiol 25 microgram/24 hours transdermal patches
  8 patch [PST] £5.19

- Elleste Solo MX (Meda Pharmaceuticals Ltd)
  Estradiol 80 microgram per 24 hour
  Elleste Solo MX 80 microgram/24 hours transdermal patches
  8 patch [PST] £5.99

- Estraderm MX (Novartis Pharmaceuticals UK Ltd)
  Estradiol 25 microgram per 24 hour
  Estraderm MX 25 microgram
  8 patch [PST] £5.50

- Estradiol 50 microgram per 24 hour
  Estraderm MX 50 microgram
  8 patch [PST] £5.51

- Estradiol 80 microgram per 24 hour
  Estraderm MX 80 microgram
  8 patch [PST] £5.80

- Estring
  Cautionary and Advisory Labels
  Vaginal delivery system

Estradiol (as Estradiol hemihydrate) 500 microgram

- FemSeven (Teva UK Ltd)
  Estradiol 6 microgram per 24 hour
  FemSeven 6 microgram
  1 tablet daily for 14 days
  14 tablet [PST] £1.46

- FemSeven Sequi Phase I
  Estradiol 8 microgram per 24 hour
  FemSeven Sequi Phase I
  1 tablet daily for 14 days
  14 tablet [PST] £1.46

Drospirenone with estradiol

The properties listed below are those particular to the combination only. For the properties of the components please consider, estradiol p. 649.

INDICATIONS AND DOSE

Menopausal symptoms in women with a uterus whose last menstrual period occurred over 12 months previously

- Osteoporosis prophylaxis in women with a uterus whose last menstrual period occurred over 12 months previously

BY MOUTH

- Adult: 1 tablet daily continuously, if changing from cyclical HRT begin treatment the day after finishing oestrogen plus progestogen phase

- CAUTIONS
  Use with care if an increased concentration of potassium might be hazardous

- REPRODUCTIVE AND BREAST FUNCTION
  Avoid if eGFR less than 30 mL/minute/1.73 m²

- MEDICAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.

Tablet

- Angelilq (Bayer Plc)
  Drospirenone 2 mg, Estradiol (as Estradiol hemihydrate) 1 mg
  Angelilq tablets
  84 tablet [PST] £29.00

Dydrogesterone with estradiol

The properties listed below are those particular to the combination only. For the properties of the components please consider, estradiol p. 649.

INDICATIONS AND DOSE

FEMOSTON®-CONTI 0.5 MG/2.5 MG

Menopausal symptoms in women with a uterus whose last menstrual period occurred over 12 months previously

BY MOUTH

- Adult: 1 tablet daily continuously, if changing from cyclical HRT begin treatment the day after finishing oestrogen plus progestogen phase

FEMOSTON®-CONTI 1 MG/5 MG

Menopausal symptoms in women with a uterus whose last menstrual period occurred over 12 months previously

- Osteoporosis prophylaxis in women with a uterus whose last menstrual period occurred over 12 months previously

BY MOUTH

- Adult: 1 tablet daily continuously, if changing from cyclical HRT begin treatment the day after finishing oestrogen plus progestogen phase

FEMOSTON® 1 MG/10 MG

Menopausal symptoms in women with a uterus

BY MOUTH

- Adult: 1 tablet daily for 14 days, white tablet to be taken and started within 5 days of onset of menstruation (or any time if cycles have ceased or are infrequent), then 1 tablet daily for 14 days, grey tablet to be taken, subsequent courses repeated without interval, Femoston® 1 mg/10 mg given initially and Femoston® 2 mg/10 mg substituted if symptoms not controlled

Osteoporosis prophylaxis in women with a uterus

BY MOUTH

- Adult: 1 tablet daily for 14 days, white tablet to be taken and started within 5 days of onset of menstruation (or any time if cycles have ceased or are infrequent), then 1 tablet daily for 14 days, grey tablet to be taken, subsequent courses repeated without interval
**FEMOSTON**® 2 MG/10 MG

**Menopausal symptoms in women with a uterus**  
**BY MOUTH**
- Adult: 1 tablet daily for 14 days, red tablet to be taken and started within 5 days of onset of menstruation (or any time if cycles have ceased or are infrequent), then 1 tablet daily for 14 days, yellow tablet to be taken, subsequent courses repeated without interval, **Femoston**® 1 mg/10 mg given initially and **Femoston**® 2 mg/10 mg substituted if symptoms not controlled

**Osteoporosis prophylaxis in women with a uterus**  
**BY MOUTH**
- Adult: 1 tablet daily for 14 days, red tablet to be taken and started within 5 days of onset of menstruation (or any time if cycles have ceased or are infrequent), then 1 tablet daily for 14 days, yellow tablet to be taken, subsequent courses repeated without interval

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Hormonin** (AMCo)  
  Estradiol 600 microgram, Estriol 270 microgram, Estrone 1.4 mg  
  Hormonin tablets | 84 tablet (POM) £7.93

**Estradiol with levonorgestrel**

The properties listed below are those particular to the combination only. For the properties of the components please consider, levonorgestrel p. 692, estradiol p. 649.

**INDICATIONS AND DOSE**

**FEMSEVEN CONTI**®  
Menopausal symptoms in women with a uterus whose last menstrual period occurred over 12 months previously  
**BY TRANSDERMAL APPLICATION**
- Adult: Apply 1 patch once weekly continuously

**FEMSEVEN SEQUI**®  
Menopausal symptoms in women with a uterus  
**BY TRANSDERMAL APPLICATION**
- Adult: Apply 1 phase 1 patch once weekly for 2 weeks, then apply 1 phase 2 patch once weekly for 2 weeks, subsequent courses are repeated without interval

**PATIENT AND CARER ADVICE**  
Patient counselling is advised for estradiol with levonorgestrel patches (application).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Transdermal patch**
- **FemSeven Conti** (Teva UK Ltd)  
  Estradiol 50 microgram per 24 hour, Levonorgestrel 7 microgram per 24 hour  
  FemSeven Conti patches | 4 patch (POM) £15.48 | 12 patch (POM) £44.12  
  **FemSeven Sequi** (Teva UK Ltd)  
  FemSeven Sequi patches | 4 patch (POM) £13.18 | 12 patch (POM) £37.54

**Estradiol with medroxyprogesterone**

The properties listed below are those particular to the combination only. For the properties of the components please consider, medroxyprogesterone acetate p. 695, estradiol p. 649.

**INDICATIONS AND DOSE**

**INDIVINA**® TABLETS  
Menopausal symptoms in women with a uterus whose last menstrual period occurred over 3 years previously | Osteoporosis prophylaxis in women with a uterus whose last menstrual period occurred over 3 years previously  
**BY MOUTH**
- Adult: Initially 1/2.5 mg daily taken continuously, adjusted according to response, to be started at end of scheduled bleed if changing from cyclical HRT

**TRIDESTRA**®  
Menopausal symptoms in women with a uterus | Osteoporosis prophylaxis in women with a uterus  
**BY MOUTH**
- Adult: 1 white tablet daily for 70 days, then 1 blue tablet daily for 14 days, then 1 yellow tablet daily for 7 days, subsequent courses are repeated without interval

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Estradiol with estriol and estrone**

The properties listed below are those particular to the combination only. For the properties of the components please consider, estradiol p. 649, estriol p. 713.

**INDICATIONS AND DOSE**

Menopausal symptoms | Osteoporosis prophylaxis  
**BY MOUTH**
- Adult: 1–2 tablets daily continuously or cyclically (21 days out of 28), started within 5 days of onset of menstruation (or at any time if cycles have ceased or are infrequent), to be taken with cyclical progesterogen for 12–14 days of each cycle in women with a uterus
### Indications and Dose

#### **CLIMASTE® 1-MG**

**Menopausal symptoms**

- **By mouth**
  - Adult: 1 grey tablet daily for 16 days, started on day 1 of menstruation (or at any time if cycles have ceased or are infrequent), then 1 white tablet daily for 12 days, subsequent courses are repeated without interval.

#### **CLIMASTE® 2-MG**

**Menopausal symptoms (if symptoms not controlled with lower strength)**

- **By mouth**
  - Adult: 1 blue tablet daily for 16 days, started on day 1 of menstruation (or at any time if cycles have ceased or are infrequent), then 1 white tablet daily for 12 days, subsequent courses are repeated without interval.

#### **CLIMAGEST®**

**Menopausal symptoms in women with a uterus whose last menstrual period occurred over 12 months previously**

- **By mouth**
  - Adult: 1 tablet daily continuously

#### **CLINORETTE®**

**Menopausal symptoms in women with a uterus**

- **By mouth**
  - Adult: 1 white tablet daily for 16 days, starting on day 5 of menstruation (or at any time if cycles have ceased or are infrequent), then 1 pink tablet daily for 12 days, subsequent courses repeated without interval.

#### **ELLESTE-DUET® CONTI**

**Menopausal symptoms in women with a uterus whose last menstrual period occurred over 12 months previously**

- **By mouth**
  - Adult: 1 tablet daily continuous basis, if changing from cyclical HRT begin treatment at the end of scheduled bleed.

#### **ELLESTE-DUET® 1-MG**

**Menopausal symptoms**

- **By mouth**
  - Adult: 1 white tablet daily for 16 days, started on day 1 of menstruation (or at any time if cycles have ceased or are infrequent), then 1 green tablet daily for 12 days, subsequent courses are repeated without interval.

#### **ELLESTE-DUET® 2-MG**

**Menopausal symptoms**

- **By mouth**
  - Adult: 1 orange tablet daily for 16 days, to be started on day 1 of menstruation (or at any time if cycles have ceased or are infrequent), then 1 grey tablet daily for 12 days, subsequent courses are repeated without interval.

#### **EVOREL® CONTI**

**Menopausal symptoms in women with a uterus**

- **By Transdermal Application**
  - Adult: Apply 1 patch twice weekly continuously

#### **EVOREL® SEQUI**

**Menopausal symptoms in women with a uterus**

- **By Transdermal Application**
  - Adult: Apply 1 Evorel® 1-MG patch twice weekly for 2 weeks, started within 5 days of onset of menstruation (or at any time if cycles have ceased or are infrequent), followed by 1 Evorel® Conti patch twice weekly, subsequent courses are repeated without interval.

#### **KLOFEM®**

**Menopausal symptoms in women with a uterus whose last menstrual period occurred over 12 months previously**

- **By mouth**
  - Adult: 1 tablet daily continuously, to be started at end of scheduled bleed if changing from cyclical HRT.

#### **KLOYVANCE®**

**Menopausal symptoms in women with a uterus whose last menstrual period occurred over 12 months previously**

- **By mouth**
  - Adult: 1 tablet daily continuously, to be started at end of scheduled bleed if changing from cyclical HRT.

#### **NOVOFEM®**

**Menopausal symptoms in women with a uterus**

- **By mouth**
  - Adult: 1 red tablet daily for 16 days, then 1 white tablet daily for 12 days, subsequent courses are repeated without interval; start treatment with red tablet at any time or if changing from cyclical HRT, start treatment the day after finishing oestrogen plus progestogen phase.

#### **NUVELLE® CONTINUOUS**

**Menopausal symptoms in women with a uterus whose last menstrual period occurred over 12 months previously**

- **By mouth**
  - Adult: 1 tablet daily continuously, if changing from cyclical HRT, start treatment the day after finishing oestrogen plus progestogen phase.

#### **TRISEQUENS®**

**Menopausal symptoms in women with a uterus**

- **By mouth**
  - Adult: 1 blue tablet daily for 12 days, followed by 1 white tablet daily for 10 days, then 1 red tablet daily for 6 days, subsequent courses are repeated without interval.
**Estradiol with norgestrel**

The properties listed below are those particular to the combination only. For the properties of the components please consider, estradiol p. 649.

**INDICATIONS AND DOSE**

**CYCLO-PROGYNova® 2MG TABLETS**

Menopausal symptoms in women with a uterus; Osteoporosis prophylaxis in women with a uterus

**BY MOUTH**

- Adult: 1 white tablet daily for 11 days; started on day 5 of menstruation (or at any time if cycles have ceased or are infrequent), then 1 brown tablet daily for 10 days, followed by a 7-day tablet free interval

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Cyclo-Progynova (Meda Pharmaceuticals Ltd)
  Cyclo-Progynova tablets 2 | 21 tablet [BNF] £3.11

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**Ethinylestradiol (Ethinyleoestradiol)**

**INDICATIONS AND DOSE**

Short-term treatment of symptoms of oestrogen deficiency

**Osteoporosis prophylaxis if other drugs cannot be used**

**BY MOUTH**

- Adult: 10–50 micrograms daily for 21 days, repeated after 7-day tablet-free period, to be given with progesterogen for 12–14 days per cycle in women with intact uterus.

**Female hypogonadism**

**BY MOUTH**

- Adult: 10–50 micrograms daily on cyclical basis, initial oestrogen therapy should be followed by combined oestrogen and progesterogen therapy.

**Menstrual disorders**

**BY MOUTH**

- Adult: 20–50 micrograms daily from day 5 to 25 of each cycle, to be given with progesterogen, added either throughout the cycle or from day 15 to 25.

**Palliative treatment of prostate cancer**

**BY MOUTH**

- Adult: 0.15–1.5 mg daily.

**CONTRA-INDICATIONS**

Acute porphyrias p. 864; active or recent arterial thromboembolic disease (e.g. angina or myocardial infarction) · active thrombophlebitis · Dubin-Johnson and Rotor syndromes (or monitor closely) · gallstones · heart disease associated with pulmonary hypertension · heart disease associated with risk of embolus · history during pregnancy of cholestatic jaundice · history during pregnancy of chorea · history during pregnancy of pempigoid gestations · history during pregnancy of puritus · history of breast cancer · history of haemolytic uraemic syndrome · liver disease (where liver function tests have failed to return to normal) · migraine with aura · oestrogen-dependent cancer · sclerosing cholangitis · systemic lupus erythematosus with (or unknown) antiphospholipid antibodies · thrombophilic disorder · transient cerebral ischaemic attacks without headaches · undiagnosed vaginal bleeding · untreated endometrial hyperplasia · venous thromboembolism · or history of recurrent venous thromboembolism (unless already on anticoagulant treatment)

**CAUTIONS**

Active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration) · seek specialist advice · cardiovascular disease (sodium retention with oedema, thromboembolism) · Crohn’s disease · diabetes (increased risk of heart disease) · gene mutations associated with breast cancer (e.g. BRCA1) · history of breast nodules or fibrocystic disease · colon cancer · endometrial hyperplasia · history of severe depression (especially if induced by hormonal contraceptive) · hyperprolactinaemia (seek specialist advice) · hypophyselial tumours · increased risk of gall-bladder disease · inflammatory bowel disease · migraine (migraine-like headaches) · personal or family history of hypertriglyceridaemia · presence of antiphospholipid antibodies · increased risk of thrombotic events · prolonged exposure to unopposed oestrogens may increase risk of developing endometrial cancer · risk factors for arterial disease · risk factors for migraine · risk factors for oestrogen-dependent tumours (e.g. breast cancer in first-degree relative) · risk factors for venous thromboembolism · sickle-cell disease · undiagnosed breast mass
656  Sex hormone responsive conditions

Endocrine system

CAUTIONS, FURTHER INFORMATION

Other conditions  The product literature advises caution in other conditions including hypertension, renal disease, asthma, epilepsy, sickle-cell disease, melanoma, otochlosis, multiple sclerosis, and systemic lupus erythematous (but care required if antiphospholipid antibodies present, see above). Evidence for caution in these conditions is unsatisfactory and many women with these conditions may stand to benefit from HRT.

Risk of venous thromboembolism  Use with caution if any of the following factors present but avoid if two or more factors present:

•  family history of venous thromboembolism in first-degree relative aged under 45 years (avoid if known prothrombotic coagulation abnormality e.g. factor V Leiden or antiphospholipid antibodies (including lupus anticoagulant));
•  obesity—body mass index $\geq 30$ kg/m$^2$ (avoid if body mass index $\geq 35$ kg/m$^2$ unless no suitable alternative); (In adolescents, caution if obese according to BMI (adjusted for age and gender); in those who are markedly obese, avoid unless no suitable alternative);
•  long-term immobilisation e.g. in a wheelchair (avoid if confined to bed or leg in plaster cast);
•  history of superficial thrombophlebitis;
•  age over 35 years (avoid if over 50 years);
•  smoking.

Risk factors for arterial disease  Use with caution if any one of following factors present but avoid if two or more factors present:

•  family history of arterial disease in first degree relative aged under 45 years (avoid if atherogenic lipid profile);
•  diabetes mellitus (avoid if diabetes complications present);
•  hypertension—blood pressure above systolic 140 mmHg or diastolic 90 mmHg (avoid if blood pressure above systolic 160 mmHg or diastolic 95 mmHg); (In adolescents, avoid if blood pressure very high);
•  smoking (avoid if smoking 40 or more cigarettes daily);
•  age over 35 years (avoid if over 50 years);
•  obesity (avoid if body mass index $\geq 35$ kg/m$^2$ unless no suitable alternative); (In adolescents, caution if obese according to BMI (adjusted for age and gender); in those who are markedly obese, avoid unless no suitable alternative);
•  migraine without aura (avoid if migraine with aura (focal symptoms), or severe migraine frequently lasting over 72 hours despite treatment, or migraine treated with ergot derivatives).

Migraine  Women should report any increase in headache frequency or onset of focal symptoms (discontinue immediately and refer urgently to neurology expert if focal neurological symptoms not typical of aura persist for more than 1 hour).

INTERACTIONS  $\rightarrow$ Appendix 1 (oestrogens).

SIDE-EFFECTS

•  Rare  Gallstones systemic lupus erythematous
•  Frequency not known  Abdominal bloating abdominal cramps absence of withdrawal bleeding altered blood lipids (may lead to pancreatitis) amenorrhea after discontinuation breast enlargement breast secretion breast tenderness cervical erosion changes in libido changes in lipid metabolism changes in vaginal discharge chloasma cholestatic jaundice chorea contact lenses may irritate depression dizziness feminising effects fluid retention glucose intolerance headache hepatic tumours hypertension irritability leg cramps (rule out venous thrombosis) liver impairment migraine mood changes nausea nervousness photosensitivity premenstrual-like syndrome rashes reduced menstrual loss skin reactions sodium retention symptoms of endometriosis may be exacerbated thrombosis (more common when factor V Leiden present or in blood groups A, B, and AB) uterine fibroids may increase in size vaginal candidiasis visual disturbances vomiting weight changes spotting in early cycles

SIDE-EFFECTS, FURTHER INFORMATION

Withdrawal bleeding  Cyclical HRT (where a progestogen is taken for 12–14 days of each 28-day oestrogen treatment cycle) usually results in regular withdrawal bleeding towards the end of the progestogen. The aim of continuous combined HRT (where a combination of oestrogen and progestogen is taken, usually in a single tablet, throughout each 28-day treatment cycle) is to avoid bleeding, but irregular bleeding may occur during the early treatment stages (if it continues endometrial abnormality should be excluded and consideration given to cyclical HRT instead).

•  PREGNANCY  Not known to be harmful.
•  BREAST FEEDING  Avoid until weaning or for 6 months after birth (adverse effects on lactation).
•  HEPATIC IMPAIRMENT  Avoid.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, oral suspension, capsule

Tablet

$\rightarrow$ ETHINYLESTRODIOL (Non-proprietary)

| Ethinylestradiol 2 microgram | Ethinylestradiol 2 microgram tablets | 100 tablet (PO) £20.00 |
| Ethinylestradiol 10 microgram | Ethinylestradiol 10 microgram tablets | 21 tablet (PO) £200.00 DT price + £20.00 |
| Ethinylestradiol 1 mg | Ethinylestradiol 1 mg tablets | 28 tablet (PO) £200.00 DT price + £20.00 |
| Ethinylestradiol 10 mg | Ethinylestradiol 10 microgram tablets | 21 tablet (PO) £200.00 DT price + £20.00 |

PROGESTOGENS

Norethisterone

INDICATIONS AND DOSE

Endometriosis

BY MOUTH

$\rightarrow$ Adult 10–15 mg daily for 4–6 months or longer, to be started on day 5 of cycle; increased to 20–25 mg daily if required, dose only increased if spotting occurs and reduced once bleeding has stopped

Dysfunctional uterine bleeding (to arrest bleeding) Menorrhagia (to arrest bleeding)

BY MOUTH

$\rightarrow$ Adult 5 mg 3 times a day for 10 days

Dysfunctional uterine bleeding (to prevent bleeding) Menorrhagia (to prevent bleeding)

BY MOUTH

$\rightarrow$ Adult 5 mg twice daily, to be taken from day 19 to day 26 of cycle

Dysmenorrhoea

BY MOUTH

$\rightarrow$ Adult 5 mg 3 times a day for 3–4 cycles, to be taken from day 5–24 of cycle

Premenstrual syndrome (but not recommended)

BY MOUTH

$\rightarrow$ Adult 5 mg 2–3 times a day for several cycles, to be taken from day 19–26 of cycle

Postponement of menstruation

BY MOUTH

$\rightarrow$ Females of childbearing potential: 5 mg 3 times a day, to be started 3 days before expected onset (menstruation occurs 2–3 days after stopping)
When used for contraception

- **CAUTIONS**
  - **With oral use**
  - **Females of childbearing potential**:
    - 200 mg, to be administered within first 5 days of cycle or immediately after parturition (duration 8 weeks), then 200 mg after 8 weeks if required
  
- **Contraception**
  - **BY MOUTH**
  - **Females of childbearing potential**:
    - 350 micrograms daily, dose to be taken at same time each day, starting on day 1 of cycle then continuously, if administration delayed for 3 hours or more it should be regarded as a ‘missed pill’

- **INTERACTIONS** → Appendix 1 (progestogens).
  - With intramuscular use
    - Effectiveness of parenteral progestogen-only contraceptives is not affected by antibacterials that do not induce liver enzymes. The effectiveness of norethisterone intramuscular injection is not affected by enzyme-inducing drugs and may be continued as normal during courses of these drugs.

- **SIDE-EFFECTS**
  - **GENERAL SIDE-EFFECTS**
    - In use as a contraceptive indications.
    - Acne, alopecia, anaphylactoid reactions, breast tenderness, change in libido, depression, disturbance of appetite, dizziness, fluid retention, headache, hirsutism, insomnia, nausea, premenstrual-like syndrome, pruritus, rash, skin reactions, urticaria, vomiting, weight change
  
  **SPECIFIC SIDE-EFFECTS**
  - With intramuscular use
    - Injection-site reactions

  **SIDE-EFFECTS, FURTHER INFORMATION**

  **Cervical cancer** Use of injectable progestogen-only contraceptives may be associated with a small increased risk of cervical cancer, similar to that seen with combined oral contraceptives (use of combined oral contraceptives for 5 years or longer is associated with a small increased risk of cervical cancer; the risk diminishes after stopping and disappears by about 10 years). The risk of cervical cancer with other progestogen-only contraceptives is not yet known.

  **PREGNANCY** Masculinisation of female fetuses and other defects reported with non-contraceptive use.

  **BREAST FEEDING** Progestogen-only contraceptives do not affect lactation. Higher doses (used in malignant conditions) may suppress lactation and alter milk composition—use lowest effective dose.

  **With intramuscular use**
  - Withhold breast-feeding for 3 days after recovery.
  - Use as a contraceptive; caution in severe liver disease and recurrent cholestatic jaundice, avoid in liver tumour. Avoid in non-contraceptive indications.

  **RENAL IMPAIRMENT** Use with caution in non-contraceptive indications.

  **PATIENT AND CARER ADVICE**
  - **Missed oral contraceptive pill** The following advice is recommended: ‘If you forget a pill, take it as soon as you remember and carry on with the next pill at the right time. If the pill was more than 3 hours overdue you are not protected. Continue normal pill-taking but you must also use another method, such as the condom, for the next 2 days.’
  
  The Faculty of Sexual and Reproductive Healthcare recommends emergency contraception if one or more progestogen-only contraceptive tablets are missed or taken more than 3 hours late and unprotected intercourse has occurred before 2 further tablets have been correctly taken.

  - Diarrhoea and vomiting with oral contraceptives
  - Vomiting and persistent, severe diarrhoea can interfere with the absorption of oral progestogen-only contraceptives.
  - If vomiting occurs within 2 hours of taking an oral progestogen-only contraceptive, another pill should be taken as soon as possible. If a replacement pill is not taken within 3 hours of the normal time for taking the progestogen-only pill, or in cases of persistent vomiting or very severe diarrhoea, additional precautions should be used during illness and for 2 days after recovery.
Starting routine for oral contraceptives One tablet daily, on a continuous basis, starting on day 1 of cycle and taken at the same time each day (if delayed by longer than 3 hours contraceptive protection may be lost). Additional contraceptive precautions are not necessary when initiating treatment. Changing from a combined oral contraceptive: start on the day following completion of the combined oral contraceptive course without a break (or in the case of ED tablets omitting the inactive ones).

After childbirth: oral progestogen-only contraceptives can be started up to and including day 21 postpartum without the need for additional contraceptive precautions. If started more than 21 days postpartum, additional contraceptive precautions are required for 2 days.

Contraceptives by injection Full counselling backed by patient information leaflet required before administration—likelihood of menstrual disturbance and the potential for a delay in return to full fertility. Delayed return of fertility and irregular cycles may occur after discontinuation of treatment but there is no evidence of permanent infertility.

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Tablet

▶ NORETHISTERONE (Non-proprietary)
   Norethisterone 350 microgram Norethisterone 350 microgram tablets | 84 tablet  £1.80
   Norethisterone 5 mg Norethisterone 5 mg tablets | 30 tablet  £0.50
   £4.50 DT price = £2.35
   Micronor (Janssen-Cilag Ltd)
   Norethisterone 350 microgram Micronor 350 microgram tablets | 84 tablet  £1.80 DT price = £1.80
   Noriday (Pfizer Ltd)
   Norethisterone 350 microgram Noriday 350 microgram tablets | 84 tablet  £2.10 DT price = £1.80
   Primolut N (Bayer Plc)
   Norethisterone 5 mg Primolut N 5 mg tablets | 30 tablet  £0.80
   £2.26 DT price = £2.35
   Utovlan (Pfizer Ltd)
   Norethisterone 5 mg Utovlan 5 mg tablets | 30 tablet  £1.40
   DT price = £2.35 | 9 tablet  £0.42
   Solution for injection
   Noristerat (Bayer Plc)
   Norethisterone enantate 200 mg per 1 ml Noristerat 200mg/1ml solution for injection ampoules | 1 ampoule  £4.05
Also available in combination with estradiol, p. 654

Progestosterone

INDICATIONS AND DOSE

UTROGESTAN® CAPSULES

Progestogenic opposition of oestrogen HRT

BY MOUTH
   Adult: 200 mg once daily on days 15–26 of each 28-day oestrogen HRT cycle, alternatively 100 mg once daily on days 1–25 of each 28-day oestrogen HRT cycle

GESTONE® SOLUTION FOR INJECTION

Dysfunctional uterine bleeding

BY DEEP INTRAMUSCULAR INJECTION
   Adult: 5–10 mg daily for 5–10 days until 2 days before expected onset of menstruation, to be administered into buttocks

Recurrent miscarriage due to inadequate luteal phase (but not recommended) or following in vitro fertilisation or gamete intra-fallopian transfer

BY DEEP INTRAMUSCULAR INJECTION
   Adult: 25–100 mg 2–7 times a week from day 15, or day of embryo or gamete transfer, until 8–16 weeks of pregnancy, to be administered into buttocks; maximum 200 mg per day

LUBION® SOLUTION FOR INJECTION

Supplementation of luteal phase during assisted reproductive technology (ART) treatment in women for whom vaginal preparations are inappropriate

BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION
   Adult: 25 mg once daily from day of oocyte retrieval up to week 12 of pregnancy

CYCLOGEST® PESSARIES

Premenstrual syndrome | Post-natal depression

BY VAGINA OR BY RECTUM
   Adult: 200–800 mg daily, doses above 200 mg to be given in 2 divided doses, for premenstrual syndrome start on day 12–14 and continue until onset of menstruation (but not recommended); rectally if barrier methods of contraception are used, in patients who have recently given birth or in those who suffer from vaginal infection or recurrent cystitis

UTROGESTAN® VAGINAL CAPSULES

Supplementation of luteal phase during assisted reproductive technology (ART) cycles

BY VAGINA
   Adult: 1 capsule 3 times a day from day of embryo transfer until at least week 7 of pregnancy up to week 12 of pregnancy

● CONTRA-INDICATIONS

Acute porphyrias p. 864 • avoid in patients with a history of liver tumours • breast cancer (unless progestogens are being used in the management of this condition) • genital cancer (unless progestogens are being used in the management of this condition) • history during pregnancy of idiopathic jaundice • history during pregnancy of pemphigoid gestationis • history during pregnancy of severe pruritus • incomplete miscarriage • missed miscarriage • severe arterial disease • undiagnosed vaginal bleeding

● CAUTIONS

Asthma • cardiac dysfunction • conditions that may worsen with fluid retention • diabetes (progestogens can decrease glucose tolerance—monitor patient closely) • epilepsy • history of depression • hypertension • migraine • susceptibility to thromboembolism (particular caution with high dose)

● INTERACTIONS → Appendix 1 (progestogens).

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

Acne • alopecia • anaphylactoid reactions • bloating • breast tenderness • change in libido • depression • dizziness • drowsiness • fluid retention • headache • hirsutism • insomnia • jaundice • menstrual disturbances • nausea • premenstrual-like syndrome • pruritus • rash • skin reactions • urticaria • weight change

SPECIFIC SIDE-EFFECTS

With intramuscular use or subcutaneous use Injection-site reactions
   With rectal use Diarrhoea • flatulence • pain
   With vaginal use Local irritation

● PREGNANCY

Not known to be harmful.

● BREAST FEEDING

Avoid—present in milk.

● HEPATIC IMPAIRMENT

Avoid in hepatic impairment. Avoid in active liver disease including disorders of hepatic excretion (e.g. Dublin-Johnson or Rotor Syndromes), infective hepatitis (until liver function returns to normal) and liver tumours.

● RENAL IMPAIRMENT

Use with caution.

● DIRECTIONS FOR ADMINISTRATION

Capsules should be taken at bedtime on an empty stomach.

● PATIENT AND CARER ADVICE

Patient counselling is advised for progesterone capsules (administration).
Anti-oestrogens 659

SELECTIVE OESTROGEN RECEPTOR MODULATORS

Raloxifene hydrochloride

INDICATIONS AND DOSE
Treatment and prevention of postmenopausal osteoporosis

BY MOUTH

Adult: 60 mg once daily

CONTRA-INDICATIONS Cholestasis - endometrial cancer - history of venous thromboembolism - undiagnosed uterine bleeding

CAUTIONS Avoid in Acute porphyrias p. 864 - breast cancer (manufacturer advises avoid during treatment for breast cancer) - history of oestrogen-induced hypertriglyceridaemia (monitor serum triglycerides) - risk factors for stroke - risk factors for venous thromboembolism (discontinue if prolonged immobilisation)

INTERACTIONS → Appendix 1 (raloxifene).

SIDE-EFFECTS

Common or very common Hot flushes - influenza-like symptoms - leg cramps - peripheral oedema

Uncommon Thrombophlebitis - venous thromboembolism - leg pain

Rare Arterial thromboembolism - breast discomfort - gastro-intestinal disturbances - headache - hypertension - migraine - rashes - thrombocytopenia

HEPATIC IMPAIRMENT Avoid.

RENAL IMPAIRMENT Caution in mild to moderate impairment. Avoid in severe impairment.

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

RALOXIFENE HYDROCHLORIDE (Non-proprietary)

Raloxifene hydrochloride 60 mg Raloxifene 60 mg tablets | 28 tablet | £16.02

Raloxifene hydrochloride 60 mg Raloxifene 60 mg tablets | 84 tablet | £14.63

Raloxifene hydrochloride 60 mg Raloxifene 60 mg tablets | 14 tablet | £6.02

Raloxifene hydrochloride 60 mg Raloxifene 60 mg tablets | 28 tablet | £17.06

Brands may include Ostiral; Razylan

Raloxifene is recommended by the NICE guideline TA161 as a treatment option for postmenopausal women for prevention of osteoporotic fractures and osteoporotic fragility fractures in postmenopausal women (October 2008) NICE TA161

8.2 Anti-oestrogens

OVULATION STIMULANTS

Clomifene citrate

Clomiphene citrate

DRUG ACTION Anti-oestrogen which induces gonadotrophin release by occupying oestrogen receptors in the hypothalamus, thereby interfering with feedback mechanisms; choriionic gonadotrophin is sometimes used as an adjunct.

INDICATIONS AND DOSE

Treatment of female infertility due to oligomenorrhoea or secondary amenorrhoea (e.g. associated with polycystic ovarian disease)

BY MOUTH

Adult: 50 mg daily for 5 days, to be started within about 5 days of onset of menstruation (preferably on 2nd day) or at any time (normally preceded by a progestogen induced withdrawal bleed) if cycles have ceased, followed by 100 mg daily if required for a further 5 days, this second course may be given in absence of ovulation; most patients who are going to respond will do so to first course, 3 courses should constitute adequate therapeutic trial; long-term cyclical therapy not recommended.

Important safety information

The CSM has recommended that clomifene should not normally be used for longer than 6 cycles (possibly increased risk of ovarian cancer).
8.3 Male sex hormone responsive conditions

Androgens, anti-androgens and anabolic steroids

Androgens

Androgens cause masculinisation; they may be used as replacement therapy in castrated adults and in those who are hypogonadal due to either pituitary or testicular disease. In the normal male they inhibit pituitary gonadotrophin secretion and depress spermatogenesis. Androgens also have an anabolic action which led to the development of anabolic steroids.

Androgens are useless as a treatment of impotence and impaired spermatogenesis unless there is associated hypogonadism; they should not be given until the hypogonadism has been properly investigated. Treatment should be under expert supervision.

When given to patients with hypopituitarism they can lead to normal sexual development and potency but not to fertility. If fertility is desired, the usual treatment is with gonadotrophins or pulsatile gonadotrophin-releasing hormone which will stimulate spermatogenesis as well as androgen production.

Intramuscular depot preparations of testosterone esters are preferred for replacement therapy. Testosterone enantate, propionate or undecanoate, or alternatively Sustanon®, which consists of a mixture of testosterone esters and has a longer duration of action, may be used.

Anti-androgens

Cyproterone acetate

Cyproterone acetate p. 662 is an anti-androgen used in the treatment of severe hypersexuality and sexual deviation in the male. It inhibits spermatogenesis and produces reversible infertillity (but is not a male contraceptive); abnormal sperm forms are produced. Fully informed consent is recommended and an initial spermogram. As hepatic tumours have been produced in animal studies, careful consideration should be given to the risk/benefit ratio before treatment. Cyproterone acetate is also licensed for use alone in patients with metastatic prostate cancer refractory to gonadorelin analogue therapy and has been used as an adjunct in prostatic cancer and in the treatment of acne and hirsutism in women.

Dutasteride and finasteride

Dutasteride p. 676 and finasteride p. 676 are alternatives to alpha-blockers particularly in men with a significantly enlarged prostate. Finasteride is also licensed for use with doxazosin in the management of benign prostatic hyperplasia.

A low strength of finasteride is licensed for treating male-pattern baldness in men.

Anabolic steroids

Anabolic steroids have some anabolic activity but they cause less virilisation than androgens in women. They are used in the treatment of some aplastic anemia. Anabolic steroids have been given for osteoporosis in women but they are no longer advocated for this purpose.

The protein-building properties of anabolic steroids have not proved beneficial in the clinical setting. Their use as body builders or tonics is unjustified; some athletes abuse them.

ANDROGENS

Androgens

- CONTRA-INDICATIONS Breast cancer in males • history of liver tumours • hypercalcaemia • prostate cancer

- CAUTIONS Cardiac impairment • diabetes mellitus • elderly • epilepsy • hypertension • ischaemic heart disease • migraine • pre-pubertal boys (fusion of epiphyses is hastened and may result in short stature)—statural growth and sexual development should be monitored • skeletal metastases—risk of hypercalcaemia or hypercalciuria (if this occurs, treat appropriately and restart treatment once normal serum calcium concentration restored) • sleep apnoea • stop treatment or reduce dose if severe polycthymia occurs • tumours—risk of hypercalcaemia or hypercalciuria (if this occurs, treat appropriately and restart treatment once normal serum calcium concentration restored)

- INTERACTIONS Appendix 1 (testosterone).

- SIDE-EFFECTS
  - Common or very common Acne • androgenic effects (to be assessed regularly in women) • anxiety • arthralgia • asthenia • changes in libido • cholestatic jaundice • depression • electrolyte disturbances • excessive duration of penile erection • excessive frequency of penile erection • gastrointestinal bleeding • gynaecomastia • headache • hirsutism • hypercalcaemia • hypertension • increased bone growth • irritability • male-pattern baldness • muscle cramps • nausea • nervousness • oedema • paraesthesia • polycythaemia • precocious sexual development in pre-pubertal males • premature closure of epiphyses in pre-pubertal males • prostate abnormalities • prostate cancer • pruritus • seborrhoea • sodium retention • suppression of virilism in women • vomiting • weight gain
Testosterone enantate

INDICATIONS AND DOSE

Hypogonadism

BY SLOW INTRAMUSCULAR INJECTION

Adult: Initially 250 mg every 2–3 weeks; maintenance 250 mg every 3–6 weeks

Breast cancer

BY SLOW INTRAMUSCULAR INJECTION

Adult: 250 mg every 2–3 weeks

SIDE-EFFECTS

Suppression of spermatogenesis

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

TESTOSTERONE ENANTATE (Non-proprietary)

Testosterone enantate 250 mg per 1 ml Testosterone enantate 250mg/1ml solution for injection ampoules | 3 ampoule [POM] £68.00 DT price = £68.00 Schedule 4 (CD Anab)
## Testosterone propionate

### INDICATIONS AND DOSE

**Androgen deficiency**
- **BY INTRAMUSCULAR INJECTION**
  - Adult: 50 mg 2–3 times a week
- Delayed puberty in males
  - **BY INTRAMUSCULAR INJECTION**
  - Adult: 50 mg once weekly

**Breast cancer in women**
- **BY INTRAMUSCULAR INJECTION**
  - Adult: 100 mg 2–3 times a week

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, cream capsule containing the same drug. There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, cream.

### SIDE-EFFECTS

Suppression of spermatogenesis

## Testosterone decanoate, isocaproate, phenylpropionate and propionate

The properties listed below are those particular to the combination only. For the properties of the components please consider, testosterone propionate above.

### INDICATIONS AND DOSE

**Androgen deficiency**
- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 1 ml every 3 weeks

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Solution for injection EXCIPIENTS: May contain Arachis (peanut) oil, benzyl alcohol
- Testosterone decanoate 100 mg per 1 ml, Testosterone isocaproate 60 mg per 1 ml, Testosterone phenylpropionate 60 mg per 1 ml, Testosterone propionate 30 mg per 1 ml
- Sustanon 250mg/1ml solution for injection ampoules | 1 ampoule £2.45 Schedule 4 (CD Anab)
- Nebido 1000mg/4ml solution for injection vials | 1 vial £80.00 Schedule 4 (CD Anab)

### SIDE-EFFECTS

Suppression of spermatogenesis

## Testosterone undecanoate

### INDICATIONS AND DOSE

**Androgen deficiency**
- **BY MOUTH**
  - Adult: 120–160 mg daily for 2–3 weeks; maintenance 40–120 mg daily

**Hypogonadism**
- **BY DEEP INTRAMUSCULAR INJECTION**
  - Adult: 1 g every 10–14 weeks, to be given over 2 minutes, if necessary, second dose may be given after 6 weeks to achieve rapid steady state plasma testosterone levels and then every 10–14 weeks.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

### Capsule

**CAUTIONARY AND ADVISORY LABELS** 21, 25
- Restandol (Merck Sharp & Dohme Ltd)
- Testosterone undecanoate 40 mg Restandol 40mg Testocaps | 30 capsule £8.55 Schedule 4 (CD Anab) | 60 capsule £17.10 DT price = £17.10 Schedule 4 (CD Anab)

### SIDE-EFFECTS

Suppression of spermatogenesis

## Cyproterone acetate

### INDICATIONS AND DOSE

**Hypersexuality | Sexual deviation**
- **BY MOUTH**
  - Adult: 50 mg twice daily, to be taken after food.

**Prevention of tumour flare with initial gonadorelin analogue therapy**
- **BY MOUTH**
  - Adult: 200 mg daily in 2–3 divided doses for 5–7 days before initiation of gonadorelin analogue, followed by 200 mg daily in 2–3 divided doses for 3–4 weeks after initiation of gonadorelin analogue; maximum 300 mg per day.

**Long-term palliative therapy where gonadorelin analogues or orchidectomy contra-indicated, not tolerated, or where oral therapy preferred**
- **BY MOUTH**
  - Adult: 200–300 mg daily in 2–3 divided doses.

**Hot flushes with gonadorelin analogue therapy or after orchidectomy**
- **BY MOUTH**
  - Adult: Initially 50 mg daily, then adjusted according to response to 50–150 mg daily in 1–3 divided doses.

### CONTRA-INDICATIONS

In hypersexuality, Dubin-Johnson syndrome - in hypersexuality, history of thromboembolic disorders - in hypersexuality, liver disease - in hypersexuality, malignant diseases - in hypersexuality, previous or existing liver tumours - in hypersexuality, Rotor syndrome - in hypersexuality, severe depression - in hypersexuality, severe diabetes (with vascular changes) - in hypersexuality, sickle-cell anaemia - in hypersexuality, wasting diseases - meningioma or history of meningioma - youths under 18 years (may arrest bone maturation and testicular development)

### CAUTIONS

Diabetes mellitus - in prostate cancer, severe depression - in prostate cancer, sickle-cell anaemia - ineffective for male hypersexuality in chronic alcoholism (relevance to prostate cancer not known)

### SIDE-EFFECTS

- Rare Hypersensitivity reactions - osteoporosis - rash
- **Frequency not known** Breathlessness - changes in hair pattern - fatigue - gynaecomastia (rarely leading to galactorrhoea and benign breast nodules) - hepatic failure - hepatitis - hepatotoxicity - inhibition of spermatogenesis - jaundice - lassitude - reduced sebum production (may clear acne) - risk of recurrence of thromboembolic disease - weight changes

### SIDE-EFFECTS, FURTHER INFORMATION

**Hepatotoxicity** Direct hepatic toxicity including jaundice, hepatitis and hepatic failure have been reported (fatalities reported, usually after several months, at dosages of 100 mg and above). If hepatotoxicity is confirmed, cyproterone should normally be withdrawn unless the hepatotoxicity can be explained by another cause such as
9 Thyroid disorders

Thyrotropin alfa
(Recombinant human thyroid stimulating hormone; rhTSH)

**DRUG ACTION** Thyrotropin alfa is a recombinant form of thyrotrophin (thyroid stimulating hormone).

**INDICATIONS AND DOSE**
Detection of thyroid remnants and thyroid cancer in post-thyroidectomy patients, together with serum thyroglobulin testing (with or without radiolodine imaging) To increase radio-iodine uptake for the ablation of thyroid remnant tissue in suitable post-thyroidectomy patients

**BY INTRAMUSCULAR INJECTION**
- Adult: 900 micrograms every 24 hours for 2 doses, dose to be administered into the gluteal muscle, consult product literature for further information on indications and dose

**CAUTIONS** Presence of thyroglobulin autoantibodies may give false negative results

**SIDE-EFFECTS**
- **Common or very common** Dizziness • fatigue • headache • nausea • vomiting
- **Uncommon** Asthenia • back pain • influenza-like symptoms • paraesthesia • rash • urticaria
- **Rare** Diarrhoea
- **Very rare** Arthralgia • dyspnoea • flushing • hyperhidrosis • injection-site pain • injection-site pruritus • injection-site rash • injection-site reactions • myalgia • pain at site of metastases • palpitation • tremor

**ALLERGY AND CROSS-SENSITIVITY** Contraindicated if previous hypersensitivity to bovine or human thyrotrophin.

**PREGNANCY** Avoid.

**BREAST FEEDING** Avoid.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**
- Thyrogen (Genzyme Therapeutics Ltd) Thyrotropin alfa 900 microgram Thyrogen 900microgram powder for solution for injection vials 2 vial £158.04

9.1 Hyperthyroidism

**Antithyroid drugs**

Antithyroid drugs are used for hyperthyroidism either to prepare patients for thyroidectomy or for long-term management. In the UK carbimazole is the most commonly used drug. Propylthiouracil p. 664 should be reserved for patients who are intolerant of carbimazole or for those who experience sensitivity reactions to carbimazole (sensitivity is not necessarily displayed to both drugs), and for whom other treatments are inappropriate. Both drugs act primarily by interfering with the synthesis of thyroid hormones.

Over-treatment with antithyroid drugs can result in the rapid development of hypothyroidism and should be avoided particularly during pregnancy because it can cause fetal goitre.

A combination of carbimazole with levothyroxine sodium daily p. 665, may be used in a blocking-replacement regimen; therapy is usually given for 18 months. The blocking-replacement regimen is not suitable during pregnancy.

Iodine has been used as an adjunct to antithyroid drugs for 10 to 14 days before partial thyroidectomy; however, there is little evidence of a beneficial effect. Iodine should not be used for long-term treatment because its antithyroid action tends to diminish.

Radioactive sodium iodide (¹³¹I) solution is used increasingly for the treatment of thyrotoxicosis at all ages, particularly where medical therapy or compliance is a problem, in patients with cardiac disease, and in patients who relapse after thyroidectomy.

Propanolol hydrochloride p. 146 is useful for rapid relief of thyrotoxic symptoms and may be used in conjunction with antithyroid drugs or as an adjunct to radioactive iodine. Beta-blockers are also useful in neonatal thyrotoxicosis and in supraventricular arrhythmias due to hyperthyroidism. Propanolol hydrochloride p. 146 has been used in conjunction with iodine to prepare mildly thyrotoxic patients for surgery but it is preferable to make the patient euthyroid with carbimazole. Laboratory tests of thyroid function are not altered by beta-blockers. Most experience in treating thyrotoxicosis has been gained with propanolol hydrochloride but nadolol p. 145 is also used.

Thyrotoxic crisis (‘thyroid storm’) requires emergency treatment with intravenous administration of fluids, propanolol hydrochloride and hydrocortisone p. 583 (as sodium succinate), as well as oral iodine solution and carbimazole or propylthiouracil which may need to be administered by nasogastric tube.

**Pregnancy**
Radioactive iodine therapy is contra-indicated during pregnancy. Propylthiouracil and carbimazole can be given but the blocking-replacement regimen is not suitable. Rarely, carbimazole has been associated with congenital defects, including aplasia cutis of the neonate, therefore...
propylthiouracil remains the drug of choice during the first trimester of pregnancy. In the second trimester, consider switching to carbimazole because of the potential risk of hepatotoxicity with propylthiouracil. Both propylthiouracil and carbimazole cross the placenta and in high doses may cause fetal goitre and hypothyroidism—the lowest dose that will control the hyperthyroid state should be used (requirements in Graves’ disease tend to fall during pregnancy).

**Drugs used for Hyperthyroidism not listed below:**
Metoprolol tartrate, p. 144; Nadolol, p. 145; Propranolol hydrochloride, p. 146

### ANTITHYROIDORS

#### Carbimazole

**INDICATIONS AND DOSE**

**Hyperthyroidism**

**BY MOUTH**

- Adult: 15–40 mg daily continue until the patient becomes euthyroid, usually after 4 to 8 weeks, higher doses should be prescribed under specialist supervision only, then reduced to 5–15 mg daily, reduce dose gradually, therapy usually given for 12 to 18 months

**Hyperthyroidism (blocking-replacement regimen) in combination with levothyroxine**

**BY MOUTH**

- Adult: 40–60 mg daily, therapy usually given for 18 months

**Dose equivalence and conversion**

When substituting, carbimazole 1 mg is considered equivalent to propylthiouracil 10 mg but the dose may need adjusting according to response.

**Important safety information**

**NEUTROPENIA AND AGRANULOCYTOSIS**

Doctors are reminded of the importance of recognising bone marrow suppression induced by carbimazole and the need to stop treatment promptly.

- Patient should be asked to report any signs suggestive of infection, especially sore throat.
- A white blood cell count should be performed if there is any clinical evidence of infection.
- Carbimazole should be stopped promptly if there is clinical or laboratory evidence of neutropenia.

**SIDE-EFFECTS**

| Common or very common | Arthralgia - fever - headache - jaundice - malaise - mild gastro-intestinal disturbances - nausea - pruritus - rash - taste disturbance |
| Rare | Agranulocytosis - alopecia - bone marrow suppression - jaundice - myopathy - pancytopenia |

Rashes and pruritus are common with carbimazole but they can be treated with antihistamines without discontinuing therapy; alternatively propylthiouracil can be substituted.

**CONTRA-INDICATIONS**

Severe blood disorders

**SIDE-EFFECTS, FURTHER INFORMATION**

**HEPATIC IMPAIRMENT**

Avoid in severe impairment.

**BREAST FEEDING**

Present in breast milk but this does not preclude breast-feeding as long as neonatal development is closely monitored and the lowest effective dose is used. Amount in milk may be sufficient to affect neonatal thyroid function therefore lowest effective dose should be used.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension, capsule

**Tablet**

- CARBIMAZOLE (Non-proprietary)
  - Carbimazole 5 mg Carbimazole 5mg tablets | 100 tablet POM
e\[11.08\] DT price = \[84.80\]
  - Carbimazole 20 mg Carbimazole 20mg tablets | 100 tablet POM
e\[72.93\] DT price = \[208.17\]

#### Propylthiouracil

**INDICATIONS AND DOSE**

**Hyperthyroidism**

**BY MOUTH**

- Adult: Initially 200–400 mg daily in divided doses until the patient becomes euthyroid, then reduced to 50–150 mg daily in divided doses, initial dose should be gradually reduced to the maintenance dose

**Dose equivalence and conversion**

When substituting, carbimazole 1 mg is considered equivalent to propylthiouracil 10 mg but the dose may need adjusting according to response.

**SIDE-EFFECTS, FURTHER INFORMATION**

**Hepatotoxicity**

Severe hepatic reactions have been reported, including fatal cases and cases requiring liver transplant—discontinue if significant liver-enzyme abnormalities develop.

**PREGNANCY**

Propylthiouracil can be given but the blocking-replacement regimen is **not** suitable. Propylthiouracil crosses the placenta and in high doses may cause fetal goitre and hypothyroidism—the lowest dose that will control the hyperthyroid state should be used (requirements in Graves’ disease tend to fall during pregnancy).

**BREAST FEEDING**

Present in breast milk but this does not preclude breast-feeding as long as neonatal development is closely monitored and the lowest effective dose is used. Amount in milk probably too small to affect infant; high doses may affect neonatal thyroid function. Monitor infant’s thyroid status.

**HEPATIC IMPAIRMENT**

Reduce dose.

**RENAL IMPAIRMENT**

Use three-quarters normal dose if eGFR 10–50 mL/minute/1.73 m². Use half normal dose if eGFR less than 10 mL/minute/1.73 m².

**MONITORING REQUIREMENTS**

Monitor for hepatotoxicity.
Liothyronine sodium by intravenous injection is the treatment of choice in hypothyroid coma. Adjunctive therapy includes intravenous fluids, hydrocortisone p. 583, and treatment of infection; assisted ventilation is often required.

**THYROID HORMONES**

**Levothyroxine sodium**
*(Thyroxine sodium)*

**INDICATIONS AND DOSE**

**Hypothyroidism**

**BY MOUTH**

- **Adult**: Initially 50–100 micrograms once daily; adjusted in steps of 25–50 micrograms every 3–4 weeks, adjusted according to response; maintenance 100–200 micrograms once daily, dose to be taken preferably at least 30 minutes before breakfast, caffeine-containing liquids (e.g. coffee, tea), or other medication.
- **Adult**: Initially 25 micrograms once daily; adjusted in steps of 25 micrograms every 4 weeks, adjusted according to response; maintenance 50–200 micrograms once daily, dose to be taken preferably at least 30 minutes before breakfast, caffeine-containing liquids (e.g. coffee, tea), or other medication.

**Hypothyroidism in patients with cardiac disease**

**Severe hypothyroidism**

**BY MOUTH**

- **Adult**: Initially 25 micrograms once daily; adjusted in steps of 25 micrograms every 4 weeks, adjusted according to response; maintenance 50–200 micrograms once daily, dose to be taken preferably at least 30 minutes before breakfast, caffeine-containing liquids (e.g. coffee, tea), or other medication.

**Hyperthyroidism (blocking-replacement regimen) in combination with carbimazole**

**BY MOUTH**

- **Adult**: 50–150 micrograms daily therapy usually given for 18 months.

**CONTRA-INDICATIONS**

- Thyrotoxicosis

**CAUTIONS**

- Cardiovascular disorders • diabetes insipidus • diabetes mellitus (dose of antidiabetic drugs including insulin may need to be increased) • elderly • hypertension • long-standing hypothyroidism • myocardial infarction • myoccardial insufficiency • panhypopituitarism (initiate corticosteroid therapy before starting levothyroxine) • predisposition to adrenal insufficiency (initiate corticosteroid therapy before starting levothyroxine).

**CAUTIONS, FURTHER INFORMATION**

- Cardiovascular disorders: Baseline ECG is valuable because changes induced by hypothyroidism can be confused with ischaemia.
- **INTERACTIONS** → Appendix 1 (thyroid hormones).
- **SIDE-EFFECTS**
  - **Anginal pain (usually at excessive dosage)** • **arrhythmias (usually at excessive dosage)** • **diarrhoea (usually at excessive dosage)** • **excitability (usually at excessive dosage)** • **fever • flushing • headache • heat intolerance • hypersensitivity reactions • insomnia (usually at excessive dosage)** • **myocardial infarction • muscle cramp • muscular weakness • oedema • palpitation (usually at excessive dosage)** • **pruritus • rash • restlessness (usually at excessive dosage)** • **sweating • tachycardia (usually at excessive dosage)** • **transient hair loss in children • tremor (usually at excessive dosage)** • **weight-loss**
## 666 Thyroid disorders

**CONTRA-INDICATIONS**

- **PREGNANCY** Levothyroxine requirement may increase during pregnancy. Levothyroxine may cross the placenta. Excessive or insufficient maternal thyroid hormones can be detrimental to fetus. Assess maternal thyroid function before conception (if possible), at diagnosis of pregnancy, at antenatal booking, during both the second and third trimesters, and after delivery (more frequent monitoring required on initiation or adjustment of levothyroxine).

- **BREAST FEEDING** Amount too small to affect tests for neonatal hypothyroidism.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: powder for solution for injection, oral suspension, oral solution, powder, capsule

**Tablet**

- **LEVOthyroxine SODIum (Non-proprietary)**
  - Levothyroxine sodium anhydrous 25 microgram tablet
  - Levothyroxine sodium 25microgram tablets | 28 tablet (PBM) £4.00 DT price = £2.95 | 500 tablet (PBM) £42.32-£52.68
  - Levothyroxine sodium anhydrous 50 microgram tablet
  - Levothyroxine sodium 50microgram tablets | 28 tablet (PBM) £3.00 DT price = £2.02 | 1000 tablet (PBM) £93.49
  - Levothyroxine sodium anhydrous 100 microgram tablet
  - Levothyroxine sodium 100microgram tablets | 28 tablet (PBM) £3.00 DT price = £2.02 | 1000 tablet (PBM) £92.51

**Oral solution**

- **LEVOthyroxine SODIum (Non-proprietary)**
  - Levothyroxine sodium anhydrous 5 microgram per 1 ml
  - Levothyroxine sodium 5microgram/5ml oral solution sugar free (sugar-free) | 100 ml (PBM) £90.92 DT price = £79.55
  - Levothyroxine sodium anhydrous 10 microgram per 1 ml
  - Levothyroxine sodium 10microgram/5ml oral solution sugar free (sugar-free) | 100 ml (PBM) £101.79 DT price = £96.16
  - Levothyroxine sodium anhydrous 20 microgram per 1 ml
  - Levothyroxine sodium 20microgram/5ml oral solution sugar free (sugar-free) | 100 ml (PBM) £142.94 DT price = £123.56

**SIDE-EFFECTS, FURTHER INFORMATION**

- **Initial dosage in patients with cardiovascular disorders** If metabolism increases too rapidly (causing diarrhoea, nervousness, rapid pulse, insomnia, tremors and sometimes anginal pain where there is latent myocardial ischaemia), reduce dose or withhold for 1–2 days and start again at a lower dose.

- **PREGNANCY** Levothyroxine requirement may increase during pregnancy. Levothyroxine may cross the placenta. Excessive or insufficient maternal thyroid hormones can be detrimental to fetus. Assess maternal thyroid function before conception (if possible), at diagnosis of pregnancy, at antenatal booking, during both the second and third trimesters, and after delivery (more frequent monitoring required on initiation or adjustment of levothyroxine).

- **BREAST FEEDING** Amount too small to affect tests for neonatal hypothyroidism.

**INDICATIONS AND DOSE**

**Hypothyroidism**

- **Adult**:
  - Initially 10–20 micrograms daily; increased to 60 micrograms daily in 2–3 divided doses, dose should be increased gradually, smaller initial doses given for the elderly

**Hypothyroid coma**

**BY SLOW INTRAVENOUS INJECTION**

- Adult: 5–20 micrograms every 12 hours, increased to 5–20 micrograms every 4 hours if required, alternatively initially 50 micrograms for 1 dose, then 25 micrograms every 8 hours, reduced to 25 micrograms twice daily

**Dose equivalence and conversion**

20–25 micrograms of liothyronine sodium is equivalent to approximately 100 micrograms of levothyroxine sodium.

Brands without a UK licence may not be bioequivalent and dose adjustment may be necessary.

**CONTRA-INDICATIONS**

- **Cardiovascular disorders**
  - Diabetes mellitus (dose of anti diabetic drugs including insulin may need to be increased)
  - Elderly
  - Hypertension
  - Long-standing hypothyroidism
  - Myocardial infarction
  - Myocardial insufficiency

**CAUTIONS, FURTHER INFORMATION**

**Cardiovascular disorders** Baseline ECG is valuable because changes induced by hypothyroidism can be confused with ischaemia.

**INTERACTIONS** Appendix 1 (thyroid hormones).

**SIDE-EFFECTS**

- Anginal pain (usually at excessive dosage)
- ARRHYNTHIAS (usually at excessive dosage)
- Nervousness, rapid pulse, insomnia, tremors and sometimes anginal pain where there is latent myocardial ischaemia.

**SIDE-EFFECTS, FURTHER INFORMATION**

**Initial dosage in patients with cardiovascular disorders** If metabolism increases too rapidly (causing diarrhoea, nervousness, rapid pulse, insomnia, tremors and sometimes anginal pain where there is latent myocardial ischaemia), reduce dose or withhold for 1–2 days and start again at a lower dose.

**PREGNANCY** Levothyroxine requirement may increase during pregnancy. Does not cross the placenta in significant amounts. Excessive or insufficient maternal thyroid hormones can be detrimental to fetus. Assess maternal thyroid function before conception (if possible), at diagnosis of pregnancy, at antenatal booking, during both the second and third trimesters, and after delivery (more frequent monitoring required on initiation or adjustment of liothyronine).

**BREAST FEEDING** Amount too small to affect tests for neonatal hypothyroidism.

**PRESCRIBING AND DISPENSING INFORMATION**

Switching to a different brand Patients switched to a different brand should be monitored (particularly if pregnant or if heart disease present) as brands without a UK licence may not be bioequivalent. Pregnant women or those with heart disease should undergo an early review of thyroid status, and other patients should have thyroid function assessed if experiencing a significant change in symptoms. If liothyronine is continued long-term, thyroid function tests should be repeated 1–2 months after any change in brand.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, solution for injection, oral suspension, oral solution, capsule

**Tablet**

- **LIOTHYRONINE SODIUM (Non-proprietary)**
  - Liothyronine sodium 20 microgram tablet
  - Liothyronine sodium 20 microgram tablets | 28 tablet (PBM) £12.02 DT price = £10.00

**Powder for solution for injection**

- **LIOTHYRONINE SODIUM (Non-proprietary)**
  - Liothyronine sodium 20 microgram powder for solution for injection vials | 5 vial (PBM) £1.425.00
Chapter 7
Genito-urinary system

1 Bladder and urinary disorders

1.1 Urinary frequency, enuresis, and incontinence

Urinary frequency, enuresis and incontinence

Urinary frequency and incontinence

Incontinence in adults which arises from detrusor instability is managed by combining drug therapy with conservative methods for managing urge incontinence such as pelvic floor exercises and bladder training; stress incontinence can be managed by non-drug methods. Duloxetine p. 288 can be added and is licensed for the treatment of moderate to severe stress incontinence in women; it may be more effective when used as an adjunct to pelvic floor exercises. Antimuscarinic drugs reduce symptoms of urgency and urge incontinence and increase bladder capacity. Oxybutynin hydrochloride p. 669 also has a direct relaxant effect on urinary smooth muscle. Side-effects limit the use of oxybutynin hydrochloride, but they may be reduced by starting at a lower dose. A modified-release preparation of oxybutynin hydrochloride is effective and has fewer side-effects; a transdermal patch is also available. The efficacy and side-effects of tolterodine tartrate p. 671 are comparable to those of modified-release oxybutynin hydrochloride. Flavoxate hydrochloride p. 669 has less marked side-effects but it is also less effective. Darifenacin p. 668, fesoterodine fumarate p. 668, propiverine hydrochloride p. 670, solifenacin succinate p. 670, and trosiptum chloride p. 671 are newer antimuscarinic drugs licensed for urinary frequency, urgency, and incontinence. The need for continuing antimuscarinic drug therapy should be reviewed every 4–6 weeks until symptoms stabilise, and then every 6–12 months.

Propantheline bromide p. 74 and tricyclic antidepressants were used for urge incontinence but they are little used now because of their side-effects. The use of imipramine hydrochloride p. 296 is limited by its potential to cause cardiac side-effects.

Mirabegron p. 671, a selective beta, agonist, is licensed for the treatment of urinary frequency, urgency, and urge incontinence associated with overactive bladder syndrome. Purified bovine collagen implant (Contigen®, Bard) is indicated for urinary incontinence caused by intrinsic sphincter deficiency (poor or non-functioning bladder outlet mechanism). The implant should be inserted only by surgeons or physicians trained in the technique for injection of the implant.

Nocturnal enuresis in children

Nocturnal enuresis is common in young children, but persists in a small proportion by 10 years of age. For children under 5 years, reassurance and advice on the management of nocturnal enuresis can be useful for some families. Treatment may be considered in children over 5 years depending on their maturity and motivation, the frequency of nocturnal enuresis, and the needs of the child and their family.

Initially, advice should be given on fluid intake, diet, toileting behaviour, and reward systems; for children who do not respond to this advice, further treatment may be necessary. An enuresis alarm should be first line treatment for motivated, well-supported children; alarms have a lower relapse rate than drug treatment when discontinued.

Treatment should be reviewed after 4 weeks, and, if there are early signs of response, continued until a minimum of 2 weeks’ uninterrupted dry nights have been achieved. If complete dryness is not achieved after 3 months, only continue if the condition is still improving and the child remains motivated to use the alarm. If initial alarm treatment is unsuccessful, consider combination treatment with desmopressin p. 574, or desmopressin alone if the alarm is no longer appropriate or desirable.

Desmopressin is given by oral or by sublingual administration. Desmopressin alone can be offered to children over 5 years of age if an alarm is inappropriate or undesirable, or when rapid or short-term results are the priority (for example to cover periods away from home); desmopressin alone can also be used if there has been a partial response to a combination of desmopressin and an alarm following initial treatment with an alarm. Treatment should be assessed after 4 weeks and continued for...
3 months if there are signs of response. Desmopressin should be withdrawn at regular intervals (for 1 week every 3 months) for full reassessment. When stopping treatment with desmopressin, gradual withdrawal should be considered.

Nocturnal enuresis associated with daytime symptoms (overactive bladder) can be managed with antimuscarinic specialist assessment and should be continued for 3 months; the course can be repeated if necessary. The tricyclic antidepressant imipramine hydrochloride p. 296 may be considered for children who have not responded to all other treatments and have undergone specialist assessment, however, behavioural disorders can occur and relapse is common after withdrawal. Treatment should not normally exceed 3 months unless a physical examination is made and the child is fully reassessed; toxicity following overdose with tricyclics is of particular concern.

ANTIMUSCARINICS

Antimuscarinics (systemic)

- **CONTRA-INDICATIONS** Gastro-intestinal obstruction - intestinal atony - myasthenia gravis (but some antimuscarinics may be used to decrease muscarinic side-effects of anticholinesterases) - paralytic ileus - prostatic enlargement - pyloric stenosis - severe ulcerative colitis - significant bladder outflow obstruction - toxic megacolon - urinary retention

- **CAUTIONS** Acute myocardial infarction - arrhythmias (may be worsened) - autonomic neuropathy - cardiac insufficiency (due to association with tachycardia) - cardiac surgery (due to association with tachycardia) - conditions characterised by tachycardia - congestive heart failure (may be worsened) - coronary artery disease (may be worsened) - diarrhoea - elderly (especially if frail) - gastro-oesophageal reflux disease - hiatus hernia with reflux oesophagitis - hypertension - hyperthyroidism (due to association with tachycardia) - individuals susceptible to angle-closure glaucoma - prostatic hyperplasia - pyrexia - ulcerative colitis

- **INTERACTIONS** Many drugs have antimuscarinic effects; concomitant use of two or more such drugs can increase side-effects such as dry mouth, urine retention, and constipation. Concomitant use of other drugs with antimuscarinic effects can also lead to confusion in the elderly.

- **SIDE-EFFECTS**
  - **Common or very common** Constipation - dilution of pupils with loss of accommodation - dry mouth - photosphobia - reduced bronchial secretions - skin dryness - skin flushing - transient bradycardia (followed by tachycardia, palpitation and arrhythmias) - urinary retention - urinary urgency
  - **Uncommon** Confusion (particularly in the elderly) - giddiness - nausea - vomiting
  - **Very rare** Angle-closure glaucoma
  - **Frequency not known** Angioedema - blurred vision - blurred vision - central nervous system stimulation - convulsion - diarrhoea - difficulty in micturition - disorientation - dizziness - drowsiness - dry eyes - euphoria - fatigue - flatulence - hallucinations - headache - impaired memory - palpitation - photosensitivity - rash - reduced sweating (may lead to heat sensations and fainting in hot environments or patients with fever) - restless - taste disturbances

- **PATIENT AND CARER ADVICE** Antimuscarinics can affect the performance of skilled tasks (e.g. driving).

**Darifenacin**

**INDICATIONS AND DOSE**

**Urinary frequency | Urinary urgency | Incontinence**

**BY MOUTH**

- **Adult:** Initially 7.5 mg once daily, increased if necessary to 15 mg after 2 weeks

- **SIDE-EFFECTS**
  - **Uncommon** Cough - dyspnoea - hypertension - impotence - insomnia - oedema - rhinitis - ulcerative stomatitis - vaginitis - weakness

- **PREGNANCY** Manufacturer advises avoid—toxicity in animal studies.

- **BREAST FEEDING** Present in milk in animal studies—manufacturer advises caution.

- **HEPATIC IMPAIRMENT** Max. 7.5 mg daily in moderate impairment. Avoid in severe impairment.

- **PRESCRIBING AND DISPENSING INFORMATION** The need for continuing therapy for urinary incontinence should be reviewed every 4–6 weeks until symptoms stabilise, and then every 6–12 months.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Modified-release tablet**
  
  **Emselex (Merus Labs Luxco S.A.R.L.)**
  
  **Darifenacin (as Darifenacin hydrobromide) 7.5 mg** Emselex 7.5mg modified-release tablets 28 tablet £25.48 DT price = £25.48
  
  **Darifenacin (as Darifenacin hydrobromide) 15 mg** Emselex 15mg modified-release tablets 28 tablet £25.48

**Fesoterodine fumarate**

**INDICATIONS AND DOSE**

**Urinary frequency | Urinary urgency | Urge incontinence**

**BY MOUTH**

- **Adult:** 4 mg once daily, increased if necessary up to 8 mg once daily

**Dose adjustments due to interactions**

Max. 4 mg daily with concomitant atazanavir, clarithromycin, indinavir, itraconazole, ritonavir, saquinavir, or telithromycin.

In patients with hepatic or renal impairment, consult product literature before concomitant use with amrrenavir, aperipitant, atazanavir, clarithromycin, diltiazem, erythromycin, fluconazole, fosamprenavir, indinavir, itraconazole, ritonavir, saquinavir, telithromycin, verapamil, or grapefruit juice

- **SIDE-EFFECTS**
  - **Common or very common** Insomnia
  - **Uncommon** Cough - nasal dryness - pharyngolaryngeal pain - vertigo

- **PREGNANCY** Manufacturer advises avoid—toxicity in animal studies.

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT** Manufacturer advises increase dose cautiously; max. 4 mg daily in moderate impairment. Avoid in severe impairment. Consult product literature before concomitant use of cytochrome P450 enzyme inhibitors.

- **RENAL IMPAIRMENT** Increase dose cautiously if eGFR 30–80 mL/minute/1.73m²; max. 4 mg daily if eGFR less than 30 mL/minute/1.73m². Consult product literature before concomitant use of cytochrome P450 enzyme inhibitors.
Flavoxate hydrochloride

INDICATIONS AND DOSE
Urinary frequency | Urinary incontinence | Dysuria | Urinary urgency | Bladder spasm due to catheterisation, cystoscopy, or surgery

BY MOUTH
- Adult: 200 mg 3 times a day

CONTRA-INDICATIONS
Gastro-intestinal haemorrhage

SIDE-EFFECTS
- Eosinophilia | erythema | leucopenia | pruritus | urticaria | vertigo

PREGNANCY
Manufacturer advises avoid unless no safer alternative.

BREAST FEEDING
Manufacturer advises caution—no information available.

PRESCRIBING AND DISPENSING INFORMATION
The need for continuing therapy for urinary incontinence should be reviewed every 4–6 weeks until symptoms stabilise, and then every 6–12 months.

MEDIcular FORMS
There can be variation in the licensing of different medicines containing the same drug.

Modified-release tablet
CAUTIONARY AND ADVISORY LABELS 3, 25
- Toviaz (Pfizer Ltd)
  - Fesoterodine fumarate 4 mg: Toviaz 4 mg modified-release tablets | 28 tablet (PO) £25.78 DT price = £25.78
  - Fesoterodine fumarate 8 mg: Toviaz 8 mg modified-release tablets | 28 tablet (PO) £25.78 DT price = £25.78

Oxybutynin hydrochloride

INDICATIONS AND DOSE
Urinary frequency | Urinary incontinence | Neurogenic bladder instability

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
- Child 5–11 years: Initially 2.5–3 mg twice daily, increased to 5 mg 2–3 times a day
- Child 12–17 years: Initially 5 mg 2–3 times a day, increased if necessary up to 5 mg 4 times a day
- Adult: Initially 5 mg 2–3 times a day, increased if necessary up to 5 mg 4 times a day
- Elderly: Initially 2.5–3 mg twice daily, increased if tolerated to 5 mg twice daily, adjusted according to response

BY TRANSDERMAL APPLICATION USING PATCHES
- Adult: Apply 1 patch twice weekly, patch is to be applied to clean, dry unbroken skin on abdomen, hip or buttock. Patch should be removed every 3–4 days and site replacement patch on a different area.

Dose equivalence and conversion
Patients taking immediate-release oxybutynin may be transferred to the nearest equivalent daily dose of Lystinel™ XL.

UNLICENSED USE

CAUTIONS
Acute porphyrias p. 864

SIDE-EFFECTS
GENERAL SIDE-EFFECTS
- Uncommon Anorexia | facial flushing
- Rare Night terrors
- Frequency not known Cognitive impairment

SPECIFIC SIDE-EFFECTS
- Rare
- With transdermal use Application site reactions with patches

PREGNANCY
Manufacturers advise avoid unless essential—toxicity in animal studies.

BREAST FEEDING
Manufacturers advise avoid—present in milk in animal studies.

HEPATIC IMPAIRMENT
Manufacturer advises caution.

RENAL IMPAIRMENT
Manufacturer advises caution.

DIRECTIONS FOR ADMINISTRATION
- With transdermal use Apply patches to clean, dry, unbroken skin on abdomen, hip or buttock, remove after every 3–4 days and site replacement patch on a different area (avoid using same area for 7 days).

PRESCRIBING AND DISPENSING INFORMATION
- In adults The need for continuing therapy for urinary incontinence should be reviewed every 4–6 weeks until symptoms stabilise, and then at regular intervals; a response usually occurs within 6 months but may take longer.
- In children The need for therapy for urinary indications should be reviewed soon after it has been commenced and then at regular intervals; a response usually occurs within 6 months but may take longer.

PATIENT AND CARER ADVICE
Medicines for Children leaflet: Oxybutynin for daytime urinary symptoms www.medicinesforchildren.org.uk/oxybutynin-for-daytime-urinary-symptoms

Patients or carers should be given advice on how to administer oxybutynin transdermal patches.

NATIONAL FUNDING/ACCESS DECISIONS
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (July 2005) that Kentera® should be restricted for use in adults who...
benefit from oral oxybutynin but cannot tolerate its side-effects.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

CAUTIONARY AND ADVISORY LABELS 3

- OXYBUTYNIN HYDROCHLORIDE (Non-proprietary)
  - Oxybutynin hydrochloride 2.5 mg: Oxybutynin 2.5mg tablets | 56 tablet (£8.68 DT price = £1.75 | 84 tablet (£10.75
  - Oxybutynin hydrochloride 3 mg: Oxybutynin 3mg tablets | 56 tablet (£8.68 DT price = £1.66 | 72 (£13.77
  - Oxybutynin hydrochloride 5 mg: Oxybutynin 5mg tablets | 56 tablet (£13.85 DT price = £2.40 | 84 tablet (£20.77
  - Oxybutynin hydrochloride 10 mg: Oxybutynin 10mg tablets | 60 (£27.54 DT price = £27.54

**Modified-release tablet**

CAUTIONARY AND ADVISORY LABELS 3, 25

- Lyriix (Janssen-Cilag Ltd)
  - Oxybutynin hydrochloride 5 mg: Lyriix 5mg tablets | 30 (£13.77 DT price = £1.73
  - Oxybutynin hydrochloride 10 mg: Lyriix 10mg tablets | 30 (£27.54 DT price = £27.54

**Oral solution**

CAUTIONARY AND ADVISORY LABELS 3

- OXYBUTYNIN HYDROCHLORIDE (Non-proprietary)
  - Oxybutynin hydrochloride 500 microgram per 1 ml: Oxybutynin 500 microgram per 1 ml or solution sugar free (sugar-free) | 150 ml (£128.15
  - Oxybutynin hydrochloride 1 mg per 1 ml: Oxybutynin 1mg/5ml oral solution sugar free (sugar-free) | 150 ml (£128.15
  - Ditropan (Sanofi)
    - Oxybutynin hydrochloride 500 microgram per 1 ml Ditropan 5mg/5ml elixir | 150 ml (£6.88 DT price = £6.88

**Transdermal patch**

CAUTIONARY AND ADVISORY LABELS 3

- Kentera (Orion Pharma (UK) Ltd)
  - Oxybutynin 3.9 mg per 24 hour Kentera 3.9mg/24hours patches | 8 patch (£27.20 DT price = £27.20

**Propiverine hydrochloride**

**INDICATIONS AND DOSE**

Urinary frequency, urgency and incontinence associated with overactive bladder

INITIALLY BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

- Adult: 15 mg 1–2 times a day, increased if necessary up to 15 mg 3 times a day

BY MOUTH USING MODIFIED-RELEASE CAPSULES

- Adult: 30 mg once daily

Urinary frequency, urgency and incontinence associated with neurogenic bladder instability

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

- Adult: 15 mg 3 times a day

**PREGNANCY**

Manufacturer advises avoid (restriction of skeletal development in animals).

**BREAST FEEDING**

Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**

Avoid in moderate to severe impairment.

**RENAL IMPAIRMENT**

Max. daily dose 30 mg if eGFR less than 30 ml/minute/1.73m². Manufacturer advises caution in mild or moderate impairment.

**PRESCRIBING AND DISPENSING INFORMATION**

The need for continuing therapy for urinary incontinence should be reviewed every 4–6 weeks until symptoms stabilise, and then every 6–12 months.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

CAUTIONARY AND ADVISORY LABELS 3

- Detrunorm (AMCo)
  - Propiverine hydrochloride 15 mg Detrunorm 15mg tablets | 56 tablet (£18.00 DT price = £18.00

**Modified-release capsule**

CAUTIONARY AND ADVISORY LABELS 3, 25

- Detrunorm XL (AMCo)
  - Propiverine hydrochloride 30 mg Detrunorm XL 30mg capsules | 28 capsule (£24.45 DT price = £24.45
  - Propiverine hydrochloride 45 mg Detrunorm XL 45mg capsules | 28 capsule (£27.00 DT price = £27.00

**Solifenacin succinate**

**INDICATIONS AND DOSE**

Urinary frequency | Urinary urgency | Urinary incontinence

BY MOUTH

- Adult: 5 mg once daily, increased if necessary to 10 mg once daily

Dose adjustments due to interactions

Max. 5 mg daily with concomitant potent inhibitors of cytochrome P450 enzyme CYP3A4 (such as itraconazole, ketoconazole, or ritonavir).

**CAUTIONS**

Neurogenic bladder disorder • susceptibility to QT-interval prolongation

**SIDE-EFFECTS**

- Uncommon
  - Gastro-oesophageal reflux • oedema
- Frequency not known
  - Dysphonie • hepatic impairment • hyperkalaemia • muscle weakness • reduced appetite • torsade de pointes

**PREGNANCY**

Manufacturer advises caution—no information available.

**BREAST FEEDING**

Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**

Max. 5 mg daily in moderate impairment, avoid in moderate impairment in those already taking potent inhibitors of cytochrome P450 enzyme CYP3A4 (such as itraconazole or ritonavir). Avoid in severe impairment.

**RENAL IMPAIRMENT**

Max. 5 mg daily if eGFR less than 30 ml/minute/1.73 m²; avoid if eGFR less than 30 ml/minute/1.73 m² in those already taking potent inhibitors of cytochrome P450 enzyme CYP3A4 (such as itraconazole or ritonavir).

**PRESCRIBING AND DISPENSING INFORMATION**

The need for continuing therapy for urinary incontinence should be reviewed every 4–6 weeks until symptoms stabilise, and then every 6–12 months.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

**Tablet**

CAUTIONARY AND ADVISORY LABELS 3

- Vesicare (Astellas Pharma Ltd)
  - Solifenacin succinate 5 mg Vesicare 5mg tablets | 30 tablet (£27.62 DT price = £27.62
  - Solifenacin succinate 10 mg Vesicare 10mg tablets | 30 tablet (£35.91 DT price = £35.91
**Tolterodine tartrate**

**INDICATIONS AND DOSE**

**Urinary frequency** | **Urinary urgency** | **Urinary incontinence**

INITIALLY BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

- Adults: 2 mg twice daily, reduced if not tolerated to 1 mg twice daily

BY MOUTH USING MODIFIED-RELEASE CAPSULES

- Adults: 4 mg once daily

- **CAUTIONS** History of QT-interval prolongation
- **INTERACTIONS** Caution with concomitant use with other drugs known to prolong QT interval.

- **SIDE-EFFECTS**
  - Common or very common: Bronchitis · chest pain · fatigue · paraesthesia · peripheral oedema · sinusitis · vertigo · weight gain
  - Uncommon: Memory impairment
  - Frequency not known: Flushing

- **PREGNANCY** Manufacturer advises avoid—toxicity in animal studies.
- **BREAST FEEDING** Manufacturer advises avoid—no information available.
- **HEPATIC IMPAIRMENT** Reduce dose to 1 mg twice daily. Avoid modified-release preparations.
- **RENAL IMPAIRMENT** Reduce dose to 1 mg twice daily if eGFR less than 30 mL/minute/1.73 m². Avoid modified-release preparations if eGFR less than 30 mL/minute/1.73 m².

**PRESCRIBING AND DISPENSING INFORMATION**

The need for continuing therapy for urinary incontinence should be reviewed every 4–6 weeks until symptoms stabilise, and then every 6–12 months.

**MEDICAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, powder

**Tablet**

CAUTIONARY AND ADVISORY LABELS 23

- **TOLTERODINE TARTRATE** (Non-proprietary)
  - Tolterodine tartrate 1 mg: Tolterodine 1mg tablets | 56 tablet [PMS] £23.03 DT price = £6.21
  - Tolterodine tartrate 2 mg: Tolterodine 2mg tablets | 56 tablet [PMS] £30.56 DT price = £7.78
  - Detrusitol (Pfizer Ltd)
    - Tolterodine tartrate 1 mg: Detrusitol 1mg tablets | 56 tablet [PMS] £23.03 DT price = £6.21
    - Tolterodine tartrate 2 mg: Detrusitol 2mg tablets | 56 tablet [PMS] £30.56 DT price = £7.78
- **Modified-release capsule**

  CAUTIONARY AND ADVISORY LABELS 3, 25

  - Detrusitol XL (Pfizer Ltd)
    - Tolterodine tartrate 4 mg: Detrusitol XL 4mg capsules | 28 capsule [PMS] £25.78 DT price = £25.78
    - Brands may include Blerone XL; Efflosomyl XL; Inconex XL; Mariosea XL; Neditol XL; Preblacon XL; Santisor X

**Trospium chloride**

**INDICATIONS AND DOSE**

**Urinary frequency** | **Urinary urgency** | **Urinary incontinence**

INITIALLY BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

- Adults: 20 mg twice daily, to be taken before food

BY MOUTH USING MODIFIED-RELEASE MEDICINES

- Adults: 60 mg once daily

- **SIDE-EFFECTS**
  - Common or very common: Tachycardia · urinary-tract infection
  - Uncommon: Atrial fibrillation · dyspepsia · gastritis · hypertension · joint swelling · palpitation · pruritus · rash · vulvovaginal infection · vulvovaginal pruritus

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

**Tablet**

CAUTIONARY AND ADVISORY LABELS 23

- **TROSPNIUM CHLORIDE** (Non-proprietary)
  - Trospium chloride 20 mg: Trospium chloride 20mg tablets | 60 tablet [PMS] £24.79 DT price = £24.78
  - Regurin (Speciality European Pharma Ltd)
    - Trospium chloride 20 mg: Regurin 20mg tablets | 60 tablet [PMS] £26.00 DT price = £24.78
    - Brands may include Flotros; Uraplex

**Modified-release capsule**

CAUTIONARY AND ADVISORY LABELS 23, 25

- **TROSPNIUM CHLORIDE** (Non-proprietary)
  - Trospium chloride 60 mg: Trospium chloride 60mg modified-release capsules | 28 capsule [PMS] no price available
  - Regurin XL (Speciality European Pharma Ltd)
    - Trospium chloride 60 mg: Regurin XL 60mg capsules | 28 capsule [PMS] £23.05

**BETA₂-ADRENOCEPTOR AGONISTS**

**Mirabegron**

**INDICATIONS AND DOSE**

**Urinary frequency, urgency, and urge incontinence**

BY MOUTH

- Adult: 50 mg once daily

- **CONTRA-INDICATIONS** Severe hypertension
- **CAUTIONS** History of QT-interval prolongation
- **INTERACTIONS** → Appendix 1 (mirabegron).

  Caution with concomitant use with drugs that prolong the QT interval.

- **HEPATIC IMPAIRMENT** With concomitant use of strong cytochrome P450 inhibitors such as itraconazole, ketoconazole, ritonavir, or clarithromycin reduce dose to 25 mg once daily in mild impairment, and avoid in moderate impairment.

- **RENAL IMPAIRMENT** With concomitant use of strong cytochrome P450 inhibitors such as itraconazole, ketoconazole, ritonavir, or clarithromycin reduce dose to 25 mg once daily if eGFR less than 30–89 mL/minute/1.73 m², and avoid if eGFR less than 30 mL/minute/1.73 m².

- **SIDE-EFFECTS**
  - Common or very common: Atrial fibrillation · dyspepsia · gastritis · hypertension · joint swelling · palpitation · pruritus · rash · vulvovaginal infection · vulvovaginal pruritus
1.2 Urinary retention

**Drugs for urinary retention**

*Acute retention* is painful and is treated by catheterisation. *Chronic retention* is painless and often long-standing. Catheterisation is unnecessary unless there is deterioration of renal function. After the cause has initially been established and treated, drugs may be required to increase detrusor muscle tone.

*Benign prostatic hyperplasia* is treated either surgically or medically with alpha-blockers. Dutasteride p. 676 and finasteride p. 676 are alternatives to alpha-blockers, particularly in men with a significantly enlarged prostate. Tadalafil p. 700, a phosphodiesterase type-5 inhibitor, may also be used in the management of benign prostatic hyperplasia.

**Alpha-blockers**

The alpha-1-selective alpha blockers, alfuzosin hydrochloride below, doxazosin p. 673, prazosin p. 674, tamsulosin hydrochloride p. 674 and terazosin p. 675 relax smooth muscle in benign prostatic hyperplasia producing an increase in urinary flow-rate and an improvement in obstructive symptoms.

**Parasympathomimetics**

The parasympathomimetic bethanechol chloride p. 676 increases detrusor muscle contraction. However, it has only a limited role in the relief of urinary retention; its use has been superseded by catheterisation.

**INDICATIONS AND DOSE**

Beanzosin hydrochloride

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

- Adult: 2.5 mg 3 times a day; maximum 10 mg per day
- Elderly: Initially 2.5 mg twice daily, adjusted according to response; maximum 10 mg per day

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

- Adult: 10 mg once daily

Acute urinary retention associated with benign prostatic hyperplasia

**BY MOUTH USING MODIFIED-RELEASE TABLETS**

- Elderly: 10 mg once daily for 2–3 days during catheterisation and for one day after removal; max. 4 days

**SIDE-EFFECTS, FURTHER INFORMATION**

First dose effect First dose may cause collapse due to hypotensive effect (therefore should be taken on retiring to bed). Patient should be warned to lie down if symptoms such as dizziness, fatigue or sweating develop, and to remain lying down until they abate completely.

**HEPATIC IMPAIRMENT** Initial dose 2.5 mg once daily, adjusted according to response to 2.5 mg twice daily in mild to moderate impairment—avoid if severe.

**RENAL IMPAIRMENT** Initial dose 2.5 mg twice daily and adjust according to response. Manufacturers advise avoid use of modified-release preparations if eGFR less than 30 mL/minute/1.73 m² as limited experience.

**PATIENT AND CARER ADVICE** May affect performance of skilled tasks e.g. driving. Patient should be counselled on the first dose effect.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

**Tablet**

- ALFUZOSIN HYDROCHLORIDE (Non-proprietary)
  - Alfuzosin hydrochloride 2.5 mg Alfuzosin 2.5mg tablets | 60 tablet £1.48 £1.39
  - Xatral (Sanofi)
  - Alfuzosin hydrochloride 2.5 mg Xatral 2.5mg tablets | 60 tablet £1.29 £1.21
Doxazosin

INDICATIONS AND DOSE

Hypertension

Adult: Initially 1 mg once daily for 1–2 weeks, then increased to 2 mg once daily, then increased if necessary to 4 mg once daily; maximum 16 mg per day

BY MOUTH USING MODIFIED-RELEASE MEDICINES

Adult: Initially 4 mg once daily, dose can be adjusted after 4 weeks, then increased if necessary to 8 mg once daily

Benign prostatic hyperplasia

Administer the initial dose in the evening. If required, increase dose in 4 mg increments to a maximum of 16 mg daily

Adult: Initially 4 mg once daily, dose can be adjusted after 4 weeks, then increased if necessary to 8 mg once daily

Dose adjustments due to interactions

Caution with concomitant antihypertensives in benign prostatic hyperplasia—reduced dosage and specialist supervision may be required

CONTRA-INDICATIONS

History of micturition syncope (in patients with benign prostatic hypertrophy) - history of postural hypotension - monotherapy in patients with overflow bladder or anuria

CAUTIONS

Care with initial dose (postural hypotension) - cataract surgery (risk of intra-operative floppy iris syndrome) - elderly - heart failure - pulmonary oedema due to aortic or mitral stenosis

INTERACTIONS

Appendix 1 (alpha-blockers).

SIDE-EFFECTS

Common or very common

Anxiety - back pain - coughing - dyspnoea - fatigue - influenza-like symptoms - myalgia - paraesthesia - sleep disturbance - vertigo

Uncommon

Agitation - angina - arthralgia - epistaxis - gout - hypoesthesia - micturition disturbance - myocardial infarction - tinnitus - tremor - weight changes

Very rare

Abnormal ejaculation - alopecia - arrhythmias - bradycardia - bronchospasm - choreostasis - gynaecomastia - hepatitis - hot flashes - jaundice - leucopenia - thrombocytopenia

Frequency not known


Pregnancy

No evidence of teratogenicity; manufacturers advise use only when potential benefit outweighs risk.

Breast feeding

Accumulates in milk in animal studies—manufacturer advises avoid.

Hepatic impairment

Use with caution. Manufacturer advises avoid in severe impairment—no information available.

PATIENT AND CARER ADVICE

May affect performance of skilled tasks e.g. driving. Patient counselling is advised for doxazosin tablets (initial dose).

MEDITICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, capsule

Tablet

DOXAZOSIN (Non-proprietary)

Doxazosin (as Doxazosin mesilate) 1 mg

Doxazosin 1 mg tablets | 28 tablet | £10.56 DT price = £0.92

Doxazosin (as Doxazosin mesilate) 2 mg

Doxazosin 2 mg tablets | 28 tablet | £14.08 DT price = £0.95

Doxazosin (as Doxazosin mesilate) 4 mg

Doxazosin 4 mg tablets | 28 tablet | £14.08 DT price = £1.12

Cardura (Pfizer Ltd)

Doxazosin (as Doxazosin mesilate) 1 mg

Cardura 1 mg tablets | 28 tablet | £10.56 DT price = £0.92

Doxazosin (as Doxazosin mesilate) 2 mg

Cardura 2 mg tablets | 28 tablet | £14.08 DT price = £0.95

Brands may include Doxadura

Modified-release tablet

CAUTIONARY AND ADVISORY LABELS

Adult: 25 mg twice daily, increased in steps of 25–50 mg every 2 weeks, maximum daily dose should be given in divided doses; maximum 200 mg per day

Benign prostate hyperplasia

BY MOUTH

Adult: 20 mg twice daily, increased in steps of 20 mg every 2 weeks if required, increased if necessary up to 100 mg daily in divided doses

Elderly: 20 mg daily, dose to be taken at night

Dose adjustments due to interactions

Caution with concomitant antihypertensives in benign prostatic hyperplasia—reduced dosage and specialist supervision may be required

CONTRA-INDICATIONS

Established heart failure - history micturition syncope (when used for benign prostatic hyperplasia) - history of postural hypotension (when used for benign prostatic hyperplasia)

CAUTIONS

Cataract surgery (risk of intra-operative floppy iris syndrome) - control incipient heart failure before initiating indoramin - elderly - epilepsy - convulsions in animal studies - history of depression - Parkinson’s disease (extrapyramidal disorders reported)

INTERACTIONS

Appendix 1 (alpha-blockers).

Avoid alcohol (enhances rate and extent of absorption).

SIDE-EFFECTS

Common or very common

Sedation

Uncommon

Failure of ejaculation - fatigue - weight gain

Frequency not known

Genito-urinary system

PREGNANCY No evidence of teratogenicity; manufacturers advise use only when potential benefit outweighs risk.

BREAST FEEDING No information available.

HEPATIC IMPAIRMENT Manufacturer advises caution.

RENAL IMPAIRMENT Manufacturer advises caution.

PATIENT AND CARER ADVICE Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol may be enhanced.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS

■ ★ INDORAMIN (Non-proprietary)
  Indoramin hydrochloride 20 mg Indoramin 20mg tablets | 60 tablet | £33.30 DT price = 18.11
  Indoramin (as Indoramin hydrochloride) 25 mg Indoramin 25mg tablets | 84 tablet | £60.26 DT price = £60.26

■ ★ Doraile Tiltab (Chemidex Pharma Ltd)
  Indoramin hydrochloride 20 mg Doraile Tiltab 20mg tablets | 60 tablet | £11.44 DT price = £8.11

Prazosin

INDICATIONS AND DOSE

Hypertension

BY MOUTH

Adult: Initially 500 micrograms 2–3 times a day for 3–7 days, the initial dose should be taken on retiring to bed at night to avoid collapse, increased to 1 mg 2–3 times a day for a further 3–7 days, then increased if necessary up to 20 mg daily in divided doses

Congestive heart failure (rarely used)

BY MOUTH

Adult: 500 micrograms 2–4 times a day, initial dose to be taken at bedtime, then increased to 4 mg daily in divided doses; maintenance 4–20 mg daily in divided doses

Raynaud’s syndrome (but efficacy not established)

BY MOUTH

Adult: Initially 500 micrograms twice daily, initial dose to be taken at bedtime, dose may be increased after 3–7 days, then increased if necessary up to 1–2 mg twice daily

Benign prostatic hyperplasia

BY MOUTH

Adult: Initially 500 micrograms twice daily for 3–7 days, subsequent doses should be adjusted according to response, maintenance 2 mg twice daily, initiate with lowest possible dose in elderly patients

Dose adjustments due to interactions

Caution with concomitant antihypertensives in benign prostatic hyperplasia—reduced dosage and specialist supervision may be required

Tamsulosin hydrochloride

INDICATIONS AND DOSE

Benign prostatic hyperplasia

BY MOUTH USING MODIFIED-RELEASE MEDICINES

Adult: 400 micrograms once daily

CONTRA-INDICATIONS History of micturition syncope - history of postural hypotension

CAUTIONS Cataract surgery (risk of intra-operative floppy iris syndrome) - comitant antihypertensives (reduced dosage and specialist supervision may be required) - elderly

INTERACTIONS → Appendix 1 (alpha-blockers).

Dutasteride with tamsulosin

The properties listed below are those particular to the combination only. For the properties of the components please consider, dutasteride p. 676, tamsulosin hydrochloride p. 674.

INDICATIONS AND DOSE

Benign prostatic hyperplasia

BY MOUTH

Adult (male): 1 capsule daily.

PATIENT AND CARER ADVICE

May affect performance of skilled tasks e.g. driving.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, powder

Modified-release tablet

CAUTIONARY AND ADVISORY LABELS 25

TAMSULOSIN HYDROCHLORIDE (Non-proprietary)

Tamsulosin hydrochloride 400 microgram Tamsulosin 400micromgram modified-release tablets | 30 tablet (Pos) £10.47 DT price = £10.47

Flomaxtra XL (Astellas Pharma Ltd)

Tamsulosin hydrochloride 400 microgram | 30 tablet (Pos) £10.47 DT price = £10.47

Brands may include Costam XL; Faramisil; Flontone XL

Modified-release capsule

CAUTIONARY AND ADVISORY LABELS 25

TAMSULOSIN HYDROCHLORIDE (Non-proprietary)

Tamsulosin hydrochloride 400 microgram | 30 capsule (Pos) £6.15 DT price = £4.52

Brands may include Contiflo XL; Diffundox XL; Flomax MR; Galebon; Losinate MR; Pamsvax XL; Petyme MR; Pinexel PR; Prosurin XL; Talphyn MR; Tamfrex XL; Tamurex

Solifenacin with tamsulosin

The properties listed below are those particular to the combination only. For the properties of the components please consider, solifenacin succinate p. 670, tamsulosin hydrochloride p. 674.

INDICATIONS AND DOSE

Moderate to severe urinary frequency, urgency, and obstructive symptoms associated with benign prostatic hyperplasia when monotherapy ineffective

BY MOUTH

Adult (male): 1 tablet daily.

Dose adjustments due to interactions

Max. 1 Vesomni® tablet daily with concomitant potent inhibitors of cytochrome P450 enzyme CYP3A4 (such as itraconazole or ritonavir).

HEPATIC IMPAIRMENT

Max. 1 Vesomni® tablet daily in moderate impairment.

RENAL IMPAIRMENT

Max. 1 Vesomni® tablet daily if eGFR less than 30 mL/minute/1.73 m².

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Modified-release tablet

CAUTIONARY AND ADVISORY LABELS 3, 25

Vesomni® (Astellas Pharma Ltd)

Solifenacin succinate 6 mg, Tamsulosin hydrochloride 400 microgram Vesomni 6mg/0.4mg modified-release tablets | 30 tablet (Pos) £27.62

Terazosin

INDICATIONS AND DOSE

Mild to moderate hypertension

BY MOUTH

Adult: 1 mg daily for 7 days, then increased if necessary to 2 mg daily, dose should be taken at bedtime; maintenance 2–10 mg once daily, doses above 20 mg rarely improve efficacy

Benign prostatic hyperplasia

BY MOUTH

Adult: Initially 1 mg daily, dose should be taken at bedtime, if necessary dose may be doubled at intervals of 1–2 weeks according to response; maintenance 5–10 mg daily; maximum 10 mg per day

CONTRA-INDICATIONS

History of micturition syncope (in benign prostatic hyperplasia) - history of postural hypotension (in benign prostatic hyperplasia)

CAUTIONS

Cataract surgery (risk of intra-operative floppy iris syndrome) - elderly - first dose

CAUTIONS, FURTHER INFORMATION

First dose First dose may cause collapse due to hypotension within 30–90 minutes, therefore should be taken on retiring to bed; may also occur with rapid dose increase.

INTERACTIONS

Appendix 1 (alpha-blockers).

SIDE-EFFECTS


PREGNANCY

No evidence of teratogenicity; manufacturers advise use only when potential benefit outweighs risk.

BREAST FEEDING

No information available.

PATIENT AND CARER ADVICE

May affect performance of skilled tasks e.g. driving. Patient counselling is advised for terazosin tablets (initial dose).

First dose effect First dose may cause collapse due to hypotensive effect (therefore should be taken on retiring to bed). Patient should be warned to lie down if symptoms such as dizziness, fatigue or sweating develop, and to remain lying down until they abate completely.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

TERAZOSIN (Non-proprietary)

Terazosin (as Terazosin hydrochloride) 2 mg Terazosin 2mg tablets | 28 tablet (Pos) £4.90 DT price = £2.45

Terazosin (as Terazosin hydrochloride) 5 mg Terazosin 5mg tablets | 28 tablet (Pos) £6.57 DT price = £2.80
Terazosin (as Terazosin hydrochloride) 10 mg Terazosin 10mg tablets | 28 tablet (P) £16.00 DT price = £8.09
▶ Hytrin (AMCo)
Terazosin (as Terazosin hydrochloride) 1 mg Hytrin 1mg tablets | 7 tablet (P) no price available
Terazosin (as Terazosin hydrochloride) 2 mg Hytrin 2mg tablets | 14 tablet (P) no price available | 21 tablet (P) no price available | 28 tablet (P) £2.20 DT price = £2.45
Terazosin (as Terazosin hydrochloride) 5 mg Hytrin 5mg tablets | 7 tablet (P) no price available | 28 tablet (P) £4.13 DT price = £2.80
Terazosin (as Terazosin hydrochloride) 10 mg Hytrin 10mg tablets | 28 tablet (P) £8.24 DT price = £8.09
▶ Hytrin (AMCo)
Hytrin BPH tablets starter pack | 28 tablet (P) £10.97
Hytrin tablets starter pack | 28 tablet (P) £13.00

PARASYMPATHOMIMETICS
Bethanechol chloride

INDICATIONS AND DOSE
Urinary retention
BY MOUTH
▶ Adult: 10–25 mg 3–4 times a day, to be taken 30 minutes before food

CONTRA-INDICATIONS Bradycardia - cardiovascular disorders - conditions where increased motility of the gastro-intestinal tract could be harmful - conditions where increased motility of the urinary tract could be harmful - epilepsy - heart block - hypothyroidism - hypotension - intestinal obstruction - obstructive airways disease - parkinsonism - peptic ulcer - recent myocardial infarction - urinary obstruction

CAUTIONS Autonomic neuropathy (use lower initial dose)

INTERACTIONS ▶ Appendix 1 (parasympathomimetics).

SIDE-EFFECTS Abdominal pain - bradycardia - bronchoconstriction - diarrhoea - eructation - flushing - headache - hypotension - increased lacrimation - increased salivation - increased sweating - nausea - rhinorrhoea - vomiting

PREGNANCY Manufacturer advises avoid—no information available.

BREAST FEEDING Manufacturer advises avoid; gastrointestinal disturbances in infant reported.

LESS SUITABLE FOR PRESCRIBING Less suitable for prescribing.

MEDICINAL FORMS
Tablet
CAUTIONARY AND ADVISORY LABELS 22
▶ Myotonine (Cheolapharm Arzneimittel GmbH)
Bethanechol chloride 10 mg Myotonine 10mg tablets | 100 tablet (P) £18.51
Bethanechol chloride 25 mg Myotonine 25mg tablets | 100 tablet (P) £27.26

5α-REDUCTASE INHIBITORS
Dutasteride

DRUG ACTION A specific inhibitor of the enzyme 5α-reductase, which metabolises testosterone into the more potent androgen, dihydrotestosterone.

INDICATIONS AND DOSE
Benign prostatic hyperplasia
BY MOUTH
▶ Adult: 500 micrograms daily, review treatment at 3–6 months and then every 6–12 months (may require several months treatment before benefit is obtained).

INTERACTIONS ▶ Appendix 1 (dutasteride).

SIDE-EFFECTS Breast enlargement - breast tenderness - decreased libido - ejaculation disorders - impotence

CONCEPTION AND CONTRACEPTION Dutasteride is excreted in semen and use of a condom is recommended if sexual partner is pregnant or likely to become pregnant.

HEPATIC IMPAIRMENT Avoid in severe impairment—no information available.

EFFECT ON LABORATORY TESTS May decrease serum concentration of prostate cancer markers such as prostate-specific antigen; reference values may need adjustment.

HANDLING AND STORAGE Women of childbearing potential should avoid handling leaking capsules of dutasteride.

PATIENT AND CARER ADVICE Cases of male breast cancer have been reported. Patients or their carers should be told to promptly report to their doctor any changes in breast tissue such as lumps, pain, or nipple discharge.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution
Capsule
CAUTIONARY AND ADVISORY LABELS 25
▶ Avarol (GlaxoSmithKline Ltd)
Dutasteride 500 microgram Avarol 500microgram capsules | 30 capsule (P) £14.60 DT price = £14.60
Also available in combination with tamsulosin, p. 675

Finasteride

DRUG ACTION A specific inhibitor of the enzyme 5α-reductase, which metabolises testosterone into the more potent androgen, dihydrotestosterone.

INDICATIONS AND DOSE
Benign prostatic hyperplasia
BY MOUTH
▶ Adult: 5 mg daily, review treatment at 3–6 months and then every 6–12 months (may require several months treatment before benefit is obtained).

Androgenetic alopecia in men
BY MOUTH
▶ Adult: 1 mg daily.

CAUTIONS Obstructive uropathy

SIDE-EFFECTS Breast enlargement - breast tenderness - decreased libido - ejaculation disorders - face swelling - hypersensitivity reactions - impotence - lip swelling - male breast cancer - pruritus - rash - testicular pain

CONCEPTION AND CONTRACEPTION Finasteride is excreted in semen and use of a condom is recommended if sexual partner is pregnant or likely to become pregnant.

EFFECT ON LABORATORY TESTS Decreases serum concentration of prostate cancer markers such as prostate-specific antigen; reference values may need adjustment.

HANDLING AND STORAGE Women of childbearing potential should avoid handling crushed or broken tablets of finasteride.
1.3 Urological pain

**Urological pain**

The acute pain of ureteric colic may be relieved with pethidine hydrochloride p. 372. **Diclofenac** by injection or as suppositories is also effective and compares favourably with pethidine hydrochloride; other non-steroidal anti-inflammatory drugs are occasionally given by injection. Lidocaine hydrochloride gel p. 1116 is a useful topical application in urethral pain or to relieve the discomfort of catheterisation.

**Alkalisation of urine**

*Alkalisation* of urine can be undertaken with potassium citrate. The alkalising action may relieve the discomfort of cystitis caused by lower urinary tract infections. Sodium bicarbonate p. 848 is used as a urinary alkalising agent in some metabolic and renal disorders.

| Drugs used for Urological pain not listed below: Sodium bicarbonate, p. 848 |

**ALKALINISING DRUGS**

**Citric acid with potassium citrate**

**INDICATIONS AND DOSE**

- Relief of discomfort in mild urinary-tract infections
- *Alkalisation of urine*

**BY MOUTH USING ORAL SOLUTION**

- Adult: 10 mL 3 times a day, diluted well with water

**CAUTIONS**

- Cardiac disease · elderly

**INTERACTIONS → Appendix 1 (potassium salts).**

**SIDE-EFFECTS**

- Hyperkalaemia on prolonged high dosage · mild diuresis

**RENAL IMPAIRMENT**

- Avoid in severe impairment. Close monitoring required in renal impairment—high risk of hyperkalaemia.

**PRESCRIBING AND DISPENSING INFORMATION**

When prepared extemporaneously, the BP states Potassium Citrate Mixture BP consists of potassium citrate 30%, citric acid monohydrate 5% in a suitable vehicle with a lemon flavour. Extemporaneous preparations should be recently prepared according to the following formula: potassium citrate 3 g, citric acid monohydrate 500 mg, syrup 2.5 mL, quillaia tincture 0.1 mL, lemon spirit 0.05 mL, double-strength chloroform water 3 mL, water to 10 mL. Contains about 28 mmol K⁺/10 mL. Flavours of oral liquid formulations may include lemon.

**CONTRA-INDICATIONS**

- With rectal use: Acute gastro-intestinal conditions

**CAUTIONS**

- With oral use: Cardiac disease · elderly · hypertension · patients on a sodium-restricted diet

- With rectal use: Debilitated patients · sodium and water retention in susceptible individuals

**INTERACTIONS**

- With oral use: Appendix 1 (potassium citrate).

**SIDE-EFFECTS**

- With oral use: Mild diuresis

**PREGNANCY**

- With oral use: Use with caution.

**RENAL IMPAIRMENT**

- With oral use: In patients with fluid retention, avoid antacids containing large amounts of sodium.

**Sodium citrate**

**INDICATIONS AND DOSE**

- **Bladder washouts**
  - Adult: (consult product literature)
- **Relief of discomfort in mild urinary-tract infections**
  - **BY MOUTH**
    - Adult: (consult product literature)
- **MICRALAX®**
- **Constipation**
  - **BY RECTUM**
    - Child 3-17 years: 5 mL for 1 dose
    - Adult: 5 mL for 1 dose
- **MICOLETTE®**
- **Constipation**
  - **BY RECTUM**
    - Child 3-17 years: 5–10 mL for 1 dose
    - Adult: 5–10 mL for 1 dose
- **RELAXIT®**
- **Constipation**
  - **BY RECTUM**
    - Child 1 month-2 years: 5 mL for 1 dose, insert only half the nozzle length
    - Child 3-17 years: 5 mL for 1 dose
    - Adult: 5 mL for 1 dose

## 7. Genito-urinary system
Bladder instillations and urological surgery

2 Bladder instillations and urological surgery

Bladder instillations and
urological surgery

Bladder infection
Various solutions are available as irrigations or washouts. Aqueous chlorhexidine p. 1051 can be used in the management of common infections of the bladder but it is ineffective against most Pseudomonas spp. Solutions containing chlorhexidine 1 in 5000 (0.02%) are used but they may irritate the mucosa and cause burning and haematuria (in which case they should be discontinued); sterile sodium chloride solution 0.9% p. 851 (physiological saline) is usually adequate and is preferred as a mechanical irrigant.

Continuous bladder irrigation with amphotericin 50 micrograms/ml p. 517 may be of value in mycotic infections in adults.

Dissolution of blood clots
Clot retention is usually treated by irrigation with sterile sodium chloride solution 0.9% but sterile sodium citrate solution for bladder irrigation 3% may also be helpful.

Bladder cancer
Bladder instillations of doxorubicin hydrochloride p. 754 and mitomycin p. 767 are used for recurrent superficial bladder tumours. Such instillations reduce systemic side-effects; adverse effects on the bladder (e.g. micturition disorders and reduction in bladder capacity) may occur.

Instillation of epirubicin hydrochloride p. 756 is used for treatment and prophylaxis of certain forms of superficial bladder cancer; instillation of doxorubicin hydrochloride p. 754 is also used for some papillary tumours.

Instillation of BCG (bacillus calmette-guérin p. 794), a live attenuated strain derived from Mycobacterium bovis is licensed for the treatment of primary or recurrent bladder carcinoma in-situ and for the prevention of recurrence following transurethral resection.

Urological surgery
Glycine irrigation solution 1.5% p. 679 is the irrigant of choice for transurethral resection of the prostate gland and bladder tumours; sterile sodium chloride solution 0.9% (physiological saline) is used for percutaneous renal surgery.

Maintenance of indwelling urinary catheters
The deposition which occurs in catheterised patients is usually chiefly composed of phosphate and to minimise this the catheter (if latex) should be changed at least as often as every 6 weeks. If the catheter is to be left for longer periods a silicone catheter should be used together with the appropriate use of catheter maintenance solutions. Repeated blockage usually indicates that the catheter needs to be changed.

Chlorhexidine with lidocaine
The properties listed below are those particular to the combination only. For the properties of the components please consider, chlorhexidine p. 1051, lidocaine hydrochloride p. 1161.
Catheter maintenance solutions

- **OptiFlo R citric acid 6% catheter maintenance solution** (Bard Ltd)
  - 50 ml: NHS indicative price = £3.53 - Drug Tariff (Part IXa) 100 ml: NHS indicative price = £3.53 - Drug Tariff (Part IXa)
- **OptiFlo S saline 0.9% catheter maintenance solution** (Bard Ltd)
  - 50 ml: NHS indicative price = £3.33 - Drug Tariff (Part IXa)
- **Uro-Tainer M sodium chloride 0.9% catheter maintenance solution** (Braun Medical Ltd)
  - 50 ml: No NHS indicative price available - Drug Tariff (Part IXa)
  - 100 ml: No NHS indicative price available - Drug Tariff (Part IXa)
- **Uro-Tainer Twin Solution R citric acid 6% catheter maintenance solution** (Braun Medical Ltd)
  - 60 ml: NHS indicative price = £4.76 - Drug Tariff (Part IXa)
- **Uro-Tainer sodium chloride 0.9% catheter maintenance solution** (Braun Medical Ltd)
  - 50 ml: NHS indicative price = £3.48 - Drug Tariff (Part IXa)

3 Contraception

**Contraceptives, hormonal**

The Fraser Guidelines (Department of Health Guidance (July 2004)): Best practice guidance for doctors and other health professionals on the provision of advice and treatment to young people under 16 on contraception, sexual and reproductive health, available at www.tinyurl.com/bpg16 should be followed when prescribing contraception for women under 16 years. The UK Medical Eligibility Criteria for Contraceptive Use (available at www.fsrh.org) is published by the Faculty of Sexual and Reproductive Healthcare; it categorises the risks of using contraceptive methods with pre-existing medical conditions.

**Hormonal contraception** is the most effective method of fertility control, but can have major and minor side-effects, especially for certain groups of women. Hormonal contraception should only be used by adolescents after menarche.

**Intra-uterine devices** are a highly effective method of contraception but may produce undesirable local side-effects. They may be used in women of all ages irrespective of parity, but are less appropriate for those with an increased risk of pelvic inflammatory disease.

**Barrier methods** alone (condoms, diaphragms, and caps) are less effective but can be reliable for well-motivated couples if used in conjunction with a spermicide. Occasionally sensitivity reactions occur. A female condom (Femidom ®) is also available; it is pre-lubricated but does not contain a spermicide.

**Combined hormonal contraceptives**

Oral contraceptives containing an oestrogen and a progestogen (‘combined oral contraceptives’) are effective preparations for general use. Advantages of combined oral contraceptives include:

- reliable and reversible;
- reduced dysmenorrhoea and menorrhagia;
- reduced incidence of premenstrual tension;
- less symptomatic fibroids and functional ovarian cysts;
- less benign breast disease;
- reduced risk of ovarian and endometrial cancer;
- reduced risk of pelvic inflammatory disease.

Combined oral contraceptives containing a fixed amount of an oestrogen and a progestogen in each active tablet are termed ‘monophasic’; those with varying amounts of the two hormones are termed ‘phasic’. A transdermal patch and a vaginal ring, both containing an oestrogen with a progestogen, are also available.
### Combined Oral Contraceptives Monophasic 21-day preparations

<table>
<thead>
<tr>
<th>Oestrogen content</th>
<th>Progestogen content</th>
<th>Brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethinylestradiol</td>
<td>Desogestrel</td>
<td>Gedarel® 20/150</td>
</tr>
<tr>
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<td>Norgestimate</td>
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### Combined Oral Contraceptives Phasic 21-day preparations

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<th>Oestrogen content</th>
<th>Progestogen content</th>
<th>Brand</th>
</tr>
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<td>Ethinylestradiol</td>
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<td>Ethinylestradiol</td>
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### Combined Oral Contraceptives Phasic 28-day preparations

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<th>Brand</th>
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<td>Dienogest</td>
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</tr>
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### Combined Oral Contraceptives Monophasic 28-day preparations

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<td>Ethinylestradiol</td>
<td>Gestodene</td>
<td>Femodene® ED</td>
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<td>75 micrograms</td>
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<td>Ethinylestradiol</td>
<td>Levonorgestrel</td>
<td>Microgynon 30 ED®</td>
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<td>Estradiol (as hemihydrate)</td>
<td>Nomegestrol acetate 2.5 mg</td>
<td>Zoely®</td>
</tr>
<tr>
<td>1.5 mg</td>
<td>2.5 mg</td>
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</tr>
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### Choice

The majority of combined oral contraceptives contain ethinylestradiol p. 655 as the oestrogen component; mestranol and estradiol are also used. The ethinylestradiol content of combined oral contraceptives ranges from 20 to 40 micrograms. Generally a preparation with the lowest oestrogen and progestogen content which gives good cycle control and minimal side-effects in the individual woman is chosen. It is recommended that combined hormonal contraceptives are not continued beyond 50 years of age since more suitable alternatives exist.
Low strength preparations (containing ethinylestradiol 20 micrograms) are particularly appropriate for women with risk factors for circulatory disease, provided a combined oral contraceptive is otherwise suitable.

Standard strength preparations (containing ethinylestradiol 30 or 35 micrograms or in 30-40 microgram phased preparations) are appropriate for standard use. Phased preparations are generally reserved for women who either do not have withdrawal bleeding or who have breakthrough bleeding with monophasic products.

The progestogens desogestrel with ethinylestradiol p. 685, drospirenone with ethinylestradiol p. 686, and ethinylestradiol with gestodene p. 687 may be considered for women who have side-effects (such as acne, headache, depression, breast symptoms, and breakthrough bleeding) with other progestogens. Drospirenone, a derivative of spironolactone, has anti-androgenic and anti-depression, breast symptoms, and breakthrough bleeding) for women who have side-effects (such as acne, headache, depression, breast symptoms, and breakthrough bleeding) with other progestogens. Drospirenone, a derivative of spironolactone, has anti-androgenic and anti-mineralocorticoid activity; it should be used with care if an increased plasma-potassium concentration might be hazardous.

Dienogest with estradiol valerate p. 685 is in the combined oral contraceptive Qlaira®. Nomegestrol is the progestogen contained in the combined oral contraceptive Zoely®, in combination with estradiol.

The progestogen norgestrelomistin is combined with ethinylestradiol in a transdermal patch (Evra®). The vaginal contraceptive ring contains the progestogen etonogestrel combined with ethinylestradiol (NuvaRing®).

Surgery

Oestrogen-containing contraceptives should preferably be discontinued (and adequate alternative contraceptive arrangements made) 4 weeks before major elective surgery and all surgery to the legs or surgery which involves prolonged immobilisation of a lower limb; they should normally be recommenced at the first menses occurring at least 2 weeks after full mobilisation. A progestogen-only contraceptive may be offered as an alternative and the oestrogen-containing contraceptive restarted after mobilisation. When discontinuation of an oestrogen-containing contraceptive is not possible, e.g. after trauma or if a patient admitted for an elective procedure is still on an oestrogen-containing contraceptive, thromboprophylaxis (with unfractionated or low molecular weight heparin and graduated compression hosiery) is advised. These recommendations do not apply to minor surgery with short duration of anaesthesia, e.g. laparoscopic sterilisation or tooth extraction, or to women using oestrogen-free hormonal contraceptives.

Reason to stop immediately

Combined hormonal contraceptives or hormone replacement therapy (HRT) should be stopped pending investigation and treatment, if any of the following occur:

- sudden severe chest pain (even if not radiating to left arm);
- sudden breathlessness (or cough with blood-stained sputum);
- unexplained swelling or severe pain in calf of one leg;
- severe stomach pain;
- serious neurological effects including unusual severe, prolonged headache especially if first time or getting progressively worse or sudden partial or complete loss of vision or sudden disturbance of hearing or other perceptive disorders or dysphasia or bad fainting attack or collapse or first unexplained epileptic seizure or weakness, motor disturbances, very marked numbness suddenly affecting one side or one part of body;
- hepatitis, jaundice, liver enlargement;
- blood pressure above systolic 160 mmHg or diastolic 95 mmHg; (in adolescents stop if blood pressure very high);
- prolonged immobility after surgery or leg injury;
- detection of a risk factor which contra-indicates treatment.

Progestogen-only contraceptives

Oral progestogen-only contraceptives

Oral progestogen-only preparations alter cervical mucus to prevent sperm penetration and may inhibit ovulation in some women; oral desogestrel-only preparations consistently inhibit ovulation and this is their primary mechanism of action. There is insufficient clinical trial evidence to compare the efficacy of oral progestogen-only contraceptives with each other or with combined hormonal contraceptives. Progestogen-only contraceptives offer a suitable alternative to combined hormonal contraceptives when oestrogens are contra-indicated (including those with venous thrombosis or a past history or predisposition to venous thrombosis, heavy smokers, those with hypertension above systolic 160 mmHg or diastolic 95 mmHg, valvular heart disease, diabetes mellitus with complications, and migraine with aura).

Parenteral progestogen-only contraceptives

Medroxyprogesterone acetate (Depo-Provera®, SAYANA PRESS®) p. 695 is a long-acting progestogen given by injection; it is at least as effective as the combined oral preparations but because of its prolonged action it should never be given without full counselling backed by the patient information leaflet. It may be used as a short-term or long-term contraceptive for women who have been counselled about the likelihood of menstrual disturbance and the potential for a delay in return to full fertility. Delayed return of fertility and irregular cycles may occur after discontinuation of treatment but there is no evidence of permanent infertility. Troublesome bleeding has been reported in patients given medroxyprogesterone acetate in the immediate puerperium; delaying the first injection until 6 weeks after birth may minimise bleeding problems. If the woman is not breast-feeding, the first injection may be given within 5 days postpartum (she should be warned that the risk of troublesome bleeding may be increased).

In adolescents, medroxyprogesterone acetate (Depo-Provera®, SAYANA PRESS®) should be used only when other methods of contraception are inappropriate;

- in all women, the benefits of using medroxyprogesterone acetate beyond 2 years should be evaluated against the risks;
- in women with risk factors for osteoporosis, a method of contraception other than medroxyprogesterone acetate should be considered.

Norethisterone enantate (Noristerat®) is a long-acting progestogen given as an oily injection which provides contraception for 8 weeks; it is used as short-term interim contraception e.g. before vasectomy becomes effective.

An etonogestrel-releasing implant (Nexplanon®) is also available. It is a highly effective long-acting contraceptive, consisting of a single flexible rod that is inserted subdermally into the lower surface of the upper arm and provides contraception for up to 3 years. The manufacturer advises that in heavier women, blood-etonogestrel concentrations are lower and therefore the implant may not provide effective contraception during the third year; they advise that earlier replacement may be considered in such patients—however, evidence to support this recommendation is lacking. Local reactions such as bruising and itching can occur at the insertion site. The contraceptive effect of etonogestrel is rapidly reversed on removal of the implant.

Intra-uterine progestogen-only device

The progestogen-only intra-uterine systems, Mirena® and Jaydess®, releases levonorgestrel p. 692 directly into the uterine cavity. Mirena® is licensed for use as a contraceptive, for the treatment of primary menorrhagia, and for the prevention of endometrial hyperplasia during

Genito-urinary system

BNF 70
oestrogen replacement therapy. Jaydess® is licensed for contraception. These may therefore be a contraceptive method of choice for women who have excessively heavy menses.

The effects of the progestogen-only intra-uterine system are mainly local and hormonal including prevention of endometrial proliferation, thickening of cervical mucus, and suppression of ovulation in some women (in some cycles). In addition to the progestogeneric activity, the intra-uterine system itself may contribute slightly to the contraceptive effect. Return of fertility after removal is rapid and appears to be complete.

Advantages of the progestogen-only intra-uterine system over copper intra-uterine devices are that there may be an improvement in any dysmenorrhea and a reduction in blood loss; there is also evidence that the frequency of pelvic inflammatory disease may be reduced (particularly in the youngest age groups who are most at risk).

In primary menorrhagia, menstrual bleeding is reduced significantly within 3–6 months of inserting the progestogen-only intra-uterine system, probably because it prevents endometrial proliferation. Another treatment should be considered if menorrhagia does not improve within this time.

Surgery All progestogen-only contraceptives (including those given by injection) are suitable for use as an alternative to combined hormonal contraceptives before major elective surgery, before all surgery to the legs, or before surgery which involves prolonged immobilisation of a lower limb.

Emergency contraception

Hormonal methods

Hormonal emergency contraceptives include levonorgestrel p. 692 and ulipristal acetate p. 691; either drug should be taken as soon as possible after unprotected intercourse to increase efficacy.

Levonorgestrel is effective if taken within 72 hours (3 days) of unprotected intercourse and may also be used between 72 and 96 hours after unprotected intercourse [unlicensed use], but efficacy decreases with time. Ulipristal acetate, a progestrone receptor modulator, is effective if taken within 120 hours (5 days) of unprotected intercourse.

Levonorgestrel is less effective than insertion of an intra-uterine device. Ulipristal acetate is as effective as levonorgestrel, but its efficacy compared to an intra-uterine device is not yet known.

Intra-uterine device

Insertion of an intra-uterine device is more effective than oral levonorgestrel p. 692 for emergency contraception. A copper intra-uterine contraceptive device can be inserted up to 120 hours (5 days) after unprotected intercourse; sexually transmitted infections should be tested for and insertion of the device should usually be covered by antibiotic prophylaxis (e.g. azithromycin p. 469). If intercourse has occurred more than 5 days previously, the device can still be inserted up to 5 days after the earliest likely calculated ovulation (i.e. within the minimum period before implantation), regardless of the number of episodes of unprotected intercourse earlier in the cycle.

Contraceptives, interactions

Combined hormonal contraceptives interactions

The effectiveness of combined oral contraceptives, progestogen-only oral contraceptives, contraceptive patches, and vaginal rings can be considerably reduced by interaction with drugs that induce hepatic enzyme activity (e.g. carbamazepine p. 387, eslicarbazepine acetate p. 390, nevirapine p. 560, oxcarbazepine p. 397, phenytoin p. 398, phenobarbital p. 409, primidone p. 401, ritonavir p. 570, St John’s Wort, topiramate p. 406 and, above all, rifabutin p. 507 and rifampicin p. 508). A condom together with a long-acting method, such as an injectable contraceptive, may be more suitable for patients with HIV infection or at risk of HIV infection; advice on the possibility of interaction with antiretroviral drugs should be sought from HIV specialists.

Women taking combined hormonal contraceptives who require enzyme-inducing drugs should be advised to change to a contraceptive method that is unaffected by enzyme-inducers (e.g. some parenteral progestogen-only contraceptives, intra-uterine devices) for the duration of treatment and for 4 weeks after stopping. If a change in contraceptive method is undesirable or inappropriate the following options should be discussed:

- For a short course (2 months or less) of an enzyme-inducing drug, continue with a combined oral contraceptive providing ethinylestradiol 30 micrograms or more daily and use a ‘tricycling’ regimen (i.e. taking 3 packets of monophasic tablets without a break followed by a shortened tablet-free interval of 4 days [unlicensed use]). Additional contraceptive precautions should also be used whilst taking the enzyme-inducing drug and for 4 weeks after stopping. Another option (except for rifampicin or rifabutin) is to follow the advice for long-term courses.

For women using combined hormonal contraceptive patches or vaginal rings, additional contraceptive precautions are also required whilst taking the enzyme-inducing drug and for 4 weeks after stopping. If concomitant administration runs beyond the 3 weeks of patch or vaginal ring use, a new treatment cycle should be started immediately, without a patch-free or ring-free break.

- For a long-term course (over 2 months) of an enzyme-inducing drug (except rifampicin or rifabutin), adjust the dose of combined oral contraceptive to provide ethinylestradiol 50 micrograms or more daily [unlicensed use] and use a ‘tricycling’ regimen; continue for the duration of treatment with the enzyme-inducing drug and for 4 weeks after stopping. If breakthrough bleeding occurs (and all other causes are ruled out) it is recommended that the dose of ethinylestradiol is increased by increments of 10 micrograms up to a maximum of 70 micrograms daily [unlicensed use], or to use additional precautions, or to change to a method unaffected by enzyme-inducing drugs.

Contraceptive patches and vaginal rings are not recommended for women taking enzyme-inducing drugs over a long period.

- For a long-term course (over 2 months) of rifampicin or rifabutin, an alternative method of contraception (such as an IUD) is always recommended because they are such potent enzyme-inducing drugs; the alternative method of contraception should be continued for 4 weeks after stopping the enzyme-inducing drug.

Antibacterials that do not induce liver enzymes

Latest recommendations are that no additional contraceptive precautions are required when combined oral contraceptives are used with antibacterials that do not induce liver enzymes, unless diarrhoea or vomiting occur. These recommendations should be discussed with the woman, who should also be advised that guidance in patient information leaflets may differ.

It is also currently recommended that no additional contraceptive precautions are required when contraceptive patches or vaginal rings are used with antibacterials that do not induce liver enzymes. There have been concerns that some antibacterials that do not induce liver enzymes (e.g. ampicillin p. 483, doxycline p. 496) reduce the efficacy of combined oral contraceptives by impairing the bacterial flora...
responsible for recycling ethinylestradiol from the large bowel. However, there is a lack of evidence to support this interaction.

**Oral progestogen-only contraceptives interactions**

Effectiveness of oral progestogen-only preparations is not affected by antibiotics that do not induce liver enzymes. The efficacy of oral progestogen-only preparations is, however, reduced by enzyme-inducing drugs and an alternative contraceptive method, unaffected by the interacting drug, is recommended during treatment with an enzyme-inducing drug and for at least 4 weeks afterwards. For a short course of an enzyme-inducing drug, if a change in contraceptive method is undesirable or inappropriate, the progestogen-only oral method may be continued in combination with additional contraceptive precautions (e.g. barrier methods) for the duration of treatment with the enzyme-inducing drug and for 4 weeks after stopping.

**Parenteral progestogen-only contraceptives interactions**

Effectiveness of parenteral progestogen-only contraceptives is not affected by antibiotics that do not induce liver enzymes. The effectiveness of norethisterone intramuscular injections and medroxyprogesterone acetate intramuscular and subcutaneous injections p. 695 is not affected by enzyme-inducing drugs and they may be continued as normal during courses of these drugs. However, effectiveness of the etonogestrel-releasing implant p. 695 may be reduced by enzyme-inducing drugs and an alternative contraceptive method, unaffected by the interacting drug, is recommended during treatment with the enzyme-inducing drug and for at least 4 weeks after stopping. For a short course of an enzyme-inducing drug, if a change in contraceptive method is undesirable or inappropriate, the implant may be continued in combination with additional contraceptive precautions (e.g. condom) for the duration of treatment with the enzyme-inducing drug and for 4 weeks after stopping it.

**Hormonal emergency contraception interactions**

The effectiveness of levonorgestrel p. 692, and possibly ulipristal acetate p. 691, is reduced in women taking enzyme-inducing drugs (and possibly for 4 weeks after stopping); a copper intra-uterine device can be offered instead. If the copper intra-uterine device is undesirable or inappropriate, the dose of levonorgestrel should be increased to a total of 3 mg taken as a single dose [unlicensed dose—advise women accordingly]. There is no need to increase the dose for emergency contraception if the patient is taking antibacterials that are not enzyme inducers.

### Contraceptives, non-hormonal

**Spermicidal contraceptives**

Spermicidal contraceptives are useful additional safeguards but do not give adequate protection if used alone unless fertility is already significantly diminished. They have two components: a spermicide and a vehicle which itself may have some inhibiting effect on sperm activity. They are suitable for use with barrier methods, such as diaphragms or caps; however, spermicidal contraceptives are not generally recommended for use with condoms, as there is no evidence of any additional protection compared with non-spermicidal lubricants.

Spermicidal contraceptives are not suitable for use in those with or at high risk of sexually transmitted infections (including HIV); high frequency use of the spermicide nonoxinol 9" of 697 has been associated with genital lesions, which may increase the risk of acquiring these infections.

Products such as petroleum jelly (Vaseline®), baby oil and oil-based vaginal and rectal preparations are likely to damage condoms and contraceptive diaphragms made from latex rubber, and may render them less effective as a barrier method of contraception and as a protection from sexually transmitted infections (including HIV).

**Contraceptive devices**

The intra-uterine device (IUD) is a suitable contraceptive for women of all ages irrespective of parity; however, it is less appropriate for those with an increased risk of pelvic inflammatory disease e.g. women under 25 years.

The most effective intra-uterine devices have at least 380 mm² of copper and have banded copper on the arms. Smaller devices have been introduced to minimise side-effects; these consist of a plastic carrier wound with copper wire or fitted with copper bands; some also have a central core of silver to prevent fragmentation of the copper.

Fertility declines with age and therefore a copper intra-uterine device which is fitted in a woman over the age of 40, may remain in the uterus until menopause.

A frameless, copper-bearing intra-uterine device (Gyne Fix®) is also available. It consists of a knotted, polypropylene thread with 6 copper sleeves; the device is anchored in the uterus by inserting the knot into the uterine fundus.

3.1 Contraception, combined

**OESTROGENS**

### Combined hormonal contraceptives

- **CONTRA-INDICATIONS** Acute porphyrias p. 864; gallstones - heart disease associated with pulmonary hypertension or risk of embolus - history during pregnancy of cholestatic jaundice - history during pregnancy of chorea - history during pregnancy of pemphigoid gestationis - history during pregnancy of pruritus - history of breast cancer (but can be used after 5 years if no evidence of disease and non-hormonal methods unacceptable) - history of haemolytic uraemic syndrome - migraine with aura - personal history of venous or arterial thrombosis - sclerosing treatment for varicose veins - severe or multiple risk factors for arterial disease - severe or multiple risk factors for venous thromboembolism - systemic lupus erythematosus with (or unknown) antiphospholipid antibodies - transient cerebral ischaemic attacks without headaches - undiagnosed vaginal bleeding

- **CAUTIONS** Active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration)—seek specialist advice - Crohn’s disease - gene mutations associated with breast cancer (e.g. BRCA 1) - history of severe depression especially if induced by hormonal contraceptive - hyperprolactinaemia (seek specialist advice) - inflammatory bowel disease - migraine - personal or family history of hypertriglyceridaemia (increased risk of pancreatitis) - risk factors for arterial disease - risk factors for venous thromboembolism - sickle cell disease - undiagnosed breast mass

**CAUTIONS, FURTHER INFORMATION**

Risk of venous thromboembolism. There is an increased risk of venous thromboembolic disease in users of combined hormonal contraceptives particularly during the first year and possibly after restarting combined hormonal
contraceptives following a break of four weeks or more. This risk is considerably smaller than that associated with pregnancy (about 60 cases of venous thromboembolic disease per 100 000 pregnancies). In all cases the risk of venous thromboembolism increases with age and in the presence of other risk factors, such as obesity. The risk also varies depending on the type of progestogen. Provided that women are informed of the relative risks of venous thromboembolism and accept them, the choice of oral contraceptive is for the woman together with the prescriber jointly to make in light of her individual medical history and any contra-indications.

Combined hormonal contraceptives also slightly increase the risk of arterial thromboembolism; however, there is no evidence to suggest that this risk varies between different preparations.

**Risk factors for venous thromboembolism** Use with caution if any of following factors present but **avoid** if two or more factors present:

- **family history of venous thromboembolism** in first-degree relative aged under 45 years (avoid contraceptive containing desogestrel or gestodene, or avoid if known prothrombotic coagulation abnormality e.g. factor V Leiden or antiphospholipid antibodies (including lupus anticoagulant));
- **obesity**; body mass index \(\geq 30\) kg/m\(^2\) (avoid if body mass index \(\geq 35\) kg/m\(^2\) unless no suitable alternative); (in adolescents, caution if obese according to BMI (adjusted for age and gender); in those who are markedly obese, avoid unless no suitable alternative);
- **long-term immobilisation** e.g. in a wheelchair (avoid if confined to bed or leg in plaster cast);
- **history of superficial thrombophlebitis**;
- **age over 35 years** (avoid if over 50 years);
- **smoking**.

### Combined Hormonal Contraception and Risk of Venous Thromboembolism

<table>
<thead>
<tr>
<th>Progestogen in Combined Hormonal Contraceptive</th>
<th>Estimated incidence per 10 000 women per year of use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-pregnant, not using combined hormonal contraception</td>
<td>2</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>5-7</td>
</tr>
<tr>
<td>Norgestimate</td>
<td>5-7</td>
</tr>
<tr>
<td>Norethisterone</td>
<td>5-7</td>
</tr>
<tr>
<td>Etonogestrel</td>
<td>6-12</td>
</tr>
<tr>
<td>Norelgestromin</td>
<td>6-12</td>
</tr>
<tr>
<td>Gestodene</td>
<td>9-12</td>
</tr>
<tr>
<td>Desogestrel</td>
<td>9-12</td>
</tr>
<tr>
<td>Drospirenone</td>
<td>Not known–insufficient data</td>
</tr>
<tr>
<td>Dienogest</td>
<td>Not known–insufficient data</td>
</tr>
<tr>
<td>&quot; Combined with ethinylestradiol &quot; Combined with estradiol</td>
<td></td>
</tr>
</tbody>
</table>

### Risk factors for arterial disease

Use with caution if any one of following factors present but **avoid** if two or more factors present:

- **family history of arterial disease** in first degree relative aged under 45 years (avoid if atherogenic lipid profile);
- **diabetes mellitus** (avoid if diabetes complications present);
- **hypertension**; blood pressure above systolic 140 mmHg or diastolic 90 mmHg (avoid if blood pressure above systolic 160 mmHg or diastolic 95 mmHg); (in adolescents, avoid if blood pressure very high);
- **smoking** (avoid if smoking 40 or more cigarettes daily);
- **age over 35 years** (avoid if over 50 years);
- **obesity** (avoid if body mass index \(\geq 35\) kg/m\(^2\) unless no suitable alternative); (in adolescents, caution if obese according to BMI (adjusted for age and gender); in those who are markedly obese, avoid unless no suitable alternative);
- **migraine without aura** (avoid if migraine with aura (focal symptoms), or severe migraine frequently lasting over 72 hours despite treatment, or migraine treated with ergot derivatives).

**Migraine** Women should report any increase in headache frequency or onset of focal symptoms (discontinue immediately and refer urgently to neurology expert if focal neurological symptoms not typical of aura persist for more than 1 hour). Combined hormonal contraceptives should be stopped (pending investigation and treatment), if serious neurological effects occur, including unusual severe, prolonged headache especially if first time or getting progressively worse or sudden partial or complete loss of vision or sudden disturbance of hearing or other perceptual disorders or dizziness or bad fainting attack or collapse or first unexplained epileptic seizure or weakness, motor disturbances, very marked numbness suddenly affecting one side or one part of body.

- **INTERACTIONS** → Appendix 1 (oestrogens, progestogens).

### SIDE-EFFECTS

- **Rare** Gallstones - systemic lupus erythematosus
- **Frequency not known** Abdominal cramps - absence of withdrawal bleeding - amenorrhoea after discontinuation - breast enlargement - breast secretion - breast tenderness - cervical erosion - changes in lihido - changes in lipid metabolism - changes in vaginal discharge - chloasma - chorea - contact lenses may irritate - depression - fluid retention - headache - hepatic tumours - hypertension - irritability - leg cramps - liver impairment - nausea - nervousness - photosensitivity - reduced menstrual loss - skin reactions - thrombosis (more common when factor V Leiden present or in blood groups A, B, and AB) - visual disturbances - vomiting - 'spotting' in early cycles.

### SIDE-EFFECTS, FURTHER INFORMATION

#### Breast cancer

There is a small increase in the risk of having breast cancer diagnosed in women taking the combined oral contraceptive pill; this relative risk may be due to an earlier diagnosis. In users of combined oral contraceptive pills the cancers are more likely to be localised to the breast. The most important factor for diagnosing breast cancer appears to be the age at which the contraceptive is stopped rather than the duration of use; any increase in the rate of diagnosis diminishes gradually during the 10 years after stopping and disappears by 10 years.

#### Cervical cancer

Use of combined oral contraceptives for 5 years or longer is associated with a small increased risk of cervical cancer; the risk diminishes after stopping and disappears by about 10 years. The possible small increase in the risk of breast cancer and cervical cancer should be weighed against the protective effect against cancers of the ovary and endometrium.

- **PREGNANCY** Not known to be harmful.
- **BREAST FEEDING** Avoid until weaning or for 6 months after birth (adverse effects on lactation).
- **HEPATIC IMPAIRMENT** Avoid in active liver disease including disorders of hepatic excretion (e.g. Dubin-Johnson or Rotor syndromes), infective hepatitis (until liver function returns to normal), liver tumours.
- **DIRECTIONS FOR ADMINISTRATION** With oral use Each tablet should be taken at approximately same time each day; if delayed, contraceptive protection may be lost. 21-day combined preparations, 1 tablet daily for 21 days; subsequent courses repeated after a 7-day
interval (during which withdrawal bleeding occurs); if reasonably certain a woman is not pregnant, first course can be started on any day of cycle—if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days. Every day (ED) combined preparations, 1 active tablet daily for 21 days, followed by 1 inactive tablet daily for 7 days; subsequent courses repeated without interval (withdrawal bleeding occurs when inactive tablets being taken); if reasonably certain a woman is not pregnant, first course can be started on any day of cycle—if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days.

Changing to combined preparation containing different progestogen If previous contraceptive used correctly, or pregnancy can reasonably be excluded, start the first active tablet of new brand immediately. See individual monographs for requirements of specific preparations.

Changing from progestogen-only tablet If previous contraceptive used correctly, or pregnancy can reasonably be excluded, start new brand immediately, additional precautions (barrier methods) necessary for first 7 days. Secondary amenorrhoea (exclude pregnancy) Start any day, additional precautions (barrier methods) necessary during first 7 days (9 days for Qlaira®).

After childbirth (not breast-feeding) Start 3 weeks after birth (increased risk of thrombosis if started earlier); later than 3 weeks postpartum additional precautions (barrier methods) necessary for first 7 days (9 days for Qlaira®).

After abortion or miscarriage Start same day.

PATIENT AND CARER ADVICE
Missed pill The critical time for loss of contraceptive protection is when a pill is omitted at the beginning or end of a cycle (which lengthens the pill-free interval). If a woman forgets to take a pill, it should be taken as soon as she remembers, and the next one taken at the normal time (even if this means taking 2 pills together). A missed pill is one that is 24 or more hours late. If a woman misses only one pill, she should take an active pill as soon as she remembers and then resume normal pill-taking. No additional precautions are necessary. If a woman misses 2 or more pills (especially from the first 7 in a packet), she may not be protected. She should take an active pill as soon as she remembers and then resume normal pill-taking. In addition, she must either abstain from sex or use an additional method of contraception such as a condom for the next 7 days. If these 7 days run beyond the end of the packet, the next packet should be started at once, omitting the pill-free interval (or, in the case of everyday (ED) pills, omitting the 7 inactive tablets). Emergency contraception is recommended if 2 or more combined oral contraceptive tablets are missed from the first 7 tablets in a packet and unprotected intercourse has occurred since finishing the last packet. Travel Women taking oral contraceptives are at an increased risk of deep vein thrombosis during travel involving long periods of immobility (over 3 hours). The risk may be reduced by appropriate exercise during the journey and possibly by wearing graduated compression hosiery.

Diarrhoea and vomiting Vomiting and persistent, severe diarrhoea can interfere with the absorption of combined oral contraceptives. If vomiting occurs within 2 hours of taking a combined oral contraceptive another pill should be taken as soon as possible. In cases of persistent vomiting or severe diarrhoea lasting more than 24 hours, additional precautions should be used during and for 7 days after recovery. If the vomiting and diarrhoea occurs during the last 7 tablets, the next pill-free interval should be omitted (in the case of ED tablets the inactive ones should be omitted).
**Genito-urinary system**

**DIRECTIONS FOR ADMINISTRATION**

**Estradiol with nomegestrol**

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Tablet**
  - **Gedarel** (Consilient Health Ltd)
    - Desogestrel 150 microgram, Ethinylestradiol 20 microgram
      - 63 tablet (PFS) £5.98
    - Desogestrel 150 microgram, Ethinylestradiol 30 microgram
      - 63 tablet (PFS) £4.19
  - **Marvelon** (Merck Sharp & Dohme Ltd)
    - Desogestrel 150 microgram, Ethinylestradiol 30 microgram
      - 63 tablet (PFS) £7.10
  - **Mercilon** (Merck Sharp & Dohme Ltd)
    - Desogestrel 150 microgram, Ethinylestradiol 20 microgram
      - 63 tablet (PFS) £8.44
  - **Brands may include Alenini; Cimitz; Lestromaly; Munalea**

**INSTRUCTIONS AND DOSE**

**Contraception with 21-day combined preparations**

- **BY MOUTH**
  - **Females of childbearing potential:** 1 tablet once daily for 21 days; subsequent courses repeated after 7-day interval

**PATIENT AND CARER ADVICE**

- **Missed dose**
  - A missed pill for a patient taking Zoely® is one that is 12 hours or more late; for information on how to manage missed pills in women taking Zoely®, refer to product literature.
  - Diarrhoea and vomiting In cases of persistent vomiting or severe diarrhoea lasting more than 12 hours in women taking Zoely®, refer to product literature.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Tablet**
  - **Zoely** (Merck Sharp & Dohme Ltd)
    - Estradiol (as Estradiol hemihydrate) 1.5 mg, Nomegestrol 2.5 mg
      - 80 tablet (PFS) £19.60 DT price £13.80

**Drospirenone with ethinylestradiol**

- **The properties listed below are those particular to the combination only. For the properties of the components please consider, ethinylestradiol p. 655.**

**INDICATIONS AND DOSE**

**Contraception with 21-day combined preparations**

**Menstrual symptoms with 21-day combined preparations**

**BY MOUTH**

| Females of childbearing potential: 1 tablet once daily for 21 days; subsequent courses repeated after 7-day interval |

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Tablet**
  - **Yasmin** (Bayer Plc)
    - Drospirenone 3 mg, Ethinylestradiol 30 microgram
      - 63 tablet (PFS) £14.70
    - **Brands may include Acondrin; Cleosensa; Dretrine; Lucette**

**Estradiol with nomegestrol**

- **The properties listed below are those particular to the combination only. For the properties of the components please consider, estradiol p. 649.**

**INDICATIONS AND DOSE**

**Contraception**

**BY MOUTH**

- **Females of childbearing potential:** 1 active tablet daily for 24 days, followed by 1 inactive tablet daily for 4 days, to be started on day 1 of cycle with first active tablet (withdrawal bleeding occurs when inactive tablets being taken); subsequent courses repeated without interval

**DIRECTIONS FOR ADMINISTRATION**

- **Zoely® (every day (ED) combined (monophasic) preparation),** 1 active tablet daily for 24 days, followed by 1 inactive tablet daily for 4 days, starting on day 1 of cycle with first active tablet; subsequent courses repeated without interval (withdrawal bleeding occurs when inactive tablets being taken). Changing to combined preparation containing different progestogen If previous contraceptive used correctly, or pregnancy can reasonably be excluded, start the first active tablet of new brand immediately.

- **Changing to Zoely®:** start the first active Zoely® tablet on the day after taking the last active tablet of the previous brand or, at the latest, the day after the tablet-free or inactive tablet interval of the previous brand

- **PATIENT AND CARER ADVICE**
  - **Missed dose**
    - A missed pill for a patient taking Zoely® is one that is 12 hours or more late; for information on how to manage missed pills in women taking Zoely®, refer to product literature.

**Ethinylestradiol with etonogestrel**

- **The properties listed below are those particular to the combination only. For the properties of the components please consider, ethinylestradiol p. 655, etonogestrel p. 695.**

**INDICATIONS AND DOSE**

**Contraception | Menstrual symptoms**

**BY VAGINA**

- **Females of childbearing potential:** 1 unit, insert the ring into the vagina on day 1 of cycle and leave in for 3 weeks; remove ring on day 22; subsequent courses repeated after 7-day ring free interval (during which withdrawal bleeding occurs)

**DIRECTIONS FOR ADMINISTRATION**

- **Changing method of contraception to vaginal ring**
  - Insert ring at the latest on the day after the usual tablet-free, patch-free, or inactive-tablet interval. If previous contraceptive used correctly, or pregnancy can reasonably be excluded, can switch to ring on any day of cycle.
  - Changing from progestogen-only method From an implant or intra-uterine progestogen-only device, insert ring on the day implant or intra-uterine progestogen-only device removed; from an injection, insert ring when next injection due; from oral preparation, first ring may be inserted on any day after stopping pill. For all methods additional precautions (barrier methods) should be used concurrently for first 7 days. After first trimester abortion Start immediately. After childbirth (not breast-feeding) or second trimester abortion Start 4 weeks after birth or abortion; if started later than 4 weeks after birth or abortion, additional precautions (barrier methods) should be used for first 7 days.

**PATIENT AND CARER ADVICE**

- **Expulsion, delayed insertion or removal, or broken vaginal ring**
  - If the vaginal ring is expelled or removed, or broken vaginal ring may be inserted on any day after stopping pill. For all methods additional precautions (barrier methods) should be used concurrently for first 7 days. If the ring remains outside the vagina for more than 3 hours, rinse the ring with cool water and reinsert immediately; no additional contraception is needed. If the ring remains outside the vagina for less than 3 hours, rinse the ring with cool water and reinsert immediately; no additional contraception is needed. If the ring remains outside the vagina for more than 3 hours, rinse the ring with cool water and reinsert immediately; no additional contraception is needed.

- **If ring expelled during week 1 or 2 of cycle, rinse ring with cool water and reinsert; use additional precautions (barrier methods) for next 7 days;**

- **If ring expelled during week 3 of cycle, either insert a new ring to start a new cycle or allow a withdrawal bleed and insert a new ring no later than 7 days after ring was expelled; later option only available if ring was used continuously for at least 7 days before expulsion.**
If insertion of a new ring at the start of a new cycle is delayed, contraceptive protection is lost. A new ring should be inserted as soon as possible; additional precautions (barrier methods) should be used for the first 7 days of the new cycle. If intercourse occurred during the extended ring-free interval, pregnancy should be considered. No additional contraception is required if removal of the ring is delayed by up to 1 week (4 weeks of continuous use). The 7-day ring-free interval should be observed and subsequently a new ring should be inserted. Contraceptive protection may be reduced with continuous use of the ring for more than 4 weeks—pregnancy should be ruled out before inserting a new ring. If the ring breaks during use, remove it and insert a new ring immediately; additional precautions (barrier methods) should be used for the first 7 days of the new cycle. Patients or carers should be given advice on how to administer vaginal ring. Counselling The presence of the ring should be checked regularly. Travel Women using the vaginal ring are at an increased risk of deep vein thrombosis during travel involving long periods of immobility (over 3 hours). The risk may be reduced by appropriate exercise during the journey and possibly by wearing graduated compression hosiery.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

#### Vaginal delivery system

- **NuvaRing** (Merck Sharp & Dohme Ltd)
  - Ethinylestradiol 2.7 mg, Etonogestrel 11.7 mg NuvaRing
  - 0.12mg/0.015mg per day vaginal delivery system | 3 system [PoS] £29.70

### Ethinylestradiol with gestodene

The properties listed below are those particular to the combination only. For the properties of the components please consider, ethinylestradiol p. 655, gestodene p. 692.

#### INDICATIONS AND DOSE

**Contraception with 21-day combined preparations**

**Menstrual symptoms with 21-day combined preparations**

**BY MOUTH**
- **Females of childbearing potential**: 1 tablet once daily for 21 days; subsequent courses repeated after 7-day interval, withdrawal bleeding occurs during the 7-day interval, if reasonably certain woman is not pregnant, first course can be started on any day of cycle—if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days, tablets should be taken at approximately the same time each day

**Contraception with 28-day combined preparations**

**Menstrual symptoms with 28-day combined preparations**

**BY MOUTH**
- **Females of childbearing potential**: 1 active tablet once daily for 21 days, followed by 1 inactive tablet daily for 7 days; subsequent courses repeated without interval, withdrawal bleeding occurs during the 7-day interval of inactive tablets being taken, if reasonably certain woman is not pregnant, first course can be started on any day of cycle—if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days, tablets should be taken at approximately the same time each day

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

#### Tablet

- **Femodene** (Bayer Plc)
  - Ethinylestradiol 30 microgram, Gestodene 75
  - microgram Femodene tablets | 63 tablet [PoS] £6.73
- **Femodette** (Bayer Plc)
  - Ethinylestradiol 20 microgram, Gestodene 75
  - microgram Femodette tablets | 63 tablet [PoS] £8.85
- **Katya** (Stragen UK Ltd)
  - Ethinylestradiol 30 microgram, Gestodene 75 microgram Katya
  - 30/75 tablets | 63 tablet [PoS] £6.01
- **Millinette** (Consilient Health Ltd)
  - Ethinylestradiol 30 microgram, Gestodene 75 microgram Millinette
  - 20/75 microgram/75microgram tablets | 63 tablet [PoS] £5.41
- **Sunya** (Stragen UK Ltd)
  - Ethinylestradiol 20 microgram, Gestodene 75 microgram Sunya
  - 20/75 tablets | 63 tablet [PoS] £6.62
- **Brands may include Aidulan**

### Ethinylestradiol with levonorgestrel

The properties listed below are those particular to the combination only. For the properties of the components please consider, ethinylestradiol p. 655, levonorgestrel p. 692.

#### INDICATIONS AND DOSE

**Contraception with 21-day combined preparations**

**Menstrual symptoms with 21-day combined preparations**

**BY MOUTH**
- **Females of childbearing potential**: 1 tablet once daily for 21 days; subsequent courses repeated after 7-day interval, withdrawal bleeding occurs during the 7-day interval, if reasonably certain woman is not pregnant, first course can be started on any day of cycle—if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days, tablets should be taken at approximately the same time each day

**Contraception with 28-day combined preparations**

**Menstrual symptoms with 28-day combined preparations**

**BY MOUTH**
- **Females of childbearing potential**: 1 active tablet once daily for 21 days, followed by 1 inactive tablet once daily for 7 days, withdrawal bleeding occurs during the 7-day interval of inactive tablets being taken, if reasonably certain woman is not pregnant, first course can be started on any day of cycle—if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days, tablets should be taken at approximately the same time each day. Subsequent courses repeated without interval

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

#### Tablet

- **Levest** (Morningside Healthcare Ltd)
  - Ethinylestradiol 30 microgram, Levonorgestrel 150
  - microgram Levest 150/30 tablets | 21 tablet [PoS] £0.85 (Hospital only) | 63 tablet [PoS] £1.80 DT price = £2.82
- **Microgynon 30** (Bayer Plc)
  - Ethinylestradiol 30 microgram, Levonorgestrel 150
  - microgram Microgynon 30 tablets | 63 tablet [PoS] £2.82 DT price = £2.82
- **Ovranette** (Pfizer Ltd)
  - Ethinylestradiol 30 microgram, Levonorgestrel 150
  - microgram Ovranette 150microgram/30microgram tablets | 63 tablet [PoS] £2.20 DT price = £2.82
Ethinylestradiol with norethisterone

The properties listed below are those particular to the combination only. For the properties of the components please consider, ethinylestradiol p. 655, norethisterone p. 656.

**INDICATIONS AND DOSE**

**Contraception with 21-day combined preparations | Menstrual symptoms with 21-day combined preparations**

- **MOUTH**
  - Females of childbearing potential: 1 tablet once daily for 21 days; subsequent courses repeated after 7-day interval, withdrawal bleeding occurs during the 7-day interval, if reasonably certain woman is not pregnant, first course can be started on any day of cycle—if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days, tablets should be taken at approximately the same time each day.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Brevinor (Pfizer Ltd)**
  - Ethinylestradiol 35 microgram, Norethisterone 500 microgram
  - 63 tablet (PRT) £1.99
- **Loestrin 20 (Galen Ltd)**
  - Ethinylestradiol 20 microgram, Norethisterone acetate
  - 1 mg Loestrin 20 tablets | 63 tablet (PRT) £2.30
- **Loestrin 30 (Galen Ltd)**
  - Ethinylestradiol 30 microgram, Norethisterone acetate
  - 1.5 mg Loestrin 30 tablets | 63 tablet (PRT) £3.32
- **Norim (Pfizer Ltd)**
  - Ethinylestradiol 35 microgram, Norethisterone 1 mg
  - Norim 1mg/35microgram tablets | 63 tablet (PRT) £2.28 DT price = £2.28
- **Ovysmen (Janssen-Cilag Ltd)**
  - Ethinylestradiol 35 microgram, Norethisterone 500 microgram
  - Ovysmen 500microgram/35microgram tablets | 63 tablet (PRT) £1.89

Ethinylestradiol with norgestimate

The properties listed below are those particular to the combination only. For the properties of the components please consider, ethinylestradiol p. 655.

**INDICATIONS AND DOSE**

**Contraception with 21-day combined preparations | Menstrual symptoms with 21-day combined preparations**

- **MOUTH**
  - Females of childbearing potential: 1 tablet once daily for 21 days; subsequent courses repeated after 7-day interval, withdrawal bleeding occurs during the 7-day interval, if reasonably certain woman is not pregnant, first course can be started on any day of cycle—if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days, tablets should be taken at approximately the same time each day.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Cilest (Janssen-Cilag Ltd)**
  - Ethinylestradiol 35 microgram, Norgestimate 250 microgram
  - Cilest 250microgram/35microgram tablets | 63 tablet (PRT) £7.16
- **Brands may include Elevin; Erlibelle; Maexeni**

Ethinylestradiol with norelgestromin

The properties listed below are those particular to the combination only. For the properties of the components please consider, ethinylestradiol p. 655.

**INDICATIONS AND DOSE**

**Contraception | Menstrual symptoms**

**BY TRANSDERMAL APPLICATION**

- Females of childbearing potential. Apply 1 patch once weekly for 3 weeks, apply first patch on day 1 of cycle, change patch on days 8 and 15; remove third patch on day 22 and apply new patch after 7-day patch-free interval to start subsequent contraceptive cycle, subsequent courses repeated after a 7-day patch-free interval (during which withdrawal bleeding occurs)

**DIRECTIONS FOR ADMINISTRATION**

- Adhesives or bandages should not be used to hold patch in place. If no longer sticky does not reapply but use a new patch.
- Changing to a transdermal combined hormonal contraceptive
- Changing from combined oral contraception

**Apply patch**

- on the first day of withdrawal bleeding; if no withdrawal bleeding within 5 days of taking last active tablet, rule out pregnancy before applying first patch.
- Unless patch is applied on first day of withdrawal bleeding, additional precautions (barrier methods) should be used concurrently for first 7 days.

**Changing from progestogen-only method**

- from an implant, apply first patch on the day implant removed
- from an injection, apply first patch when next injection due
- from oral progestogen, first patch may be applied on any day after stopping pill

**After childbirth (not breast-feeding)**

- Start 4 weeks after birth; if started later than 4 weeks after birth additional precautions (barrier methods) should be used for first 7 days.

**After abortion or miscarriage**

- Before 20 weeks’ gestation start immediately; no additional contraception required if started immediately. After 20 weeks’ gestation start on day 21 after abortion or on the first day of first spontaneous menstruation; additional precautions (barrier methods) should be used for first 7 days.

**After birth**

- If a patch is partly detached for less than 24 hours, reapply to the same site or replace with a new patch immediately; no additional contraception is needed and the next patch should be applied on the usual ‘change day’. If a patch remains detached for more than 24 hours or if the user is not aware when the patch became detached, then stop the current contraceptive cycle and start a new cycle by applying a new patch, giving a new ‘Day 1’; an additional non-hormonal contraceptive must be used concurrently for the first 7 days of the new cycle.

- If application of a new patch at the start of a new cycle is delayed, contraceptive protection is lost. A new patch

- should be used as soon as remembered giving a new ‘Day 1’; additional non-hormonal methods of contraception should be used for the first 7 days of the
new cycle. If application of a patch in the middle of the cycle is delayed (i.e. the patch is not changed on day 8 or day 15):

- for up to 48 hours, apply a new patch immediately; next patch ‘change day’ remains the same and no additional contraception is required;
- for more than 48 hours, contraceptive protection may have been lost. Stop the current cycle and start a new 4-week cycle immediately by applying a new patch giving a new ‘Day 1’; additional non-hormonal contraception should be used for the first 7 days of the new cycle.

If the patch is not removed at the end of the cycle (day 22), remove it as soon as possible and start the next cycle on the usual ‘change day’, the day after day 28; no additional contraception is required. Patients and carers should be given advice on how to administer patches.

Travel Women using patches are at an increased risk of deep vein thrombosis during travel involving long periods of immobility (over 3 hours). The risk may be reduced by appropriate exercise during the journey and possibly by wearing graduated compression hosiery.

NATIONAL FUNDING/ACCESS DECISIONS Scottish Medicines Consortium (SMC) Decisions The Scottish Medicines Consortium has advised (September 2003) that Evra® patches should be restricted for use in women who are likely to comply poorly with combined oral contraceptives.

Mestranol with norethisterone The properties listed below are those particular to the combination only. For the properties of the components please consider, norethisterone p. 656.

INDICATIONS AND DOSE Contraception | Menstrual symptoms By Mouth

- Females of childbearing potential: 1 tablet once daily for 21 days; subsequent courses repeated after 7-day interval, withdrawal bleeding can occur during the 7-day interval, if reasonably certain a woman is not pregnant, first course can be started on any day of cycle — if starting on day 6 of cycle or later, additional precautions (barrier methods) necessary during first 7 days, tablets should be taken at the same time each day.

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

Tablet

- Norinyl®-1 (Pfeizer Ltd)
- Mestranol 50 microgram, Norethisterone 1 mg Norinyl-1 tablets | 63 tablet (PBM) £2.19 DT price = £2.19

3.2 Contraception, devices Drugs used for Contraception, devices not listed below; Levonorgestrel, p. 692

CONTRACEPTIVE DEVICES Intra-uterine contraceptive devices (copper)

INDICATIONS AND DOSE Contraception By INTRA-UTERINE ADMINISTRATION

- Females of childbearing potential: (consult product literature)

- CONTRA-INDICATIONS Active trophoblastic disease (until return to normal of urine and plasma-gonadotrophin concentration) — distorted uterine cavity — established or marked immunosuppression — genital malignancy — medical diathery — pelvic inflammatory disease — recent sexually transmitted infection (if not fully investigated and treated) — severe anaemia — small uterine cavity — unexplained uterine bleeding — Wilson’s disease

CAUTIONS Anaemia — anticoagulant therapy (avoid if possible) — diabetes — disease-induced immunosuppression (risk of infection — avoid if marked immunosuppression) — drug-induced immunosuppression (risk of infection — avoid if marked immunosuppression) — endometritis — epilepsy (risk of seizure at time of insertion) — fertility problems — history of pelvic inflammatory disease — increased risk of expulsion if inserted before uterine involution — menorrhagia (progestogen intra-uterine system might be preferable) — nulliparity — severe cervical stenosis — severe primary dysmenorrhoea — severely scarred uterus (including after endometrial resection) — young age

CAUTIONS, FURTHER INFORMATION Risk of infection The main excess risk of infection occurs in the first 20 days after insertion and is believed to be related to existing carriage of a sexually transmitted infection. Women are considered to be at a higher risk of sexually transmitted infections if:

- they are under 25 years old or
- they are over 25 years old and have a new partner or
- have had more than one partner in the past year or their regular partner has other partners.

In these women, pre-insertion screening (for chlamydia and, depending on sexual history and local prevalence of disease, Neisseria gonorrhoeae) should be performed. If results are unavailable at the time of fitting an intra-uterine device for emergency contraception, appropriate prophylactic antibacterial cover should be given. The woman should be advised to attend as an emergency if she experiences sustained pain during the next 20 days. An intra-uterine device should not be removed in mid-cycle unless an additional contraceptive was used for the previous 7 days. If removal is essential post-coital contraception should be considered.

SIDE-EFFECTS Allergy — bleeding (on insertion) — cervical perforation — displacement — dysmenorrhoea — expulsion — menorrhagia — occasionally epileptic seizure (on insertion) — pain (on insertion, alleviated by NSAID such as ibuprofen 50 minutes before insertion) — pelvic infection may be exacerbated — uterine perforation — vasovagal attack (on insertion)

SIDE-EFFECTS, FURTHER INFORMATION Presence of significant symptoms (especially pain) Advise the patient to seek medical attention promptly in case of significant symptoms.

ALLERGY AND CROSS-SENSITIVITY Contraindicated if patient has a copper allergy.

PREGNANCY If an intra-uterine device fails and the woman wishes to continue to full-term the device should be removed in the first trimester if possible. Remove
device; if pregnancy occurs, increased likelihood that it may be ectopic.

- **BREAST FEEDING** Not known to be harmful.
- **MONITORING REQUIREMENTS** Gynaecological examination before insertion, 6–8 weeks after insertion, then annually.
- **DIRECTIONS FOR ADMINISTRATION** The timing and technique of fitting an intra-uterine device are critical for its subsequent performance. The healthcare professional inserting (or removing) the device should be fully trained in the technique and should provide full counselling backed, where available, by the patient information leaflet. Devices should not be fitted during the heavy days of the period; they are best fitted after the end of menstruation and before the calculated time of implantation.

### Prescribing and dispensing information

- **ANCORA – 375 CU PRODUCTS**
  - For uterine length over 6.5 cm; replacement every 5 years.
  - **COPPER – T380 PRODUCTS**
    - For uterine length 6.5–9 cm; replacement every 10 years.
    - **FLEXI-T – 300 PRODUCTS**
      - For uterine length over 5 cm; replacement every 5 years.
    - **FLEXI-T – 380 PRODUCTS**
      - For uterine length over 6 cm; replacement every 5 years.
    - **GYNEFLEX PRODUCTS**
      - Suitable for all uterine sizes; replacement every 5 years.
    - **LOAD PRODUCTS**
      - Suitable for uterine length over 7 cm; replacement every 5 years.
    - **MINI T380 PRODUCTS**
      - For minimum uterine length 5 cm; replacement every 5 years.
    - **MULTILOAD CU 375 PRODUCTS**
      - For uterine length 6–9 cm; replacement every 5 years.
    - **MULTI-SAFE 375 PRODUCTS**
      - For uterine length over 6–9 cm; replacement every 5 years.
    - **NEO-SAFE T380 PRODUCTS**
      - For uterine length 6.5–9 cm; replacement every 5 years.
    - **NOVAPLUS T 380 AG**
      - For uterine length 6.5–9 cm; replacement every 5 years.
    - **NOVAPLUS T 380 CU**
      - For uterine length 6.5–9 cm; replacement every 5 years.
    - **NOVA-T PRODUCTS**
      - For uterine length 6.5–9 cm; replacement every 5 years.
    - **T-SAFE PRODUCTS**
      - For uterine length 6.5–9 cm; replacement every 10 years.
    - **TT380 PRODUCTS**
      - For uterine length 6.5–9 cm; replacement every 10 years.
    - **UT380 PRODUCTS**
      - For uterine length 5–7 cm; replacement every 5 years.
    - **UT380 STANDARD PRODUCTS**
      - For uterine length 6.5–9 cm; replacement every 5 years.

### Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

#### Contraceptive devices

- **INTRA-UTERINE CONTRACEPTIVE DEVICES (COPPER) (Non-proprietary)**
  - Copper T380 A intra-uterine contraceptive device | 1 device £8.95
  - Steriload intra-uterine contraceptive device | 1 device £8.65
  - Load 375 intra-uterine contraceptive device | 1 device £8.52
  - Novaplex T 380 Ag intra-uterine contraceptive device mini | 1 device £12.50
  - T-Safe 380A QL intra-uterine contraceptive device | 1 device £10.47
  - UT380 Standard intra-uterine contraceptive device | 1 device £11.22
  - Nova-T 380 intra-uterine contraceptive device | 1 device £15.20

- **FLEXI-T 380 intra-uterine contraceptive device** | 1 device £10.06
- **Mini TT380 Slimline intra-uterine contraceptive device** | 1 device £12.46
- **FLEXI-T 300 intra-uterine contraceptive device** | 1 device £9.47
- **Multi-Safe 375 intra-uterine contraceptive device** | 1 device £8.96
- **Multiload Cu375 intra-uterine contraceptive device** | 1 device £9.24
- **Optima Tcu 380A intra-uterine contraceptive device** | 1 device £9.65
- **Novaplex T 380 Ag intra-uterine contraceptive device normal** | 1 device £12.50
- **Gynex intra-uterine contraceptive device** | 1 device £27.11
- **Novaplex T 380 Cu intra-uterine contraceptive device mini** | 1 device £10.95
- **TT380 Slimline intra-uterine contraceptive device** | 1 device £12.46
- **Ancora T380 Cu intra-uterine contraceptive device** | 1 device £7.95
- **Novaplex T 380 Cu intra-uterine contraceptive device normal** | 1 device £10.95
- **Neo-Safe T380 intra-uterine contraceptive device** | 1 device £13.31
- **UT380 Short intra-uterine contraceptive device** | 1 device £11.22

### Vaginal contraceptives

- **SILICONE CONTRACEPTIVE DIAPHRAGMS**
  - **Milex arcing spring silicone diaphragm 60mm (Durbin Plc)**
    - 1 device - NHS indicative price = £9.31 - Drug Tariff (Part Ixa)
  - **Milex arcing spring silicone diaphragm 65mm (Durbin Plc)**
    - 1 device - NHS indicative price = £9.31 - Drug Tariff (Part Ixa)
  - **Milex arcing spring silicone diaphragm 70mm (Durbin Plc)**
    - 1 device - NHS indicative price = £9.31 - Drug Tariff (Part Ixa)
  - **Milex arcing spring silicone diaphragm 75mm (Durbin Plc)**
    - 1 device - NHS indicative price = £9.31 - Drug Tariff (Part Ixa)
  - **Milex arcing spring silicone diaphragm 80mm (Durbin Plc)**
    - 1 device - NHS indicative price = £9.31 - Drug Tariff (Part Ixa)
  - **Milex arcing spring silicone diaphragm 90mm (Durbin Plc)**
    - 1 device - NHS indicative price = £9.31 - Drug Tariff (Part Ixa)
  - **Milex omniflex coil spring silicone diaphragm 60mm (Durbin Plc)**
    - 1 device - NHS indicative price = £9.31 - Drug Tariff (Part Ixa)
  - **Milex omniflex coil spring silicone diaphragm 65mm (Durbin Plc)**
    - 1 device - NHS indicative price = £9.31 - Drug Tariff (Part Ixa)
  - **Milex omniflex coil spring silicone diaphragm 70mm (Durbin Plc)**
    - 1 device - NHS indicative price = £9.31 - Drug Tariff (Part Ixa)
  - **Milex omniflex coil spring silicone diaphragm 75mm (Durbin Plc)**
    - 1 device - NHS indicative price = £9.31 - Drug Tariff (Part Ixa)
  - **Milex omniflex coil spring silicone diaphragm 80mm (Durbin Plc)**
    - 1 device - NHS indicative price = £9.31 - Drug Tariff (Part Ixa)
  - **Milex omniflex coil spring silicone diaphragm 85mm (Durbin Plc)**
    - 1 device - NHS indicative price = £9.31 - Drug Tariff (Part Ixa)
  - **Ortho All-Flex arcing spring silicone diaphragm 65mm (Janssen-Cilag Ltd)**
    - 1 device - NHS indicative price = £8.35 - Drug Tariff (Part Ixa)
  - **Ortho All-Flex arcing spring silicone diaphragm 70mm (Janssen-Cilag Ltd)**
    - 1 device - NHS indicative price = £8.35 - Drug Tariff (Part Ixa)
  - **Ortho All-Flex arcing spring silicone diaphragm 75mm (Janssen-Cilag Ltd)**
    - 1 device - NHS indicative price = £8.35 - Drug Tariff (Part Ixa)
  - **Ortho All-Flex arcing spring silicone diaphragm 80mm (Janssen-Cilag Ltd)**
    - 1 device - NHS indicative price = £8.35 - Drug Tariff (Part Ixa)
  - **Ortho All-Flex arcing spring silicone diaphragm 85mm (Janssen-Cilag Ltd)**
    - 1 device - NHS indicative price = £8.35 - Drug Tariff (Part Ixa)

- **SILICONE CONTRACEPTIVE PESSARIES**
  - **FemCap 22mm (Durbin Plc)**
    - 1 device - NHS indicative price = £15.29 - Drug Tariff (Part Ixa)
  - **FemCap 26mm (Durbin Plc)**
    - 1 device - NHS indicative price = £15.29 - Drug Tariff (Part Ixa)
  - **FemCap 30mm (Durbin Plc)**
    - 1 device - NHS indicative price = £15.29 - Drug Tariff (Part Ixa)
3.3 Contraception, oral progestogen-only

### Ulipristal acetate

**DRUG ACTION** Ulipristal acetate is a progesterone receptor modulator with a partial progesterone antagonist effect.

<table>
<thead>
<tr>
<th>INDICATIONS AND DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency contraception</td>
</tr>
<tr>
<td>BY MOUTH</td>
</tr>
<tr>
<td>Females of childbearing potential: 30 mg for 1 dose, to be taken as soon as possible after coitus, but no later than after 120 hours</td>
</tr>
<tr>
<td>Pre-operative treatment of moderate to severe symptoms of uterine fibroids</td>
</tr>
<tr>
<td>BY MOUTH</td>
</tr>
<tr>
<td>Adults: 5 mg daily for up to 3 months starting during the first week of menstruation, course may be repeated once if necessary, starting during the second menstruation after the first course completed, maximum 2 courses of 3 months</td>
</tr>
</tbody>
</table>

**CONTRA-INDICATIONS**

**GENERAL CONTRA-INDICATIONS**
Repeated use as an emergency contraceptive within a menstrual cycle

**SPECIFIC CONTRA-INDICATIONS**
- When used for uterine fibroids
  - Breast cancer
  - Cervical cancer
  - Ovarian cancer
  - Undiagnosed vaginal bleeding
  - Uterine cancer
  - Vaginal bleeding not caused by uterine fibroids

**CAUTIONS**
- Uncontrolled severe asthma

**INTERACTIONS** 
- Appendix 1 (ulipristal).

The effectiveness of ulipristal as an emergency contraceptive is possibly reduced in women taking enzyme-inducing drugs (and possibly for 4 weeks after stopping); a copper intra-uterine device can be offered instead. There is no need to increase the dose for emergency contraception if the patient is taking antibacterials that are not enzyme inducers.

**SIDE-EFFECTS**
- Common or very common
  - Abdominal pain
  - Back pain
  - Diarrhoea
  - Dizziness
  - Fatigue
  - Gastro-intestinal disturbances
  - Headache
  - Menstrual irregularities
  - Muscle spasms
  - Nausea
  - Vomiting

**When used for uterine fibroids**
- Abdominal pain
- Acne
- Breast pain
- Dizziness
- Endometrial thickening
- Headache
- Hot flushes
- Hypertension
- Malaise
- Menstrual disturbances
- Myalgia
- Nausea
- Oedema
- Ovarian cyst (including rupture)
- Pelvic pain
- Uterine haemorrhage

**Uncommon**
- Abnormal bleeding
- Blurred vision
- Breast tenderness
- Dry mouth
- Hot flushes
- Pruritus
- Rash
- Tremor
- Uterine spasm

**When used for uterine fibroids**
- Anxiety
- Constipation
- Dyspepsia
- Epistaxis
- Flatulence
- Urinary incontinence

**CONCEPTION AND CONTRACEPTION**
- When ulipristal is given as an emergency contraceptive the effectiveness of combined hormonal and progestogen-only contraceptives may be reduced—additional precautions (barrier methods) required for 14 days for combined and parenteral progestogen-only hormonal contraceptives (16 days for Qlaira®) and 9 days for oral progestogen-only contraceptives. When ulipristal is given for uterine fibroids non-hormonal contraceptive methods (barrier methods or intra-uterine device) should be used both during treatment and for 12 days after stopping, if required.

**PREGNANCY**
- Manufacturer advises avoid for uterine fibroids—no information available. Limited information available when used as an emergency contraceptive.

**BREAST Feeding**
- When used for uterine fibroids, manufacturer advises avoid—no information available. In emergency contraception manufacturer advises avoid for 1 week after administration—present in milk.

**HEPATIC IMPAIRMENT**
- Caution with use in uterine fibroids in moderate to severe hepatic impairment—no information available. Manufacturer advises avoiding use as an emergency contraceptive in severe hepatic impairment—no information available.

**RENAL IMPAIRMENT**
- Caution in severe renal impairment when used for uterine fibroids—no information available.

**PATIENT AND CARER ADVICE**
- When ulipristal is given as an emergency contraceptive, if vomiting occurs within 3 hours of taking a dose, a replacement dose should be given. When prescribing or supplying hormonal emergency contraception, women should be advised:
  - that their next period may be early or late;
  - that a barrier method of contraception needs to be used until the next period;
  - to seek medical attention promptly if any lower abdominal pain occurs because this could signify an ectopic pregnancy;
  - to return in 3 to 4 weeks if the subsequent menstrual bleed is abnormally light, heavy or brief, or is absent, or if she is otherwise concerned (if there is any doubt as to whether menstruation has occurred, a pregnancy test should be performed at least 3 weeks after unprotected intercourse).

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

<table>
<thead>
<tr>
<th>Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ellaine (IRA Pharma UK Ltd)</td>
</tr>
<tr>
<td>Ulipristal acetate 30 mg EllaOne 30 mg tablets</td>
</tr>
<tr>
<td>Esmya (Gedeon Richter (UK) Ltd)</td>
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<tr>
<td>Ulipristal acetate 5 mg Esmya 5 mg tablets</td>
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</tbody>
</table>

### Desogestrel

**INDICATIONS AND DOSE**

<table>
<thead>
<tr>
<th>Contraception</th>
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<tbody>
<tr>
<td>BY MOUTH</td>
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<tr>
<td>Females of childbearing potential: 75 micrograms daily, dose to be taken at same time each day, starting on day 1 of cycle (if you have any delay then the pill must be taken as soon as possible)</td>
</tr>
</tbody>
</table>

**CONTRA-INDICATIONS**
- Acute porphyrias p. 864 • history of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal contraceptive methods unacceptable • severe arterial disease • undiagnosed vaginal bleeding

**CAUTIONS**
- Active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration)—seek specialist advice • arterial disease • functional ovarian cysts • history of jaundice in pregnancy • malabsorption syndromes • past ectopic pregnancy • sex-steroid dependent cancer • systemic lupus erythematosus with positive (or unknown) antiphospholipid antibodies
Levonorgestrel

INDICATIONS AND DOSE

Emergency contraception

BY MOUTH

- Females of childbearing potential: 1.5 mg for 1 dose, taken as soon as possible after coitus, preferably within 12 hours but no later than after 72 hours

Contraception

BY MOUTH

- Females of childbearing potential: 1 tablet daily starting on day 1 of the cycle then continuously, dose is to be taken at the same time each day, if administration delayed for 3 hours or more it should be regarded as a "missed pill"

JAYDESS® 13.5MG INTRA-UTERINE DEVICE

Contraception

BY VAGINA

- Females of childbearing potential: Insert into uterine cavity within 7 days of onset of menstruation, or any time if replacement, or immediately after first-trimester termination; postpartum insertions should be delayed until at least 6 weeks after delivery (12 weeks if uterus involution is substantially delayed); effective for 3 years

MIRENA® 20MICROGRAMS/24HOURS INTRA-UTERINE DEVICE

Contraception | Menorrhagia

BY INTRA-UTERINE ADMINISTRATION

- Females of childbearing potential: Insert into uterine cavity within 7 days of onset of menstruation, or any time if replacement, or any time if reasonably certain woman is not pregnant and there is no risk of conception (additional precautions (e.g. barrier methods) necessary for next 7 days), or immediately after first-trimester termination by curettage; postpartum insertions should be delayed until at least 4 weeks after delivery; effective for 5 years

Prevention of endometrial hyperplasia during oestrogen replacement therapy

BY INTRA-UTERINE ADMINISTRATION

- Females of childbearing potential: Insert during last days of menstruation or withdrawal bleeding or at any time if amenorrhoeic; effective for 4 years

CONTRA-INDICATIONS

- With intra-uterine use Active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration - acute cervicitis - acute vaginitis - distorted uterine cavity - established immunosuppression - genital
malignancy · history of breast cancer but can be considered for a woman in long-term remission who has menorrhagia and requires effective contraception · infected abortion during the previous three months · marked immunosuppression · not suitable for emergency contraception · pelvic inflammatory disease · postpartum endometritis · recent sexually transmitted infection (if not fully investigated and treated) · severe anemia · small uterine cavity · unexplained uterine bleeding

- With oral use Acute porphyrias p. 864
- With oral use for contraception History of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal contraceptive methods unacceptable · severe arterial disease · undiagnosed vaginal bleeding

- CAUTIONS
  - With intra-uterine use Anaemia · anticoagulant therapy (avoid if possible) · diabetes · disease-induced immunosuppression (risk of infection—avoid if marked immunosuppression) · drug-induced immunosuppression (risk of infection—avoid if marked immunosuppression) · endometriosis · epilepsy (risk of seizure at time of insertion) · fertility problems · history of pelvic inflammatory disease · increased risk of expulsion if inserted before uterine involution · menorrhagia (progestogen intra-uterine system might be preferable) · multiparity · severe cervical stenosis · severe primary dysmenorrhea · severely scarred uterus (including after endometrial resection) · young age
  - With oral use for contraception Active trophoblastic disease (until return to normal of urine- and plasma-gondotrophin concentration)—seek specialist advice · arterial disease · functional ovarian cysts · history of jaundice in pregnancy · malabsorption syndromes · past ectopic pregnancy · sex-steroi dependent cancer · systemic lupus erythematosus with positive (or unknown) antiphospholipid antibodies
  - With oral use for emergency contraception Active trophoblastic disease (until return to normal of urine- and plasma-gondotrophin concentration)—seek specialist advice · past ectopic pregnancy · severe malabsorption syndromes

CAUTIONS, FURTHER INFORMATION

Risk of infection with intra-uterine devices The main excess risk of infection occurs in the first 20 days after insertion and is believed to be related to existing carriage of a sexually transmitted infection. Women are considered to be at a higher risk of sexually transmitted infections if:

- they are under 25 years old or
- they are over 25 years old and have a new partner or
- have had more than one partner in the past year or
- their regular partner has other partners.

In these women, pre-insertion screening (for chlamydia and, depending on sexual history and local prevalence of disease, Neisseria gonorrhoeae) should be performed. If results are unavailable at the time of fitting an intra-uterine device for emergency contraception, appropriate prophylactic antibacterial cover should be given. The woman should be advised to attend as an emergency if she experiences sustained pain during the next 20 days. An intra-uterine device should not be removed in mid-cycle unless an additional contraceptive was used for the previous 7 days. If removal is essential post-coital contraception should be considered.

- With oral use

Use as a contraceptive in co-morbidities The product literature advises caution in patients with history of thromboembolism, hypertension, diabetes mellitus and migraine; evidence for caution in these conditions is unsatisfactory.

MIRENA® 50MICROGRAMS/24HOURS INTRA-UTERINE DEVICE

Advanced uterine atrophy

- INTERACTIONS → Appendix 1 (progestogens).

When used orally as an emergency contraceptive, the effectiveness of levonorgestrel is reduced in women taking enzyme-inducing drugs (and possibly for 4 weeks after stopping); a copper intra-uterine device can be offered instead. If the copper intra-uterine device is undesirable or inappropriate, the dose of levonorgestrel should be increased to a total of 3 mg taken as a single dose [unlicensed dose—advise women accordingly]. There is no need to increase the dose for emergency contraception if the patient is taking antibiotics that are not enzyme inducers.

With the progestogen-only intra-uterine device, levonorgestrel is released close to the site of the main contraceptive action (on cervical mucosa and endometrium) and therefore prostogestinic side-effects and interactions are less likely; in particular, enzyme-inducing drugs are unlikely to significantly reduce the contraceptive effect of the progestogen-only intra-uterine system and additional contraceptive precautions are not required.

- SIDE-EFFECTS

GENERAL SIDE-EFFECTS

- Common or very common Depression (sometimes severe) · headache · nausea
- Frequency not known Vomiting

SPECIFIC SIDE-EFFECTS

- Common or very common
  - With intra-uterine use Abdominal pain · acne · alopecia · back pain · breast pain · changes in the pattern and duration of menstrual bleeding (spotting or prolonged bleeding) · expulsion · hirsutism · migraine · nervousness · pelvic pain · peripheral oedema · salpingitis
  - Uncommon
  - With intra-uterine use Abdominal distension · cervicitis · eczema · pelvic inflammatory disease · pruritus · skin hyperpigmentation
- Rare
  - With intra-uterine use Rash · uterine perforation
  - Frequency not known
  - With intra-uterine use Allergy · bleeding (on insertion) · cervical perforation · displacement · dysmenorrhea · epileptic seizures (on insertion) · functional ovarian cysts (usually asymptomatic and usually resolve spontaneously—ultrasound monitoring recommended) · menorrhagia · pain (on insertion, alleviated by NSAID such as ibuprofen 50 minutes before insertion) · pelvic infection may be exacerbated · vasovagal attack (on insertion)
- With oral use Breast discomfort · breast tenderness · changes in libido · disturbances of appetite · dizziness · fatigue · menstrual irregularities · skin disorders

SIDE-EFFECTS, FURTHER INFORMATION

Endometrial disorders should be ruled out before insertion and the patient should be fully counselled (and provided with a patient information leaflet). Improvement in prostogestinic side-effects, such as mastalgia and in the bleeding pattern may often become very light or absent.

Breast cancer There is a small increase in the risk of having breast cancer diagnosed in women using, or who have recently used, a progestogen-only contraceptive pill; this relative risk may be due to an earlier diagnosis. The most important risk factor appears to be the age at which the contraceptive is stopped rather than the duration of use; the risk disappears gradually during the 10 years after stopping and there is no excess risk by 10 years. A possible small increase in the risk of breast cancer should be weighed against the benefits.

Although the progestogen-only intra-uterine system produces little systemic prostogestinic activity, it is usually avoided for 5 years after any evidence of breast cancer. However, the system can be considered for a
woman in long-term remission from breast cancer who has menorrhagia and requires effective contraception. Removal of the intra-uterine system should be considered if the patient experiences migraine or severe headache, jaundice, marked increase of blood pressure, or severe arterial disease.

- **PREGNANCY**
  - With oral use Not known to be harmful.
  - With vaginal use If an intra-uterine device fails and the woman wishes to continue to full-term the device should be removed in the first trimester if possible. Avoid; if pregnancy occurs remove intra-uterine system.

- **BREAST FEEDING**
  - Progestogen-only contraceptives do not affect lactation.

- **HEPATIC DISEASE**
  - Caution in severe liver disease and recurrent cholestatic jaundice. Avoid in liver tumour.

- **MONITORING REQUIREMENTS**
  - Caution in recurrent cholestatic jaundice. Avoid in liver tumour.

- **DIRECTIONS FOR ADMINISTRATION**
  - With intra-uterine use The doctor or nurse administering (or removing) the system should be fully trained in the technique and should provide full counselling reinforced by the patient information leaflet.

- **PRESCRIBING AND DISPENSING INFORMATION**

  - **JAYDESS 13.5MG INTRA-UTERINE DEVICE**
    When system is removed (and not replaced immediately) and pregnancy is not desired, remove within 7 days of the onset of menstruation; additional precautions (e.g. barrier methods) should be used if the system is removed at some other time during the cycle and there is intercourse within 7 days.

  - **MIRENA®20MICROGRAMS/24HOURS INTRA-UTERINE DEVICE**
    When system is removed (and not immediately replaced) and pregnancy is not desired, remove during first few days of menstruation, otherwise additional precautions (e.g. barrier methods) should be used for at least 7 days before removal.

- **PATIENT AND CARER ADVICE**

  - **Missed doses**
    When used as an oral contraceptive, the following advice is recommended. If you forget a pill, take it as soon as you remember and carry on with the next pill at the right time. If the pill was more than 3 hours overdue you are not protected. Continue normal pill-taking but you must also use another method, such as the condom, for the next 2 days. The Faculty of Sexual and Reproductive Healthcare recommends emergency contraception if one or more progestogen-only contraceptive tablets are missed or taken more than 3 hours late and unprotected intercourse has occurred before 2 further tablets have been correctly taken. Diarrhoea and vomiting Vomiting and persistent, severe diarrhoea can interfere with the absorption of oral progestogen-only contraceptives. If vomiting occurs within 2 hours of taking an oral progestogen-only contraceptive, another pill should be taken as soon as possible. If a replacement pill is not taken within 3 hours of the normal time for taking the progestogen-only pill, or in cases of persistent vomiting or very severe diarrhoea, additional precautions should be used during illness and for 2 days after recovery.

  - With oral use for Contraception
    Starting routine One tablet daily, on a continuous basis, starting on day 1 of cycle and taken at the same time each day (if delayed by longer than 3 hours contraceptive protection may be lost). Additional contraceptive precautions are not necessary when initiating treatment. Changing from a combined oral contraceptive Start on the day following completion of the combined oral contraceptive course without a break (or in the case of ED tablets omitting the inactive ones).

- **With oral use for Emergency contraception**
  - If vomiting occurs within 2 hours of taking levonorgestrel, a replacement dose should be given.

- **With vaginal use**
  - If an intra-uterine device fails and the woman wishes to continue to full-term the device should be removed in the first trimester if possible. Avoid; if pregnancy occurs remove intra-uterine system.

- **With oral use for Contraception**
  - If vomiting occurs within 2 hours of taking levonorgestrel, a replacement dose should be given.

- **When prescribing or supplying hormonal emergency contraception, women should be advised:**
  - that their next period may be early or late;
  - that a barrier method of contraception needs to be used until the next period;
  - to seek medical attention promptly if any lower abdominal pain occurs because this could signify an ectopic pregnancy;
  - to return in 3 to 4 weeks if the subsequent menstrual bleed is abnormally light, heavy or brief, or is absent, or if she is otherwise concerned (if there is any doubt as to whether menstruation has occurred, a pregnancy test should be performed at least 3 weeks after unprotected intercourse).

  - With intra-uterine use Counsel women to seek medical attention promptly in case of significant symptoms, especially pain.

- **EXCEPTIONS TO LEGAL CATEGORY**
  - Levonelle® One Step can be sold to women over 16 years; when supplying emergency contraception to the public, pharmacists should refer to guidance issued by the Royal Pharmaceutical Society.

- **MEDI CINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

| Tablet | Levonorgestrel 1.5 mg | Levonorgestrel 1.5mg tablets | 1 tablet (£5.20–£13.83 DT price = £5.20) | 1 tablet (NHS) £5.20 DT price = £5.20
|--------|----------------------|-----------------------------|----------------------------------------|----------------------------------------
|        | Levonorgestrel 1.5 mg | Levonorgestrel 1.5mg tablets | 1 tablet (£5.20–£13.83 DT price = £5.20) | 1 tablet (NHS) £5.20 DT price = £5.20
|        | Levonelle® One Step 1.5mg tablets | 1 tablet (£5.20–£13.83 DT price = £5.20) | 1 tablet (NHS) £5.20 DT price = £5.20
|        | Norgeston 30 microgram tablets | 1 tablet (£0.92 DT price = £0.92) | 1 tablet (£0.92 DT price = £0.92)
|        | Upostelle 1500 microgram tablets | 1 tablet (£3.75 DT price = £5.20) | 1 tablet (£3.75 DT price = £5.20)
|        | Intra-uterine device | Jaydess® 13.5 mg Jaydess 13.5mg intra-uterine device | 1 device (£69.22) | 1 device (£69.22)
|        | Levosert® 20 microgram per 24 hour | Levosert 20micrograms/24hours intra-uterine device | 1 device (£66.00) | 1 device (£66.00)
|        | Mirena® 20 microgram per 24 hour | Mirena 20micrograms/24hours intra-uterine device | 1 device (£88.00) | 1 device (£88.00)

3.4 Contraception, parenteral progestogen-only

**Drugs used for Contraception, parenteral progestogen-only not listed below; Norethisterone, p. 656**
**PROGESTOGENS**

**Etonogestrel**

**INDICATIONS AND DOSE**

Contraception (no hormonal contraceptive use in previous month)

* BY SUBDERMAL IMPLANTATION
  - Females of childbearing potential: 1 implant inserted during first 5 days of cycle, implant should be removed within 3 years of insertion

Contraception (postpartum)

* BY SUBDERMAL IMPLANTATION
  - Females of childbearing potential: 1 implant to be inserted after 28 days postpartum in breast-feeding mothers, implant should be removed within 3 years of insertion

Contraception following abortion or miscarriage in the second trimester

* BY SUBDERMAL IMPLANTATION
  - Females of childbearing potential: 1 implant to be inserted 21–28 days after abortion or miscarriage, implant should be removed within 3 years of insertion

Contraception following abortion or miscarriage in the first trimester

* BY SUBDERMAL IMPLANTATION
  - Females of childbearing potential: 1 implant to be inserted within 5 days, implant should be removed within 3 years of insertion

Contraception (changing from other hormonal contraceptive)

* BY SUBDERMAL IMPLANTATION
  - Females of childbearing potential: Implant should be removed within 3 years of insertion (consult product literature)

**CONTRA-INDICATIONS**

- Acute porphyria - history of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal contraceptive methods unacceptable - severe arterial disease - undiagnosed vaginal bleeding

**CAUTIONS**

- Active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration)—seek specialist advice - arterial disease - disturbances of lipid metabolism - history during pregnancy of deterioration of otosclerosis - history during pregnancy of pruritus - history of jaundice in pregnancy - malabsorption syndromes - possible risk of breast cancer - sex-steroid dependent cancer - systemic lupus erythematosus with positive (or unknown) antiphospholipid antibodies

**INTERACTIONS**

- Appendix 1 (progestogens).
  - Effectiveness of parenteral progestogen-only contraceptives is not affected by antibacterial that do not induce liver enzymes. Effectiveness of the etonogestrel-releasing implant may be reduced by enzyme-inducing drugs and an alternative contraceptive method, unaffected by the interacting drug, is recommended during treatment with the enzyme-inducing drug and for at least 4 weeks after stopping. For a short course of an enzyme-inducing drug, if a change in contraceptive method is undesirable or inappropriate, the implant may be continued in combination with additional contraceptive precautions (e.g. condom) for the duration of treatment with the enzyme-inducing drug and for 4 weeks after stopping it.

**SIDE-EFFECTS**

- Breast discomfort - changes in libido - depression - disturbance of appetite - dizziness - headache

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Implant**
  - ETONOGESTREL (Non-proprietary)
    - Etonogestrel 68 mg: Etonogestrel 68 mg implant | 1 device [commercial price not available]
    - Nexplanon (Merck Sharp & Dohme Ltd)
    - Etonogestrel 68 mg: Nexplanon 68 mg implant | 1 device [commercial price £83.43]

**Medroxyprogesterone acetate**

**INDICATIONS AND DOSE**

Dysfunctional uterine bleeding

* BY MOUTH
  - Adult: 2.5–10 mg daily for 5–10 days, repeated for 2 cycles, begin treatment on day 16–21 of cycle

Secondary amenorrhoea

* BY MOUTH
  - Adult: 2.5–10 mg daily for 5–10 days, repeated for 3 cycles, begin treatment on day 16–21 of cycle

Mild to moderate endometriosis

* BY MOUTH
  - Adult: 10 mg 3 times a day for 90 consecutive days, begin treatment on day 1 of cycle

Progestogenic opposition of oestrogen HRT

* BY MOUTH
  - Adult: 10 mg daily for the last 14 days of each 28-day oestrogen HRT cycle

Endometrial cancer | Renal cell cancer

* BY MOUTH
  - Adult: 200–600 mg daily

Breast cancer

* BY MOUTH
  - Adult: 0.4–1.5 g daily

SIDE-EFFECTS, FURTHER INFORMATION

Cervical cancer

- Use of injectable progestogen-only contraceptives may be associated with a small increased risk of cervical cancer, similar to that seen with combined oral contraceptives. The risk of cervical cancer with other progestogen-only contraceptives is not yet known.

Breast cancer

- There is a small increase in the risk of having breast cancer diagnosed in women using, or who have recently used, a progestogen-only contraceptive pill; this relative risk may be due to an earlier diagnosis. The most important risk factor appears to be the age at which the contraceptive is stopped rather than the duration of use; the risk disappears gradually during the 10 years after stopping and there is no excess risk by 10 years. A possible small increase in the risk of breast cancer should be weighed against the benefits.

Pregnancy

- Not known to be harmful, remove implant if pregnancy occurs.

Breast feeding

- Progestogen-only contraceptives do not affect lactation.

DIRECTIONS FOR ADMINISTRATION

The doctor or nurse administering (or removing) the system should be fully trained in the technique and should provide full counselling reinforced by the patient information leaflet.

PATIENT AND CARER ADVICE

- Full counselling backed by patient information leaflet required before administration.

continued →
Contraception

BY DEEP INTRAMUSCULAR INJECTION
- Females of childbearing potential: 150 mg, to be administered within the first 5 days of cycle or within first 5 days after parturition (delay until 6 weeks after parturition if breast-feeding)

BY SUBCUTANEOUS INJECTION
- Females of childbearing potential: 104 mg, to be administered within first 5 days of cycle or within 5 days postpartum (delay until 6 weeks postpartum if breast-feeding), injected into anterior thigh or abdomen, dose only suitable if no hormonal contraceptive use in previous month

Contraception (when patient changing from other hormonal contraception)
BY SUBCUTANEOUS INJECTION
- Females of childbearing potential: (consult product literature)

• CONTRA-INDICATIONS
  • GENERAL CONTRA-INDICATIONS
    Acute porphyrias p. 864 · severe arterial disease · undiagnosed vaginal bleeding
  • SPECIFIC CONTRA-INDICATIONS
    - With intramuscular or subcutaneous use History of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal contraceptive methods unacceptable
    - With oral use Breast cancer (unless progestogens are being used in the management of this condition) · genital cancer (unless progestogens are being used in the management of this condition) · history of liver tumours
  • CAUTIONS
    • GENERAL CAUTIONS:
      Possible risk of breast cancer
    • SPECIFIC CAUTIONS:
      - With intramuscular or subcutaneous use History during pregnancy in disturbances of lipid metabolism · history during pregnancy of pruritus
      - With oral use Asthma · cardiac dysfunction · conditions that may worsen with fluid retention · diabetes (progestogens can decrease glucose tolerance—monitor patient closely) · epilepsy · history of depression · hypertension · migraine · susceptibility to thromboembolism (particular caution with high dose)
  • INTERACTIONS → Appendix 1 (progestogens).
    Effectiveness of parental progestogen-only contraceptives is not affected by antibiotics that do not induce liver enzymes. The effectiveness of medroxyprogesterone acetate intramuscular and subcutaneous injections is not affected by enzyme-inducing drugs and they may be continued as normal during courses of these drugs.
  • SIDE-EFFECTS
    • GENERAL SIDE-EFFECTS
      Breast discomfort · changes in libido · depression · dizziness · headache · indigestion · loss of vision during treatment (discontinue treatment if papilloedema or retinal vascular lesions) · menstrual irregularities · nausea · pruritus · vomiting · weight gain
    • SPECIFIC SIDE-EFFECTS
      - Rare
        - With intramuscular or subcutaneous use Osteoporosis · osteoporotic fractures
      - Frequency not known
        - With intramuscular or subcutaneous use Disturbance of appetite · injection site-reactions · reduced bone mineral density · skin disorders
        - With oral use Acne · adrenergic-like effects (when used for malignant disease) · alopecia · anaphylactoid reactions · bloating · breast tenderness · cervical erosions (when used for malignant disease) · confusion (when used for malignant disease) · congestive heart failure (when used for malignant disease) · constipation (when used for malignant disease) · diarrhoea (when used for malignant disease) · drowsiness · dry mouth (when used for malignant disease) · euphoria (when used for malignant disease) · fluid retention · galactorrhoea (when used for malignant disease) · glucocorticoid effects may lead to a cushingoid syndrome (with high doses for malignant disease) · hirsutism · hypercalcaemia (when used for malignant disease) · hyperpyrexia (when used for malignant disease) · hypertension (when used for malignant disease) · insomnia · jaundice · loss of concentration (when used for malignant disease) · nervousness (when used for malignant disease) · palpitation (when used for malignant disease) · premenstrual-like syndrome · raised platelet count (when used for malignant disease) · raised white blood cell count (when used for malignant disease) · rash · retinal thrombosis (when used for malignant disease) · skin reactions · tachycardia (when used for malignant disease) · urticaria · vision disorders (when used for malignant disease)
    • SIDE-EFFECTS, FURTHER INFORMATION
      Cervical cancer Use of injectable progestogen-only contraceptives may be associated with a small increased risk of cervical cancer, similar to that seen with combined oral contraceptives. The risk of cervical cancer with other progestogen-only contraceptives is not yet known. Reduction in bone mineral density occurs in the first 2–3 years of use then stabilises.
    • CONCEPTION AND CONTRACEPTION
      - With intramuscular use If interval between dose is greater than 12 weeks and 5 days (in long-term contraception), rule out pregnancy before next injection and advise patient to use additional contraceptive measures (e.g. barrier) for 14 days after the injection.
      - With subcutaneous use If interval between dose is greater than 13 weeks and 7 days (in long-term contraception), rule out pregnancy before next injection.
    • PREGNANCY
      - With oral use Avoid—genital malformations and cardiac defects reported.
      - With intramuscular use or subcutaneous use Not known to be harmful.
    • BREAST FEEDING
      Present in milk—no adverse effects reported. Progesterone-only contraceptives do not affect lactation.
      - With intramuscular use or subcutaneous use The manufacturers advise that in women who are breast-feeding, the first dose should be delayed until 6 weeks after birth; however, evidence suggests no harmful effect to infant if given earlier. The benefits of using medroxyprogesterone acetate in breast-feeding women outweigh any risks.
    • HEPATIC IMPAIRMENT
      - With oral use Avoid in hepatic impairment.
3.5 Contraception, spermicidal

SPERMICIDALS

Nonoxinol

INDICATIONS AND DOSE
Spermicidal contraceptive in conjunction with barrier methods of contraception such as diaphragms or caps by vagina

INTERNATIONAL PHARMACEUTICAL FORMULARY

Nonoxinol 9 20 mg per 1 ml Gygel 2% contraceptive jelly

30 gram (GSS) £4.25 | 81 gram (GSS) £11.00

4 Erectile and ejaculatory conditions

4.1 Erectile dysfunction

Erectile dysfunction

Reasons for failure to produce a satisfactory erection include psychogenic, vascular, neurogenic, and endocrine abnormalities; impotence can also be drug-induced.

Intracavernosal, urethral or topical application of vasoactive drugs under careful medical supervision are used for the management of erectile dysfunction. Intracavernosal or intrathecal preparations can also be used in the diagnosis of erectile dysfunction.

Erectile disorders may also be treated with drugs given by mouth which increase the blood flow to the penis. Drugs should be used with caution if the penis is deformed (e.g. in angulation, cavernosal fibrosis, and Peyronie’s disease).

Priapism

If priapism occurs with alprostadil p. 701, treatment should not be delayed more than 6 hours and is as follows:

- Initial therapy by penile aspiration; using aseptic technique a 19–21 gauge butterfly needle inserted into the corpus cavernosum and 20–50 mL of blood aspirated; if necessary the procedure may be repeated on the opposite side.
- If initial aspiration is unsuccessful a second 19–21 gauge butterfly needle can be inserted into the opposite corpus cavernosum and sterile physiological saline introduced through the first needle and drained through the second.
- If aspiration and lavage of corpora are unsuccessful, cautious intracavernosal injection of a sympathomimetic with action on alpha-adrenergic receptors, continuously monitoring blood pressure and pulse (extreme caution: coronary heart disease, hypertension, cerebral ischaemia or if taking antidepressant) can be given.
- If necessary the sympathomimetic injections can be followed by further aspiration of blood through the same butterfly needle.
- If sympathomimetic unsuccessful, urgent surgical referral for management (possibly including shunt procedure).

Prescribing on the NHS

Some drug treatments for erectile dysfunction may only be prescribed on the NHS under certain circumstances; for details see the criteria listed in part XVIIIIB of the Drug Tariff (Part XII of the Northern Ireland Drug Tariff, Part 12 of the Scottish Drug Tariff). The Drug Tariffs can be accessed online at: National Health Service Drug Tariff for England and Wales: www.ppa.org.uk/ppa/edt_intro.htm

Health and Personal Social Services for Northern Ireland Drug Tariff: www.dhsspsni.gov.uk/pas-tariff

Scottish Drug Tariff: www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Scottish-Drug-Tariff/
Alprostadil
Alprostadil p. 701 (prostaglandin E₃) is given by intracavernosal injection, intrarectal application, or topical application for the management of erectile dysfunction (after exclusion of treatable medical causes). Intracavernosal or intrarectal preparations can also be used in the diagnosis of erectile dysfunction.

Phosphodiesterase type-5 inhibitors
Avanafil below, sildenafil below, tadalafil p. 700 and vardenafil p. 701 are phosphodiesterase type-5 inhibitors licensed for the treatment of erectile dysfunction; they are not recommended for use with other treatments for erectile dysfunction. The patient should be assessed appropriately before prescribing avanafil, sildenafil, tadafalil or vardenafil. Since these drugs are given by mouth there is a potential for drug interactions.

Papaverine and phentolamine
Although not licensed the smooth muscle relaxant papaverine has also been given by intracavernosal injection for erectile dysfunction. Patients with neurological or psychogenic impotence are more sensitive to the effect of papaverine than those with vascular abnormalities. Phentolamine mesilate p. 161 is added if the response is inadequate [unlicensed indication]. Persistence of the erection for longer than 4 hours is an emergency.

PHOSPHODIESTERASE TYPE-5 INHIBITORS

Avanafil

INDICATIONS AND DOSE
Erectile dysfunction
BY MOUTH
Adult: Initially 100 mg, to be taken approximately 30 minutes before sexual activity, then adjusted according to response to 50–200 mg (max. per dose 200 mg), to be taken as a single dose as needed; maximum 1 dose per day

Erectile dysfunction in patients on alpha-blocker therapy
BY MOUTH
Adult: Initially 50 mg, to be taken approximately 30 minutes before sexual activity, then adjusted according to response to 50–200 mg (max. per dose 200 mg), to be taken as a single dose as needed; maximum 1 dose per day

Dose adjustments due to interactions
Max. 100 mg once every 48 hours with concomitant moderate inhibitors of cytochrome P450 enzyme CYP3A4 e.g. aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, or verapamil.

Concomitant treatment with a phosphodiesterase type-5 inhibitor and an alpha-blocker can increase the risk of postural hypotension—initiate treatment with a phosphodiesterase type-5 inhibitor (at a low dose) only once the patient is stable on the alpha-blocker.

CONTRA-INDICATIONS Avoid if systolic blood pressure below 90 mmHg (no information available) - blood pressure > 170/100 mmHg - hereditary degenerative retinal disorders - history of non-articent anterior ischaemic optic neuropathy - life-threatening arrhythmia in previous 6 months - mild to severe heart failure - patients in whom vasodilatation or sexual activity are inappropriate 

CAUTIONS Active peptic ulceration - anatomical deformation of the penis (e.g. angulation, cavernosal fibrosis, Peyronie’s disease) - bleeding disorders - cardiovascular disease - left ventricular outflow obstruction - predisposition to priapism (e.g. in sickle-cell disease, multiple myeloma, or leukaemia)

INTERACTIONS → Appendix 1 (avanafil).
Avoid concomitant use of nitrates.

SIDE-EFFECTS

Common or very common Back pain - dizziness - dyspepsia - flushing - headache - migraine - myalgia - nasal congestion - nausea - visual disturbances - vomiting

Uncommon Drowsiness - epistaxis - hypertension - hypotension - malaise - painful red eyes - palpitation - tachycardia

Rare Abdominal pain - diarrhoea - dry mouth - facial oedema - gastritis - genital irritation - gout - haematuria - hyperactivity - hyperbilirubinaemia - hyperosmolarity - increased serum creatinine - insomnia - muscle spasms - peripheral oedema - pollakiuria - priapism - rash - Stevens-Johnson syndrome - syncope - weight gain

Frequency not known Arrhythmia - myocardial infarction - non-articent anterior ischaemic optic neuropathy (stop drug if sudden visual impairment occurs) - retinal vascular occlusion - seizures - serious cardiovascular events - sudden hearing loss (discontinue drug and seek medical advice) - unstable angina

HEPATIC IMPAIRMENT Use lowest effective initial dose in mild to moderate impairment, adjusted according to response. Manufacturer advises avoid in severe impairment—no information available.

RENAL IMPAIRMENT Avoid if eGFR less than 30 mL/minute/1.73 m².

PATIENT AND CARER ADVICE Onset of effect may be delayed if taken with food.

NATIONAL FUNDING/ACCESS DECISIONS

NHS restrictions Spedra ™ is not prescribable under the NHS for treatment of erectile dysfunction except in men who meet the criteria listed in part XVIII B of the Drug Tariff (Part XII of the Northern Ireland Drug Tariff, Part 12 of the Scottish Drug Tariff). The prescription must be endorsed ‘SLS’.

The Drug Tariffs can be accessed online at: National Health Service Drug Tariff for England and Wales: www.ppa.org.uk/ppa/edt_intro.htm; Health and Personal Social Services for Northern Ireland Drug Tariff; www.dhsspsni.gov.uk/pas-tariff; Scottish Drug Tariff: www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Scottish-Drug-Tariff/

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
Spedra (A. Menarini Farmaceutica Internazionale SRL) ▼
Avanafil 50 mg Spedra 50mg tablets | 4 tablet (£2.90) £10.94 | 8 tablet (£5.10) £19.70
Avanafil 100 mg Spedra 100mg tablets | 4 tablet (£2.90) £14.08 | 8 tablet (£5.10) £26.26
Avanafil 200 mg Spedra 200mg tablets | 4 tablet (£2.90) £21.90 | 8 tablet (£5.10) £39.40

Sildenafil

INDICATIONS AND DOSE
Pulmonary arterial hypertension
BY MOUTH
Adult: 20 mg 3 times a day

BY INTRAVENOUS INJECTION
Adult: 10 mg 3 times a day, use intravenous route when the oral route is not appropriate
Erectile dysfunction

**BY MOUTH**
- Adult: Initially 50 mg, to be taken approximately 1 hour before sexual activity, adjusted according to response to 25–100 mg (max. per dose 100 mg) as required, to be taken as a single dose; maximum 1 dose per day

**CONTRA-INDICATIONS**

**GENERAL CONTRA-INDICATIONS**
Hereditary degenerative retinal disorders · history of non-articentric anterior ischaemic optic neuropathy · recent history of myocardial infarction · recent history of stroke

**SPECIFIC CONTRA-INDICATIONS**
- When used for erectile dysfunction Avoid if systolic blood pressure below 90 mmHg (no information available) · patients in whom vasodilation or sexual activity are inadvisable · recent unstable angina
- When used for pulmonary arterial hypertension Sickle-cell anaemia

**CAUTIONS**

**GENERAL CAUTIONS**
Active peptic ulceration · bleeding disorders · cardiovascular disease · left ventricular outflow obstruction

**SPECIFIC CAUTIONS**
- When used for erectile dysfunction Anatomical deformation of the penis (e.g. angulation, cavernous fibrosis, Peyronie’s disease) · predisposition to priapism (e.g. in sickle-cell disease, multiple myeloma, or leukaemia)
- When used for pulmonary arterial hypertension Anatomical deformation of the penis · autonomic dysfunction · hypotension (avoid if systolic blood pressure below 90 mmHg) · intravascular volume depletion · predisposition to priapism · pulmonary veno-occlusive disease

**INTERACTIONS** → Appendix 1 (sildenafil).

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**
Back pain · dyspepsia · flushing · migraine · myalgia · nasal congestion · visual disturbances

**Frequency not known** Non-articentric anterior ischaemic optic neuropathy (discontinue if sudden visual impairment occurs) · sudden hearing loss · myalgia · vertigo · flushing · syncope

**SPECIFIC SIDE-EFFECTS**
- Common or very common
  - When used for erectile dysfunction Nausea · dizziness · vomiting
  - When used for pulmonary arterial hypertension Abdominal distension · alopecia · anemia · anxiety · bronchitis · cellulitis · cough · diarrhoea · dry mouth · epistaxis · fever · gastritis · gastro-oesophageal reflux · haemorrhoids · headache · influenza-like symptoms · insomnia · limb pain · night sweats · oedema · painful red eyes · paraesthesia · photophobia · retinal haemorrhage · tremor · vertigo
- Uncommon
  - When used for erectile dysfunction Chest pain · drowsiness · dry mouth · epistaxis · fatigue · hypertension · hypoaesthesia · hypotension · painful red eyes · palpitation · tachycardia · tinnitus · vertigo
  - When used for pulmonary arterial hypertension Gynaecomastia · haematuria · penile haemorrhage · priapism
- Rare
  - When used for erectile dysfunction Atrial fibrillation · cerebrovascular accident · facial oedema · hypersensitivity reactions · priapism · rash · Stevens-Johnson syndrome · syncope
- Frequency not known
  - When used for erectile dysfunction Arrhythmia · myocardial infarction · seizures · unstable angina
  - When used for pulmonary arterial hypertension Rash · retinal vascular occlusion
- **PREGNANCY** Use only if potential benefit outweighs risk—no evidence of harm in animal studies.
- **BREAST FEEDING** Manufacturer advises avoid—no information available.
- **HEPATIC IMPAIRMENT** In pulmonary arterial hypertension, if usual dose not tolerated, reduce oral dose to 20 mg twice daily and intravenous dose to 10 mg twice daily. For erectile dysfunction, use initial dose of 25 mg. Manufacturer advises avoid in severe impairment.
- **RENAL IMPAIRMENT** Use initial dose of 25 mg in erectile dysfunction if eGFR less than 30 mL/minute/1.73 m².

In pulmonary hypertension, if usual dose not tolerated, reduce oral dose to 20 mg twice daily and intravenous dose to 10 mg twice daily.

**TREATMENT CESSATION**
- When used for Pulmonary arterial hypertension Consider gradual withdrawal.

**PATIENT AND CARER ADVICE**
- When used for Erectile dysfunction Onset of effect may be delayed if taken with food.

**NATIONAL FUNDING/ACCESS DECISIONS**

**Scottish Medicines Consortium (SMC) Decisions**
The Scottish Medicines Consortium has advised (January 2010 and February 2011) that sildenafil tablets (Revatio®) should be initiated for patients with pulmonary arterial hypertension only by specialists in the Scottish Pulmonary Vascular Unit or other similar specialists and that sildenafil injection (Revatio®) should be prescribed only on the advice of specialists in the Scottish Pulmonary Vascular Unit or the Scottish Adult Congenital Cardiac Service.

**NHS restrictions** Viagra® is not prescribable under NHS for treatment of erectile dysfunction except in men who meet the criteria listed in part XVIII B of the Drug Tariff (Part XII of the Northern Ireland Drug Tariff, Part 12 of the Scottish Drug Tariff). The prescription must be endorsed ‘SLS’. For more information see Prices in the BNF, under How to use BNF publications p. xi.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: pessary, oral suspension, oral solution

**Tablet**

| SILDENAFIL (Non-proprietary) | Sildenafil (as Sildenafil citrate) 25 mg | Sildenafil 25mg tablets | 4 tablet (PFS) £16.93 DT price = £1.09 | 8 tablet (PFS) £33.19 |
| Sildenafil (as Sildenafil citrate) 50 mg | Sildenafil 50mg tablets | 4 tablet (PFS) £21.27 DT price = £1.15 | 8 tablet (PFS) £42.54 |
| Sildenafil (as Sildenafil citrate) 100 mg | Sildenafil 100mg tablets | 4 tablet (PFS) £35.50 DT price = £1.23 | 8 tablet (PFS) £64.99 |

| **Revatio** (Pfizer Ltd) | Sildenafil (as Sildenafil citrate) 20 mg | Revatio 20mg tablets | 90 tablet (PFS) £446.33 |
| Viagra® (Pfizer Ltd) | Sildenafil (as Sildenafil citrate) 25 mg | Viagra 25mg tablets | 4 tablet (PFS) £16.93 DT price = £1.09 | 8 tablet (PFS) £33.19 |
| Sildenafil (as Sildenafil citrate) 50 mg | Viaga 50mg tablets | 4 tablet (PFS) £21.27 DT price = £1.15 | 8 tablet (PFS) £42.54 |
| Sildenafil (as Sildenafil citrate) 100 mg | Viaga 100mg tablets | 4 tablet (PFS) £35.50 DT price = £1.23 | 8 tablet (PFS) £64.99 |

| **Prices in the BNF** |  |  |  |  |

| **BRANDS** |  |  |  |  |
| Manufacturers may include Vivasin |  |  |  |  |
Tadalafil

INDICATIONS AND DOSE
Pulmonary arterial hypertension
BY MOUTH
Adult: 40 mg once daily
Erectile dysfunction
BY MOUTH
Adult: Initially 10 mg once daily (max. per dose 20 mg), to be taken at least 30 minutes before sexual activity, subsequent doses adjusted according to response, the effect of intermittent dosing may persist for longer than 24 hours, daily dose of 10–20 mg not recommended; maximum 1 dose per day
Erectile dysfunction; for patients who anticipate sexual activity at least twice a week
BY MOUTH
Adult: 5 mg once daily, reduced to 2.5 mg once daily, adjusted according to response, the effect of intermittent dosing may persist for longer than 24 hours
Benign prostatic hyperplasia
BY MOUTH
Adult: 5 mg once daily

CONTRA-INDICATIONS
GENERAL CONTRA-INDICATIONS
History of non-arteritic anterior ischaemic optic neuropathy
SPECIFIC CONTRA-INDICATIONS
When used for benign prostatic hyperplasia or erectile dysfunction Hypotension (avoid if systolic blood pressure below 90 mmHg) - left ventricular dysfunction - life-threatening arrhythmias - pericardial constriction - predisposition to priapism - pulmonary veno-occlusive disease - uncontrolled hypertension
INTERACTIONS → Appendix 1 (tadalafil).
SIDE-EFFECTS
GENERAL SIDE-EFFECTS
Common or very common Back pain - dyspepsia - flushing - headache - myalgia - nausea - vomiting
Uncommon Hypertension - tachycardia
Frequency not known Arrhythmia - myocardial infarction - non-arteritic anterior ischaemic optic neuropathy (stop drug if sudden visual impairment occurs) - retinal vascular occlusion - sudden hearing loss (discontinue drug and seek medical advice) - unstable angina
SPECIFIC SIDE-EFFECTS
Common or very common
When used for benign prostatic hyperplasia or erectile dysfunction Dizziness - migraine - nasal congestion - visual disturbances
When used for pulmonary arterial hypertension Blurred vision - chest pain - epistaxis - facial oedema - gastrointestinal reflux - hypotension - increased uterine bleeding - limb pain - nasopharyngitis - palpitation - rash
Uncommon
When used for benign prostatic hyperplasia or erectile dysfunction Epistaxis - hypotension - painful red eyes - palpitation
When used for pulmonary arterial hypertension or erectile dysfunction Amnesia - hyperhidrosis - priapism - seizures
Rare
When used for benign prostatic hyperplasia or erectile dysfunction Facial oedema - hypersensitivity reactions - priapism - rash - Stevens-Johnson syndrome - syncope
Frequency not known
When used for benign prostatic hyperplasia or erectile dysfunction Abdominal pain - increased sweating - seizures - serious cardiovascular events - transient amnesia
When used for pulmonary arterial hypertension Stevens-Johnson syndrome - stroke - visual field defect
PREGNANCY Manufacturer advises avoid.
BREAST FEEDING Manufacturer advises avoid—present in milk in animal studies.
HEPATIC IMPAIRMENT When used for pulmonary arterial hypertension use initial dose of 20 mg once daily in mild to moderate impairment and avoid in severe impairment. Use maximum dose of 10 mg in erectile dysfunction and benign prostatic hyperplasia. Manufacturer advises caution in severe impairment and for regular once-daily dosing in erectile dysfunction and benign prostatic hyperplasia—no information available.
RENAL IMPAIRMENT In pulmonary arterial hypertension for patients with mild to moderate impairment, initially use 20 mg once daily, increased to 40 mg once daily if tolerated; avoid in severe impairment. For erectile dysfunction and benign prostatic hyperplasia, maximum dose 10 mg if eGFR less than 30 mL/minute/1.73 m² (avoid regular once-daily dosing).
NATIONAL FUNDING/ACCESS DECISIONS
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (June 2012) that tadalafil (Adcirca®) should be initiated only by specialists in the Scottish Pulmonary Vascular Unit or other similar specialists.
NHS restrictions Cialis® is not prescribable under the NHS for treatment of erectile dysfunction except in men who meet the criteria listed in part XVIII B of the Drug Tariff (Part XII of the Northern Ireland Drug Tariff, Part 12 of

Chewable tablet

CAUTIONARY AND ADVISORY LABELS 24 EXCIPENTS: May contain Aspartame

REVATIO
Sildenafil (as Sildenafil citrate) 10 mg per 1 ml Revatio 10mg/ml oral suspension (sugar-free) £106.75
Solution for injection
Revatio (Pfizer Ltd)
Sildenafil (as Sildenafil citrate) 8 mg per 1 ml Revatio 10mg/12.5ml solution for injection vials £45.28

700 Erectile and ejaculatory conditions
Vardenafil

INDICATIONS AND DOSE

Erectile dysfunction

BY MOUTH USING TABLETS
• Adult: Initially 10 mg (max. per dose 20 mg), to be taken approximately 25–60 minutes before sexual activity, subsequent doses adjusted according to response, onset of effect may be delayed if taken with high-fat meal; maximum 1 dose per day

BY MOUTH USING ORODISPERSIBLE TABLET
• Adult: 10 mg, to be taken approximately 25–60 minutes before sexual activity; maximum 10 mg per day

Erectile dysfunction (patients on alpha-blocker therapy)

BY MOUTH USING TABLETS
• Adult: Initially 5 mg (max. per dose 20 mg), to be taken approximately 25–60 minutes before sexual activity, subsequent doses adjusted according to response, onset of effect may be delayed if taken with high-fat meal; maximum 1 dose per day

Dose adjustments due to interactions
Concomitant treatment with phosphodiesterase type-5 inhibitor and an alpha-blocker can increase the risk of postural hypotension—initiate treatment with a phosphodiesterase type-5 inhibitor (at a low dose) only once the patient is stable on the alpha-blocker.

Dose equivalence and conversion
Levitra® 10 mg orodispersible tablets and Levitra® 10 mg film coated tablets are not bioequivalent.

CONTRA-INDICATIONS
Avoid if systolic blood pressure below 90 mmHg • hereditary degenerative retinal disorders • myocardial infarction • patients in whom vasodilatation or sexual activity are inadvisable • previous history of non-arteritic anterior ischaemic optic neuropathy • recent stroke • unstable angina

CAUTIONS
Active peptic ulceration • anatomical deformation of the penis (e.g. angulation, cavernosal fibrosis, Peyronie’s disease) • bleeding disorders • cardiovascular disease • elderly • left ventricular outflow obstruction • predisposition to priapism (e.g. in sickle-cell disease, multiple myeloma, or leukaemia) • susceptibility to prolongation of QT interval

INTERACTIONS
• Appendix 1 (vardenafil)
Caution with concomitant use of drugs which prolong QT interval. Avoid concomitant use of nitrates.

SIDE-EFFECTS
• Common or very common Back pain • dizziness • dyspepsia • flushing • headache • migraine • myalgia • nasal congestion • nausea • visual disturbances • vomiting

• Uncommon Drowsiness • dyspnoea • epistaxis • hypertension • hypotension • increased lacrimation • painful red eyes • palpitation • photosensitivity • tachycardia

• Rare Anxiety • facial oedema • hypersensitivity reactions • hypotonia • priapism • raised intraocular pressure • rash • Stevens-Johnson syndrome • syncope • transient amnesia

• Frequency not known Arrhythmia • myocardial infarction • non-arteritic anterior ischaemic optic neuropathy (stop drug if sudden visual impairment occurs) • retinal vascular occlusion • seizures • serious cardiovascular events • sudden hearing loss (discontinue drug and seek medical advice) • unstable angina

• HEPATIC IMPAIRMENT
Initial dose 5 mg if eGFR less than 30 mL/minute/1.73 m². Orodispersible tablets not suitable if eGFR less than 30 mL/minute/1.73 m².

• PRESCRIBING AND DISPENSING INFORMATION
Orodispersible tablets not suitable for initiation of therapy in patients taking alpha-blockers.

• NATIONAL FUNDING/ACCESS DECISIONS
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (September 2011) that vardenafil orodispersible tablets (Levitra®) are accepted for restricted use within NHS Scotland for men for whom an orodispersible tablet is an appropriate formulation.

NHS restrictions Levitra® is not prescribable under the NHS for the treatment of erectile dysfunction except in men who meet the criteria listed in part XVIIIB of the Drug Tariff (Part XIIb of the Northern Ireland Drug Tariff, Part 12 of the Scottish Drug Tariff). The prescription must be endorsed ‘SLS’. For more information see Prices in the BNF, under How to use BNF publications p. xi.

• MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
• Levitra (Bayer Plc)
Vardenafil (as Vardenafil hydrochloride trihydrate) 5 mg Levitra 5mg tablets | 4 tablet (POM) £7.56 DT price = £7.56 | 8 tablet (POM) £15.12

Vardenafil (as Vardenafil hydrochloride trihydrate) 10 mg Levitra 10mg tablets | 4 tablet (POM) £14.08 DT price = £14.08 | 8 tablet (POM) £28.16

Vardenafil (as Vardenafil hydrochloride trihydrate) 20 mg Levitra 20mg tablets | 4 tablet (POM) £23.48 DT price = £23.48 | 8 tablet (POM) £46.96

ORODISPERSIBLE TABLET
EXCipients: May contain Aspartame
• Levitra (Bayer Plc)
Vardenafil (as Vardenafil hydrochloride trihydrate) 10 mg Levitra 10mg orodispersible tablets (sugar-free) | 4 tablet (POM) £17.88 DT price = £17.88

PROSTAGLANDINS (ERECTILE DYSFUNCTION)

Alprostadil

INDICATIONS AND DOSE
Erectile dysfunction (initiated under specialist supervision)
BY URETHRAL APPLICATION
• Adult: Initially 250 micrograms, adjusted according to response; usual dose 0.125–1 mg; maximum 2 doses per day; maximum 7 doses per week continued
**Erectile and ejaculatory conditions**

**CAVERJECT®**

**Erectile dysfunction**

**BY INTRACAVERNOSAL INJECTION**

- Adult: Initially 2.5 micrograms for 1 dose (first dose), followed by 5 micrograms for 1 dose (second dose), then 5 micrograms for 1 dose (third dose), increased in steps of 5–10 micrograms, to obtain a dose suitable for producing erection not lasting more than 1 hour; usual dose 10–20 micrograms (max. per dose 40 micrograms), maximum frequency of injection not more than 3 times per week with at least 24 hour interval between injections; reduce dose if erection lasts longer than 2 hours

**Erectile dysfunction associated with neurological dysfunction**

**BY INTRACAVERNOSAL INJECTION**

- Adult: Initially 2.5 micrograms for 1 dose (first dose), followed by 5 micrograms for 1 dose (second dose), then 2.5 micrograms for 1 dose (third dose), increased in steps of 5–10 micrograms, to obtain a dose suitable for producing erection not lasting more than 1 hour; usual dose 10–20 micrograms (max. per dose 40 micrograms), maximum frequency of injection not more than 3 times per week with at least 24 hour interval between injections; reduce dose if erection lasts longer than 2 hours

**BY URETHRAL APPLICATION**

- Adult: 500 micrograms for 1 dose

**TO THE SKIN**

- Adult: 300 micrograms, to the tip of the penis, 30 minutes before sexual activity; max 1 dose in 24 hours not more than 2–3 times per week

**VIRIDAL® DUO STARTER PACK**

Neurogenic erectile dysfunction

**BY INTRACAVERNOSAL INJECTION**

- Adult: 40 micrograms, increased in steps of 5–10 micrograms, maximum frequency of injection not more than 2–3 times per week with at least 24 hour interval between injections; reduce dose if erection lasts longer than 2 hours

**Erectile dysfunction**

**BY INTRACAVERNOSAL INJECTION**

- Adult: 5 micrograms, increased in steps of 2.5–5 micrograms, to obtain dose suitable for producing erection not lasting more than 1 hour; usual dose 10–20 micrograms (max. per dose 40 micrograms), maximum frequency of injection not more than 2–3 times per week with at least 24 hour interval between injections; reduce dose if erection lasts longer than 2 hours

**C A V E R J E C T ® D U A L C H A M B E R**

**Erectile dysfunction**

**BY INTRACAVERNOSAL INJECTION**

- Adult: Initially 2.5 micrograms for 1 dose (first dose), followed by 5 micrograms for 1 dose (second dose), to be given if some response to first dose, alternatively 7.5 micrograms for 1 dose (second dose), to be given if no response to first dose, then increased in steps of 5–10 micrograms, to obtain a dose suitable for producing erection not lasting more than 1 hour; if no response to dose then next higher dose can be given within 1 hour, if there is a response the next dose should not be given for at least 24 hours; usual dose 20 micrograms (max. per dose 60 micrograms), maximum frequency of injection not more than 3 times per week with at least 24 hour interval between injections; reduce dose if erection lasts longer than 2 hours

**Erectile dysfunction associated with neurological dysfunction**

**BY INTRACAVERNOSAL INJECTION**

- Adult: Initially 5 micrograms, increased in steps of 2.5–5 micrograms, to obtain dose suitable for producing erection not lasting more than 1 hour; usual dose 10–20 micrograms (max. per dose 40 micrograms), maximum frequency of injection not more than 2–3 times per week with at least 24 hour interval between injections; reduce dose if erection lasts longer than 2 hours

**BY URETHRAL APPLICATION**

- Adult: 300 micrograms, to the tip of the penis, 30 minutes before sexual activity; max 1 dose in 24 hours not more than 2–3 times per week

**TO THE SKIN**

- Adult: 300 micrograms, to the tip of the penis, 30 minutes before sexual activity; max 1 dose in 24 hours not more than 2–3 times per week

**VIRIDAL® DUO CONTINUATION PACK**

**Erectile dysfunction**

**BY INTRACAVERNOSAL INJECTION**

- Adult: 5 micrograms, increased in steps of 2.5–5 micrograms, to obtain dose suitable for producing erection not lasting more than 1 hour; usual dose 10–20 micrograms (max. per dose 40 micrograms), maximum frequency of injection not more than 2–3 times per week with at least 24 hour interval between injections; reduce dose if erection lasts longer than 2 hours

**Neurogenic erectile dysfunction**

**BY INTRACAVERNOSAL INJECTION**

- Adult: Initially 5 micrograms, increased in steps of 2.5–5 micrograms, to obtain dose suitable for producing erection not lasting more than 1 hour; usual dose 10–20 micrograms (max. per dose 40 micrograms), maximum frequency of injection not more than 2–3 times per week with at least 24 hour interval between injections; reduce dose if erection lasts longer than 2 hours

**CONTRA-INDICATIONS**

**GENERAL CONTRA-INDICATIONS**

Not for use in patients with penile implants or when sexual activity medically inadvisable (e.g. orthostatic hypotension, myocardial infarction, and syncope); not for use with other agents for erectile dysfunction - predisposition to prolonged erection (as in thrombocytopenia, polycythemia, sickle cell anaemia,
multiple myeloma or leukaemia) - urethral application contra-indicated in balanitis - urethral application contra-indicated in severe curvature - urethral application contra-indicated in severe hypospadia - urethral application contra-indicated in urethral stricture - urethral application contra-indicated in urethritis

**SPECIFIC CONTRA-INDICATIONS**

- With topical use: Balanitis - severe curvature - severe hypospadia - urethral stricture - urethritis

**CAUTIONS**

- Anatomical deformations of penis (painful erection more likely) — follow up regularly to detect signs of penile fibrosis (consider discontinuation if angulation, cavernosal fibrosis or Peyronie’s disease develop) — priapism (patients should be instructed to report any erection lasting 4 hours or longer)

**INTERACTIONS**

- Appendix 1 (alprostadil).

**SIDE-EFFECTS**

- Common or very common: Dizziness - haematoma - haemosiderin deposits - headache - hypertension - hypotension - influenza-like syndrome - injection site reactions - other localised pain (buttocks, leg, testicular, abdominal) - penile fibrosis - penile oedema - penile pain - penile rash - urethral bleeding - urethral burning


- Rare: Anaphylaxis - erythema - hypersensitivity reactions - rash - urinary-tract injection - urticaria - vertigo

**CONCEPTION AND CONTRACEPTION**

- With urethral use: If partner is pregnant, barrier contraception should be used. No evidence of harm to latent condoms and diaphragms.

- With topical use: Condoms should be used to avoid exposure to women of child-bearing age, pregnant or lactating women. No evidence of harm to latent condoms.

**DIRECTIONS FOR ADMINISTRATION**

- With intraurethral use: The first dose of the intraurethral injection must be given by medically trained personnel; self-administration may only be undertaken after proper training.

- With urethral use: During initiation of treatment the urethral application should be used under medical supervision; self-administration may only be undertaken after proper training.

**PATIENT AND CARER ADVICE**

- Patients should be instructed to report any erection lasting 4 hours or longer.

- With topical use: Counsel patients that condoms should be used to avoid local reactions and exposure of alprostadil to women of childbearing age, pregnant, or lactating women.

**NATIONAL FUNDING/ACCESS DECISIONS**

- NHS restrictions: Caverject®, Viridal®, Duo, Vitaros® and MUSE® are not prescribable under the NHS for treatment of erectile dysfunction except in men who meet the criteria listed in part XVIIIb of the Drug Tariff (Part XIIb of the Northern Ireland Drug Tariff, Part 12 of the Scottish Drug Tariff). The prescription must be endorsed “SLS” for more information see Prices in the BNF, under How to use BNF publications p. xi.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

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**Premature ejaculation**

**SELECTIVE SEROTONIN RE-UPTAKE INHIBITORS**

- **Dapoxetine**

  **DRUG ACTION**

  Dapoxetine is a short-acting selective serotonin re-uptake inhibitor.

  **INDICATIONS AND DOSE**

  Premature ejaculation in men who meet all the following criteria: poor control over ejaculation, a history of premature ejaculation over the past 6 months, marked distress or interpersonal difficulty as a consequence of premature ejaculation, and an intravaginal ejaculatory latency time of less than two minutes

  **BY MOUTH**

  - Adult: Initially 30 mg, to be taken approximately 1–3 hours before sexual activity, subsequent doses adjusted according to response; review treatment after 4 weeks (or 6 doses) and at least every 6 months thereafter, not recommended for adults 65 years and over; maximum 1 dose per day; maximum 60 mg per day

  **continued**

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Premature ejaculation in men who meet all the following criteria: poor control over ejaculation, a history of premature ejaculation over the past 6 months, marked distress or interpersonal difficulty as a consequence of premature ejaculation, and an intravaginal ejaculatory latency time of less than two minutes (with concomitant apreparit, clarihormycin, ditiazem, erythromycin, flucinazone, fosamprenavir, and verapamil).

BY MOUTH
- Adult: Up to 30 mg, to be taken approximately 1–3 hours before sexual activity; review treatment after 4 weeks (or 6 doses) and at least every 6 months thereafter, not recommended for adults 65 years and over; maximum 1 dose per day.

Dose adjustments due to interactions
Max. single dose 30 mg with concomitant apreparit, clarihormycin, ditiazem, erythromycin, flucinazone, fosamprenavir, and verapamil. Use 60-mg dose with caution with concomitant potent inhibitors of cytochrome P450 enzyme CYP2D6.

• CONTRA-INDICATIONS History of bipolar disorder • history of mania • history of severe depression • history of syncope • significant cardiac disease • uncontrolled epilepsy

• CAUTIONS Bleeding disorders • epilepsy (discontinue if convulsions develop) • susceptibility to angle-closure glaucoma

• INTERACTIONS → Appendix 1 (dapoxetine).
Caution with concomitant use of drugs that increase risk of bleeding.

• SIDE-EFFECTS
- Common or very common Abdominal distension • abdominal pain • abnormal dreams • agitation • anxiety • constipation • diarrhea • dizziness • drowsiness • dry mouth • dyspepsia • flushing • headache • hypertension • impaired attention • irritability • malaise • nausea • paraesthesia • sexual dysfunction • sleep disturbances • sweating • tinnitus • tremor • visual disturbances • vomiting
- Uncommon Abnormal thoughts • bradycardia • bruxism • confusion • depression • eye pain • hypotension • mood disturbances • mydriasis • postural hypotension • pruritus • restlessness • sinus arrest • syncope • tachycardia • taste disturbances • vertigo
- Rare Defaecation urgency • sudden onset of sleep

SIDE-EFFECTS, FURTHER INFORMATION
Discontinue if psychiatric disorder develops. Avoid if postural hypotension occurs during test dose.

• HEPATIC IMPAIRMENT
Avoid in moderate to severe impairment.

• RENAL IMPAIRMENT
Use with caution if eGFR 30–80 mL/minute/1.73 m²; avoid if eGFR less than 30 mL/minute/1.73 m².

• PRE-TREATMENT SCREENING
Test for postural hypotension before starting treatment.

• PATIENT AND CARER ADVICE
Postural hypotension and syncope Patients should be advised to maintain hydration and to sit or lie down until prodromal symptoms such as nausea, dizziness, and sweating abate.

• MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
Table
CAUTIONARY AND ADVISORY LABELS 2, 25
- Priligy (A. Menarini Farmaceutica Internazionale SRL)
  Dapoxetine 30 mg Priligy 30mg tablets | 3 tablet (P) £14.71 | 6 tablet (P) £26.48
  Dapoxetine 60 mg Priligy 60mg tablets | 3 tablet (P) £19.12 | 6 tablet (P) £34.42

5 Obstetrics

Obstetrics

Prostaglandins and oxytocics
Prostaglandins and oxytocics are used to induce abortion or induce or augment labour and to minimise blood loss from the placental site. They include oxytocin p. 705, carbocetin p. 706, ergometrine maleate p. 707, and the prostaglandins. All induce uterine contractions with varying degrees of pain according to the strength of contractions induced.

Induction of abortion
Gemeprost p. 709, a prostaglandin administered vaginally as pessaries, is suitable for the medical induction of late therapeutic abortion; gemeprost is also used to ripen the cervix before surgical abortion, particularly in primigravidas. The prostaglandin misoprostol p. 709 is given by mouth, buccally, sublingually, or vaginally, to induce medical abortion [unlicensed indication].

Intravaginal use ripens the cervix before surgical abortion [unlicensed indication]. Extra-anniotic dinoprostone p. 706 is rarely used nowadays.

Pre-treatment with mifepristone p. 708 can facilitate the process of medical abortion. It sensitises the uterus to subsequent administration of a prostaglandin and, therefore, abortion occurs in a shorter time and with a lower dose of prostaglandin.

Induction and augmentation of labour
Dinoprostone p. 706 is available as vaginal tablets, pessaries and vaginal gels for the induction of labour. The intravenous solution is rarely used; it is associated with more side-effects.

Oxytocin p. 705 (Syntocinon®) is administered by slow intravenous infusion, using an infusion pump, to induce or augment labour, usually in conjunction with amniotomy.

Uterine activity must be monitored carefully and hyperstimulation avoided. Large doses of oxytocin may result in excessive fluid retention.

Misoprostol p. 709 is given orally or vaginally for the induction of labour [unlicensed indication].


Prevention and treatment of haemorrhage
Bleeding due to incomplete miscarriage or abortion can be controlled with ergometrine maleate and oxytocin (Syntometrine®) given intramuscularly, the dose is adjusted according to the patient’s condition and blood loss. This is commonly used before surgical evacuation of the uterus, particularly when surgery is delayed. Oxytocin and ergometrine maleate combined are more effective in early pregnancy than either drug alone.

Active management of the third stage of labour reduces the risk of postpartum haemorrhage; oxytocin is given by intramuscular injection [unlicensed] on delivery of the anterior shoulder or, at the latest, immediately after the baby is delivered. Alternatively, ergometrine maleate with oxytocin (Syntometrine®) can be given by intramuscular injection in the absence of hypertension; oxytocin alone causes less nausea, vomiting, and hypertension than when given with ergometrine maleate p. 707.

In excessive uterine bleeding, any placental products remaining in the uterus should be removed. Oxytocic drugs are used to treat postpartum haemorrhage caused by uterine atony; treatment options are as follows:

- oxytocin by slow intravenous injection, followed in severe cases by intravenous infusion of oxytocin at a rate that controls uterine atony or
- ergometrine by intramuscular injection or
contracts not established after a total of 5 units, stop induction attempt (may be repeated next day starting again at 0.001–0.004 units/minute)

Caesarean section
BY SLOW INTRAVENOUS INJECTION
- Adult: 5 units immediately after delivery

Prevention of postpartum haemorrhage after delivery of placenta
BY SLOW INTRAVENOUS INJECTION
- Adult: 5 units, if infusion previously used for induction or enhancement of labour, increase rate during third stage and for next few hours
BY INTRAMUSCULAR INJECTION
- Adult: 10 units, can be used instead of oxytocin with ergometrine (Symptometrine®)

Treatment of postpartum haemorrhage
BY SLOW INTRAVENOUS INJECTION
- Adult: 5 units, repeated if necessary

Treatment of severe cases of postpartum haemorrhage
(following intravenous injection)
BY INTRAVENOUS INFUSION
- Adult: 40 units in 500 mL infusion fluid given at a rate sufficient to control uterine atony

Incomplete, inevitable, or missed miscarriage
INITIALLY BY SLOW INTRAVENOUS INJECTION
- Adult: 5 units, followed by (by intravenous infusion) 0.02–0.04 units/minute if required, the rate of infusion can be faster if necessary

UNLICENSED USE Oxytocin doses in the BNF may differ from those in the product literature.

Important safety information
Prolonged intravenous administration at high doses with large volume of fluid (which is possible in inevitable or missed miscarriage or postpartum haemorrhage) may cause water intoxication with hyponatraemia. To avoid: use electrolyte-containing diluent (i.e. not glucose), increase oxytocin concentration to reduce fluid, restrict fluid intake by mouth; monitor fluid and electrolytes.

CONTRA-INDICATIONS Any condition where spontaneous labour inadvisable • any condition where vaginal delivery inadvisable • avoid intravenous injection during labour • avoid prolonged administration in oxytocin-resistant uterine inertia • avoid rapid intravenous injection (may transiently reduce blood pressure) • fetal distress (discontinue immediately if this occurs) • hypertonic uterine contractions (discontinue immediately if this occurs) • severe cardiovascular disease • severe pre-eclamptic toxaemia

CAUTIONS Avoid large infusion volumes and restrict fluid intake by mouth (risk of hyponatraemia and water-intoxication) • enhancement of labour—presence of borderline cephalopelvic disproportion (avoid if significant) • history of lower-uterine segment caesarean section • induction of labour—presence of borderline cephalopelvic disproportion (avoid if significant) • mild pregnancy-induced cardiac disease • mild pregnancy-induced hypertension • moderate pregnancy-induced cardiac disease • moderate pregnancy-induced hypertension • risk factors for disseminated intravascular coagulation • secondary uterine inertia • women over 35 years

INTERACTIONS → Appendix 1 (oxytocin).
Effects enhanced by concomitant prostaglandins (very careful monitoring of uterine activity). Caudal block anaesthesia (may enhance hypertensive effects of sympathomimetic vasopressors).
706 Obstetrics

SIDE-EFFECTS

- Common or very common: Arrhythmia · headache · nausea · vomiting
- Rare: Anaphylactoid reactions (with dyspnoea, hypotension, or shock) · disseminated intravascular coagulation · hyponatraemia associated with high doses with large infusion volumes of electrolyte-free fluid · rash · uterine hyperstimulation (usually with excessive doses—may cause fetal distress, asphyxia, and death, or may lead to hypertonicity, tetanic contractions, soft-tissue damage or uterine rupture) · uterine spasm (may occur at low doses) · water intoxication associated with high doses with large infusion volumes of electrolyte-free fluid

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

- Pabal (Ferring Pharmaceuticals Ltd)

Carbetocin 100 microgram per 1 ml

Pabal 100micrograms/1ml solution for injection ampoules | 5 ampoule £88.20 (Hospital only)

CARBOPROSTOP

INDICATIONS AND DOSE

Postpartum haemorrhage due to uterine atony in patients unresponsive to ergometrine and oxytocin

BY DEEP INTRAMUSCULAR INJECTION

- Adult: 250 micrograms at least every 15 minutes, repeated if necessary, total dose should not exceed 2 mg (8 doses)

CONTRA-INDICATIONS

- Cardiac disease · pulmonary disease
- Untreated pelvic infection

CAUTIONS

- Excessive dosage may cause uterine rupture · history of anaemia · history of asthma · history of diabetes · history of epilepsy · history of glaucoma · history of hypertension · history of hypotension · history of jaundice · history of raised intra-ocular pressure · uterine scars

INTERACTIONS

- Appendix 1 (prostaglandins)

SIDE-EFFECTS

- Bronchospasm · cardiovascular collapse · chills · diaphoresis · diarrhoea · dizziness · dyspnoea · erythema at injection site · flushing · headache · hyperthermia · nausea · pain at injection site · pulmonary oedema · raised blood pressure · vomiting

HEPATIC IMPAIRMENT

Manufacturer advises avoid.

RENAL IMPAIRMENT

Manufacturer advises avoid.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

- Hemabate (Pfizer Ltd)

Carboprost (as Carboprost trometamol) 250 microgram per 1 ml

Hemabate 250micrograms/1ml solution for injection ampoules | 5 ampoule £182.01 (Hospital only)

DINO PROSTOPNE

INDICATIONS AND DOSE

PROSTIN E2® VAGINAL GEL

Induction of labour

BY VAGINA

- Adult: 1 mg, inserted high into the posterior fornix (avoid administration into the cervical canal), followed by 1–2 mg after 6 hours if required; max. dose 3 mg

Induction of labour (unfavourable primigravida)

BY VAGINA

- Adult: 2 mg, inserted high into the posterior fornix (avoid administration into the cervical canal), followed by 1–2 mg if required; max. dose 4 mg

5.2 Postpartum haemorrhage

PROSTAGLANDINS AND OXYTOCICS

Carbetocin

INDICATIONS AND DOSE

Prevention of uterine atony after caesarean section

BY SLOW INTRAVENOUS INJECTION

- Adult: 100 micrograms for 1 dose, to be given over 1 minute, administer as soon as possible after delivery, preferably before removal of placenta

CONTRA-INDICATIONS

- Eclampsia · epilepsy · pre-eclampsia

CAUTIONS

- Asthma · cardiovascular disease (avoid if severe) · hyponatraemia · migraine
**PROSTIN E2® VAGINAL TABLETS**

Induction of labour

**BY VAGINA**

- Adult: 3 mg, inserted high into the posterior fornix, followed by 3 mg after 6–8 hours (max. per dose 6 mg), to be given if labour not established

**Dose equivalence and conversion**

Prostin E2 Vaginal tablets and Vaginal Gel are not bioequivalent.

**PROPESES®**

Cervical ripening and induction of labour at term

**BY VAGINA**

- Adult: 1 pessary, insert pessary (in retrieval device) high into posterior fornix and remove when cervical ripening adequate; if oxytocin necessary, remove 30 minutes before oxytocin infusion; remove if cervical ripening inadequate after 24 hours (dose not to be repeated).

**CONTRA-INDICATIONS**

- Active cardiac disease
- Active pulmonary disease
- Avoid extra-anniotic route in cervicitis or vaginitis
- Fetal distress
- Fetal malpresentation
- Grand multiparas
- History of caesarean section
- History of difficult or traumatic delivery
- Major cephalopelvic disproportion
- Myocardial infarction
- Neurological disease
- Severe bradycardia
- Severe cardiac disease
- Severe uterine contractions
- Stillbirth or neonatal death
- Uterine hypercontractility with or without fetal bradycardia
- Uterine hypertonus
- Uterine scarring
- Untreated pelvic infection

**CAUTIONS**

- Effect of oxytocin enhanced
- History of asthma
- History of epilepsy
- History of glaucoma and raised intraocular pressure
- Hypertension
- Risk factors for disseminated intravascular coagulation
- Uterine rupture
- Uterine scarring

**INTERACTIONS**

- Appendix 1 (prostaglandins).

**SIDE-EFFECTS**

- Abruptio placenta
- Amniotic fluid embolism
- Backache
- Bronchospasm
- Cardiac arrest
- Diarrhoea
- Disseminated intravascular coagulation
- Fetal distress
- Fever
- Low Apgar scores
- Maternal hypertension
- Nausea
- Pulmonary embolism
- Rapid cervical dilation
- Severe uterine contractions
- Stillbirth or neonatal death
- Uterine hypercontractility with or without fetal bradycardia
- Uterine hypertonus
- Uterine rupture
- Vaginal symptoms (warmth, irritation, pain)
- Vomiting

**HEPATIC IMPAIRMENT**

Manufacturers advise avoid.

**RENAL IMPAIRMENT**

Manufacturers advise avoid.

**MONITORING REQUIREMENTS**

- Monitor for disseminated intravascular coagulation after parturition.
- Monitor uterine activity and fetal status (particular care if history of uterine hypertony)
- Care needed in monitoring uterine activity when used in sequence following oxytocin.

**DIRECTIONS FOR ADMINISTRATION**

For intravenous infusion (Prostin E2®), give continuously or intermittently in Glucose 5% or Sodium Chloride 0.9%.

**PRESCRIBING AND DISPENSING INFORMATION**

Important: Do not confuse dose of Prostin E2® vaginal gel with that of Prostin E2® vaginal tablets—not bioequivalent.

**LESS SUITABLE FOR PRESCRIBING**

Intravenous solution rarely used and is considered less suitable for prescribing. Extra-anniotic solution less commonly used and is considered less suitable for prescribing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- **Prostin E2** (Pfizer Ltd)
  - Dinoprostone 1 mg per 1 ml Prostin E2 750 micrograms/0.75ml solution for infusion ampoules | 1 ampoule (POM) £8.52 (Hospital only)
  - Dinoprostone 10 mg per 1 ml Prostin E2 5mg/0.5ml solution for infusion ampoules | 1 ampoule (POM) £18.40 (Hospital only)

**Pessary**

- **Prostin E2** (Pfizer Ltd)
  - Dinoprostone 3 mg Prostin E2 3mg vaginal tablets | 8 pessary (POM) £106.23 (Hospital only)

**Vaginal gel**

- **Prostin E2** (Pfizer Ltd)
  - Dinoprostone 1 mg Prostin E2 1mg vaginal gel | 1mg/2.5ml (POM) £13.28 (Hospital only)
  - Dinoprostone 2 mg Prostin E2 2mg vaginal gel | 2mg/2.5ml (POM) £13.28 (Hospital only)

**Vaginal device**

- **Propess** (Ferring Pharmaceuticals Ltd)
  - Dinoprostone 10 mg Propess 10mg vaginal delivery system | 5 device (POM) £150.00

**Vaginal gel**

- **Prostin E2** (Pfizer Ltd)
  - Dinoprostone 1 mg Prostin E2 1mg vaginal gel | 1mg/2.5ml (POM) £13.28 (Hospital only)
  - Dinoprostone 2 mg Prostin E2 2mg vaginal gel | 2mg/2.5ml (POM) £13.28 (Hospital only)

**Liquid**

- **Prostin E2** (Pfizer Ltd)
  - Dinoprostone 10 mg Prostin E2 10mg per 1 ml Prostin E2 5mg/0.5ml extraamniotic solution ampoules | 1 ampoule (POM) £18.40 (Hospital only)

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**Ergometrine maleate**

**INDICATIONS AND DOSE**

Postpartum haemorrhage caused by uterine atony

**BY INTRAMUSCULAR INJECTION OR BY SLOW INTRAVENOUS INJECTION**

- Adult: 250–500 micrograms

**CONTRA-INDICATIONS**

- Eclampsia - first stage of labour - induction of labour - second stage of labour - sepsis - severe cardiac disease - severe hypertension - vascular disease

**CAUTIONS**

- Acute porphyrias
- Cardiac disease
- Hypertension
- Multiple pregnancy
- Risk of hypertension associated with intravenous administration

**INTERACTIONS**

- Appendix 1 (ergot alkaloids).

**SIDE-EFFECTS**

- Common or very common
  - Abdominal pain
  - Arrhythmias
  - Brachycardia
  - Chest pain
  - Dizziness
  - Dyspnoea
  - Headache
  - Hypertension
  - Nausea
  - Palpitations
  - Pulmonary oedema
  - Rash
  - Tinnitus
  - Vasoconstriction
  - Vomiting

**VERY RARE**

- Myocardial infarction

**HEPATIC IMPAIRMENT**

Manufacturer advises caution in mild or moderate impairment. Manufacturer advises avoid in severe impairment.

**RENAL IMPAIRMENT**

Manufacturer advises caution in mild or moderate impairment. Manufacturer advises avoid in severe impairment.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **ERGOMETRINE MALEATE** (Non-proprietary)
  - Ergometrine maleate 500 microgram per 1 ml Ergometrine 500 micrograms/2ml solution for injection ampoules | 10 ampoule (POM) £13.00
Ergometrine with oxytocin

The properties listed below are those particular to the combination only. For the properties of the components please consider, ergometrine maleate p. 707, oxytocin p. 705.

**INDICATIONS AND DOSE**
Active management of the third stage of labour
Postpartum haemorrhage caused by uterine atony

**BY INTRAMUSCULAR INJECTION**
- Adult: 1 ml for one dose.

**BLEEDING DUE TO INCOMPLETE MISCARRIAGE OR ABORTION**
**BY INTRAMUSCULAR INJECTION**
- Adult: Adjusted according to response to, the patient’s condition and blood loss.

**SIDE-EFFECTS**
Common or very common
- Dizziness · headache · hot flushes · hyperglycaemia · hypotension · injection-site reaction · nausea · tachycardia · vomiting

**CONTRA-INDICATIONS**
Abruptio placentae · antepartum haemorrhage (requiring immediate delivery) · eclampsia · intra-uterine fetal death · intra-uterine infection · intra-uterine growth restriction with abnormal fetal heart rate · placenta praevia · premature rupture of membranes after 30 weeks’ gestation · severe pre-eclampsia

**CAUTIONS**
Abnormal placental site · intra-uterine growth restriction

**HEPATIC IMPAIRMENT**
No information available.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- [ATOSIBAN](https://www.alliancepharma.co.uk/) (Non-proprietary)
  - Atosiban (as Atosiban acetate) 7.5 mg per 1 ml
    - Atosiban 6.75 mg/0.9 ml solution for injection vials | 1 vial (£52.82) (Hospital only)
  - Tractocile (Ferring Pharmaceuticals Ltd)
    - Atosiban (as Atosiban acetate) 7.5 mg per 1 ml
      - Tractocile 6.75 mg/0.9 ml solution for injection vials | 1 vial (£52.82) (Hospital only)

**Solution for infusion**
- [ATOSIBAN](https://www.alliancepharma.co.uk/) (Non-proprietary)
  - Atosiban (as Atosiban acetate) 7.5 mg per 1 ml
    - Atosiban 37.5 mg/ml for solution for infusion vials | 1 vial (£52.82) (Hospital only)
  - Tractocile (Ferring Pharmaceuticals Ltd)
    - Atosiban (as Atosiban acetate) 7.5 mg per 1 ml
      - Tractocile 37.5 mg/ml for solution for infusion vials | 1 vial (£52.82) (Hospital only)

5.3 Premature labour

**OXYTOCIN RECEPTOR ANTAGONISTS**

**Atosiban**

**INDICATIONS AND DOSE**
Uncomplicated premature labour between 24 and 33 weeks of gestation

**INITIALLY BY INTRAVENOUS INJECTION**
- Adult: Initially 6.75 mg over 1 minute, then (by intravenous infusion) 18 mg/hour for 3 hours, then (by intravenous infusion) reduced to 6 mg/hour for up to 45 hours. Maximum duration of treatment is 48 hours

**CONTRA-INDICATIONS**
Abruptio placentae · antepartum haemorrhage · eclampsia · intra-uterine fetal death · intra-uterine infection · intra-uterine growth restriction with abnormal fetal heart rate · placenta praevia · premature rupture of membranes after 30 weeks’ gestation · severe pre-eclampsia

**SIDE-EFFECTS**
Common or very common
- Dizziness · headache · hot flushes · hyperglycaemia · hypotension · injection-site reaction · nausea · tachycardia · vomiting

**UNCOMMON**
- Fever · insomnia · pruritus · rash

**HEPATIC IMPAIRMENT**
No information available.

**RENAL IMPAIRMENT**
No information available.

**MONITORING REQUIREMENTS**
Monitor blood loss after delivery.

**DIRECTIONS FOR ADMINISTRATION**
For intravenous infusion (Tractocile® concentrate for intravenous infusion), give continuously in Glucose 5% or Sodium chloride 0.9%. Withdraw 10 ml infusion fluid from 100-ml bag and replace with 10 ml atosiban concentrate (7.5 mg/ml) to produce a final concentration of 750 micrograms/ml.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

5.4 Termination of pregnancy

**PROGESTERONE RECEPTOR MODULATORS**

**Mifepristone**

**DRUG ACTION**
Mifepristone, an antiprogestogenic steroid, sensitises the myometrium to prostaglandin-induced contractions and ripens the cervix.

**INDICATIONS AND DOSE**
Cervical ripening before mechanical cervical dilatation for termination of pregnancy of up to 64 days gestation (under close medical supervision)

**BY MOUTH**
- Adult: 200 mg for 1 dose, to be taken 36–48 hours before procedure

Labour induction in fetal death in utero where prostaglandin or oxytocin inappropriate (under close medical supervision)

**BY MOUTH**
- Adult: 600 mg once daily for 2 days, if labour not started within 72 hours of first dose, another method should be used

Medical termination of intra-uterine pregnancy of up to 49 days gestation (under close medical supervision)

**BY MOUTH**
- Adult: 600 mg for 1 dose, dose followed 24–36 hours later (unless abortion already complete) by gemeprost 1 mg by vagina or misoprostol 400 micrograms by mouth, alternatively 200 mg for 1 dose, dose followed 36–48 hours later (unless abortion already complete) by gemeprost 1 mg by vagina; observe for at least 3 hours (or until bleeding or pain at acceptable level); follow-up visit within 2 weeks to verify complete expulsion and to assess vaginal bleeding

Medical termination of intra-uterine pregnancy of 50–63 days gestation (under close medical supervision)

**BY MOUTH**
- Adult: 600 mg for 1 dose, alternatively 200 mg for 1 dose, dose followed 36–48 hours later (unless abortion already complete) by gemeprost 1 mg by vagina; observe for at least 3 hours (or until bleeding or pain at acceptable level); follow-up visit within 2 weeks to verify complete expulsion and to assess vaginal bleeding
Gemeprost

**INDICATIONS AND DOSE**

Cervical ripening prior to first trimester surgical abortion
- **BY VAGINA**
  - Adult: 1 mg, dose to be inserted into posterior fornix 3 hours before surgery

Second trimester abortion
- **BY VAGINA**
  - Adult: 1 mg every 3 hours for maximum 5 administrations, to be inserted into posterior fornix

Second course may begin 24 hours after start of treatment (if treatment fails, pregnancy should be terminated by another method)

**Second trimester intra-uterine death**

- **BY VAGINA**
  - Adult: 1 mg every 3 hours for maximum 5 administrations only, to be inserted into posterior fornix

**Medical termination of intra-uterine pregnancy of up to 49 days gestation following mifepristone**

- **BY VAGINA**
  - Adult: 1 mg

**Termination of pregnancy of 13-24 weeks gestation (in combination with a prostaglandin) (under close medical supervision)**

**By Mouth**
- Adult: 600 mg for 1 dose, alternatively 200 mg for 1 dose, dose followed 36–48 hours later by gemeprost 1 mg by vagina every 3 hours up to max. 5 mg or misoprostol; if abortion does not occur, 24 hours after start of treatment repeat course of gemeprost 1 mg by vagina up to max. 5 mg; follow-up visit after appropriate interval to assess vaginal bleeding recommended

- **CONTRA-INDICATIONS**
  - Acute porphyrias p. 864 - chronic adrenal failure - suspected ectopic pregnancy (use other specific means of termination) - uncontrolled severe asthma

- **CAUTIONS**
  - Adrenal suppression (may require corticosteroid) - anticoagulant therapy - asthma (avoid if severe and uncontrolled) - existing cardiovascular disease - haemorrhagic disorders - history of endocarditis - prosthetic heart valve - risk factors for cardiovascular disease

- **INTERACTIONS** → Appendix 1 (mifepristone).

- **SIDE-EFFECTS**
  - **Common or very common** Gastro-intestinal cramps - uterine contractions - vaginal bleeding (sometimes severe) may occur between administration of mifepristone and surgery (and rarely abortion may occur before surgery)
  - **Uncommon** Hypersensitivity reactions - rash - urticaria
  - **Rare** Chills - dizziness - fever - headache - hot flushes - hypotension - malaise

- **Frequency not known** Infections - toxic shock syndrome

- **HEPATIC IMPAIRMENT** Manufacturer advises avoid.

- **RENAL IMPAIRMENT** Manufacturer advises avoid.

- **MONITORING REQUIREMENTS** Careful monitoring of blood pressure and pulse essential for 3 hours after administration of gemeprost pessary (risk of profound hypotension).

- **PRESCRIBING AND DISPENSING INFORMATION** Supplied to NHS hospitals and premises approved under Abortion Act 1967.

- **PATIENT AND CARER ADVICE** Patient information leaflet to be provided.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS 10**
  - **MIFEPRISTONE (Non-proprietary)**
    - Mifepristone 200 mg Mifepristone 200mg tablets | 1 tablet £25.50 no price available (Hospital only)
  - **Mifegyne (Nordic Pharma Ltd)**
    - Mifepristone 200 mg Mifegyne 200mg tablets | 3 tablet £52.66 (Hospital only)

**PROSTAGLANDINS AND OXYTOCICS**

**Gemeprost**

**INDICATIONS AND DOSE**

Cervical ripening prior to first trimester surgical abortion
- **BY VAGINA**
  - Adult: 1 mg, dose to be inserted into posterior fornix 3 hours before surgery

Second trimester abortion
- **BY VAGINA**
  - Adult: 1 mg every 3 hours for maximum 5 administrations, to be inserted into posterior fornix

- **CONTRA-INDICATIONS**
  - Placenta praevia - unexplained vaginal bleeding - uterine scarring

- **CAUTIONS**
  - Cardiovascular insufficiency - cervicitis - obstructive airways disease - raised intra-ocular pressure - vaginitis

- **INTERACTIONS** → Appendix 1 (prostaglandins).

- **SIDE-EFFECTS**
  - Backache - chest pain - chills - coronary artery spasm - diarrhoea - dizziness - dyspnoea - flushing - headache - mild pyrexia - muscle weakness - myocardial infarction - nausea - palpitation - severe hypotension - uterine pain - uterine rupture (most commonly in multiparas or if history of uterine surgery or if given with intravenous oxytocics) - vaginal bleeding - vomiting

- **RENAL IMPAIRMENT** Manufacturer advises avoid.

- **MONITORING REQUIREMENTS**
  - If used in combination with mifepristone, carefully monitor blood pressure and pulse for 3 hours.
  - When used for second trimester intra-uterine death, monitor for coagulopathy during treatment.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Pessary**
  - **GEMEPROST (Non-proprietary)**
    - Gemeprost 1mg Gemeprost 1mg pessaries | 5 pessary £25.50 no price available

**PROSTAGLANDINS**

**Misoprostol**

- **DRUG ACTION** Misoprostol is a synthetic prostaglandin analogue that has antisecretory and protective properties, promoting healing of gastric and duodenal ulcers. It also acts as a potent uterine stimulant.

**INDICATIONS AND DOSE**

Termination of pregnancy following mifepristone (gestation up to 49 days)
- **BY MOUTH**
  - Adult: 400 micrograms for 1 dose, dose to be given 24–48 hours after mifepristone
Termination of pregnancy following mifepristone (gestation 50 to 63 days)
INITIALLY BY VAGINA OR BY BUCCAL ADMINISTRATION OR BY SUBLINGUAL ADMINISTRATION
- Adult: 800 micrograms for 1 dose, dose to be given 24–48 hours after mifepristone, if abortion has not occurred 4 hours after first misoprostol dose a further dose may be given, (by mouth or by vagina)
- 400 micrograms for 1 dose

Termination of pregnancy following mifepristone (gestation of 9 to 13 weeks)
INITIALLY BY VAGINA
- Adult: 800 micrograms for 1 dose, dose to be given 36–48 hours after mifepristone, followed by (by vagina or by mouth) 400 micrograms every 3 hours if required for a maximum of 4 doses

Termination of pregnancy following mifepristone (gestation of 13 to 24 weeks)
INITIALLY BY VAGINA
- Adult: 800 micrograms for 1 dose, dose to be given 36–48 hours after mifepristone, followed by (by vagina or by mouth) 400 micrograms every 3 hours if required for a maximum of 4 doses, if abortion has not occurred 3 hours after the last dose of misoprostol, a further dose of mifepristone may be given, and misoprostol may be recommenced 12 hours later

Benign gastric ulceration | Benign duodenal ulceration | NSAID-associated ulceration
BY MOUTH
- Adult: 800 micrograms daily in 2–4 divided doses continued for at least 4 weeks or may be continued for up to 8 weeks if required, dose to be taken with breakfast (or main meals) and at bedtime

Prophylaxis of NSAID-induced gastric ulcer | Prophylaxis of duodenal ulcer
BY MOUTH
- Adult: 200 micrograms 4 times a day, reduced if not tolerated to 200 micrograms 2–3 times a day, use lower dose is less effective

- UNLICENSED USE Use of misoprostol for termination of pregnancy is an unlicensed use.
- CAUTIONS Conditions where hypotension might precipitate severe complications (e.g. cerebrovascular disease, cardiovascular disease) - inflammatory bowel disease
- SIDE-EFFECTS
  - Common or very common Diarrhoea
  - Postmenopausal bleeding - rashes - vomiting

SIDE-EFFECTS, FURTHER INFORMATION
Diarrhoea May occasionally be severe and require withdrawal, reduced by giving single doses not exceeding 200 micrograms and by avoiding magnesium-containing antacids.

- CONCEPTION AND CONTRACEPTION Manufacturer advises that misoprostol should not be used in women of childbearing age unless pregnancy has been excluded. In such patients it is advised that misoprostol should only be used if the patient takes effective contraceptive measures and has been advised of the risks of taking misoprostol if pregnant.
- PREGNANCY Avoid—potent uterine stimulant (has been used to induce abortion). Teratogenic risk in first trimester.
- BREAST FEEDING Present in milk, but amount probably too small to be harmful.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.
- Tablet
  CAUTIONARY AND ADVISORY LABELS 21
  - MISOPROSTOL (Non-proprietary)
    - Misoprostol 200 microgram Misoprostol 200microgram vaginal tablets | 4 tablet | no price available (Hospital only)
    - Cytotec (Pfizer Ltd)
      - Misoprostol 200 microgram Cytotec 200microgram tablets | 56 tablet | no price available | 60 tablet | £10.03 DT price = £10.03
      - Topogyn (Nordic Pharma Ltd)
        - Misoprostol 400 microgram Topogyn 400microgram tablets | 16 tablet | £128.00 (Hospital only)

Vaginal delivery system
- Mysodelle (Ferring Pharmaceuticals Ltd)
  - Misoprostol 7 microgram per 1 hour Mysodelle 200micrograms vaginal delivery system | 5 unit | £465.00

6 Vaginal and vulval conditions

Vaginal and vulval conditions
Symptoms are often restricted to the vulva, but infections almost invariably involve the vagina which should also be treated. Applications to the vulva alone are likely to give only symptomatic relief without cure.

Aqueous medicated douches may disturb normal vaginal acidity and bacterial flora.

Topical anaesthetic agents give only symptomatic relief and may cause sensitivity reactions. They are indicated only in cases of pruritus where specific local causes have been excluded.

Systemic drugs are required in the treatment of infections such as gonorrhoea and syphilis.

Preparations for vaginal and vulval changes
A cream containing an oestrogen may be applied on a short-term basis to improve the vaginal epithelium in menopausal atrophic vaginitis. It is important to bear in mind that topical oestrogens should be used in the smallest effective amount to minimise systemic effects. Modified-release vaginal tablets and an impregnated vaginal ring are now also available.

The risk of endometrial hyperplasia and carcinoma is increased when systemic oestrogens are administered alone for prolonged periods. The endometrial safety of long-term or repeated use of topical vaginal oestrogens is uncertain; treatment should be reviewed at least annually, with special consideration given to any symptoms of endometrial hyperplasia or carcinoma.

Topical oestrogens are also used in postmenopausal women before vaginal surgery for prolapse when there is epithelial atrophy.

Non-hormonal preparations for vaginal atrophy
Several non-hormonal vaginal moisturisers are available and some are prescribable on the NHS (consult Drug Tariff).

Vaginal and vulval infections
Effective specific treatments are available for the common vaginal infections.

Fungal infections
Candidal vulvitis can be treated locally with cream, but is almost invariably associated with vaginal infection which should also be treated. Vaginal candidiasis is treated primarily with antifungal pessaries or cream inserted high into the vagina (including during menstruation). Single-
Vaginal and vulval infections, bacterial **711**

6.1 **Vaginal and vulval infections, bacterial**

**CARBOXYLIC ACIDS**

### Lactic acid

**INDICATIONS AND DOSE**

**BALANCE ACTIV RX® GEL**

**Prevention of bacterial vaginosis**

BY VAGINA

- Adult: 5 mL 1–2 times a week, insert the content of 1 tube

**RELACTAGEL® GEL**

**Prevention of bacterial vaginosis**

BY VAGINA

- Adult: 5 mL daily for 2–3 nights after menstruation, insert the contents of one tube

- **SIDE-EFFECTS**

  RELACTAGEL® GEL

  Mild irritation

- **CONCEPTION AND CONTRACEPTION**

  RELACTAGEL® GEL

  Not recommended if trying to conceive.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  **Vaginal gel**

  EXCIPIENTS: May contain Propylene glycol

  - Balance Activ (BBI Healthcare Ltd)
    Balance Activ BV vaginal pH correction gel | 7 device £5.25
    Balance Activ pessaries | 7 pessary £5.25
  - Relactagel (KoRa Healthcare)
    Relactagel vaginal pH correction gel | 7 device £5.25

#### Clindamycin

**INDICATIONS AND DOSE**

**DALACIN® 2% CREAM**

**Bacterial vaginosis**

BY VAGINA

- Adult: 1 applicatorful daily for 3–7 nights, dose to be administered at night

**Dose equivalence and conversion**

1 applicatorful delivers a 5 g dose of clindamycin 2%.

- **SIDE-EFFECTS**

  Cervicitis - irritation - vaginitis

  SIDE-EFFECTS, FURTHER INFORMATION

  Systemic side-effects Clindamycin 2% cream is poorly absorbed into the blood—low risk of systemic effects.

- **CONCEPTION AND CONTRACEPTION**

  DALACIN® 2% CREAM

  Damages latex condoms and diaphragms.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  **Cream**

  EXCIPIENTS: May contain Benzyl alcohol, cetosteareth alcohol (including cetyl and stearyl alcohol), polyborates, propylene glycol

  - Dalacin (Pfizer Ltd)
    Clindamycin (as Clindamycin phosphate) 20 mg per 1 gram Dalacin 2% cream | 40 gram | £10.86
    Dalacin 2% cream | 40 gram | £10.86
Metronidazole

- **DRUG ACTION** Metronidazole is an antimicrobial drug with high activity against anaerobic bacteria and protozoa.

### INDICATIONS AND DOSE

**Bacterial vaginosis**

- **BY VAGINA USING VAGINAL GEL**
  - Adult: 1 applicatorful daily for 5 days, dose to be administered at night

- **CAUTIONS** Not recommended during menstruation - some systemic absorption may occur with vaginal gel

- **SIDE-EFFECTS** Abnormal vaginal discharge - local irritation - pelvic discomfort - vaginal candidiasis

### MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug.

#### Vaginal gel

- **EXCEPTIONS TO LEGAL CATEGORY** Brands for sale to the public include Canesten® Internal Cream.

#### Medicinal forms

- **CLOTRIMAZOLE (Non-proprietary)**
  - Clotrimazole 500 mg. Clotrimazole 500mg pessaries | 1 pessary [P] £4.00 DT price = £3.47
  - Canesten (clotrimazole) (Bayer Plc) Clotrimazole 100 mg. Canesten 100mg pessaries | 6 pessary [P] £3.50 DT price = £3.50
  - Clotrimazole 200 mg. Canesten 200mg pessaries | 3 pessary [P] £3.10 DT price = £3.10
  - Clotrimazole 500 mg. Canesten 500mg Soft Gel pessaries | 1 pessary [P] £6.41 DT price = £3.47

- **EXCIPIENTS:** May contain Benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol), polysorbates.

### INDICATIONS AND DOSE

- **Superficial sites of infection in vaginal and vulval candidiasis (dose for 1% or 2% cream)**
  - **BY VAGINA USING CREAM**
    - Adult: Apply 2–3 times a day, to be applied to anogenital area

- **Vaginal candidiasis (dose for 10% intravaginal cream)**
  - **BY VAGINA USING CREAM**
    - Adult: 5 g for 1 dose, one applicatorful to be inserted into the vagina at night, dose can be repeated once if necessary

- **Vaginal candidiasis**
  - **BY VAGINA USING PESSARIES**
    - Adult: 200 mg for 3 nights, course can be repeated once if necessary, alternatively 100 mg for 6 nights, course can be repeated once if necessary, alternatively 500 mg for 1 night, dose can be repeated once if necessary

- **Recurrent vulvovaginal candidiasis**
  - **BY VAGINA USING PESSARIES**
    - Adult: 500 mg every 1 week for 6 months, dose to be administered following topical imidazole for 10–14 days

### UNLICENSED USE

- Consult product literature for individual preparations.

### SIDE-EFFECTS

- Local irritation

### CONCEPTION AND CONTRACEPTION

- Cream and pessaries may damage latex condoms and diaphragms.

### PREGNANCY

- Pregnant women need a longer duration of treatment, usually about 7 days, to clear the infection. Oral antifungal treatment should be avoided during pregnancy.

### ECONAZOLE NITRATE (Non-proprietary)

#### INDICATIONS AND DOSE

- **GYNO-PEVARYL® CREAM**
  - **BY VAGINA**
    - Adult: 1 pessary for 1 dose, pessary to be inserted at night, dose to be repeated once if necessary

- **GYNO-PEVARYL® ONCE**
  - **BY VAGINA**
    - Adult: 1 pessary daily for 3 days, pessary to be inserted at night, course can be repeated once if necessary

- **GYNO-PEVARYL® PESSARY**
  - **BY VAGINA**
    - Adult: 1 pessary for 1 dose, pessary to be inserted at night, dose to be repeated once if necessary

### SIDE-EFFECTS

- Occasional local irritation

### CONCEPTION AND CONTRACEPTION

- Cream and pessaries damage latex condoms and diaphragms.

### PREGNANCY

- Pregnant women need a longer duration of treatment, usually about 7 days, to clear the infection.

### MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug.

#### Pessary

- **GYNO-PEVARYL® ONCE**
  - Econazole nitrate 150 mg. Gyno-Pevaryl Once 150mg vaginal pessary | 1 pessary [P] £3.69
  - Econazole Nitrate 150mg vaginal pessaries | 3 pessary [P] £4.17
### Fenticonazole nitrate

**INDICATIONS AND DOSE**

**Vaginal and vulva candidiasis**
- **Adult:** 200 mg daily for 3 days, alternatively 600 mg daily for 1 dose, to be inserted at night
- **By Vagina Using Cream**
- **Adult:** 5 g twice daily for 3 days

**SIDE-EFFECTS**
- Local irritation

**CONCEPTION AND CONTRACEPTION**
- Intravaginal cream and vaginal capsules damage latex condoms and diaphragms.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Capsule**
- **Excipients:** May contain Hydroxybenzoates (parabens)
- **Fenticonazole nitrate 200 mg** Gynoxin 200mg vaginal capsules | 3 capsule [PAX] £2.42
- **Fenticonazole nitrate 600 mg** Gynoxin 600mg vaginal capsules | 1 capsule [PAX] £2.62

**Cream**
- **Excipients:** May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), propylene glycol, wool fat and related substances including lanolin
- **Gynoxin** Capsule
- **Fenticonazole nitrate 20 mg per 1 gram** Gynoxin 2% vaginal cream | 30 gram [PAX] £3.74

### Ketoconazole

**INDICATIONS AND DOSE**

**Vaginal and vulva candidiasis**
- **By Vagina Using Cream**
- **Adult:** Apply 1–2 times a day, to be applied to the anogenital area

**INTERACTIONS**
- Appendix 1 (antifungals, imidazole).

**SIDE-EFFECTS**
- Occasional local irritation

**CONCEPTION AND CONTRACEPTION**
- Effect on latex condoms and diaphragms not yet known.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Capsule**
- **Excipients:** May contain Hydroxybenzoates (parabens)
- **Gyno-Daktarin (Janssen-Cilag Ltd)**
- **Miconazole nitrate 1.2 gram** Gyno-Daktarin 1200mg vaginal capsules | 1 capsule [PAX] £2.94 DT price = £2.94

**Cream**
- **Excipients:** May contain Butylated hydroxyanisole, fragrances
- **Gyno-Daktarin (Janssen-Cilag Ltd)**
- **Miconazole nitrate 20 mg per 1 gram** Gyno-Daktarin 2% vaginal cream | 78 gram [PAX] £4.33

### Miconazole

**INDICATIONS AND DOSE**

**Vaginal and vulva candidiasis**
- **Child:** 1 capsule daily, ovule to be inserted at night as a single dose, dose can be repeated once if necessary

**BY VAGINA USING CREAM**
- **Adult:** 1 capsule daily, ovule to be inserted at night as a single dose, dose can be repeated once if necessary

**INTERACTIONS**
- Appendix 1 (antifungals, imidazole).

**SIDE-EFFECTS**
- Occasional local irritation

**CONCEPTION AND CONTRACEPTION**
- Cream and pessaries damage latex condoms and diaphragms.

**PREGNANCY**
- Pregnant women need a longer duration of treatment, usually about 7 days, to clear the infection.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Capsule**
- **Excipients:** May contain Hydroxybenzoates (parabens)
- **Gyno-Pevaryl (Janssen-Cilag Ltd)**
- **Econazole nitrate 10 mg per 1 gram** Gyno-Pevaryl 1% cream | 15 gram [PAX] £2.11 | 30 gram [PAX] £3.78

**6.3 Vaginal atrophy**

**OESTROGENS**

**Estriol**

**INDICATIONS AND DOSE**

**GYNEST™**
- Improve the vaginal epithelium in menopausal atrophic vaginitis (short-term use)
- **By Vagina**
- **Adult:** Apply 1 applicatorful daily until improvement occurs, dose to be applied preferably in the evening, reduced to 1 applicatorful twice weekly, attempts to discontinue should be made at 3–6 month intervals with re-examination

**OVESTIN™**
- Improve the vaginal epithelium in menopausal atrophic vaginitis (short-term use)
- **By Vagina**
- **Adult:** Apply 1 applicatorful daily for 2–3 weeks, then reduced to 1 applicatorful twice weekly, discontinue every 2–3 months for 4 weeks to assess need for further treatment

**Vaginal surgery for prolapse when there is epithelial atrophy in postmenopausal women (before surgery)**
- **By Vagina**
- **Adult:** Apply 1 applicatorful daily for 2 weeks before surgery, resume 2 weeks after surgery

**CONTRA-INDICATIONS**
- Active arterial thromboembolic disease (e.g. angina or myocardial infarction) - active thrombophlebitis - Dublin-Johnson syndrome (or monitor closely) - history of breast cancer - history of recurrent venous thromboembolism (unless already on anticoagulant treatment) - oestrogen-dependent cancer - recent arterial thromboembolic disease (e.g. angina or...
myocardial infarction) - Rotor syndrome (or monitor closely) - thrombophilic disorder - undiagnosed vaginal bleeding - untreated endometrial hyperplasia - venous thromboembolism

**CAUTIONS**
- Acute porphyrias p. 864 - diabetes (increased risk of heart disease) - factors predisposing to thromboembolism - history of breast nodules - closely monitor breast status (risk of breast cancer) - history of endometrial hyperplasia - history of fibrocystic disease - closely monitor breast status (risk of breast cancer) - hypophysal tumours - increased risk of gall-bladder disease - migraine (or migraine-like headaches) - presence of antiphospholipid antibodies (increased risk of thrombotic events) - prolonged exposure to unopposed oestrogens may increase risk of developing endometrial cancer - risk factors for oestrogen-dependent tumours (e.g. breast cancer in first-degree relative) - symptoms of endometriosis may be exacerbated - uterine fibroids may increase in size - interrupt treatment periodically to assess need for continued treatment

**CAUTIONS, FURTHER INFORMATION**

**Risk of breast cancer**
- It is estimated that using all types of HRT increases the risk of breast cancer within 1–2 years of initiating treatment. The increased risk is related to the duration of HRT use (but not to the age at which HRT is started) and this excess risk disappears within 5 years of stopping. Radiological detection of breast cancer can be made more difficult as mammographic density can increase with HRT use.

**Risk of endometrial cancer**
- The increased risk of endometrial cancer depends on the dose and duration of oestrogen-only HRT. In women with a uterus, the addition of a progestogen cyclically (for at least 10 days per 28-day cycle) reduces the additional risk of endometrial cancer; this additional risk is eliminated if a progestogen is given continuously. However, this should be weighed against the increased risk of breast cancer.

**Risk of ovarian cancer**
- Long-term use of combined HRT or oestrogen-only HRT is associated with a small increased risk of ovarian cancer. This excess risk disappears within a few years of stopping.

**Risk of venous thromboembolism**
- Women using combined or oestrogen-only HRT are at an increased risk of deep vein thrombosis and of pulmonary embolism especially in the first year of use. In women who have predisposing factors (such as a personal or family history of deep vein thrombosis or pulmonary embolism, severe varicose veins, obesity, trauma, or prolonged bed-rest) it is prudent to review the need for HRT, as in some cases the risks of HRT may exceed the benefits. Travel involving prolonged immobility further increases the risk of deep vein thrombosis.

**Risk of stroke**
- Risk of stroke increases with age, therefore older women have a greater absolute risk of stroke. Combined HRT or oestrogen-only HRT slightly increases the risk of stroke.

**Risk of coronary heart disease**
- HRT does not prevent coronary heart disease and should not be prescribed for this purpose. There is an increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause. Although very little information is available on the risk of coronary heart disease in younger women who start HRT close to the menopause, studies suggest a lower relative risk compared with older women.

**Other conditions**
- The product literature advises caution in other conditions including hypertension, renal disease, asthma, epilepsy, sickle-cell disease, melanoma, otosclerosis, multiple sclerosis, and systemic lupus erythematosus (but care required if antiphospholipid antibodies present). Evidence for caution in these conditions is unsatisfactory and many women with these conditions may stand to benefit from HRT.

**INTERACTIONS**
- Appendix 1 (oestrogens).

**SIDE-EFFECTS**
- Abdominal bloating - abdominal cramps - altered blood lipids (may lead to pancreatitis, rashes and chloasma) - breast enlargement - breast tenderness - changes in libido - cholestatic jaundice - contact lenses may irritate - depression - dizziness - fluid retention - glucose intolerance - headache - leg cramps - migraine - mood changes - nausea - premenstrual-like syndrome - sodium retention - vaginal candidiasis - vomiting - weight changes - local irritation

**SIDE-EFFECTS, FURTHER INFORMATION**

**Leg Cramps**
- Venous thrombosis should be ruled out.

**Withdrawal Bleeding**
- Cyclical HRT (where a progestogen is taken for 12–14 days of each 28-day oestrogen treatment cycle) usually results in regular withdrawal bleeding towards the end of the progestogen. The aim of continuous combined HRT (where a combination of oestrogen and progestogen is taken, usually in a single tablet, throughout each 28-day treatment cycle) is to avoid bleeding, but irregular bleeding may occur during the early treatment stages (if it continues endometrial abnormality should be excluded and consideration given to cyclical HRT instead).

**CONCEPTION AND CONTRACEPTION**
- Intravaginal cream may damage latex condoms and diaphragms.

**Gynest®**
- May damage latex condoms and diaphragms.

**Ovestin®**
- Effect on latex condoms and diaphragms not yet known.

**PREGNANCY**
- Not known to be harmful.

**RÆST FEEDING**
- Avoid; adverse effects on lactation.

**HEPATIC IMPAIRMENT**
- Avoid in active liver disease including disorders of hepatic excretion (e.g. Dubin-Johnson or Rotor syndromes), infective hepatitis (until liver function returns to normal), and liver tumours.

**RENAL IMPAIRMENT**
- Manufacturer advises caution in renal disease. Evidence for caution is unsatisfactory and many women with these conditions may stand to benefit from HRT.

**MONITORING REQUIREMENTS**
- Closely monitor breast status if history of breast nodules or fibrocystic disease (risk of breast cancer).
- The endometrial safety of long-term or repeated use of topical vaginal oestrogens is uncertain; treatment should be reviewed at least annually, with special consideration given to any symptoms of endometrial hyperplasia or carcinoma.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Cream**

**EXCIPIENTS:** May contain Arachis (peanut) oil, cetostearyl alcohol (including cetyl and stearyl alcohol), polysorbates

- ESTRIOL (Non-proprietary)
- Estriol 100 micrograms per 1 gram
- Estriol 0.01% cream | 80 gram (£4.45)
- Ovestin (Aspen Pharma Trading Ltd)
- Estriol 1 mg per 1 gram
- Ovestin 1mg cream | 15 gram (£4.45)
- DT price = £4.45
- Gynest (Marlborough Pharmaceuticals Ltd)
- Estriol 100 micrograms per 1 gram
- Gynest 0.01% cream | 80 gram (£4.51

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**714 Vaginal and vulval conditions BNF 70**
Chapter 8
Malignant disease

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1 Immune system

1.1 Immune system disorders and transplantation

Immune response
Azathioprine p. 716, ciclosporin p. 717, mercaptopurine p. 762, and methotrexate p. 762 have a role in the treatment of inflammatory bowel disease.

Corticosteroids and other immunosuppressants

Antiproliferative immunosuppressants
Azathioprine is widely used for transplant recipients and it is also used to treat a number of auto-immune conditions, usually when corticosteroid therapy alone provides inadequate control. It is metabolised to mercaptopurine, and doses should be reduced when allopurinol p. 909 is given concurrently.

Mycophenolate mofetil p. 725 is metabolised to mycophenolic acid which has a more selective mode of action than azathioprine.

There is evidence that compared with similar regimens incorporating azathioprine, mycophenolate mofetil reduces the risk of acute rejection episodes; the risk of opportunistic infections (particularly due to tissue-invasive cytomegalovirus) and the occurrence of blood disorders such as leucopenia may be higher.

Cyclophosphamide p. 750 is less commonly prescribed as an immunosuppressant.

Corticosteroids and other immunosuppressants
Prednisolone p. 585 is widely used in oncology. It has a marked antitumour effect in acute lymphoblastic leukaemia, Hodgkin’s disease, and the non-Hodgkin lymphomas. It has a role in the palliation of symptomatic end-stage malignant disease when it may enhance appetite and produce a sense of well-being.

The corticosteroids are also powerful immunosuppressants. They are used to prevent organ transplant rejection, and in high dose to treat rejection episodes.

Ciclosporin p. 717 a calcineurin inhibitor, is a potent immunosuppressant which is virtually non-myelotoxic but markedly nephrotoxic. It has an important role in organ and tissue transplantation, for prevention of graft rejection following bone marrow, kidney, liver, pancreas, heart, lung, and heart-lung transplantation, and for prophylaxis and treatment of graft-versus-host disease.

Tacrolimus p. 720 is also a calcineurin inhibitor. Although not chemically related to ciclosporin it has a similar mode of action and side-effects, but the incidence of neurotoxicity appears to be greater; cardiomyopathy has also been reported. Disturbance of glucose metabolism also appears to be significant.

Sirolimus p. 719 is a non-calcineurin inhibiting immunosuppressant licensed for renal transplantation. Basiliximab p. 724 is used for prophylaxis of acute rejection in allogeneic renal transplantation. It is given with ciclosporin and corticosteroid immunosuppression regimens; its use should be confined to specialist centres.

Belatacept p. 726 is a fusion protein and co-stimulation blocker that prevents T-cell activation; it is licensed for prophylaxis of graft rejection in adults undergoing renal transplantation who are seropositive for the Epstein-Barr virus. It is used with interleukin-2 receptor antagonist...
Malignant disease

induction, in combination with corticosteroids and a mycophenolic acid.

Antithymocyte immunoglobulin (rabbit) p. 723 is licensed for the prophylaxis of organ rejection in renal and heart allograft recipients and for the treatment of corticosteroid-resistant allograft rejection in renal transplantation. Tolerability is increased by pretreatment with an intravenous corticosteroid and antihistamine; an antipyretic drug such as paracetamol may also be beneficial.

NICE technology appraisals (TAs)
For induction therapy in the prophylaxis of organ rejection, either basiliximab or daclizumab [discontinued] are options for combining with a calcineurin inhibitor. For each individual, ciclosporin or tacrolimus is chosen as the calcineurin inhibitor on the basis of side-effects. Mycophenolate mofetil is recommended as part of an immunosuppressive regimen if intolerance necessitates the withdrawal of a calcineurin inhibitor. These recommendations may not be consistent with the marketing authorisation of some of the products. www.nice.org.uk/TA85

NICE has recommended that for induction therapy in the prophylaxis of organ rejection, either basiliximab or daclizumab [discontinued] are options for combining with a calcineurin inhibitor. For each individual, ciclosporin or tacrolimus is chosen as the calcineurin inhibitor on the basis of side-effects. Mycophenolate mofetil is recommended as part of an immunosuppressive regimen only if:

- the calcineurin inhibitor is not tolerated, particularly if nephrotoxicity endangers the transplanted kidney; or
- there is very high risk of nephrotoxicity from the calcineurin inhibitor, requiring a reduction in the dose of the calcineurin inhibitor or its avoidance.

Sirolimus is recommended as a component of an immunosuppressive regimen only if intolerance necessitates the withdrawal of a calcineurin inhibitor. These recommendations may not be consistent with the marketing authorisation of some of the products. www.nice.org.uk/TA99

ANTIMETABOLITES
Azathioprine

- **DRUG ACTION** Azathioprine is metabolised to mercaptopurine.

INDICATIONS AND DOSE
Severe acute Crohn’s disease | Maintenance of remission of Crohn’s disease | Maintenance of remission of acute ulcerative colitis

**BY MOUTH**
- **Adult:** 2–2.5 mg/kg daily, some patients may respond to lower doses

Rheumatoid arthritis that has not responded to other disease-modifying drugs | Severe systemic lupus erythematosus and other connective tissue disorders | Polymyositis in cases of corticosteroid resistance

**BY MOUTH**
- **Adult:** Initially up to 2.5 mg/kg daily in divided doses, adjusted according to response, rarely more than 3 mg/kg daily; maintenance 1–3 mg/kg daily, consider withdrawal if no improvement within 3 months

Autoimmune conditions

**BY MOUTH OR BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION**
- **Adult:** 1–3 mg/kg daily, adjusted according to response, consider withdrawal if no improvement within 3 months, oral administration preferable, if not possible then can be given by intravenous injection (intravenous solution very irritant) or by intravenous infusion

Suppression of transplant rejection

**BY MOUTH OR BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION**
- **Adult:** 1–2.5 mg/kg daily, adjusted according to response, oral administration preferable, if not possible then can be given by intravenous injection (intravenous solution very irritant) or by intravenous infusion

Severe refractory eczema, normal or high TPMT activity

**BY MOUTH**
- **Adult:** 1–3 mg/kg daily

Severe refractory eczema, intermediate TPMT activity

**BY MOUTH**
- **Adult:** 0.5–1.5 mg/kg daily

Generalised myasthenia gravis

**INITIALLY BY MOUTH OR BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION**
- **Adult:** Initially 0.5–1 mg/kg daily, then increased to 2–2.5 mg/kg daily, dose is increased over 3–4 weeks, azathioprine is usually started at the same time as the corticosteroid and allows a lower maintenance dose of the corticosteroid to be used, oral administration preferable, if not possible then can be given by intravenous injection (intravenous solution very irritant) or by intravenous infusion

- **UNLICENSED USE** Azathioprine doses given in BNF for suppression of transplant rejection and autoimmune conditions may differ from those in product literature. Use for severe refractory eczema is unlicensed.

- **CONTRA-INDICATIONS**
  - When used for severe refractory eczema absent thiopurine methyltransferase (TPMT) activity | very low thiopurine methyltransferase (TPMT) activity

- **CAUTIONS**
  - Reduce dose in elderly | reduced thiopurine methyltransferase activity

- **INTERACTIONS** → Appendix 1 (azathioprine).
Infections in patients also receiving corticosteroids - interstitial nephritis - liver impairment - malaise - myalgia - nausea - neutropenia - rash - rigors - thrombocytopenia - vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

**Red cell aplasia** Cases of pure red cell aplasia have been reported with azathioprine; dose reduction or discontinuation should be considered under specialist supervision.

**Neutropenia and thrombocytopenia** Usually resolved by reducing the dose.

**Nausea, vomiting and diarrhoea** Nausea, vomiting and diarrhoea may occur, usually starting early during the course of treatment, and in rheumatoid arthritis it may be appropriate to withdraw the drug.

**Hypersensitivity reactions** Hypersensitivity reactions (including malaise, dizziness, vomiting, diarrhoea, fever, rigors, myalgia, arthralgia, rash, hypotension and interstitial nephritis) call for immediate withdrawal.

**ALLERGY AND CROSS-SENSITIVITY** Contra-indicated in hypersensitivity to mercaptopurine.

**PREGNANCY** Transplant patients immunosuppressed with azathioprine should not discontinue it on becoming pregnant. However, there have been reports of premature birth and low birth-weight following exposure to azathioprine, particularly in combination with corticosteroids. Spontaneous abortion has been reported following maternal or paternal exposure. Azathioprine is teratogenic in *animal* studies. The use of azathioprine during pregnancy needs to be supervised in specialist units. Treatment should not generally be initiated during pregnancy.

**BREAST FEEDING** Present in milk in low concentration. No evidence of harm in small studies—use if potential benefit outweighs risk.

**HEPATIC IMPAIRMENT** Reduce dose. Monitor liver function.

**RENAL IMPAIRMENT** Reduce dose.

**PRE-TREATMENT SCREENING**
Thiopurine methyltransferase The enzyme thiopurine methyltransferase (TPMT) metabolises thiopurine drugs (azathioprine, mercaptopurine, tioguanine); the risk of myelosuppression is increased in patients with reduced activity of the enzyme, particularly for the few individuals in whom TPMT activity is undetectable. Consider measuring TPMT activity before starting azathioprine, mercaptopurine, or tioguanine therapy. Patients with absent TPMT activity should not receive thiopurine drugs; those with reduced TPMT activity may be treated under specialist supervision.

**MONITORING REQUIREMENTS**
- Monitor for toxicity throughout treatment.
- Monitor full blood count weekly (more frequently with higher doses or if severe hepatic or renal impairment) for first 4 weeks (manufacturer advises weekly monitoring for 8 weeks but evidence of practical value unsatisfactory), thereafter reduce frequency of monitoring to at least every 3 months.
- Blood tests and monitoring for signs of myelosuppression are essential in long-term treatment.

**DIRECTIONS FOR ADMINISTRATION** For *intravenous injection*, give over at least 1 minute (followed by 50 mL sodium chloride intravenous infusion). For *intravenous infusion (Imuran*)*, give intermittently in Glucose 5% or Sodium Chloride 0.9%. Reconstitute 50 mg with 5–15 mL Water for Injections; dilute requisite dose to a volume of 20–200 mL with infusion fluid. Intravenous injection is alkaline and very irritant; intravenous route should therefore be used only if oral route not feasible.

**PATIENT AND CARER ADVICE**
Bone marrow suppression Patients and their carers should be warned to report immediately any signs or symptoms of bone marrow suppression e.g. inexplicable bruising or bleeding, infection.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution, capsule injection 20–80 mg/mL, give over at least 1 minute (followed by 50 mL sodium chloride intravenous infusion). For *intravenous infusion (Imuran*)*, give intermittently in Glucose 5% or Sodium Chloride 0.9%. Reconstitute 50 mg with 5–15 mL Water for Injections; dilute requisite dose to a volume of 20–200 mL with infusion fluid. Intravenous injection is alkaline and very irritant; intravenous route should therefore be used only if oral route not feasible.

**IMMUNE SYSTEM DISORDERS AND TRANSPLANTATION**

**CALCINEURIN INHIBITORS AND RELATED DRUGS**

**Ciclosporin** (Cyclosporin)

**DRUG ACTION** Ciclosporin is a calcineurin inhibitor.

**INDICATIONS AND DOSE**

**Severe acute ulcerative colitis refractory to corticosteroid treatment**
- **BY CONTINUOUS INTRAVENOUS INFUSION**
  - Adult: 2 mg/kg, to be given over 24 hours, dose adjusted according to blood-ciclosporin concentration and response

**Severe active rheumatoid arthritis when conventional second-line therapy ineffective or inappropriate**
- **ADMINISTERED ON EXPERT ADVICE**

**Short-term treatment of severe atopic dermatitis**
- **ADMINISTERED ON EXPERT ADVICE**

**Short-term treatment of very severe atopic dermatitis**
- **ADMINISTERED ON EXPERT ADVICE**

**Severe psoriasis**
- **ADMINISTERED ON EXPERT ADVICE**

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**Tablet**

**CAUTIONARY AND ADVISORY LABELS**

- **AZATHIOPRINE (Non-proprietary)**
  - Azathioprine 25 mg | 28 tablet | £23.00
  - Azathioprine 50 mg | 56 tablet | £41.00
  - Imuran (Aspen Pharma Trading Ltd)
  - Azathioprine 25 mg | 28 tablet | £10.99
  - Azathioprine 50 mg | 56 tablet | £17.99

- **Brands may include Azapress**

**Powder for solution for injection**
- **Imuran (Aspen Pharma Trading Ltd)**
  - Azathioprine 50 mg | Imuran 50mg powder for solution for injection vials | 1 vial | £15.38
1 month, initial dose of 2.5 mg/kg twice daily justified if condition requires rapid improvement; discontinue if inadequate response after 3 months at the optimum dose; max. duration of treatment usually 1 year unless other treatments cannot be used

Organ transplantation (used alone) BY MOUTH
  ▶ Adult: 10–15 mg/kg, to be administered 4–12 hours before transplantation, followed by 10–15 mg/kg daily for 1–2 weeks postoperatively, then maintenance 2–6 mg/kg daily, reduce dose gradually to maintenance. Dose should be adjusted according to blood-ciclosporin concentration and renal function; dose is lower if given concomitantly with other immunosuppressant therapy (e.g. corticosteroids); if necessary one-third corresponding oral dose can be given by intravenous infusion over 2–6 hours

Bone-marrow transplantation | Prevention and treatment of graft-versus-host disease
INITIALLY BY INTRAVENOUS INFUSION
  ▶ Adult: 1–5 mg/kg daily, to be administered over 2–6 hours from day before transplantation to 2 weeks postoperatively, alternatively (by mouth) 12.5–15 mg/kg daily, then (by mouth) 12.5 mg/kg daily for 3–6 months and then tailed off (may take up to a year after transplantation)

Nephrotic syndrome BY MOUTH
  ▶ Adult: 5 mg/kg daily in 2 divided doses, for maintenance reduce to lowest effective dose according to proteinuria and serum creatinine measurements; discontinue after 3 months if no improvement in glomerulonephritis or glomerulosclerosis (after 6 months in membranous glomerulonephritis)

● UNLICENSED USE Not licensed for use in severe acute ulcerative colitis refractory to corticosteroid treatment

Important safety information
Patients should be stabilised on a particular brand of oral ciclosporin because switching between formulations without close monitoring may lead to clinically important changes in blood-ciclosporin concentration.

● CONTRA-INDICATIONS Abnormal renal function (in non-transplant indications) · malignancy (in non-transplant indications) · uncontrolled hypertension (in non-transplant indications) · uncontrolled infections (in non-transplant indications) · use with tacrolimus specifically contraindicated

● CAUTIONS Hyperuricaemia · in atopic dermatitis Staphylococcus aureus skin infections—not absolute contra-indication providing controlled (but avoid erythromycin unless no other alternative) · in atopic dermatitis allow herpes simplex infections to clear before starting (if they occur during treatment withdraw if severe) · in atopic dermatitis and psoriasis discontinue if lymphoproliferative disorder develops · in psoriasis treat patients with malignant or pre-malignant conditions of skin only after appropriate treatment (and if no other option)

● INTERACTIONS → Appendix 1 (ciclosporin).
  For patients other than transplant recipients, preferably avoid other immunosuppressants (increased risk of infection and malignancies, including lymphoma and skin cancer).

● SIDE-EFFECTS GENERAL SIDE-EFFECTS
  ▶ Common or very common Abdominal pain · anorexia · diarrhoea · fatigue · gingival hyperplasia · headache · hepatic dysfunction · hypercholesterolaemia · hyperkalaemia · hyperlipidaemia · hypertension · hypertrichosis · hyperuricaemia · hypomagnesaemia · muscle cramps · myalgia · nausea · paraesthesia · renal dysfunction (renal structural changes on long-term administration) · tremor · vomiting

  ▶ Uncommon Anaemia · oedema · signs of encephalopathy · thrombocytopenia · weight gain

  ▶ Rare Gynaecomastia · haemolytic uraemic syndrome · hyperglycaemia · menstrual disturbances · microangiopathic haemolytic anaemia · motor polyneuropathy · muscle weakness · myopathy · pancreatitis · visual disturbances secondary to benign intracranial hypertension

SPECIFIC SIDE-EFFECTS
  ▶ With intravenous use anaphylaxis

SIDE-EFFECTS, FURTHER INFORMATION
Visual disturbances Discontinue if visual disturbances secondary to benign intracranial hypertension occur.

● PREGNANCY Crosses placenta. There is less experience of ciclosporin in pregnancy but it does not appear to be any more harmful than azathioprine. The use of ciclosporin during pregnancy needs to be supervised in specialist units.

● BREAST FEEDING Present in milk—manufacturer advises avoid.

● HEPATIC IMPAIRMENT Dosage adjustment based on bilirubin and liver enzymes may be needed.

● RENAL IMPAIRMENT In patients with nephrotic syndrome and renal impairment initially 2.5 mg/kg daily. Reduce dose by 25–50% if serum creatinine more than 36% above baseline on more than one measurement. In rheumatoid arthritis, reduce dose if serum creatinine increases more than 30% above baseline in more than 1 measurement; if above 50%, reduce dose by 50% (even if within normal range) and discontinue if reduction not successful within 1 month.
  In psoriasis and atopic dermatitis, reduce dose by 25–50% if serum creatinine increases more than 30% above baseline (even if within normal range) and discontinue if reduction not successful within 1 month.

● PRE-TREATMENT SCREENING In psoriasis, exclude malignancies (including those of skin and cervix) before starting (biopsy any lesions not typical of psoriasis).

● MONITORING REQUIREMENTS
  ▶ Dermatological and physical examination, including blood pressure and renal function measurements required at least twice before starting treatment for psoriasis or atopic dermatitis.
  ▶ Monitor liver function.
  ▶ Monitor serum potassium especially in renal dysfunction (risk of hyperkalaemia).
  ▶ Monitor serum magnesium.
  ▶ Measure blood lipids before treatment and after the first month of treatment.
  ▶ In psoriasis and atopic dermatitis monitor serum creatinine every 2 weeks for first 3 months then every month.
  ▶ Investigate lymphadenopathy that persists despite improvement in atopic dermatitis.
  ▶ Monitor kidney function—dose dependent increase in serum creatinine and urea during first few weeks may necessitate dose reduction in transplant patients (exclude rejection if kidney transplant) or discontinuation in non-transplant patients.
  ▶ Monitor blood pressure—discontinue if hypertension develops that cannot be controlled by antihypertensives.
  ▶ In long-term management of nephrotic syndrome, perform renal biopsies at yearly intervals.
  ▶ In rheumatoid arthritis measure serum creatinine at least twice before treatment. During treatment, monitor serum
creatinine every 2 weeks for first 3 months, then every month for a further 3 months, then every 4–8 weeks depending on the stability of the disease, concomitant medication, and concomitant diseases (or more frequently if dose increased or concomitant NSAIDs introduced or increased).

- **Monitor hepatic function if concomitant NSAIDs given.**

**DIRECTIONS FOR ADMINISTRATION**

- **With oral use** Mix solution with orange juice (or squash) or apple juice (to improve taste) or with water immediately from other liquids (including water).
- **For intravenous infusion** (Sandimmun®), give intermittently or continuously in Glucose 5% or Sodium Chloride 0.9%; dilute to a concentration of 50 mg in 20–100 ml, give intermittent infusion over 2–6 hours; not to be used with PVC equipment. Observe patient for signs of anaphylaxis for at least 30 minutes after starting infusion and at frequent intervals thereafter.

**PRESCRIBING AND DISPENSING INFORMATION**

Brand name prescribing. Prescribing and dispensing of ciclosporin should be by brand name to avoid inadvertent confusion.

**EXCIPIENTS:** May contain Ethanol, ethyl lactate, propylene glycol (including sunlight. In psoriasis and atopic dermatitis, counselled on the administration of ciclosporin capsules and oral solution are available including special-order equipment. Observe patient for signs of anaphylaxis for at least 30 minutes after starting infusion and at frequent intervals thereafter.

**HANDLING AND STORAGE** Keep medicine measure away from other liquids (including water).

**PATIENT AND CARER ADVICE** Patients and carers should be counselled on the administration of ciclosporin capsules and oral solution. Avoid excessive exposure to UV light, including sunlight. In psoriasis and atopic dermatitis, avoid use of UVB or PUVA.

**MEDICINAL FORMS**

There can be variations in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops, eye ointment, capsules.

**Capsule**

- **Excipients:** May contain Alcohol, propylene glycol.
- **Ciclosporin (Non-proprietary)**
  - Ciclosporin 25 mg: Ciclosporin 25 mg capsules | 30 capsule | £8.50
  - Ciclosporin 50 mg: Ciclosporin 50 mg capsules | 30 capsule | £16.50
  - Ciclosporin 100 mg: Ciclosporin 100 mg capsules | 30 capsule | £24.50

**Capimune (Mylan Ltd)**

- Ciclosporin 25 mg: Capimune 25 mg capsules | 30 capsule | £11.05
  - Ciclosporin 50 mg: Capimune 50 mg capsules | 30 capsule | £22.50
  - Ciclosporin 100 mg: Capimune 100 mg capsules | 30 capsule | £45.00

**Neoral (Novartis Pharmaceuticals UK Ltd)**

- Ciclosporin 10 mg: Neoral 10 mg capsules | 60 capsule | £6.68
  - Ciclosporin 25 mg: Neoral 25 mg capsules | 30 capsule | £6.79
  - Ciclosporin 50 mg: Neoral 50 mg capsules | 30 capsule | £12.88
  - Ciclosporin 100 mg: Neoral 100 mg capsules | 30 capsule | £62.61

**Sandimmun (Novartis Pharmaceuticals UK Ltd)**

- Ciclosporin 25 mg: Sandimmun 25 mg capsules | 30 capsule | £24.65
  - Ciclosporin 50 mg: Sandimmun 50 mg capsules | 30 capsule | £48.27
  - Ciclosporin 100 mg: Sandimmun 100 mg capsules | 30 capsule | £91.61
  - Vanquoral (Teva UK Ltd)
    - Ciclosporin 25 mg: Vanquoral 25 mg capsules | 30 capsule | £13.05
    - Ciclosporin 50 mg: Vanquoral 50 mg capsules | 30 capsule | £25.59
    - Ciclosporin 100 mg: Vanquoral 100 mg capsules | 30 capsule | £48.89

**Solution for infusion**

- **Excipients:** May contain Alcohol, propylene glycol.
- **Neoral (Novartis Pharmaceuticals UK Ltd)**
  - Ciclosporin 100 mg per 1 ml: Neoral 100 mg/ml oral solution (sugar-free) | 50 ml | £55.51
  - Sandimmun (Novartis Pharmaceuticals UK Ltd)
    - Ciclosporin 100 mg per 1 ml: Sandimmun 100 mg/ml oral solution (sugar-free) | 50 ml | £131.27

**Solution for infusion**

- **Excipients:** May contain Alcohol, polyoxyxyl castor oils.
- **Neoral (Novartis Pharmaceuticals UK Ltd)**
  - Ciclosporin 50 mg per 1 ml: Sandimmun 250mg/5ml concentrate for solution for infusion | 10 ampoule | £91.71
  - Sandimmun 50 mg/5 ml concentrate for solution for infusion | 10 ampoule | £193.90

**Sirolimus**

**Drug action** Sirolimus is a non-calcineurin inhibiting immunosuppressant.

**Indications and dose**

Prophylaxis of organ rejection in kidney allograft recipients.

- **By mouth**
  - Adult: Initially 6 mg for 1 dose, to be given after surgery once wound has healed, then 2 mg once daily for 2–3 months (in combination with ciclosporin and corticosteroid); sirolimus dose should be given 4 hours after ciclosporin), followed by maintenance 2 mg once daily, ciclosporin should then be withdrawn over 4–8 weeks if not possible, sirolimus should be discontinued and an alternate immunosuppressive regimen used), dose to be adjusted according to whole blood-sirolimus trough concentration.

**Dose equivalence and conversion**

The 500 microgram tablet is not bioequivalent to the 1 mg and 2 mg tablets. Multiples of 500 microgram tablets should not be used as a substitute for other tablet strengths.

**Side-effects**

- **Common or very common** Abdominal pain - acne - anaemia - arthralgia - ascites - constipation - diarrhoea - epistaxis - haemolytic uraemic syndrome - headache - hypercholesterolaemia - hyperglycaemia - hypertension - hypertriglyceridaemia - hypokalaemia - hypophosphataemia - impaired healing - leucopenia - lymphocele - Nausea - neutropenia - oedema - osteonecrosis - pleural effusion - pneumonitis - proteinuria...
Malignant disease

- pyrexia · rash · stomatitis · tachycardia · thrombocytopenia · thrombotic thrombocytopenic purpura · venous thromboembolism
- Uncommon Nephrotic syndrome · pancreatitis · pancytopenia · pericardial effusion · pulmonary embolism · pulmonary haemorrhage
- Rare Alveolar proteinosis · anaphylactic reactions · angioedema · exfoliative dermatitis · hepatic necrosis · hypersensitivity reactions · hypersensitivity vasculitis · interstitial lung disease · lymphoedema
- Frequency not known Focal segmental glomerulosclerosis · reversible impairment of male fertility
- Conception and contraception Effective contraception must be used during treatment and for 12 weeks after stopping.
- Pregnancy Avoid unless essential—toxicity in animal studies.
- Breast feeding Discontinue breast-feeding.

Hepatic impairment
- In severe impairment decrease dose by 50% and monitor whole blood-sirolimus trough concentration every 5–7 days until 3 consecutive measurements have shown stable blood-sirolimus concentration. Clearance reduced in mild to moderate impairment.
- Monitor whole blood-sirolimus level closely and consult local treatment protocol in hepatic impairment.

Monitoring requirements
- Monitor whole blood-sirolimus trough concentration (Afro-Caribbean patients may require higher doses).
- Manufacturer advises pre-dose (‘trough’) whole blood-sirolimus concentration (using chromatographic assay) when used with ciclosporin should be 4–12 micrograms/litre (local treatment protocols may differ); after withdrawal of ciclosporin pre-dose whole blood-sirolimus concentration should be 12–20 micrograms/litre (local treatment protocols may differ).
- Close monitoring of whole blood-sirolimus concentration required if concomitant treatment with potent inducers or inhibitors of metabolism and after discontinuing them, or if ciclosporin dose reduced significantly or stopped.
- When changing between oral solution and tablets, measurement of whole blood ‘trough’ sirolimus concentration after 1–2 weeks is recommended.
- Sirolimus whole-blood concentration is measured using either high performance liquid chromatography (HPLC) or immunoassay. Switching between different immunoassays or between an immunoassay and HPLC can lead to clinically significant differences in results and therefore incorrect dose adjustments. Adjustment to the target therapeutic dose range should be made with knowledge of the assay used and corresponding reference range.
- Monitor kidney function when given with ciclosporin; monitor lipids; monitor urine proteins.

Directions for administration
- Food may affect absorption (take at the same time with respect to food). Sirolimus oral solution should be mixed with at least 60 mL water or orange juice in a glass or plastic container immediately before taking; refill container with at least 120 mL of water or orange juice and drink immediately (to ensure total dose). Do not mix with any other liquids.
- Patient and carer advice Patient or carers should be given advice on how to administer sirolimus. Patients should be advised to avoid excessive exposure to UV light.

Medicinal forms
- There can be variation in the licensing of different medicines containing the same drug.
- Tablet
  - Rapamune (Pfizer Ltd)
  - Sirolimus 500 microgram Rapamune 0.5mg tablets
  - 30 tablet [POM] £69.00 DT price = £69.00

- Sirolimus
  - Rapamune 1mg tablets | 30 tablet [POM] £86.49 DT price = £86.49
  - Sirolimus 2 mg Rapamune 2mg tablets | 30 tablet [POM] £172.98 DT price = £172.98

Oral solution
- EXCIPIENTS: May contain Ethanol
- Rapamune (Pfizer Ltd)
  - Sirolimus 1 mg per 1 ml Rapamune 1mg/ml oral solution (sugar-free) | 60 ml [POM] £162.41

Tacrolimus

- Drug action Tacrolimus is a calcineurin inhibitor.

Indications and dose

Adoprt®
Prophylaxis of graft rejection following liver transplantation, starting 12 hours after transplantation
- Adult: Initially 100–200 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation
- Adult: Initially 200–300 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation
- Adult: Initially 75 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation without antibody induction, starting within 12 hours of transplantation
- Adult: 75 micrograms/kg daily in 2 divided doses

Allograft rejection resistant to conventional immunosuppressive therapy
- Adult: Seek specialist advice

Advagraf®
Prophylaxis of graft rejection following liver transplantation, starting 12–18 hours after transplantation
- Adult: 100–200 micrograms/kg once daily, to be taken in the morning

Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation
- Adult: 200–300 micrograms/kg once daily, to be taken in the morning

Allograft rejection resistant to conventional immunosuppressive therapy
- Adult: Seek specialist advice

Capexion®
Prophylaxis of graft rejection following liver transplantation, starting 12 hours after transplantation
- Adult: Initially 100–200 micrograms/kg daily in 2 divided doses
Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation

**BY MOUTH**
- Adult: Initially 200–300 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation

**BY MOUTH**
- Adult: Initially 75 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation without antibody induction, starting within 12 hours of transplantation

**BY MOUTH**
- Adult: Initially 75 micrograms/kg daily in 2 divided doses

Allograft rejection resistant to conventional immunosuppressive therapy

**BY MOUTH**
- Adult: Seek specialist advice

**ENVARSUS®**

Prophylaxis of graft rejection following liver transplantation, starting within 24 hours of transplantation

**BY MOUTH**
- Adult: 110–130 micrograms/kg once daily, to be taken in the morning

Prophylaxis of graft rejection following renal transplantation, starting within 24 hours of transplantation

**BY MOUTH**
- Adult: 170 micrograms/kg once daily, to be taken in the morning

Rejection therapy

**BY MOUTH**
- Adult: Seek specialist advice

**MODIGRAF®**

Prophylaxis of graft rejection following liver transplantation, starting 12 hours after transplantation

**BY MOUTH**
- Adult: Initially 100–200 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation

**BY MOUTH**
- Adult: Initially 200–300 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation

**BY MOUTH**
- Adult: Initially 75 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation without antibody induction, starting within 12 hours of transplantation

**BY MOUTH**
- Adult: Initially 75 micrograms/kg daily in 2 divided doses

Rejection therapy

**BY MOUTH**
- Adult: Seek specialist advice

**PROGRAF® CAPSULES**

Prophylaxis of graft rejection following liver transplantation, starting 12 hours after transplantation

**BY MOUTH**
- Adult: Initially 100–200 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation

**BY MOUTH**
- Adult: Initially 200–300 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation

**BY MOUTH**
- Adult: Initially 75 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation without antibody induction, starting within 12 hours of transplantation

**BY MOUTH**
- Adult: Initially 75 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation

**BY MOUTH**
- Adult: Initially 75 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation without antibody induction, starting within 12 hours of transplantation

**BY MOUTH**
- Adult: Initially 75 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation

**BY MOUTH**
- Adult: Initially 75 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation without antibody induction, starting within 12 hours of transplantation

**BY MOUTH**
- Adult: Initially 75 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation

**BY MOUTH**
- Adult: Initially 75 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation without antibody induction, starting within 12 hours of transplantation

**BY MOUTH**
- Adult: Initially 75 micrograms/kg daily in 2 divided doses

Allograft rejection resistant to conventional immunosuppressive therapy

**BY CONTINUOUS INTRAVENOUS INFUSION**
- Adult: Seek specialist advice (consult local protocol)

**TACNI®**

Prophylaxis of graft rejection following liver transplantation, starting 12 hours after transplantation when oral route not appropriate

**BY INTRAVENOUS INFUSION**
- Adult: Initially 10–50 micrograms/kg daily for up to 7 days (then transfer to oral therapy), dose to be administered over 24 hours

Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation when oral route not appropriate

**BY INTRAVENOUS INFUSION**
- Adult: Initially 50–100 micrograms/kg daily for up to 7 days (then transfer to oral therapy), dose to be administered over 24 hours

Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation

**BY INTRAVENOUS INFUSION**
- Adult: Initially 10–20 micrograms/kg daily for up to 7 days (then transfer to oral therapy), dose to be administered over 24 hours

Prophylaxis of graft rejection following heart transplantation without antibody induction, starting within 12 hours of transplantation

**BY INTRAVENOUS INFUSION**
- Adult: Initially 10–20 micrograms/kg daily for up to 7 days (then transfer to oral therapy), dose to be administered over 24 hours

Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation

**BY INTRAVENOUS INFUSION**
- Adult: Initially 10–20 micrograms/kg daily for up to 7 days (then transfer to oral therapy), dose to be administered over 24 hours

Allograft rejection resistant to conventional immunosuppressive therapy

**BY CONTINUOUS INTRAVENOUS INFUSION**
- Adult: Seek specialist advice (consult local protocol)

Rejection therapy

**BY CONTINUOUS INTRAVENOUS INFUSION**
- Adult: Seek specialist advice (consult local protocol)
Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation

BY MOUTH

- Adult: Initially 200–300 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation

BY MOUTH

- Adult: Initially 75 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation without antibody induction, starting within 12 hours of transplantation

BY MOUTH

- Adult: Initially 75 micrograms/kg daily in 2 divided doses

Allograft rejection resistant to conventional immunosuppressive therapy

BY MOUTH

- Adult: Seek specialist advice

VIVADEX®

Prophylaxis of graft rejection following liver transplantation, starting 12 hours after transplantation

BY MOUTH

- Adult: Initially 100–200 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation

BY MOUTH

- Adult: Initially 200–300 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation

BY MOUTH

- Adult: Initially 75 micrograms/kg daily in 2 divided doses

Allograft rejection resistant to conventional immunosuppressive therapy

BY MOUTH

- Adult: Seek specialist advice

Important safety information

MHRA/CHM ADVICE: ORAL TACROLIMUS PRODUCTS: PRESCRIBE AND DISPENSE BY BRAND NAME ONLY, TO MINIMISE THE RISK OF INADVERTENT SWITCHING BETWEEN PRODUCTS, WHICH HAS BEEN ASSOCIATED WITH REPORTS OF TOXICITY AND GRAFT REJECTION (JUNE 2012)

Inadvertent switching between oral tacrolimus products has been associated with reports of toxicity and graft rejection. To ensure maintenance of therapeutic response when a patient is stabilised on a particular brand, oral tacrolimus products should be prescribed and dispensed by brand name only.

- Advagraf® is a prolonged-release capsule that is taken once daily in the morning.
- Advagraf® is not interchangeable with other oral tacrolimus containing products; the MHRA has advised (June 2012) that oral tacrolimus products should be prescribed and dispensed by brand name only.
- CAUTIONS UV light (avoid excessive exposure to sunlight and sunlamps) - increased risk of infections - lymphoproliferative disorders - malignancies - neurotoxicity - QT-interval prolongation
- INTERACTIONS → Appendix 1 (tacrolimus).
- Contra-indication—avoid concurrent administration with ciclosporin (care if patient has previously received ciclosporin).
- SIDE-EFFECTS
  - Rare blindness - dehydration - hirsutism - pericardial effusion - posterior reversible encephalopathy syndrome - respiratory distress syndrome - thrombotic thrombocytopenic purpura - toxic epidermal necrolysis
  - Very rare haemorrhagic cystitis - myasthenia - Stevens-Johnson syndrome

Frequency not known agranulocytosis - haemolytic anaemia - pure red cell aplasia

SIDE-EFFECTS, FURTHER INFORMATION

Cardiomyopathy Cardiomyopathy has been reported in children. Patients should be monitored by echocardiography for hypertrophic changes—consider dose reduction or discontinuation if these occur.

ALLERGY AND CROSS-SENSITIVITY Contraindicated if history of hypersensitivity to macrolides.

CONCEPTION AND CONTRACEPTION Exclude pregnancy before treatment.

PREGNANCY Avoid unless potential benefit outweighs risk—crosses the placenta and risk of premature delivery, intra-uterine growth restriction, and hyperkalaemia.

BRST FEEDING Avoid—present in breast milk.

HEPATIC IMPAIRMENT Dose reduction may be necessary in severe impairment.

twice daily, once in the morning and once in the evening;

Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation

BY MOUTH

- Adult: Initially 200–300 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation

BY MOUTH

- Adult: Initially 75 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation without antibody induction, starting within 12 hours of transplantation

BY MOUTH

- Adult: Initially 75 micrograms/kg daily in 2 divided doses

Allograft rejection resistant to conventional immunosuppressive therapy

BY MOUTH

- Adult: Seek specialist advice

VIVADEX®

Prophylaxis of graft rejection following liver transplantation, starting 12 hours after transplantation

BY MOUTH

- Adult: Initially 100–200 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following kidney transplantation, starting within 24 hours of transplantation

BY MOUTH

- Adult: Initially 200–300 micrograms/kg daily in 2 divided doses

Prophylaxis of graft rejection following heart transplantation following antibody induction, starting within 5 days of transplantation

BY MOUTH

- Adult: Initially 75 micrograms/kg daily in 2 divided doses

Allograft rejection resistant to conventional immunosuppressive therapy

BY MOUTH

- Adult: Seek specialist advice

Important safety information

MHRA/CHM ADVICE: ORAL TACROLIMUS PRODUCTS: PRESCRIBE AND DISPENSE BY BRAND NAME ONLY, TO MINIMISE THE RISK OF INADVERTENT SWITCHING BETWEEN PRODUCTS, WHICH HAS BEEN ASSOCIATED WITH REPORTS OF TOXICITY AND GRAFT REJECTION (JUNE 2012)

Inadvertent switching between oral tacrolimus products has been associated with reports of toxicity and graft rejection. To ensure maintenance of therapeutic response when a patient is stabilised on a particular brand, oral tacrolimus products should be prescribed and dispensed by brand name only.

- Advagraf®, Prograf®, Capexion®, Tacni®, and Vivadex® are immediate-release capsules that are taken twice daily, once in the morning and once in the evening;
- Midigraf® granules are used to prepare an immediate-release oral suspension which is taken
**MONITORING REQUIREMENTS**

- After initial dosing, and for maintenance treatment, tacrolimus doses should be adjusted according to whole-blood concentration. Monitor whole blood-tacrolimus trough concentration (especially during episodes of diarrhoea)—consult local treatment protocol for details.
- Monitor blood pressure, ECG (for hypertrophic changes—risk of cardiomyopathy), fasting blood-glucose concentration, haematological and neurological (including visual) and coagulation parameters, electrolytes, hepatitis and renal function.

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Prograf®): give continuously in Glucose 5% or Sodium Chloride 0.9%. Dilute concentrate in infusion fluid to a final concentration of 4–100 micrograms/mL; give over 24 hours. Tacrolimus is incompatible with PVC.

**PATIENT AND CARER ADVICE**

May affect performance of skilled tasks (e.g. driving). Avoid excessive exposure to UV light including sunlight.

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (November 2010) that tacrolimus granules for oral suspension (Modigraf®) are accepted for restricted use within NHS Scotland in patients for whom tacrolimus is an appropriate choice of immunosuppressive therapy and where small changes (less than 500 micrograms) in dosing increments are required (such as, in paediatric patients) or in seriously ill patients who are unable to swallow tacrolimus capsules.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, paste, oral solution, mouthwash.

**Modified-release tablet**

- **Envarsus** (Chiesi Ltd)
  - Tacrolimus (as Tacrolimus monohydrate) 750 microgram Envarsus 750 microgram modified-release tablets | 30 tablet | £44.33
  - Tacrolimus (as Tacrolimus monohydrate) 1 mg Envarsus 1 mg modified-release tablets | 30 tablet | £59.10
  - Tacrolimus (as Tacrolimus monohydrate) 4 mg Envarsus 4 mg modified-release tablets | 30 tablet | £236.40

**Capsule**

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- **Adoport** (Sandoz Ltd)
  - Tacrolimus 500 microgram Adoport 0.5 mg capsules | 50 capsule | £42.92 DT price = £61.88
  - Tacrolimus 750 microgram Adoport 0.75 mg capsules | 50 capsule | £51.75
  - Tacrolimus 1 mg Adoport 1 mg capsules | 50 capsule | £35.69 DT price = £80.28 | 100 capsule | £111.36
  - Tacrolimus 2 mg Adoport 2 mg capsules | 50 capsule | £111.00
  - Tacrolimus 5 mg Adoport 5 mg capsules | 50 capsule | £205.74 DT price = £296.58

- **Capexion (Mylan Ltd)**
  - Tacrolimus 500 microgram Capexion 0.5 mg capsules | 50 capsule | £52.50 DT price = £61.88
  - Tacrolimus 1 mg Capexion 1 mg capsules | 50 capsule | £68.20 DT price = £80.28 | 100 capsule | £112.70
  - Tacrolimus 5 mg Capexion 5 mg capsules | 50 capsule | £252.00 DT price = £296.58

- **Prograf (Astellas Pharma Ltd)**
  - Tacrolimus 500 microgram Prograf 500 microgram capsules | 50 capsule | £61.88 DT price = £61.88
  - Tacrolimus 1 mg Prograf 1 mg capsules | 50 capsule | £80.28 DT price = £80.28 | 100 capsule | £160.54
  - Tacrolimus 5 mg Prograf 5 mg capsules | 50 capsule | £296.58 DT price = £296.58

- **Tacni (TEVA UK)**

**Medicines not identified**

- **Vivadex (Dexcel-Pharma Ltd)**
  - Tacrolimus 500 microgram Vivadex 0.5 mg capsules | 50 capsule | £61.88

**Tacrolimus 1 mg**

Vivadex 1 mg capsules | 50 capsule | £66.21 DT price = £80.28 | 100 capsule | £120.41

**Tacrolimus 5 mg**

Vivadex 5 mg capsules | 50 capsule | £222.44 DT price = £296.58

**Modified-release capsule**

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- **Advagraf** (Astellas Pharma Ltd)
  - Tacrolimus (as Tacrolimus monohydrate) 500 microgram Advagraf 0.5 mg modified-release capsules | 50 capsule | £35.79
  - Tacrolimus (as Tacrolimus monohydrate) 1 mg Advagraf 1 mg modified-release capsules | 50 capsule | £71.59 | 100 capsule | £143.17
  - Tacrolimus (as Tacrolimus monohydrate) 3 mg Advagraf 3 mg modified-release capsules | 50 capsule | £214.76
  - Tacrolimus (as Tacrolimus monohydrate) 5 mg Advagraf 5 mg modified-release capsules | 50 capsule | £266.92

**Granules**

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- **Modigraf** (Astellas Pharma Ltd)
  - Tacrolimus (as Tacrolimus monohydrate) 200 microgram Modigraf 0.2 mg granules sachets (sugar-free) | 50 sachet | £71.30 DT price = £71.30
  - Tacrolimus (as Tacrolimus monohydrate) 1 mg Modigraf 1 mg granules sachets (sugar-free) | 50 sachet | £35.65 DT price = £35.65

**Solution for infusion**

EXCIPIENTS: May contain Polyoxyl castor oils

- **Prograf** (Astellas Pharma Ltd)
  - Tacrolimus 5 mg per 1 ml Prograf 5 mg/1 ml solution for infusion ampoules | 10 ampoule | £59.51

**IMMUNOGLOBULINS**

**Antithymocyte immunoglobulin**

(rabbit)

**INDICATIONS AND DOSE**

Prophylaxis of organ rejection in heart allograft recipients

**BY INTRAVENOUS INFUSION**

- Adult: 1–2.5 mg/kg daily for 3–5 days, to be given over at least 6 hours

Prophylaxis of organ rejection in renal allograft recipients

**BY INTRAVENOUS INFUSION**

- Adult: 1–1.5 mg/kg daily for 3–9 days, to be given over at least 6 hours

Treatment of corticosteroid-resistant allograft rejection in renal transplantation

**BY INTRAVENOUS INFUSION**

- Adult: 1.5 mg/kg daily for 7–14 days, to be given over at least 6 hours

**Doses at extremes of body-weight**

To avoid excessive dosage in obese patients, calculate dose on the basis of ideal body weight.

**CONTRA-INDICATIONS**

Infection

**SIDE-EFFECTS**

Anaphylaxis - cytokine release syndrome—diarrhoea - dysphagia - fever - hypotension - increased susceptibility to infection - increased susceptibility to malignancy - infusion-related reactions - lymphopenia - myalgia - nausea - neutropenia - pruritus - rash - serum sickness - shivering - thrombocytopenia - vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

Tolerability is increased by pretreatment with an intravenous corticosteroid and antithistamine; an antipyretic drug such as paracetamol may also be beneficial.

**PREGNANCY**

Manufacturer advises use only if potential benefit outweighs risk—no information available.

**BREAST FEEDING**

Manufacturer advises avoid—no information available.

**MONITORING REQUIREMENTS**

Monitor blood count.
• **DIRECTIONS FOR ADMINISTRATION** For continuous intravenous infusion (Thymoglobuline®) in Glucose 5% or Sodium chloride 0.9%; reconstitute each vial with 5 mL water for injections to produce a solution of 5 mg/mL; gently rotate to dissolve. Dilute requisite dose with infusion fluid to a total volume of 50–500 mL (usually 50 mL/vial); begin infusion immediately after dilution; give through an in-line filter (pore size 0.22 micron); not to be given with unfractionated heparin and hydrocortisone in glucose infusion—precipitation reported.

• **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - Canakinumab
    - **Drug Action** Canakinumab is a recombinant human monoclonal antibody that selectively inhibits interleukin-1 beta receptor binding.

**INDICATIONS AND DOSE**

- **Acute gout** in patients whose condition has not responded adequately to treatment with NSAIDs or colchicine, or who are intolerant of them
  - **By Subcutaneous Injection**
    - **Adult:** 150 mg for 1 dose, dose may be repeated at least 12 weeks after initial response if symptoms recur, patients who do not respond to initial dose should not be retreated
  - Treatment of cryopyrin-associated periodic syndromes, including severe forms of familial cold auto-inflammatory syndrome (or familial cold urticaria), Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease (also known as chronic infantile neurological cutaneous and articular syndrome)
  - **By Subcutaneous Injection**
    - **Adult:** consult product literature

• **Contra-Indications** Active infection - leucopenia - neutropenia

• **CAUTIONS**
  - History of recurrent infection - latent and active tuberculosis - predisposition to infection

**CAUTIONS, FURTHER INFORMATION**

- **Vaccinations** Patients should receive all recommended vaccinations (including pneumococcal and inactivated influenza vaccine) before starting treatment; avoid live vaccines unless potential benefit outweighs risk—consult product literature for further information.

• **INTERACTIONS** → Appendix 1 (canakinumab).

- Contra-indicated with concomitant use with tumour necrosis factor inhibitors (possible increased risk of infections).

• **SIDE-EFFECTS**
  - **Common or very common** Back pain - increased susceptibility to infection (including serious infection) - injection-site reactions - malaise - neutropenia - vertigo
  - **Uncommon** Gastro-oesophageal reflux
  - **Frequency not known** Malignancy - vomiting

• **CONCEPTION AND CONTRACEPTION** Effective contraception required during treatment and for up to 3 months after last dose.

• **PREGNANCY**
  - Manufacturer advises avoid unless potential benefit outweighs risk.

• **BREAST FEEDING**
  - Consider if benefit outweighs risk—not known if present in human milk.

• **HEPATIC IMPAIRMENT**
  - No information available.

• **RENAL IMPAIRMENT**
  - Limited information available but manufacturer advises no dose adjustment required.

• **PRE-TREATMENT SCREENING**
  - Patients should be evaluated for latent and active tuberculosis before starting treatment.

• **MONITORING REQUIREMENTS**
  - Monitor full blood count including neutrophil count before starting treatment, 1–2 months after starting treatment, and periodically thereafter.
  - Monitor for signs and symptoms of tuberculosis during and after treatment.

• **MEDICINAL FORMS**
  - Canakinumab 150 mg ilaris 150mg powder for solution for injection vials | 1 vial £9.927.80

**MONOCLONAL ANTIBODIES (ANTI-LYMPHOCYTE)**

**Basiliximab**

• **Drug Action** Basiliximab is a monoclonal antibody that acts as an interleukin-2 receptor antagonist and prevents T-lymphocyte proliferation.

**INDICATIONS AND DOSE**

- **Prophylaxis of acute rejection in allogeneic renal transplantation used in combination with ciclosporin and corticosteroid-containing immunosuppression regimes (specialist use only)**
  - **By Intravenous Injection or By Intravenous Infusion**
    - **Adult:** Initially 20 mg, administered within 2 hours before transplant surgery, followed by 20 mg after 4 days, dose to be administered after surgery; withhold second dose if severe hypersensitivity or graft loss occurs

• **CAUTIONS**
  - Off-label use in cardiac transplantation—increased risk of serious cardiac side-effects

• **INTERACTIONS** → Appendix 1 (basiliximab).

• **SIDE-EFFECTS**
  - Atrial flutter - cardiac arrest - cytokine release syndrome - palpitations - severe hypersensitivity reactions

• **CONCEPTION AND CONTRACEPTION**
  - Adequate contraception must be used during treatment and for 16 weeks after last dose.

• **PREGNANCY**
  - Manufacturer advises avoid—no information available.

• **BREAST FEEDING**
  - Manufacturer advises avoid—no information available.

• **DIRECTIONS FOR ADMINISTRATION**
  - For intravenous infusion (Simulect®) give intermittently in Glucose 5% or Sodium chloride 0.9%; reconstitute 10 mg with 2.5 mL water for injections then dilute to at least 25 mL with infusion fluid; reconstitute 20 mg with 5 mL water for injections then dilute to at least 50 mL with infusion fluid; give over 20–30 minutes.

• **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for solution for injection**

- **Simulect (Novartis Pharmaceuticals UK Ltd)**
  - **Basiliximab 10 mg** Simulect 10mg powder and solvent for solution for injection vials | 1 vial £758.69 (Hospital only)
  - **Basiliximab 20 mg** Simulect 20mg powder and solvent for solution for injection vials | 1 vial £842.38 (Hospital only)
Belimumab

INDICATIONS AND DOSE
Adjunctive therapy in patients with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity despite standard therapy

BY INTRAVENOUS INFUSION
- Adult: 400 mg every 4 weeks

BY MOUTH
- Adult: 10 mg/kg every 2 weeks for 3 doses, then 10 mg/kg every 4 weeks, review treatment if no response within 6 months

- CAUTIONS Do not initiate until active infections controlled - history or development of malignancy - predisposition to infection
- INTERACTIONS → Appendix 1 (belimumab).
- SIDE-EFFECTS
  - Common or very common Infusion-related reactions
  - Frequency not known Depressions - diarrhoea - hypersensitivity reactions - infections - insomnia - pyrexia - vomiting

SIDE-EFFECTS, FURTHER INFORMATION
Infusion-related side-effects are reported commonly, including severe or life-threatening hypersensitivity and infusion reactions. Premedication with an antihistamine, with or without an antipyretic may be considered.

- CONCEPTION AND CONTRACEPTION Manufacturer advises adequate contraception during treatment and for at least 4 months after last dose.
- PREGNANCY Avoid unless essential.
- BREAST FEEDING Avoid—present in milk in animal studies.
- RENAL IMPAIRMENT Caution in severe impairment—no information available.
- MONITORING REQUIREMENTS Delay in the onset of acute hypersensitivity reactions has been observed; patients should remain under clinical supervision for several hours following at least the first 2 infusions.
- DIRECTIONS FOR ADMINISTRATION For intravenous infusion (Benlysta®), give intermittently in Sodium chloride 0.9%; reconstitute with water for injections (120 mg in 1.5 mL, 400 mg in 4.8 mL) to produce a solution containing 80 mg/mL; gently swirl vial for 60 seconds, then allow to stand; swirl vial (without shaking) for 60 seconds every 5 minutes until dissolved; dilute requisite dose with infusion fluid to a final volume of 250 mL and give over 1 hour.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.
  Powder for solution for infusion
    - Benlysty (GlaxoSmithKline UK Ltd)
      Belimumab 120 mg Benlysta 120mg powder for concentrate for solution for infusion vials | 1 vial (POZ) £121.50 (Hospital only)
      Belimumab 400 mg Benlysta 400mg powder for concentrate for solution for infusion vials | 1 vial (POZ) £405.00 (Hospital only)

PURINE SYNTHESIS INHIBITORS

Mycophenolate mofetil

INDICATIONS AND DOSE
Prophylaxis of acute rejection in renal transplantation (in combination with a corticosteroid and ciclosporin) (under expert supervision)

BY MOUTH
- Adult: 1 g twice daily, to be started within 72 hours of transplantation

- CAUTIONS Active serious gastro-intestinal disease (risk of haemorrhage, ulceration and perforation) - children (higher incidence of side-effects may call for temporary reduction of dose or interruption) - delayed graft function - elderly (increased risk of infection, gastrointestinal haemorrhage and pulmonary oedema) - increased susceptibility to skin cancer (avoid exposure to strong sunlight) - risk of hypogammaglobulinaemia or bronchiectasis when used in combination with other immunosuppressants

CAUTIONS, FURTHER INFORMATION
Hypogammaglobulinaemia or bronchiectasis Measure serum immunoglobulin levels if recurrent infections develop, and consider bronchiectasis or pulmonary fibrosis if persistent respiratory symptoms such as cough and dyspnoea develop.

- INTERACTIONS → Appendix 1 (mycophenolate).
- Live vaccines Specialist advice should be sought for those being treated with immunosuppressive drugs.

SIDE-EFFECTS
- Frequency not known Interstitial lung disease - intestinal villous atrophy - progressive multifocal leucoencephalopathy - pulmonary fibrosis

SIDE-EFFECTS, FURTHER INFORMATION
Cases of pure red cell aplasia have been reported with mycophenolate mofetil; dose reduction or...
discontinuation should be considered under specialist supervision.

- **CONCEPTION AND CONTRACEPTION** Exclude pregnancy before starting treatment. Effective contraception required before treatment, during treatment, and for 6 weeks after discontinuation of treatment. **MYFORTIC** Manufacturer advises that men should use condoms during treatment and for 13 weeks after last dose.

- **PREGNANCY** Manufacturer advises avoid—congenital malformations reported.

- **BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

- **RENAL IMPAIRMENT** No data available in cardiac or hepatic transplant patients with renal impairment.

- **MONITORING REQUIREMENTS** Monitor full blood count every week for 4 weeks then twice a month for 2 months then every month in the first year (consider interrupting treatment if neutropenia develops).

- **DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (CellCept®), give intermittently in Glucose 5%; reconstitute each 500–mg vial with 14 mL glucose 5% and dilute the contents of 2 vials in 140 mL infusion fluid; give over 2 hours.

- **PATIENT AND CARER ADVICE**

  - Bone marrow suppression Patients should be warned to report immediately any signs or symptoms of bone marrow suppression e.g. infection or inexplicable bruising or bleeding.

- **MEDICINAL FORMS**

  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

    - **MYCOPHENOLATE MOFETIL (Non-proprietary)**
      - Mycophenolate moifetil 500 mg Mycophenolate moifetil 500mg tablets | 50 tablet [Pos] £42.50 DT price = £10.15
      - CellCept (Roche Products Ltd)
      - Mycophenolate moifetil 500 mg CellCept 500mg tablets | 50 tablet [Pos] £82.26 DT price = £10.15
      - Brands may include Myfenax

  - **Gastro-resistant tablet** CAUTIONARY AND ADVISORY LABELS 25

    - Myfortic (Novartis Pharmaceuticals UK Ltd)
      - Mycophenolic acid (as Mycophenolate sodium) 180 mg Myfortic 180mg gastro-resistant tablets | 120 tablet [Pos] £96.72
      - Mycophenolic acid (as Mycophenolate sodium) 360 mg Myfortic 360mg gastro-resistant tablets | 120 tablet [Pos] £193.43

  - **Capsule**

    - **MYCOPHENOLATE MOFETIL (Non-proprietary)**
      - Mycophenolate moifetil 250 mg Mycophenolate moifetil 250mg capsules | 100 capsule [Pos] £82.26 DT price = £82.26
      - CellCept (Roche Products Ltd)
      - Mycophenolate moifetil 250 mg CellCept 250mg capsules | 100 capsule [Pos] £82.26 DT price = £82.26
      - Brands may include Myfenax

  - **Oral suspension** EXCIPIENTS: May contain Aspartame

    - CellCept (Roche Products Ltd)
      - Mycophenolate moifetil 200 mg per 1 ml CellCept 1g/5ml oral suspension (sugar-free) | 175 ml [Pos] £115.16

  - **Powder for solution for infusion**

    - CellCept (Roche Products Ltd)
      - Mycophenolate moifetil (as Mycophenolate moefetil hydrochloride) 500 mg CellCept 500mg powder for solution for infusion vials | 4 vial [Pos] £36.49

- **SIDE-EFFECTS, FURTHER INFORMATION**

  - **Fampridine**

    - **INDICATIONS AND DOSE** Improvement of walking disability in multiple sclerosis (specialist use only)

      - **BY MOUTH**
        - Adult. 10 mg every 12 hours, discontinue treatment if no improvement within 2 weeks

      - **CONTRA-INDICATIONS** History of seizures (discontinue treatment if seizures occur)

      - **CAUTIONS** Atioventricular conduction disorders - predisposition to seizures - sinoatrial conduction disorders - symptomatic cardiac rhythm disorders

      - **INTERACTIONS** Appendix 1 (fampridine). Caution in concomitant use of drugs that lower seizure threshold.
Multiple sclerosis 727

* SIDE-EFFECTS
  * Common or very common: Anxiety, back pain, constipation, dizziness, dyspepsia, dysphoria, headache, insomnia, malaise, nausea, paraesthesia, pharyngolaryngeal pain, tremor, urinary tract infection, vomiting.
  * Uncommon: Seizures.
  * Pregnancy: Avoid—toxicity in animal studies.
  * Breast feeding: Avoid—no information available.
  * Renal impairment: Avoid if eGFR less than 80 mL/minute/1.73 m².
  * Prescribing and dispensing information: Dispense in original container (pack contains a desiccant) and discard any tablets remaining 7 days after opening.

* Medicinal forms
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule
  - Modified-release tablet

**Dimethyl fumarate**

**Drug action**: Dimethyl fumarate has immunomodulatory and anti-inflammatory properties.

**Indications and dose**
- Treatment of adults with relapsing-remitting multiple sclerosis (initiated by a specialist)
- **By mouth**
  - **Adult**: 120 mg twice daily for 7 days, then increased to 240 mg twice daily, for dose adjustment due to side effects—consult product literature

**Caution**
- Reduced lymphocyte count - risk of serious infections (do not start treatment until resolved and consider suspending treatment if infection develops during treatment) - severe active gastro-intestinal disease

**Side-effects**
- Abdominal pain - burning sensation - diarrhoea - dyspepsia - erythema - flushing (may be severe and indicate hypersensitivity) - gastritis - gastroenteritis - leucopenia - lymphopenia - nausea - proteinuria - pruritus - rash - vomiting

**Side-effects, further information**
- Progressive multifocal leuкоencephalopathy (PML): Severe prolonged lymphopenia reported, and patients are exposed to a potential risk of PML. Treatment should be stopped immediately if PML is suspected.
- Conception and contraception: Contraception required in women of child-bearing potential (consider non-hormonal methods).
- Pregnancy: Manufacturer advises avoid unless essential and potential benefit outweighs risk—toxicity in animal studies.
- Breast feeding: Manufacturer advises avoid.
- Hepatic impairment: Manufacturer advises caution in severe impairment.
- Renal impairment: Manufacturer advises caution in severe impairment.
- Monitoring requirements
  - Monitor full blood count (including lymphocytes) before treatment (within 6 months before initiation), then every 6 to 12 months thereafter, and as clinically indicated.
  - Monitor patient closely for features of progressive multifocal leuкоencephalopathy (PML) (e.g. signs and symptoms of neurological dysfunction) and other opportunistic infections.
  - Monitor renal and hepatic function before treatment, after 3 and 6 months of treatment, then every 6 to 12 months thereafter, and as clinically indicated.

**Patient and carer advice**
- Patient information leaflet should be provided. Counselling is advised on progressive multifocal leuкоencephalopathy.

**National funding/access decisions**
- **NICE technology appraisals (TAs)**
  - Dimethyl fumarate for treating relapsing-remitting multiple sclerosis (August 2014) NICE TA320
  - Dimethyl fumarate is recommended for the treatment of active relapsing-remitting multiple sclerosis, only if:
    - the patient does not have highly active or rapidly evolving severe relapsing-remitting multiple sclerosis and
    - the manufacturer provides dimethyl fumarate with the discount agreed in the patient access scheme
  - Patients currently receiving dimethyl fumarate whose disease does not meet the above criteria should be able to continue treatment until they and their clinician consider it appropriate to stop. [www.nice.org.uk/TA320](http://www.nice.org.uk/TA320)

**Medicinal forms**
- There can be variation in the licensing of different medicines containing the same drug.

**Gastro-resistant capsule**
- Cautionary and advisory labels 23, 25
  - **Fingolimod (Biogen Idec Ltd)**
  - Dimethyl fumarate 120 mg Tecfidera 120mg gastro-resistant capsules | 14 capsule | £343.00
  - Dimethyl fumarate 240 mg Tecfidera 240mg gastro-resistant capsules | 56 capsule | £1,373.00

**ImmunoModulating drugs**

**Fingolimod**

**Drug action**: Fingolimod is an immunomodulating drug.

**Indications and dose**
- Treatment of highly active relapsing-remitting multiple sclerosis in patients who have high disease activity despite treatment with at least one disease modifying therapy or in those with rapidly evolving severe relapsing-remitting multiple sclerosis (initiated under specialist supervision)
- **By mouth**
  - **Adult**: 500 micrograms once daily

**Important safety information**
- **MHRA/CHM advice**: FINGOLIMOD—NOT RECOMMENDED FOR PATIENTS AT KNOWN RISK OF CARDIOVASCULAR EVENTS. ADVICE FOR EXTENDED MONITORING FOR THOSE WITH SIGNIFICANT Bradycardia or heart block after the first dose and following treatment interruption (January 2013)
  - Fingolimod is known to cause transient bradycardias and heart block after the first dose. Fingolimod is not recommended in the following patient groups who are at high risk of cardiovascular events unless the anticipated benefits outweigh the potential risks, and advice from a cardiologist is sought before initiation:
    - Patients with the following medical conditions:
      1. 2nd degree Mobitz Type II or higher degree atrioventricular block, sick sinus syndrome, or sino-atrial heart block
      2. Significant QT prolongation (QT-interval greater than 470 milliseconds in women or greater than 450 milliseconds in men)
      3. History of symptomatic bradycardia or recurrent syncope, known ischaemic heart disease, cerebrovascular disease, history of myocardial
infarction, congestive heart failure, history of cardiac arrest, uncontrolled hypertension, or severe sleep apnoea.

**Patients receiving the following antiarrhythmic or heart-rate lowering drugs:**
- class Ia or class III antiarrhythmics
- beta blockers
- heart rate-lowering calcium channel blockers
- other substances which may decrease heart rate (e.g. digoxin, anticholinesteratic drugs or pilocarpine).

All patients receiving fingolimod should be monitored at treatment initiation, (first dose monitoring), and after treatment interruption (see note below); monitoring should include:

**Pre-treatment**
- a 12-lead ECG and blood pressure measurement before starting
- continuous ECG monitoring for 6 hours
- blood pressure and heart rate measurement every hour

**During the first 6 hours of treatment**
- a further 12-lead ECG and blood pressure measurement

If heart rate at the end of the 6 hour period is at its lowest since fingolimod was first administered, monitoring should be extended by at least 2 hours and until heart rate increases.

Extended monitoring, (at least overnight), should be performed in patients with evidence of clinically important cardiac effects during first dose monitoring. Monitoring in patients requiring pharmacological intervention for bradyarrhythmia-related symptoms during first dose monitoring should be extended at least overnight, and first dose monitoring should be repeated after the second dose.

**Note**
First dose monitoring as above should be repeated in all patients whose treatment is interrupted for:
- 1 day or more during the first 2 weeks of treatment
- more than 7 days during weeks 3 and 4 of treatment
- more than 2 weeks after one month of treatment

If the treatment interruption is of shorter duration than the above, repeated monitoring is not required and treatment should be continued with the next dose as planned.

**CONTRA-INDICATIONS** Active infection - active malignancies (except cutaneous basal cell carcinoma) - immunosuppression

**CAUTIONS** Check varicella zoster virus status—consult product literature for further information - chronic obstructive pulmonary disease - pulmonary fibrosis - risk of macular oedema - severe respiratory disease - susceptibility to QT-interval prolongation (including electrolyte disturbances)

**INTERACTIONS** → Appendix 1 (fingolimod).

Caution with concomitant use of drugs that prolong QT interval.

**SIDE-EFFECTS**
- Uncommon Macular oedema - neutropenia - pneumonia
- Frequency not known Haemophagocytic syndrome - lymphoma

**CONCEPTION AND CONTRACEPTION** Exclude pregnancy before treatment. Ensure effective contraception during and for at least 2 months after treatment.

**PREGNANCY** Avoid (toxicity in animal studies).

**BREAST FEEDING** Avoid.

**HEPATIC IMPAIRMENT** Use with caution in mild to moderate impairment. Avoid in severe impairment.

**MONITORING REQUIREMENTS**
- Eye examination recommended 3–4 months after initiation of treatment (and before initiation of treatment in patients with diabetes or history of uveitis).
- Monitor hepatic transaminases before treatment, then every 3 months for 1 year, then periodically thereafter.
- Monitor full blood count before treatment, at 3 months, then at least yearly thereafter and if signs of infection—interrupt treatment if lymphocyte count reduced—consult product literature.

- Monitor for signs and symptoms of haemophagocytic syndrome (including pyrexia, asthenia, hepatitis, splenomegaly and adenopathy)—may be associated with hepatic failure and respiratory distress; also progressive cytopenia, elevated serum-ferritin concentrations, hypertriglyceridaemia, hypofibrinogenaemia, coagulopathy, hepatic cytolysis, hyponatraemia)—initiate treatment immediately.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**
- Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis (April 2012) NICE TA254

Fingolimod is recommended as an option for the treatment of highly active relapsing-remitting multiple sclerosis in adults, only if:
- they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with interferon beta, and
- the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme

Patients currently receiving fingolimod whose disease does not meet the above criteria should be able to continue treatment until they and their clinician consider it appropriate to stop. www.nice.org.uk/TA254

**Scottish Medicines Consortium (SMC) Decisions**
The Scottish Medicines Consortium has advised (August 2012) that fingolimod (Gilenya®) is accepted for restricted use within NHS Scotland as single disease modifying therapy in highly active relapsing-remitting multiple sclerosis despite treatment with interferon beta, with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Capsule**
- Gilenya (Novartis Pharmaceuticals UK Ltd) ▼
- Fingolimod (as Fingolimod hydrochloride) 500 microgram Gilenya 0.5mg capsules | 7 capsule (PO) £367.50 | 28 capsule (PO) £1,470.00

**Glartiramer acetate**

**DRUG ACTION** Glartiramer is an immunomodulating drug comprising synthetic polypeptides.

**INDICATIONS AND DOSE**
Treatment of initial symptoms in patients at high risk of developing multiple sclerosis (initiated under specialist supervision) / Reducing frequency of relapses in ambulatory patients with relapsing-remitting multiple sclerosis who have had at least 2 clinical relapses in the past 2 years (initiated under specialist supervision) by subcutaneous injection
- Adult: 20 mg daily
INTERFERONS

Interferon beta

INDICATIONS AND DOSE

**REBIF® PRE-FILLED PEN AND SYRINGE**

For relapsing, remitting multiple sclerosis (characterised by at least two attacks of neurological dysfunction over the previous 2 or 3 years, followed by complete or incomplete recovery) who are able to walk unaided | For a single demyelinating event with an active inflammatory process (if severe enough to require intravenous corticosteroid and patient at high risk of developing multiple sclerosis) BY SUBCUTANEOUS INJECTION

- **Adult:** (consult product literature)

**CONTRA-INDICATIONS**

Decompensated liver disease • severe depressive illness

**CONTRA-INDICATIONS, FURTHER INFORMATION**

Consult product literature for further information on contra-indications.

**CAUTIONS**

History of cardiac disorders • history of depressive disorders (avoid in severe depression or in those with suicidal ideation) • history of seizures • history of severe myelosuppression

**CAUTIONS, FURTHER INFORMATION**

Consult product literature for further information on cautions.
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Malignant disease

Malignant disease

▶ NATIONAL FUNDING/ACCESS DECISIONS

PRESCRIBING AND DISPENSING INFORMATION

Patients should also be monitored for signs and symptoms of hepatic impairment.

▶ CONCEPTION AND CONTRAINDICATIONS

Effective contraception is required during treatment—consult product literature.

▶ PREGNANCY

Avoid unless potential benefit outweighs risk (toxicity in animal studies).

▶ BREAST FEEDING

Avoid—no information available.

▶ HEPATIC IMPAIRMENT

Caution in severe hepatic impairment.

▶ RENAL IMPAIRMENT

Caution in severe renal impairment.

▶ MONITORING REQUIREMENTS

Monitor for signs of hepatic injury—hepatic failure has been reported rarely.

▶ Patients should be monitored for clinical features of thrombotic microangiopathy (TMA), including thrombocytopenia, new onset hypertension, fever, central nervous system symptoms (e.g. confusion and paresis), and impaired renal function. Any signs of TMA should be investigated fully and, if diagnosed, interferon beta should be stopped immediately and treatment for TMA promptly initiated (consult product literature for details).

▶ Patients should also be monitored for signs and symptoms of nephrotic syndrome, including oedema, proteinuria, and impaired renal function—monitor renal function periodically. If nephrotic syndrome develops, treatment should be stopped immediately and considering interferon beta treatment.

▶ PRESCRIBING AND DISPENSING INFORMATION

BETAFERON® INJECTION

An auto-injector device is available from Bayer Schering.

EXTAVIA®

An auto-injector device (ExtaviPro® 30g) is supplied as part of the ExtaviPro® 30g kit.

REBIF®

Cartridges for use with RebiSmart® auto-injector device.

▶ NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

Interferon beta and glatiramer for multiple sclerosis (January 2002) NICE T32

Interferon beta and glatiramer acetate are not recommended for the treatment of multiple sclerosis in the NHS in England and Wales.

Patients who are currently receiving interferon beta or glatiramer acetate for multiple sclerosis, whether as routine therapy or as part of a clinical trial, should have the option to continue treatment until they and their consultant consider it appropriate to stop, having regard to the established criteria for withdrawal from treatment. www.nice.org.uk/TA32

NHS restrictions

 Provision of disease-modifying therapies for multiple sclerosis

The Department of Health, the National Assembly for Wales, the Scottish Executive, the Northern Ireland Department of Health, Social Services & Public Safety, and the manufacturers have reached agreement on a risk-sharing scheme for the NHS supply of interferon beta and glatiramer acetate for multiple sclerosis. Health Service Circular (HSC 2002/004) explains how patients can participate in the scheme. It is available on the Department of Health website (www.dh.gov.uk).

▶ MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

EXCIPIENTS: May contain Benzyl alcohol

Avonex (Biogen Idec Ltd)

Interferon beta-1a 12 mega u per 1 ml Avonex 30micrograms/0.5ml (6million units) solution for injection pre-filled syringes | 4 pre-filled disposable injection (P) £654.00 | 12 pre-filled disposable injection (P) £1,962.00

Interferon beta-1a 5 mega u per 1 ml Avonex 15micrograms/0.25ml (3million units) solution for injection pre-filled syringes | 4 pre-filled disposable injection (P) £317.52

Avonex 30micrograms/0.5ml (6million units) solution for injection pre-filled pen | 4 pre-filled disposable injection (P) £654.00 | 12 pre-filled disposable injection (P) £1,962.00

Rebif (Merck Serono Ltd)

Interferon beta-1a 12 mega u per 1 ml Rebif 22micrograms/0.5ml (6million units) solution for injection 1.5ml cartridges | 4 cartridge (P) £613.52

Rebif 8.8micrograms/0.2ml (2.4million units) solution for injection pre-filled syringes | 6 pre-filled disposable injection (P) no price available

Rebif 8.8micrograms/0.2ml (2.4million units) solution for injection pre-filled pen | 6 pre-filled disposable injection (P) no price available

Rebif 22micrograms/0.5ml (6million units) solution for injection pre-filled pen | 6 pre-filled disposable injection (P) no price available

Rebif 22micrograms/0.5ml (6million units) solution for injection pre-filled syringes | 12 pre-filled disposable injection (P) £613.52

Rebif 22micrograms/0.5ml (6million units) solution for injection pre-filled syringes | 12 pre-filled disposable injection (P) £1,962.00

Interferon beta-1a 24 mega u per 1 ml Rebif 44micrograms/0.5ml (12million units) solution for injection pre-filled pen | 12 pre-filled disposable injection (P) £813.21

Rebif 44micrograms/0.5ml (12million units) solution for injection pre-filled syringes | 12 pre-filled disposable injection (P) £813.21

Rebif 44micrograms/0.5ml (12million units) solution for injection pre-filled syringes | 12 pre-filled disposable injection (P) £1,962.00

Powder and solvent for solution for injection

Avonex (Biogen Idec Ltd)

Interferon beta-1a 30 microgram Avonex 30microgram powder and solvent for solution for injection vials | 4 vial (P) £654.00

Betalferon (Bayer Plc)

Interferon beta-1b 300 microgram Betalferon 300microgram powder and solvent for solution for injection vials | 15 vial (P) £596.63

Extavia (Novartis Pharmaceuticals UK Ltd)

Interferon beta-1b 300 microgram Extavia 300microgram powder and solvent for solution for injection vials | 15 vial (P) £596.63

Peginterferon beta-1a

▶ DRUG ACTION

Peginterferon beta-1a is a polyethylene glycol-conjugated (‘pegylated’) derivative of interferon beta; pegylation increases the persistence of interferon in the blood.

INDICATIONS AND DOSE

Treatment of relapsing, remitting multiple sclerosis

BY SUBCUTANEOUS INJECTION

Adults: (consult product literature)

▶ CONTRA-INDICATIONS

Severe depression - suicidal ideation

▶ CAUTIONS

History of cardiac disorders - history of depressive disorders (avoid in severe depression or in those with suicidal ideation) - history of seizures - history of severe myelosuppression

CAUTIONS, FURTHER INFORMATION

Consult product literature for further information about cautions.

▶ SIDE-EFFECTS

Consult product literature for information about side effects.
**CONCEPTION AND CONTRACEPTION** Effective contraception required during treatment—consult product literature.

**PREGNANCY** Do not initiate during pregnancy. Avoid unless potential benefit outweighs risk.

**BOOSTER FEEDING** Avoid—no information available.

**HEPATIC IMPAIRMENT** Caution in severe hepatic impairment.

**RENAL IMPAIRMENT** Caution in severe renal impairment.

**MONITORING REQUIREMENTS**
- Monitor for signs of hepatic injury—hepatic failure has been reported rarely.
- Thrombotic microangiopathy Patients should be monitored for clinical features of thrombotic microangiopathy (TMA), including thrombocytopenia, new onset hypertension, fever, central nervous system symptoms (e.g. confusion and paresis), and impaired renal function. Any signs of TMA should be investigated fully and, if diagnosed, interferon beta should be stopped immediately and treatment for TMA promptly initiated (consult product literature for details).
- Nephrotic syndrome Patients should also be monitored for signs and symptoms of nephrotic syndrome, including oedema, proteinuria, and impaired renal function—monitor renal function periodically. If nephrotic syndrome develops, treat promptly and consider stopping interferon beta treatment.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- Plegridy (Biogen Idec Ltd)
- Peginterferon beta-1a 126 microgram per 1 ml Plegridy 63 micrograms/0.5 ml solution for injection pre-filled pen | 1 pre-filled disposable injection (no price available)
- Peginterferon beta-1a 188 microgram per 1 ml Plegridy 94 micrograms/0.5 ml solution for injection pre-filled pen | 1 pre-filled disposable injection (no price available)
- Peginterferon beta-1a 250 microgram per 1 ml Plegridy 125 micrograms/0.5 ml solution for injection pre-filled pen | 2 pre-filled disposable injection (no price available) 1554.00 | 6 pre-filled disposable injection £1,962.00

**MONOCLONAL ANTIBODIES (ANTI-LYMPHOCYTE)**

**Anti-lymphocyte monoclonal antibodies**
- **DRUG ACTION** The anti-lymphocyte monoclonal antibodies cause lysis of B lymphocytes.

**Important safety information**

All anti-lymphocyte monoclonal antibodies should be given under the supervision of an experienced specialist, in an environment where full resuscitation facilities are immediately available.

**SIDE-EFFECTS**
- **Common or very common** Allergic reactions - angioedema - bronchospasm - chills - cytokine release syndrome - dyspnoea - fever - flushing - nausea - pruritus - rash - tumour pain - vomiting
- **Frequency not known** Cardiac events

**SIDE-EFFECTS, FURTHER INFORMATION**

**Infusion-related side-effects** In rare cases infusion reactions may be fatal. Infusion-related side-effects occur predominantly during the first infusion. Patients should receive premedication before administration of anti-lymphocyte monoclonal antibodies to reduce these effects—consult product literature for details of individual regimens. The infusion may have to be stopped temporarily and the infusion-related effects treated—consult product literature for appropriate management. Evidence of pulmonary infiltration and features of tumour lysis syndrome should be sought if infusion-related effects occur.

**Cytokine release syndrome** Fatalities following severe cytokine release syndrome (characterised by severe dyspnoea) and associated with features of tumour lysis syndrome have occurred after infusions of anti-lymphocyte monoclonal antibodies. Patients with a high tumour burden as well as those with pulmonary insufficiency or infiltration are at increased risk and should be monitored very closely (and a slower rate of infusion considered).

**PRE-TREATMENT SCREENING** All patients should be screened for hepatitis B before treatment.

**MONITORING REQUIREMENTS** Patients should also be monitored for cytopenias—consult product literature for specific recommendations.

**Alemtuzumab**

**INDICATIONS AND DOSE**

Treatment of adults with relapsing-remitting multiple sclerosis with active disease defined by clinical or imaging features

**BY INTRAVENOUS INFUSION**
- Adult: (consult product literature)

**UNLICENSED USE** Although no longer licensed for oncological and transplant indications, alemtuzumab is also available through a patient access programme for these indications.

**CONTRA-INDICATIONS**

Human immunodeficiency virus

**CAUTIONS**

- Hepatitis B carriers - hepatitis C carriers - in patients with active infection, a delay in initiation of alemtuzumab treatment should be considered until the infection is fully controlled - not recommended for inactive disease - not recommended for stable disease - patients should receive oral prophylaxis for herpes infection starting on the first day of treatment and continuing for at least a month following each treatment course - patients with previous autoimmune conditions other than multiple sclerosis - pretreatment before administration is required (consult product literature)

**CAUTIONS, FURTHER INFORMATION**

**Autoimmune mediated conditions** The risk of autoimmune mediated conditions may increase during treatment, including immune thrombocytopenic purpura, thyroid disorders, nephropathies, and cytopenias, and should be monitored for throughout the course of treatment (consult product literature).

For full details of cautions, consult product literature.

**INTERACTIONS**

- Appendix 1 (alemtuzumab).

**SIDE-EFFECTS**

For full side effects details (including monitoring and management) consult product literature.

**CONCEPTION AND CONTRACEPTION**

Women of childbearing potential should use effective contraception during and for 4 months after treatment.

**PREGNANCY**

Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies. Autoimmune thyroid disease during treatment may affect fetus (consult product literature).
Malignant disease

CAUTIONS

l Drug Action Natalizumab is a monoclonal antibody that inhibits the migration of leucocytes into the central nervous system, hence reducing inflammation and demyelination.

Indications and dose

Highly active relapsing-remitting multiple sclerosis (initiated under specialist supervision)

By intravenous infusion

l Adult: 300 mg every 4 weeks, treatment should be discontinued if no response after 6 months

Contra-indications

Active infection • active malignancies (except cutaneous basal cell carcinoma) • immunosuppression • progressive multifocal leucoencephalopathy

Cautions

Contra-indications. Further information

Progressive Multifocal Leucoencephalopathy Natalizumab is associated with an increased risk of opportunistic infection and progressive multifocal leucoencephalopathy (PML) caused by JC virus. The risk of developing PML increases with the presence of anti-JCV antibodies, previous use of immunosuppressant therapy, and treatment duration (especially beyond 2 years of treatment); the risk beyond 4 years of treatment is not known. Patients with all three risk factors should only be treated with natalizumab if the benefits of treatment outweigh the risks. Treatment should be suspended until PML has been excluded. If a patient develops an opportunistic infection or PML, natalizumab should be permanently discontinued. For information on cautions consult product literature.

Interactions

Appendix 1 (natalizumab).

SIDE-EFFECTS

l Common or very common Arthralgia • autoantibodies • nasopharyngitis • urinary-tract infection

l Uncommon Hypersensitivity reactions (discontinue permanently)

Frequency not known Arthralgia (during infusion) • dizziness (during infusion) • fatigue (during infusion) • flushing (during infusion) • headache (during infusion) • increased risk of opportunistic infection • liver toxicity • nausea (during infusion) • pruritus (during infusion) • pyrexia (during infusion) • rigors (during infusion) • urticaria (during infusion) • vomiting (during infusion)

SIDE-EFFECTS, FURTHER INFORMATION

Progressive Multifocal Leucoencephalopathy If Progressive Multifocal Leucoencephalopathy (PML) is suspected, treatment should be suspended until PML has been excluded. If a patient develops an opportunistic infection or PML, natalizumab should be permanently discontinued.

Liver toxicity Discontinue treatment if significant liver injury occurs.

Pregnancy

Avoid unless essential—toxicity in animal studies.

Breast feeding Present in milk in animal studies—avoid.

Pre-treatment screening

Progressive Multifocal Leucoencephalopathy A magnetic resonance image (MRI) scan is recommended before starting treatment with natalizumab. Testing for serum anti-JCV antibodies before starting treatment or in those with unknown antibody status already receiving natalizumab is recommended and should be repeated every 6 months (consult product literature for full details).

Monitoring requirements

Monitor liver function.

Arthralgia (during infusion) • dizziness (during infusion) • fatigue (during infusion) • flushing (during infusion) • headache (during infusion) • increased risk of opportunistic infection • liver toxicity • nausea (during infusion) • pruritus (during infusion) • pyrexia (during infusion) • rigors (during infusion) • urticaria (during infusion) • vomiting (during infusion)

Malignant disease

BREAST FEEDING

Manufacturer advises avoid during and for 4 months after each treatment course unless potential benefit outweighs risk.

Pre-treatment screening

Screening patients at high risk of hepatitis B or C is recommended before treatment. All patients should be evaluated for active or latent tuberculosis before starting treatment.

Monitoring requirements

HPV screening should be carried out annually in female patients.

Prescribing and dispensing information

All patients should receive oral prophylaxis for herpes infection starting on the first day of treatment and continuing for at least a month following each treatment course.

Patient and carer advice

Patients should be provided with a Patient Alert Card and Patient Guide.

National funding/access decisions

NICE technology appraisals (TAs)

Alemtuzumab for treating relapsing-remitting multiple sclerosis (May 2014) NICE TA312

Alemtuzumab is recommended as an option, within its marketing authorisation, for treating adults with active relapsing-remitting multiple sclerosis. www.nice.org.uk/TA312

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

Solution for infusion

l Lemtrada (Genzyme Therapeutics Ltd) v

Alemtuzumab 10 mg per 1 ml

Lemtrada 12mg/1.2ml concentrate for solution for infusion vials | 1 vial (POD) £7,045.00 (Hospital only)

Natalizumab

Drug action

Natalizumab is a monoclonal antibody that inhibits the migration of leucocytes into the central nervous system, hence reducing inflammation and demyelination.

Indications and dose

By intravenous infusion

l Adult: 300 mg every 4 weeks, treatment should be discontinued if no response after 6 months

Contra-indications

Active infection • active malignancies (except cutaneous basal cell carcinoma) • immunosuppression • progressive multifocal leucoencephalopathy

Cautions

Contra-indications. Further information

Progressive Multifocal Leucoencephalopathy Natalizumab is associated with an increased risk of opportunistic infection and progressive multifocal leucoencephalopathy (PML) caused by JC virus. The risk of developing PML increases with the presence of anti-JCV antibodies, previous use of immunosuppressant therapy, and treatment duration (especially beyond 2 years of treatment); the risk beyond 4 years of treatment is not known. Patients with all three risk factors should only be treated with natalizumab if the benefits of treatment outweigh the risks. Treatment should be suspended until PML has been excluded. If a patient develops an opportunistic infection or PML, natalizumab should be permanently discontinued. For information on cautions consult product literature.

Interactions

Appendix 1 (natalizumab).

Side-effects

l Common or very common Arthralgia • autoantibodies • nasopharyngitis • urinary-tract infection

l Uncommon Hypersensitivity reactions (discontinue permanently)

Frequency not known Arthralgia (during infusion) • dizziness (during infusion) • fatigue (during infusion) • flushing (during infusion) • headache (during infusion) • increased risk of opportunistic infection • liver toxicity • nausea (during infusion) • pruritus (during infusion) • pyrexia (during infusion) • rigors (during infusion) • urticaria (during infusion) • vomiting (during infusion)

Side-effects, further information

Progressive Multifocal Leucoencephalopathy If Progressive Multifocal Leucoencephalopathy (PML) is suspected, treatment should be suspended until PML has been excluded. If a patient develops an opportunistic infection or PML, natalizumab should be permanently discontinued.

Liver toxicity Discontinue treatment if significant liver injury occurs.

Pregnancy

Avoid unless essential—toxicity in animal studies.

Breast feeding Present in milk in animal studies—avoid.

Pre-treatment screening

Progressive Multifocal Leucoencephalopathy A magnetic resonance image (MRI) scan is recommended before starting treatment with natalizumab. Testing for serum anti-JCV antibodies before starting treatment or in those with unknown antibody status already receiving natalizumab is recommended and should be repeated every 6 months (consult product literature for full details).

Monitoring requirements

Monitor liver function.

Arthralgia (during infusion) • dizziness (during infusion) • fatigue (during infusion) • flushing (during infusion) • headache (during infusion) • increased risk of opportunistic infection • liver toxicity • nausea (during infusion) • pruritus (during infusion) • pyrexia (during infusion) • rigors (during infusion) • urticaria (during infusion) • vomiting (during infusion)

Malignant disease

BREAST FEEDING

Manufacturer advises avoid during and for 4 months after each treatment course unless potential benefit outweighs risk.

Pre-treatment screening

Screening patients at high risk of hepatitis B or C is recommended before treatment. All patients should be evaluated for active or latent tuberculosis before starting treatment.

Monitoring requirements

HPV screening should be carried out annually in female patients.

Prescribing and dispensing information

All patients should receive oral prophylaxis for herpes infection starting on the first day of treatment and continuing for at least a month following each treatment course.

Patient and carer advice

Patients should be provided with a Patient Alert Card and Patient Guide.

National funding/access decisions

NICE technology appraisals (TAs)

Alemtuzumab for treating relapsing-remitting multiple sclerosis (May 2014) NICE TA312

Alemtuzumab is recommended as an option, within its marketing authorisation, for treating adults with active relapsing-remitting multiple sclerosis. www.nice.org.uk/TA312

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

Solution for infusion

l Lemtrada (Genzyme Therapeutics Ltd) v

Alemtuzumab 10 mg per 1 ml

Lemtrada 12mg/1.2ml concentrate for solution for infusion vials | 1 vial (POD) £7,045.00 (Hospital only)
Teriflunomide

**INDICATIONS AND DOSE**

Treatment of relapsing-remitting multiple sclerosis (initiated under specialist supervision)

**BY MOUTH**

- Adult: 14 mg once daily

- **CONTRA-INDICATIONS**
  - Anaemia
  - Leucopenia
  - Neutropenia
  - Serious infection
  - Severe hypoproteinaemia
  - Severe immunodeficiency
  - Significantly impaired bone-marrow function
  - Thrombocytopenia

- **CAUTIONS**
  - Adult over 65 years: anaemia, dyspnoea—assess for interstitial lung disease and consider suspending treatment
  - Hypoproteinaemia (avoid if severe)
  - Impaired bone-marrow function (avoid if severe)
  - Latent tuberculosis
  - Leucopenia
  - Persistent cough—assess for interstitial lung disease and consider suspending treatment
  - Severe infection—delay or suspend treatment until resolved
  - Significant alcohol consumption—signs or symptoms of serious skin reactions (including ulcerative stomatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis)—discontinue treatment—switching between other immunomodulating drugs
  - Thrombocytopenia

- **INTERACTIONS**
  - Appendix 1 (teriflunomide)

- **SIDE-EFFECTS**
  - Common or very common: Acne, alopecia, anxiety, carpal tunnel syndrome, cystitis, diarrhoea, elevated liver enzymes, gastroenteritis, hyperaesthesia, hypertension, laryngitis, leucopenia, menorrhagia, musculoskeletal pain, myalgia, nausea, neuralgia, neutropenia, oral infection, paraesthesia, peripheral neuropathy, pollakiuria, rash, respiratory tract infection, sciatica, tinea pedis, urinary tract infection, vomiting, weight loss

- **Uncommon**
  - Anaemia
  - Thrombocytopenia

- **Very rare**
  - Interstitial lung disease
  - Pancreatitis

**SIDE-EFFECTS, FURTHER INFORMATION**

**Accelerated elimination procedure**

**Important**

Accelerated elimination procedure recommended following discontinuation due to serious adverse effects (consult product literature).

**Hepatic injury**

Discontinue treatment if signs or symptoms of hepatic injury, or if liver enzymes exceed 3 times the upper limit of reference range.

**CONCEPTION AND CONTRACEPTION**

Effective contraception essential for women of child-bearing potential during treatment and for up to 2 years after treatment.

In patients undergoing treatment with teriflunomide that are planning to conceive, the accelerated elimination procedure should be used prior to conception.

Use of non-oral contraception is recommended during the accelerated elimination procedure—consult product literature.

**PREGNANCY**

Avoid—toxicity in animal studies.

**BREAST FEEDING**

Present in milk in animal studies—manufacturer advises avoid.

**HEPATIC IMPAIRMENT**

Avoid in severe impairment.

**MONITORING REQUIREMENTS**

- Monitor full blood count (including differential white cell count and platelet count) before treatment and as clinically indicated during treatment.

- Monitor blood pressure before treatment and periodically thereafter.

- Hepatic monitoring: Monitor liver function before treatment and every 2 weeks for first 6 months then every 8 weeks thereafter or as clinically indicated (pre-existing liver disease may increase risk). Increase to weekly monitoring if alanine aminotransferase (ALT) is 2–3 times the upper limit of reference range: discontinue treatment if signs or symptoms of hepatic injury, or if liver enzymes exceed 3 times the upper limit of reference range.

**TREATMENT CESSATION**

Accelerated elimination procedure

To aid drug elimination in case of serious adverse effect or before conception, stop treatment and give either colestyramine p. 173 or charcoal, activated p. 1130. After the accelerated elimination procedure a plasma concentration of less than 20 micrograms/litre (measured on 2 occasions at least 14 days apart) and a waiting period of one and a half months are necessary before conception.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis (August 2007) NICE TA127

Natalizumab is an option for the treatment only of rapidly evolving severe relapsing-remitting multiple sclerosis (RES). RES is defined by 2 or more disabling relapses in 1 year, and 1 or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI.

- **Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (August 2007) that natalizumab is accepted for restricted use as single disease-modifying therapy in highly active relapsing-remitting multiple sclerosis only in patients with rapidly evolving severe relapsing-remitting multiple sclerosis defined by 2 or more disabling relapses in 1 year and with 1 or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI.

**PYRIMIDINE SYNTHESIS INHIBITORS**

**Teriflunomide**

**DRUG ACTION**

Teriflunomide is a metabolite of leflunomide which has immunomodulating and anti-inflammatory properties.
2 Malignant disease

2.1 Antibody responsive malignancy

MONOCLONAL ANTIBODIES (ANTI-LYMPHOCYTE)

Rituximab

The properties listed below are those particular to the drug only. For properties common to the class, see Anti-lymphocyte monoclonal antibodies, p. 731.

INDICATIONS AND DOSE

Treatment of severe active rheumatoid arthritis in patients whose condition has not responded adequately to other disease-modifying antirheumatic drugs (including one or more tumour necrosis factor inhibitors) or who are intolerant of them (in combination with methotrexate)

BY INTRAVENOUS INFUSION

Adult: 1 g, then 1 g after 2 weeks, patients should receive premedication before each infusion (consult product literature for details)

Treatment of previously untreated stage III-IV follicular lymphoma (in combination with other chemotherapy)

Maintenance therapy in patients with follicular non-Hodgkin’s lymphoma that has responded to induction therapy (in combination with other chemotherapy)

Treatment of diffuse large B-cell non-Hodgkin’s lymphoma (in combination with other chemotherapy)

Treatment of chemotherapy-resistant or relapsed stage III-IV follicular non-Hodgkin’s lymphoma

Previously untreated or relapsed chronic lymphocytic leukaemia

Induction of remission in patients with severe, active granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis (in combination with glucocorticoids)

BY INTRAVENOUS INFUSION

Adult: Patients should receive premedication before each dose (consult product literature for details)

(consult product literature or local protocols)

CONTRA-INDICATIONS

Severe heart failure (when used to treat granulomatosis with polyangiitis or microscopic polyangiitis) - severe infection - severe, uncontrolled heart disease (when used to treat granulomatosis with polyangiitis or microscopic polyangiitis)

CONTRA-INDICATIONS, FURTHER INFORMATION

For full details on contra-indications, consult product literature.

CAUTIONS

GENERAL CAUTIONS

History of cardiovascular disease; in adults exacerbation of angina, arrhythmia, and heart failure have been reported - patients receiving cardiotoxic chemotherapy; in adults exacerbation of angina, arrhythmia, and heart failure have been reported - transient hypotension occurs frequently during infusion (anti-hypertensives may need to be withheld for 12 hours before infusion)

SPECIFIC CAUTIONS

When used for rheumatoid arthritis predisposition to infection

CAUTIONS, FURTHER INFORMATION

Hepatitis B infection and reactivation

Hepatitis B infection and reactivation (including fatal cases) have been reported in patients taking rituximab. Patients with positive hepatitis B serology should be referred to a liver specialist for monitoring and initiation of antiviral therapy before treatment initiation; treatment should not be initiated in patients with evidence of current hepatitis B infection until the infection has been adequately treated. Patients should be closely monitored for clinical and laboratory signs of active hepatitis B infection during treatment and for up to a year following the last infusion (consult product literature).

For full details on cautions, consult product literature or local treatment protocol.

INTERACTIONS

Appendix 1 (rituximab).

SIDE-EFFECTS


SIDE-EFFECTS, FURTHER INFORMATION

Associated with infections, sometimes severe, including tuberculosis, septicemia, and hepatitis B reactivation.

Progressive multifocal leucoencephalopathy

Progressive multifocal leucoencephalopathy (which is usually fatal or causes severe disability) has been reported in association with rituximab; patients should be monitored for cognitive, neurological, or psychiatric signs and symptoms. If progressive multifocal leucoencephalopathy is suspected, suspend treatment until it has been excluded.

For full details, including management of side-effects, consult product literature.

CONCEPTION AND CONTRACEPTION

Effective contraception (in both sexes) required during and for 12 months after treatment.

PREGNANCY

Avoid unless potential benefit to mother outweighs risk of B-lymphocyte depletion in fetus.

BREAST FEEDING

Avoid breast-feeding during and for 12 months after treatment.

MONITORING REQUIREMENTS

For full details on monitoring requirements consult product literature.

DIRECTIONS FOR ADMINISTRATION

For intravenous infusion (MabThera®), give intermittently in Glucose 5% or Sodium chloride 0.9%; dilute to 1-4 mg/mL and gently invert bag to avoid foaming.

PATIENT AND CARER ADVICE

Alert card Patients treated for granulomatosis with polyangiitis and microscopic polyangiitis or rheumatoid arthritis should be provided with a patient alert card with each infusion.

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

Rituximab for aggressive non-Hodgkin’s lymphoma

This NICE guidance was issued for rituximab by intravenous infusion. Rituximab, in combination with cyclophosphamide, doxorubicin, vincristine, and prednisolone, is recommended for first-line treatment of
CD20-positive diffuse large-B-cell lymphoma at clinical stage II, III or IV. The use of rituximab for localised (stage I) disease should be limited to clinical trials. www.nice.org.uk/TA65

- **Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin’s lymphoma (February 2008) NICE TA57**
  This NICE guidance was issued for rituximab by intravenous infusion. Rituximab, in combination with chemotherapy, is an option for the induction of remission in patients with relapsed stage III or IV follicular non-Hodgkin’s lymphoma.
  Rituximab monotherapy as maintenance therapy is an option for the treatment of patients with relapsed stage III or IV follicular non-Hodgkin’s lymphoma, in remission induced with chemotherapy (with or without rituximab). Rituximab monotherapy is an option for the treatment of patients with relapsed stage III or IV follicular non-Hodgkin’s lymphoma, when all alternative treatment options have been exhausted (that is, if there is resistance to or intolerance of chemotherapy). www.nice.org.uk/TA137

- **Rituximab for the first-line treatment of chronic lymphocytic leukaemia (July 2009) NICE TA174**
  This NICE guidance was issued for rituximab by intravenous infusion. Rituximab, in combination with fludarabine and cyclophosphamide, is recommended as an option for the first-line treatment of chronic lymphocytic leukaemia. www.nice.org.uk/TA174

- **Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia (July 2010) NICE TA193**
  This NICE guidance was issued for rituximab by intravenous infusion. Rituximab in combination with fludarabine and cyclophosphamide is recommended as a treatment option for people with relapsed or refractory chronic lymphocytic leukaemia except when the condition:
  - is refractory to fludarabine (that is, it has not responded to fludarabine, or has relapsed within 6 months of treatment), or
  - has previously been treated with rituximab, unless it was in the context of a clinical trial, or a dose lower than the dose currently licensed for chronic lymphocytic leukaemia or with chemotherapy other than fludarabine and cyclophosphamide.

- **Adalimumab, etanercept, infliximab, rituximab, and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (August 2010) NICE TA195**
  Rituximab, in combination with methotrexate, is an option for the treatment of severe active rheumatoid arthritis in adults who have had an inadequate response to, or are intolerant of, other disease-modifying antirheumatic drugs (DMARDs), including at least 1 tumour necrosis factor (TNF) inhibitor. Repeat courses of rituximab should be given no more frequently than every 6 months, and should only be continued if an adequate response is achieved and maintained. www.nice.org.uk/TA195

- **Rituximab for the first-line maintenance treatment of follicular non-Hodgkin’s lymphoma (June 2011) NICE TA226**
  This NICE guidance was issued for rituximab by intravenous infusion. Rituximab maintenance therapy is recommended as an option for the treatment of people with follicular non-Hodgkin’s lymphoma that has responded to first-line induction therapy with rituximab in combination with chemotherapy. www.nice.org.uk/TA226

- **Rituximab for the first-line treatment of stage III-IV follicular lymphoma (January 2012) NICE TA243**
  This NICE guidance was issued for rituximab by intravenous infusion. Rituximab, in combination with:
  - cyclophosphamide, vincristine and prednisolone (CVP);
  - cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP);
  - mitoxantrone, chlorambucil and prednisolone (MCP);
  - cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-alfa (CHVPi); or
  - chlorambucil is recommended as an option for the treatment of symptomatic stage III and IV follicular lymphoma in previously untreated patients. www.nice.org.uk/TA243

- **Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmatic antibody-associated vasculitis (March 2014) NICE TA308**
  This NICE guidance was issued for rituximab by intravenous infusion. Rituximab, in combination with glucocorticoids, is recommended as an option for inducing remission in adults with anti-neutrophil cytoplasmatic antibody (ANCA)-associated vasculitis (severely active granulomatosis with polyangiitis [Wegener’s] and microscopic polyangiitis), only if:
  - further cyclophosphamide treatment would exceed the maximum cumulative cyclophosphamide dose, or
  - cyclophosphamide is contraindicated or not tolerated, or
  - the patient has not completed their family, and treatment with cyclophosphamide may materially affect their fertility, or
  - the disease has remained active or progressed despite a course of cyclophosphamide lasting 3–6 months or
  - the patient has had uroepithelial malignancy. www.nice.org.uk/TA308

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (August 2013) that Rituximab (MabThera®) is accepted for restricted use within NHS Scotland, in combination with glucocorticoids for the induction of remission in adult patients with severe, active granulomatosis with polyangiitis (Wegener’s) and microscopic polyangiitis. It is restricted to use in patients who have relapsed following treatment with cyclophosphamide or who are intolerant to or unable to receive cyclophosphamide.

The Scottish Medicines Consortium has advised (June 2014) that subcutaneous rituximab (MabThera®) is accepted for restricted use within NHS Scotland, in accordance with UK licensing, except in the maintenance setting, where use is restricted to patients who have responded to induction therapy with rituximab plus chemotherapy.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **MabThera (Roche Products Ltd)**
  Rituximab 119.66 mg per 1 ml MabThera 1400mg/11.7ml solution for injection vials | 1 vial £34.65 (Hospital only)

**Solution for infusion**

- **MabThera (Roche Products Ltd)**
  Rituximab 10 mg per 1 ml MabThera 100mg/10ml concentrate for solution for infusion vials | 1 vial £873.15
MONOClonAL ANTibodies (ANTIneoPlastic)

Bevacizumab

DRUG ACTION Bevacizumab is a monoclonal antibody that inhibits vascular endothelial growth factor.

INDICATIONS AND DOSE

Treatment of metastatic colorectal cancer in combination with fluoropyrimidine-based chemotherapy / First-line treatment of metastatic breast cancer in combination with paclitaxel when treatment with other chemotherapy, including taxanes or anthracyclines is not appropriate / First-line treatment of metastatic breast cancer in combination with capcitabine when treatment with other chemotherapy, including taxanes or anthracyclines is not appropriate (patients who have received adjuvant taxane or anthracycline-containing regimens in the previous 12 months should not be treated with bevacizumab in combination with capcitabine) / Advanced or metastatic renal cell carcinoma in combination with interferon alfa-2a / First-line treatment of unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology (in combination with platinum-based chemotherapy) / First-line treatment of advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer (in combination with carboplatin and paclitaxel) / First recurrence of platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who have not been treated previously with bevacizumab or other drugs that target vascular endothelial growth factor (in combination with carboplatin and gemcitabine)

BY INTRAVENOUS INFUSION

Adult: (consult local protocol)

Important safety information

MHRA/CHM ADVICE: BEVACIZUMAB AND SUNITINIB: RISK OF OSTEONECROSIS OF THE JAW (JANUARY 2011)

Treatment with bevacizumab or sunitinib may be a risk factor for the development of osteonecrosis of the jaw. Patients treated with bevacizumab or sunitinib, who have previously received bisphosphonates, or are treated concurrently with bisphosphonates, may be particularly at risk.

Dental examination and appropriate preventive dentistry should be considered before treatment with bevacizumab or sunitinib.

If possible, invasive dental procedures should be avoided in patients treated with bevacizumab or sunitinib who have previously received, or who are currently receiving, intravenous bisphosphonates.

CAUTIONS Elective surgery (withhold treatment and avoid for at least 28 days after major surgery or until wound fully healed) / history of arterial thromboembolism / history of cardiovascular disease (increased risk of cardiovascular events, especially in the elderly) / history of hypertension (increased risk of proteinuria—discontinue if nephrotic syndrome) / increased risk of fistulas (discontinue permanently if tracheo-oesophageal or grade 4 fistula develops) / increased risk of tumour-associated haemorrhage / intra-abdominal inflammation (risk of gastro-intestinal perforation and gall bladder perforation) / uncontrolled hypertension - untreated CNS metastases

INTERACTIONS ➔ Appendix 1 (bevacizumab).


CONCEPTION AND CONTRACEPTION Effective contraception required during and for at least 6 months after treatment in women

PREGNANCY Avoid—toxicity in animal studies. See also Pregnancy and reproductive function in cytotoxic drugs, p. 746.

BREAST FEEDING Manufacturer advises avoid breast-feeding during and for at least 6 months after treatment.

MONITORING REQUIREMENTS

Monitor for necrotising fasciitis (usually secondary to wound healing complications, gastro-intestinal perforation or fistula formation)—discontinue and initiate treatment promptly.

Monitor blood pressure.

Monitor for congestive heart failure.

Monitor for posterior reversible encephalopathy syndrome (presenting as seizures, headache, altered mental status, visual disturbance or cortical blindness, with or without hypertension).

Consider dental check-up before initiating treatment (risk of osteonecrosis of the jaw).

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer (January 2007) NICE TA118

Bevacizumab in combination with fluorouracil plus folinic acid, with or without irinotecan, is not recommended for the first-line treatment of metastatic colorectal cancer; see also NICE guidance Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy. www.nice.org.uk/TA118

Bevacizumab (first-line), sorafenib (firstand second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced or metastatic renal cell carcinoma (August 2009) NICE TA178

Bevacizumab, sorafenib, and temsirolimus are not recommended as first-line treatments for people with advanced or metastatic renal cell carcinoma. Sorafenib and sunitinib are not recommended as second-line treatments for people with advanced or metastatic renal cell carcinoma. www.nice.org.uk/TA178

Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capcitabine for the treatment of metastatic colorectal cancer (December 2010) NICE TA212

Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capcitabine is not recommended for the treatment of metastatic colorectal cancer. www.nice.org.uk/TA212

Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer (February 2011) NICE TA214

Bevacizumab in combination with a taxane is not recommended for the first-line treatment of metastatic breast cancer. www.nice.org.uk/TA214
Brentuximab vedotin and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy (January 2012) NICE TA242

Bevacizumab in combination with non-oxaliplatin (fluoropyrimidine-based) chemotherapy is not recommended for the treatment of patients with metastatic colorectal cancer that has progressed after first-line chemotherapy; see also NICE guidance Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer (January 2007). www.nice.org.uk/TA242

Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer (August 2012) NICE TA263

Bevacizumab in combination with capecitabine is not recommended within its marketing authorisation for the first-line treatment of metastatic breast cancer, that is, when treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate, or when taxanes or anthracyclines have been used as part of adjuvant treatment in the previous 12 months. www.nice.org.uk/TA263

Bevacizumab in combination with paclitaxel and carboplatin for the first-line treatment of advanced ovarian cancer (May 2013) NICE TA284

Bevacizumab in combination with paclitaxel and carboplatin is not recommended for the first-line treatment of advanced ovarian cancer (including fallopian tube and primary peritoneal cancer). www.nice.org.uk/TA284

Bevacizumab in combination with gemcitabine and carboplatin for the treatment of the first recurrence of platinum-sensitive advanced ovarian cancer (May 2013) NICE TA285

Bevacizumab in combination with gemcitabine and carboplatin is not recommended within its marketing authorisation, that is, for the treatment of the first recurrence of platinum-sensitive advanced ovarian cancer (including fallopian tube and primary peritoneal cancer) that has not been previously treated with bevacizumab or other vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor-targeted agents. www.nice.org.uk/TA285

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (April 2012) that bevacizumab (Avastin®) is not recommended for use within NHS Scotland for the first line treatment of patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate.

MEDICAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

Solution for infusion

Avastin® (Roche Products Ltd)

Bevacizumab 25 mg per 1 ml Avastin 400mg/16ml solution for infusion vials | 1 vial (POD) £324.40 (Hospital only)

Avastin 100mg/4ml solution for infusion vials | 1 vial (POD) £242.66 (Hospital only)

Brentuximab vedotin

INDICATIONS AND DOSE

Treatment of relapsed or refractory CD-30 positive Hodgkin’s disease following autologous stem cell transplant or following at least two prior therapies, when autologous stem cell transplant or multi-agent chemotherapy is not a treatment option | Relapsed or refractory systemic anaplastic large cell lymphoma

BY INTRAVENOUS INFUSION

Adult: (consult product literature)

CAUTIONS

Elevated BMI—risk of hyperglycaemia • high tumour burden—risk of tumour lysis syndrome • rapidly proliferating tumours—risk of tumour lysis syndrome

INTERACTIONS

Appendix 1 (brentuximab vedotin).

SIDE-EFFECTS

Common or very common

Abdominal pain • anorexia • anxiety • arthralgia • cholangitis • constipation • cough • dehydration • diarrhoea • dizziness • dyspepsia • dyspnoea • electrolyte disturbances • fatigue • headache • hyperglycaemia • hypertension • hypotension • hypoesthesia • ileus • infection • insomnia • leukocytosis • myalgia • pleural effusion • proteinuria • rash • skin reactions • sweating • tachycardia • vertigo

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

Solution for infusion

Avastin® (Roche Products Ltd)

Bevacizumab 25 mg per 1 ml Avastin 400mg/16ml solution for infusion vials | 1 vial (POD) £324.40 (Hospital only)

Avastin 100mg/4ml solution for infusion vials | 1 vial (POD) £242.66 (Hospital only)

Catumaxomab

INDICATIONS AND DOSE

Treatment of malignant ascites in patients with epithelial cell adhesion molecule (EpCAM) positive carcinomas, where standard therapy is not available or no longer feasible

BY INTRAPERITONEAL INFUSION

Adult: (consult product literature)

CAUTIONS

Haemodynamic insufficiency • hypoproteinaemia • oedema

INTERACTIONS

Appendix 1 (catumaxomab).

SIDE-EFFECTS

Common or very common

Abdominal pain • anorexia • anxiety • arthralgia • cholangitis • constipation • cough • dehydration • diarrhoea • dizziness • dyspepsia • dyspnoea • electrolyte disturbances • fatigue • headache • hyperglycaemia • hypertension • hypotension • hypoesthesia • ileus • infection • insomnia • leukocytosis • myalgia • pleural effusion • proteinuria • rash • skin reactions • sweating • tachycardia • vertigo
Cetuximab

**INDICATIONS AND DOSE**

Treatment of wild-type RAS metastatic colorectal cancer in patients with tumours expressing epidermal growth factor receptor, as combination therapy, or as monotherapy if oxaliplatin- and irinotecan-based therapy has failed or if irinotecan is not tolerated. Treatment of locally advanced squamous cell cancer of the head and neck (in combination with radiotherapy). Treatment of recurrent or metastatic squamous cell cancer of the head and neck (in combination with platinum-based chemotherapy).

**BY INTRAVENOUS INFUSION**

- Adult (initiated by a specialist): consult product literature or local protocols.

**IMPORTANT SAFETY INFORMATION**

MHRA/CHM ADVICE: EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) INHIBITORS: SERIOUS CASES OF KERATITIS AND ULCERATIVE KERATITIS (MAY 2012)

Keratitis and ulcerative keratitis have been reported following treatment with epidermal growth factor receptor (EGFR) inhibitors who present with acute or worsening signs and symptoms suggestive of keratitis should be referred promptly to an ophthalmology specialist. Treatment should be interrupted or discontinued if ulcerative keratitis is diagnosed.

Patients must receive an antihistamine and a corticosteroid at least one hour before infusion. Resuscitation facilities should be available and treatment should be initiated by a specialist.

**CONTRA-INDICATIONS**

RAS mutated colorectal tumours (or if RAS tumour status unknown) - combination of cetuximab with oxaliplatin-containing chemotherapy is contra-indicated in patients with metastatic colorectal cancer who have mutant or unknown RAS status.

**CAUTIONS**

Cardiopulmonary disease - cardiovascular disease - history of keratitis - pulmonary disease - discontinue if interstitial lung disease - risk factors for keratitis - severe dry eye - ulcerative keratitis (including contact lens use).

**INTERACTIONS**

Appendix 1 (cetuximab).

**SIDE-EFFECTS**


- Very rare: Stevens-Johnson syndrome - toxic epidermal necrolysis.

**PREGNANCY**

Use only if potential benefit outweighs risk—no information available. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

**BREAST FEEDING**

Avoid breast-feeding during and for 2 months after treatment—no information available.

**PRE-TREATMENT SCREENING**

Evidence of non-mutated (wild-type) RAS status (at exons 2, 3 and 4 of KRAS and NRAS) is required before cetuximab is initiated for the treatment of metastatic colorectal cancer, and should be determined by an experienced laboratory using a validated test method.

**DIRECTIONS FOR ADMINISTRATION**

Resuscitation facilities should be available.

**NATIONAL FUNDING/ACCESS DECISIONS**

NICE technology appraisals (TAs)

- Cetuximab for the treatment of locally advanced squamous cell cancer of the head and neck (June 2008) NICE TA145.

- Cetuximab in combination with radiotherapy is an option for the treatment of locally advanced squamous cell cancer of the head and neck in patients who have a Karnofsky performance status of 90% or greater and when all forms of platinum-based chemoradiotherapy treatment are contra-indicated. www.nice.org.uk/TA145

- Cetuximab for the treatment of recurrent or metastatic squamous cell cancer of the head and neck (June 2009) NICE TA172.

- Cetuximab in combination with platinum-based chemotherapy is not recommended for the treatment of recurrent or metastatic squamous cell cancer of the head and neck. www.nice.org.uk/TA172.


Cetuximab in combination with fluorouracil, folinic acid and oxaliplatin is an option for the first-line treatment of metastatic colorectal cancer under the following circumstances:

- the primary tumour has been resected or is potentially operable;
- the metastatic disease is confined to the liver and is unresectable; and
- the patient is fit to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab.

In patients unable to tolerate oxaliplatin, or in whom oxaliplatin is contra-indicated, cetuximab in combination with fluorouracil, folinic acid and irinotecan can be used as an alternative.

In addition, the manufacturer is required to rebate 16% of the amount of cetuximab used per patient when used in combination with fluorouracil, folinic acid, and oxaliplatin.

Patients who meet the above criteria should receive cetuximab for no more than 16 weeks. At 16 weeks, cetuximab should be stopped and the patient should be...
assessed for resection of liver metastases. www.nice.org.uk/TA176

- Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy (January 2012) NICE TA242

Cetuximab monotherapy or combination chemotherapy is not recommended for the treatment of patients with metastatic colorectal cancer that has progressed after first-line chemotherapy. www.nice.org.uk/TA242

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (December 2014) that cetuximab (Erbitux®) is accepted for restricted use within NHS Scotland, in combination with irinotecan or oxaliplatin-based chemotherapy, for the treatment of RAS wild-type metastatic colorectal cancer in patients who have not previously received chemotherapy for their metastatic disease (first-line treatment).

- MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- Erbitux (Merck-Serono Ltd)
  
  Cetuximab 5 mg per 1 ml 100mg/20ml solution for infusion vials | 1 vial (£0.178.10 (Hospital only))
  
  Erbitux 500mg/100ml solution for infusion vials | 1 vial (£0.180.50 (Hospital only))

Ipilimumab

- **DRUG ACTION** Ipilimumab causes T-cell activation.

**INDICATIONS AND DOSE**

Treatment of unresectable or metastatic advanced melanoma

**BY INTRAVENOUS INFUSION**

- Adult: (consult product literature)

- **CAUTIONS** For full details consult product literature.

- **INTERACTIONS** Appendix 1 (ipilimumab).

- **SIDE-EFFECTS, FURTHER INFORMATION**

**SIDE-EFFECTS** Infusion-related side-effects

**IMMUNE-RELATED REACTIONS** A corticosteroid can be used after starting ipilimumab, to treat immune-related reactions.

For further information on side-effects, (including monitoring and management of side effects) consult product literature.

- **CONCEPTION AND CONTRACEPTION** Use effective contraception.

- **PREGNANCY** Avoid unless potential benefit outweighs risk (toxicity in animal studies).

- **BREAST FEEDING** Discontinue breast-feeding—no information available.

- **HEPATIC IMPAIRMENT** Use with caution if plasma-bilirubin concentration greater than 3 times upper limit of normal range or if plasma-transaminase concentration 5 times or greater than the upper limit of normal range.

- **MONITORING REQUIREMENTS** For information on monitoring of side effects, consult product literature.

- **PRESCRIBING AND DISPENSING INFORMATION** Infusion-related side-effects have been reported; premedication with paracetamol and an antihistamine is recommended.

- **NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (December 2012) NICE TA268

Ipilimumab is recommended as an option for the treatment of advanced (unresectable or metastatic) melanoma in patients who have received prior therapy, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme. www.nice.org.uk/TA268

- Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma (July 2014) NICE TA319

Ipilimumab is recommended, within its marketing authorisation, as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme. www.nice.org.uk/TA319

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (March 2013) that ipilimumab (Yervoy®) is accepted for restricted use within NHS Scotland for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy, only whilst ipilimumab is available at the price agreed in the patient access scheme.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- Yervoy (Bristol-Myers Squibb Pharmaceuticals Ltd)
  
  Ipilimumab 5 mg per 1 ml 50mg/10ml concentrate for solution for infusion vials | 1 vial (£3,750.00 (Hospital only))
  
  Ipilimumab 200mg/40ml concentrate for solution for infusion vials | 1 vial (£15,000.00 (Hospital only))

Obinutuzumab

The properties listed below are those particular to the drug only. For properties common to the class, see Anti-lymphocyte monoclonal antibodies, p. 731.

**INDICATIONS AND DOSE**

Treatment of previously untreated chronic lymphocytic leukaemia in patients for whom full-dose fludarabine-based therapy is unsuitable due to co-morbidities

**BY INTRAVENOUS INFUSION**

- Adult: (consult product literature or local protocols)

- **CONTRA-INDICATIONS** For obinutuzumab contra-indications, consult product literature.

- **CAUTIONS**

**CAUTIONS, FURTHER INFORMATION**

Hepatitis B infection and reactivation

Hepatitis B infection and reactivation (including fatal cases) have been reported in patients taking obinutuzumab. Patients with positive hepatitis B serology should be referred to a liver specialist for monitoring and initiation of antiviral therapy before treatment initiation; treatment should not be initiated in patients with evidence of current hepatitis B infection until the infection has been adequately treated. Patients should be closely monitored for clinical and laboratory signs of active hepatitis B infection during treatment and for up to a year following the last infusion (consult product literature).

For full details on the cautions of obinutuzumab, consult product literature.

- **INTERACTIONS** Appendix 1 (obinutuzumab).

- **SIDE-EFFECTS** For full side effect details for obinutuzumab (including monitoring and management), consult product literature.

- **CONCEPTION AND CONTRACEPTION** Use effective contraception during and for 18 months after treatment.

- **PREGNANCY** Avoid unless potential benefit outweighs risk of B-lymphocyte depletion in fetus.
**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**
- Gazyvaro (Roche Products Ltd)
  - Obinutuzumab 25 mg per 1 ml Gazyvaro 1000mg/40ml concentrate for solution for infusion vials | 1 vial (£3,312.00 (Hospital only)

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**Ofatumumab**
The properties listed below are those particular to the drug only. For properties common to the class, see Anti-lymphocyte monoclonal antibodies, p. 731.

**INDICATIONS AND DOSE**
- Treatment of chronic lymphocytic leukaemia (CLL) in patients refractory to fludarabine and alemtuzumab
- Treatment of CLL in patients who have not received prior therapy and who are not eligible for fludarabine based therapy (in combination with chlorambucil or bendamustine)

**BY INTRAVENOUS INFUSION**
- Adult: Premedication must be given 30 minutes to 2 hours before each dose—consult product literature for details (consult local protocol)

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**CONTRA-INDICATIONS**
For full details on the contra-indications for ofatumumab, consult product literature.

**CAUTIONS**
History of cardiac disease—monitor closely and discontinue treatment if cardiac arrhythmias occur

**CAUTIONS, FURTHER INFORMATION**
- Hepatitis B infection and reactivation
  - Hepatitis B infection and reactivation (including fatal cases) have been reported in patients taking ofatumumab. Patients with positive hepatitis B serology should be referred to a liver specialist for monitoring and initiation of antiviral therapy before treatment initiation; treatment should not be initiated in patients with evidence of current hepatitis B infection until the infection has been adequately treated. Patients should be closely monitored for clinical and laboratory signs of active hepatitis B infection during treatment and for up to a year following the last infusion (consult product literature).

For full details about the cautions for ofatumumab, consult product literature.

**INTERACTIONS**
- Appendix 1 (ofatumumab).
Panitumumab

**DRUG ACTION** Panitumumab is a monoclonal antibody that binds to the epidermal growth factor receptor (EGFR).

**INDICATIONS AND DOSE**
Treatment of non-mutated RAS metastatic colorectal cancer (combination therapy) / Treatment of non-mutated RAS metastatic colorectal cancer (monotherapy after failure of fluoropyrimidine-, oxaliplatin- and irinotecan-containing chemotherapy regimens) BY INTRAVENOUS INFUSION

- Adult: (consult product literature)

**INTERACTIONS**

- Contraindications and precautions
  - INTERACTIONS
  - CONTRA-INDICATIONS
  - Common or very common
  - Anorexia, anxiety, back pain, biochemical disturbances, cellulitis, cheilitis, chills, cough, deep vein thrombosis, dyspnea, dysphonia, electrolyte disturbances, epistaxis, eyelash growth, flushing, folliculitis, gastro-oesophageal reflux disease, hyperhydrosis, insomnia, malaise, pain in extremities, peripheral oedema, pulmonary embolism, pyrexia, rectal haemorrhage, severe hypersensitivity reactions (possibly delayed), urinary tract infection, weight loss
  - Uncommon
  - Bronchospasm, cyanosis, hirsutism, infusion-related reactions, nasal dryness
  - Rare
  - Keratitis, skin necrosis, Stevens-Johnson syndrome
  - Toxic epidermal necrolysis
  - Frequency not known
  - Abdominal pain, acne, alopecia, bone-marrow suppression, conjunctivitis, constipation, dehydration, diarrhoea, dizziness, dry eyes, dry mouth, dry skin, erythema, extravasation, hand-foot syndrome, headache, hypertension, hypertrichosis, hyperuricaemia, hypocalcaemia, hypomagnesaemia, hypotension, increased lacrimation, interstitial lung disease, mucosal inflammation, nail disorders, nausea, ocular disorders, ocular hyperaemia, oral mucositis, pruritus, rash, skin reactions, tachycardia, thromboembolism, tumour lysis syndrome, vomiting

**CONCEPTION AND CONTRACEPTION**
Manufacturer advises effective contraception during and for at least 6 months after treatment in women

**PREGNANCY**
Avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

**BREAST FEEDING**
Manufacturer advises avoid breastfeeding during and for 2 months after treatment.

**PRE-TREATMENT SCREENING**
Evidence of non-mutated RAS status (at exons 2, 3 and 4 of KRAS and NRAS) is required before panitumumab treatment is initiated, and should be determined by an experienced laboratory using a validated test method.

**MONITORING REQUIREMENTS**

- Monitor for hypomagnesaemia.
- Monitor for hypocalcaemia.
- Monitor for dermatological reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (consult product literature).

**NATIONAL FUNDING/ACCESS DECISIONS**
NICE technology appraisals (TAs)

- Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy (January 2012) NICE TA242
- Panitinumab monotherapy is not recommended for the treatment of patients with metastatic colorectal cancer that has progressed after first-line chemotherapy. www.nice.org.uk/TA242

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- ELECTROLYTES: May contain Sodium
  - Vectibix (Amgen Ltd)
    - Panitumumab 20 mg per 1 ml Vectibix 400mg/20ml concentrate for solution for infusion vials | 1 vial (P) £1.517.16 (Hospital only)
    - Vectibix 100mg/5ml concentrate for solution for infusion vials | 1 vial (P) £1379.29 (Hospital only)

Pertuzumab

**DRUG ACTION** Pertuzumab is a recombinant humanised monoclonal antibody, and acts by inhibiting human epidermal growth factor receptor 2 protein (HER2) dimerisation.

**INDICATIONS AND DOSE**
Treatment of HER2-positive metastatic or locally recurrent unresectable breast cancer in combination with trastuzumab and docetaxel, in patients who have not received previous anti-HER2 therapy or chemotherapy (initiated by a specialist) BY INTRAVENOUS INFUSION

- Adult: (consult product literature)

**CAUTIONS**
Conditions that could impair left ventricular function, history of congestive heart failure, impaired left ventricular function, prior anthracycline exposure, radiotherapy to the chest area, recent myocardial infarction, serious cardiac arrhythmia, uncontrolled hypertension

**INTERACTIONS**

- Appendix 1 (pertuzumab).
Siltuximab

**DRUG ACTION** Siltuximab is a monoclonal antibody that inhibits interleukin-6 receptor binding.

**INDICATIONS AND DOSE**

Treatment of multicentric Castleman’s disease (MCD) in patients who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative

*By intravenous infusion*

- Adult: 11 mg/kg every 3 weeks

**CAUTIONS** Patients at increased risk of gastrointestinal perforation—promptly investigate those presenting with symptoms suggestive of gastrointestinal perforation—severe infection—withdraw treatment until resolved—treat infection prior to treatment

**CAUTIONS, FURTHER INFORMATION**

Hypersensitivity reactions Infusion-related side-effects are reported commonly with siltuximab; resuscitation facilities should be available during treatment. Consult product literature for further information about siltuximab cautions.

**INTERACTIONS** Appendices 1 (siltuximab).

Live vaccines should not be given concurrently or within 4 weeks before starting siltuximab treatment.

**SIDE-EFFECTS**

- **Common or very common** When used in combination with trastuzumab and docetaxel: anaemia; arthralgia; chills; constipation; cough; decreased appetite; diarrhoea; dizziness; dry skin; dyspepsia; dyspnoea; febrile neutropenia; headache; increased lacrimation; infusion-related reactions; insomnia; left ventricular dysfunction; leucopenia; malaise; myalgia; nail disorder; nasopharyngitis; neutropenia; oedema; pain; paronychia; peripheral neuropathy; pleural effusion; pruritus; pyrexia; rash; severe hypersensitivity reactions; taste disturbance; upper respiratory tract infection

- **Uncommon** Interstitial lung disease (when used in combination with trastuzumab and docetaxel)

- **Frequency not known** Alopecia; bone-marrow suppression; extravasation; hyperuricaemia; nausea; oral mucositis; thromboembolism; tumour lysis syndrome; vomiting

**CONCEPTION AND CONTRACEPTION** Ensure effective contraception during and for at least six months after treatment in women of childbearing potential

**PREGNANCY** Avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

**BREAST FEEDING** Avoid—no information available.

**HEPATIC IMPAIRMENT** Caution—no information available.

**RENAL IMPAIRMENT** Caution in severe impairment—no information available.

**MONITORING REQUIREMENTS**

- Assess for signs and symptoms of congestive heart failure (including left ventricular ejection fraction) before and during treatment—consult product literature, and withhold treatment if necessary.
- Monitor for febrile neutropenia.

**DIRECTIONS FOR ADMINISTRATION** Resuscitation facilities should be available.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- Perjeta (Roche Products Ltd)

  - Pertuzumab 30 mg per 1 ml Perjeta 420mg/14ml concentrate for solution for infusion vials | 1 vial (£2,395.00 Hospital only)

- Sylvant (Janssen-Cilag Ltd)

  - Siltuximab 100 mg Sylvant 100mg powder for concentrate for solution for infusion vials | 1 vial (£415.00 Hospital only)
  - Siltuximab 400 mg Sylvant 400mg powder for concentrate for solution for infusion vials | 1 vial (£1,661.00 Hospital only)

**SIDE-EFFECTS, FURTHER INFORMATION** Infusion-related side effects Siltuximab therapy should be discontinued permanently in the event of a severe infusion-related reaction, anaphylaxis, a severe allergic reaction, or the occurrence of cytokine-release syndrome. Mild to moderate infusion-related reactions may improve by temporarily reducing the rate or stopping the infusion. When restarting treatment, a reduced infusion rate and the administration of antihistamines, paracetamol, and corticosteroids should be considered. Consider discontinuation of siltuximab if more than 2 doses are delayed due to treatment-related toxicities during the first 48 weeks—for full details consult product literature.

**CONCEPTION AND CONTRACEPTION** Women of childbearing potential should use effective contraception during and for 3 months after treatment.

**PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

**BREAST FEEDING** Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT** Use with caution in hepatic impairment.

**MONITORING REQUIREMENTS**

- Monitor neutrophil and platelet count, and haemoglobin levels prior to each dose of siltuximab treatment for the first 12 months and thereafter prior to every third dosing cycle. Consider delaying treatment if required neutrophil, platelet, and haemoglobin levels not achieved—consult product literature for details.
- Monitor for infection during treatment.

**DIRECTIONS FOR ADMINISTRATION** For Intravenous infusion (Sylvant®), give intermittently in Glucose 5%. Allow vials to reach room temperature over approximately 30 minutes, then reconstitute each 100 mg vial with 5.2 mL of water for injection, and each 400 mg vial with 20 mL of water for injection, to produce a 20 mg/mL solution. Gently swirl without shaking to dissolve. Further dilute to 250 mL with glucose 5% and gently mix. Use within 6 hours of dilution and give over 60 minutes using an administration set lined with polyvinyl chloride or polyurethane, through a low-protein binding in-line 0.2 micron filter.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**

- Sylvant (Janssen-Cilag Ltd)

  - Siltuximab 100 mg Sylvant 100mg powder for concentrate for solution for infusion vials | 1 vial (£415.00 Hospital only)
  - Siltuximab 400 mg Sylvant 400mg powder for concentrate for solution for infusion vials | 1 vial (£1,661.00 Hospital only)
Trastuzumab

INDICATIONS AND DOSE
Treatment of early breast cancer which overexpresses human epidermal growth factor receptor-2 (HER2) (initiated by a specialist) | Treatment of metastatic breast cancer in patients with HER2-positive tumours who have not received chemotherapy for metastatic breast cancer and in whom anthracycline treatment is inappropriate (in combination with paclitaxel or docetaxel) (initiated by a specialist) | Treatment of metastatic breast cancer in postmenopausal patients with hormone-receptor positive HER2-positive tumours not previously treated with trastuzumab (in combination with an aromatase inhibitor) (initiated by a specialist)

BY INTRAVENTRUS INFUSION OR BY SUBCUTANEOUS INJECTION
Adult: (consult product literature or local protocols)
Monotherapy for metastatic breast cancer in patients with tumours that overexpress HER2 who have received at least 2 chemotherapy regimens including, where appropriate, an anthracycline and a taxane (initiated by a specialist)

BY INTRAVENTRUS INFUSION OR BY SUBCUTANEOUS INJECTION
Adult: Women with oestrogen-receptor-positive breast cancer should also have received hormonal therapy (consult product literature or local protocols)

Treatment of metastatic gastric cancer in patients with HER2-positive tumours who have not received treatment for metastatic gastric cancer (in combination with capecitabine or fluorouracil and cisplatin) (initiated by a specialist)

BY INTRAVENTRUS INFUSION
Adult: (consult product literature or local protocols)

CONTRA-INDICATIONS
Severe dyspnoea at rest

CAUTIONS
Coronary artery disease | history of hypertension | symptomatic heart failure | uncontrolled arrhythmias

INTERACTIONS
Appendix 1 (trastuzumab)

Use with anthracyclines
Concomitant use of trastuzumab with anthracyclines is associated with cardiotoxicity. The use of anthracyclines even after stopping trastuzumab can increase the risk of cardiotoxicity and if possible should be avoided for up to 24 weeks. If an anthracycline needs to be used, cardiac function should be monitored closely.

SIDE-EFFECTS
Acne | alopecia | anaphylaxis | angioedema | anxiety | arthralgia | arthritis | asthenia | bone pain | bone-marrow suppression | cardiotoxicity | chest pain | chills | depression | dizziness | drowsiness | dry eye | dry skin | ecchymosis | extravasation | fever | gastrointestinal symptoms | headache | hepatitis | hypersensitivity reactions | hypertension | hypotonia | hyperuricaemia | hypotension | increased lacrimation | infection | infusion-related side-effects (possibly delayed onset) | insomnia | leg cramps | malaise | mastitis | myalgia | nail disorders | nausea | oedema | oral mucositis | paraesthesia | paresthesia | peripheral neuropathy | pruritus | pulmonary events (possibly delayed onset) | rash | sweating | taste disturbance | thromboembolism | tremor | tumour lysis syndrome | urticaria | vomiting | weight loss

PREGNANCY
Manufacturer advises avoid—oligohydramnios reported. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

BREAST FEEDING
Avoid breast-feeding during treatment and for 7 months afterwards.

MONITORING REQUIREMENTS
Cardiotoxicity Monitor cardiac function before and during treatment—for details of monitoring and managing cardiotoxicity, consult product literature.

DIRECTIONS FOR ADMINISTRATION
Resuscitation facilities should be available during administration of trastuzumab.

PRESCRIBING AND DISPENSING INFORMATION
When prescribing, dispensing or administering, check that this is the correct preparation—trastuzumab is not interchangeable with trastuzumab emtansine.

NATIONAL FUNDING/ACCESS DECISIONS
NICE technology appraisals (TAs)
Guidance on the use of trastuzumab for the treatment of advanced breast cancer (March 2002) NICE TA34
Trastuzumab in combination with paclitaxel is recommended as an option for patients with tumours expressing human epidermal growth factor receptor 2 (HER2) scored at levels of 3+ who have not received chemotherapy for metastatic breast cancer, and in whom anthracycline treatment is inappropriate.
Trastuzumab monotherapy is recommended as an option for patients with tumours expressing HER2 scored at levels of 3+ who have received at least two chemotherapy regimens for metastatic breast cancer. Prior chemotherapy must have included at least an anthracycline and a taxane where these treatments are appropriate. It should also have included hormonal therapy in suitable oestrogen-receptor-positive patients. www.nice.org.uk/TA34

Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer (August 2006) NICE TA107
Trastuzumab, given at 3-week intervals for 1 year or until disease recurrence (whichever is the shorter period), is recommended as an option for women with early-stage HER2-positive breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable). www.nice.org.uk/TA107

Trastuzumab for the treatment of HER2-positive metastatic gastric cancer (November 2010) NICE TA208
Trastuzumab in combination with cisplatin and capecitabine or fluorouracil is recommended for human epidermal growth factor receptor-2-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction in patients who:
• have not received treatment for metastatic disease and
• have tumours expressing high levels of HER2 as defined by a positive immunohistochemistry score of 3.
www.nice.org.uk/TA208

Lapatinib or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2 (June 2012) NICE TA257
Lapatinib or trastuzumab in combination with an aromatase inhibitor is not recommended for first-line treatment in postmenopausal women of metastatic hormone-receptor-positive breast cancer that overexpresses human epidermal growth factor receptor 2 (HER2).
Postmenopausal women currently receiving lapatinib or trastuzumab in combination with an aromatase inhibitor for this indication should have the option to continue treatment until they and their clinician consider it appropriate to stop. www.nice.org.uk/TA257

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (December 2013) that subcutaneous trastuzumab injection (Herceptin®) is accepted for restricted use within NHS Scotland for the treatment of adults with HER2 positive metastatic breast cancer and early breast cancer, when used within licensed indications excluding use in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive metastatic breast cancer, not previously treated with trastuzumab.
Trastuzumab emtansine

- **DRUG ACTION** Trastuzumab emtansine is an antibody-drug conjugate that contains trastuzumab covalently linked to DM1, a cytotoxic microtubule inhibitor.

### INDICATIONS AND DOSE

**Monotherapy for the treatment of HER2-positive, unresectable, locally advanced or metastatic breast cancer, in adult patients who have previously received trastuzumab and a taxane separately or in combination (initiated by a specialist).**

**Monotherapy for the treatment of HER2-positive, unresectable, locally advanced or metastatic breast cancer, in adult patients who have developed disease recurrence during or within 6 months of completing adjuvant therapy (initiated by a specialist).**

**BY INTRAVENOUS INFUSION**

- Adult: (consult product literature or local protocols)

### CAUTIONS

- Dyspnoea at rest—increased risk of pulmonary events - history of congestive heart failure - patients over 75 years - peripheral neuropathy (temporarily discontinue treatment—consult product literature) - recent history of myocardial infarction - recent history of unstable angina - risk of left ventricular dysfunction - consult product literature for specific risks with trastuzumab treatment - serious arrhythmias

### INTERACTIONS

- Appendix 1 (trastuzumab), Caution with concomitant anticoagulant medication—increased risk of thrombocytopenia with haemorrhagic events.

### SIDE-EFFECTS


- Uncommon Hepatic failure - hepatic toxicity - interstitial lung disease - nodular regenerative hyperplasia - pneumonitis - portal hypertension

- Frequency not known Alopecia - bone-marrow suppression - extravasation - hyperuricaemia - nausea - oral mucositis - thromboembolism - tumour lysis syndrome - vomiting

### CONCEPTION AND CONCEPTION

- Effective contraception must be used during and for 6 months after stopping treatment in women and men.

### PREGNANCY

- Manufacturer advises avoid—oligohydramnios reported with trastuzumab. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

### BREAST FEEDING

- Manufacturer advises avoid breast-feeding during and for 6 months after treatment.

### MEDICINAL FORMS

<table>
<thead>
<tr>
<th>Powder for solution for infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab emtansine 100 mg</td>
</tr>
<tr>
<td>Kadcyla (Roche Products Ltd)</td>
</tr>
<tr>
<td>1 vial £1,641.01</td>
</tr>
<tr>
<td>Trastuzumab emtansine 160 mg</td>
</tr>
<tr>
<td>Kadcyla 160mg powder for</td>
</tr>
<tr>
<td>concentrate for solution for</td>
</tr>
<tr>
<td>infusion vials</td>
</tr>
</tbody>
</table>

### MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug.

### DIRECTIONS FOR ADMINISTRATION

- Resuscitation facilities should be available during administration of trastuzumab emtansine.

### PRESCRIBING AND DISPENSING INFORMATION

- When prescribing, dispensing or administering, check that this is the correct preparation—trastuzumab emtansine and trastuzumab are not interchangeable.

### HEPATIC IMPAIRMENT

- Consult product literature for dose modification in cases of abnormal liver function tests. Consult product literature for initiating treatment and discontinuation in cases of abnormal liver function tests.

### RENAL IMPAIRMENT

- No information available—manufacturer advises caution in severe impairment.

### MONITORING REQUIREMENTS

- Monitor hepatic function before each dose.
- Monitor for signs and symptoms of neurotoxicity.
- Monitor closely for infusion-related and hypersensitivity reactions.
- Monitor platelet count before each dose and as clinically indicated (consult product literature for treatment modification in thrombocytopenia).
- Test cardiac function before treatment and regularly during treatment—delay or discontinue treatment in cases of left ventricular dysfunction.
- Monitor for dyspnoea, cough, fatigue and pulmonary infiltrates—discontinue if interstitial lung disease or pneumonitis confirmed (fatal cases reported).

### DIRECTIONS FOR ADMINISTRATION

- Resuscitation facilities should be available during administration of trastuzumab emtansine.

### PRESCRIBING AND DISPENSING INFORMATION

- When prescribing, dispensing or administering, check that this is the correct preparation—trastuzumab emtansine and trastuzumab are not interchangeable.

### MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug.

### Powder for solution for infusion

- Trastuzumab emtansine 100 mg
- Kadcyla (Roche Products Ltd)
- 1 vial £1,641.01
- Trastuzumab emtansine 160 mg
- Kadcyla 160mg powder for
- concentrate for solution for
- infusion vials | 1 vial £2,625.62

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### 2.2 Cytotoxic responsive malignancy

#### Cytotoxic drugs

The chemotherapy of cancer is complex and should be confined to specialists in oncology. Cytotoxic drugs have both anti-cancer activity and the potential to damage normal tissue; most cytotoxic drugs are teratogenic. Chemotherapy may be given with a curative intent or it may aim to prolong life or to palliate symptoms. In an increasing number of cases chemotherapy may be combined with radiotherapy or surgery or both as either neoadjuvant treatment (initial chemotherapy aimed at shrinking the primary tumour, thereby rendering local therapy less destructive or more effective) or as adjuvant treatment (which follows definitive treatment of the primary disease, when the risk of subclinical metastatic disease is known to be high). All cytotoxic drugs cause side-effects and a balance has to be struck between likely benefit and acceptable toxicity.

Combinations of cytotoxic drugs, as continuous or pulsed cycles of treatment, are frequently more toxic than single drugs but have the advantage in certain tumours of enhanced response, reduced development of drug resistance and increased survival. However for some tumours, single-agent chemotherapy remains the treatment of choice.

Cytotoxic drugs fall into a number of classes, each with characteristic antitumour activity, sites of action, and toxicity. A knowledge of sites of metabolism and excretion
is important because impaired drug handling as a result of disease is not uncommon and may result in enhanced toxicity.

**Guidelines for handling cytotoxic drugs**

- Trained personnel should reconstitute cytotoxics
- Reconstitution should be carried out in designated pharmacy areas
- Protective clothing (including gloves, gowns, and masks) should be worn
- The eyes should be protected and means of first aid should be specified
- Pregnant staff should avoid exposure to cytotoxic drugs (all females of child-bearing age should be informed of the reproductive hazard)
- Use local procedures for dealing with spillages and safe disposal of waste material, including syringes, containers, and absorbent material
- Staff exposure to cytotoxic drugs should be monitored

**Intrathecal chemotherapy**

A Health Service Circular (HSC 2008/001) provides guidance on the introduction of safe practice in NHS Trusts where intrathecal chemotherapy is administered; written local guidance covering all aspects of national guidance should be available. Support for training programmes is also available.

Copies, and further information may be obtained from: Department of Health PO Box 777 London SE1 6XH Fax: 01623 724524

It is also available from the Department of Health website (www.dh.gov.uk).

**Safe systems for cytotoxic medicines**

NHS cancer networks have been established across the UK to bring together all stakeholders in all sectors of care, to work collaboratively to plan and deliver high quality cancer services for a given population. NHS cancer networks have websites containing information on local chemotherapy services and treatment (see www.cancer.nhs.uk/networks.htm).

Safe system requirements:

- cytotoxic drugs for the treatment of cancer should be given as part of a wider pathway of care coordinated by a multidisciplinary team
- cytotoxic drugs should be prescribed, dispensed, and administered only in the context of a written protocol or treatment plan
- injectable cytotoxic drugs should only be dispensed if they are prepared for administration
- oral cytotoxic medicines should be dispensed with clear directions for use

**Important safety information**

**Risks of incorrect dosing of oral anti-cancer medicines**

The National Patient Safety Agency has advised (January 2008) that the prescribing and use of oral cytotoxic medicines should be carried out to the same standard as parenteral cytotoxic therapy.

Standards to be followed to achieve this include:

- non-specialists who prescribe or administer on-going oral cytotoxic medication should have access to written protocols and treatment plans, including guidance on the monitoring and treatment of toxicity;
- staff dispensing oral cytotoxic medicines should confirm that the prescribed dose is appropriate for the patient. Patients should have written information that includes details of the intended oral anti-cancer regimen, the treatment plan, and arrangements for monitoring, taken from the original protocol from the initiating hospital. Staff dispensing oral cytotoxic medicines should also have access to this information, and to advice from an experienced cancer pharmacist in the initiating hospital.

**Doses**

Doses of cytotoxic drugs are determined using a variety of different methods including body-surface area or body-weight. Alternatively, doses may be fixed. Doses may be further adjusted following consideration of a patient’s neutrophil count, renal and hepatic function, and history of previous adverse effects to the cytotoxic drug. Doses may also differ depending on whether a drug is used alone or in combination.

Because of the complexity of dosage regimens in the treatment of malignant disease, dose statements have been omitted from some of the drug entries in this chapter. However, even where dose statements have been provided, detailed specialist literature, individual hospital chemotherapy protocols, or local cancer networks (www.cancer.nhs.uk/networks.htm) should be consulted before prescribing, dispensing, or administering cytotoxic drugs.

Prescriptions should not be repeated except on the instructions of a specialist.

**Side-effects of cytotoxic drugs**

Side-effects common to most cytotoxic drugs are discussed below whilst side-effects characteristic of a particular drug or class of drugs (e.g. neurotoxicity with vinca alkaloids) are mentioned in the appropriate sections. Manufacturers’ product literature, hospital-trust protocols, and cancer-network protocols should be consulted for full details of side-effects associated with individual drugs and specific chemotherapy regimes.

Many side-effects of cytotoxic drugs often do not occur at the time of administration, but days or weeks later. It is therefore important that patients and healthcare professionals can identify symptoms that cause concern and can contact an expert for advice. Toxicities should be accurately recorded using a recognised scoring system such as the Common Toxicity Criteria for Adverse Events (CTCAE) developed by the National Cancer Institute.

**Extravasation of intravenous drugs**

A number of cytotoxic drugs will cause severe local tissue necrosis if leakage into the extravascular compartment occurs. To reduce the risk of extravasation injury it is recommended that cytotoxic drugs are administered by appropriately trained staff. See information on the prevention and management of extravasation injury.

**Oral mucositis**

A sore mouth is a common complication of cancer chemotherapy; it is most often associated with fluorouracil p. 761, methotrexate p. 762, and the anthracyclines. It is best to prevent the complication. Good oral hygiene (rinsing the mouth frequently and effective brushing of the teeth with a soft brush 2–3 times daily) is probably beneficial. For fluorouracil, sucking ice chips during short infusions of the drug is also helpful.

Once a sore mouth has developed, treatment is much less effective. Saline mouthwashes should be used but there is no good evidence to support the use of antiseptic or anti-inflammatory mouthwashes. In general, mucositis is self-limiting but with poor oral hygiene it can be a focus for blood-borne infection.

**Tumour lysis syndrome**

Tumour lysis syndrome occurs secondary to spontaneous or treatment-related rapid destruction of malignant cells. Patients at risk of tumour lysis syndrome include those with non-Hodgkin’s lymphoma (especially if high grade and...
Malignant disease

bulky disease), Burkitt’s lymphoma, acute lymphoblastic leukaemia and acute myeloid leukaemia (particularly if high white blood cell counts or bulky disease), and occasionally those with solid tumours. Pre-existing hyperuricaemia, dehydration, and renal impairment are also predisposing factors. Features include hyperkalaemia, hyperuricaemia (see below), and hyperphosphataemia with hypocalcaemia; renal damage and arrhythmias can follow. Early identification of patients at risk, and initiation of prophylaxis or therapy for tumour lysis syndrome, is essential.

Hyperuricaemia
Hyperuricaemia, which may be present in high-grade lymphoma and leukaemia, can be markedly worsened by chemotherapy and is associated with acute renal failure. Allopurinol p. 909 should be started 24 hours before treating such tumours and patients should be adequately hydrated. The dose of mercaptopurine p. 762 or azathioprine p. 716 should be reduced if allopurinol needs to be given concomitantly.

Rasburicase p. 784, a recombinant urate oxidase, is licensed for hyperuricaemia in patients with haematological malignancy. It rapidly reduces plasma-uric acid concentration and may be of particular value in preventing complications following treatment of leukaemias or bulky lymphomas.

Bone-marrow suppression
All cytotoxic drugs except vincristine sulfate p. 773 and bleomycin p. 766 cause bone-marrow suppression. This commonly occurs 7 to 10 days after administration, but is delayed for certain drugs, such as carmustine p. 749, lomustine p. 752, and melphalan p. 752. Peripheral blood counts must be checked before each treatment, and doses should be reduced or therapy delayed if bone-marrow has not recovered.

Cytotoxic drugs may be contra-indicated in patients with acute infection; any infection should be treated before, or when starting, cytotoxic drugs.

Fever in a neutropenic patient (neutrophil count less than 1.06 × 10^9/litre) requires immediate broad-spectrum antibacterial therapy. Appropriate bacteriological investigations should be conducted as soon as possible. Patients taking cytotoxic drugs who have signs or symptoms of infection should be advised to seek prompt medical attention. All patients should initially be investigated and treated under the supervision of the appropriate oncology or haematology specialist.

In selected patients, the duration and the severity of neutropenia can be reduced by the use of recombinant human granulocyte-colony stimulating factors.

Symptomatic anaemia is usually treated with red blood cell transfusions. For guidance on the use of erythropoietins in patients with cancer, see MHRA/CHM advice and NICE guidance.

See advice on the use of live vaccines in individuals with impaired immune response.

Alopecia
Reversible hair loss is a common complication, although it varies in degree between drugs and individual patients. No pharmacological methods of preventing this are available.

Thromboembolism
Venous thromboembolism can be a complication of cancer itself, but chemotherapy increases the risk.

Pregnancy and reproductive function
Most cytotoxic drugs are teratogenic and should not be administered during pregnancy, especially during the first trimester. Considerable caution is necessary if a pregnant woman presents with cancer requiring chemotherapy, and specialist advice should always be sought.

Exclude pregnancy before treatment with cytotoxic drugs. Contraceptive advice should be given before cytotoxic therapy begins—women of childbearing age should use effective contraception during and after treatment. Regimens that do not contain an alkylating drug or procarbazine may have less effect on fertility, but those with an alkylating drug or procarbazine carry the risk of causing permanent male sterility (there is no effect on potency). Pretreatment counselling and consideration of sperm storage may be appropriate. Women are less severely affected, though the span of reproductive life may be shortened by the onset of a premature menopause. No increase in fetal abnormalities or abortion rate has been recorded in patients who remain fertile after cytotoxic chemotherapy.

Alkylating drugs often severely affect gametogenesis and carry the risk of causing permanent male sterility (there is no effect on potency). Pretreatment counselling and consideration of sperm storage may be appropriate. Women are less severely affected, though the span of reproductive life may be shortened by the onset of a premature menopause. No increase in fetal abnormalities or abortion rate has been recorded in patients who remain fertile after cytotoxic chemotherapy.

Nausea and vomiting
Nausea and vomiting cause considerable distress to many patients who receive chemotherapy and to a lesser extent abdominal radiotherapy, and may lead to refusal of further treatment; prophylaxis of nausea and vomiting is therefore extremely important. Symptoms may be acute (occurring within 24 hours of treatment), delayed (first occurring more than 24 hours after treatment), or anticipatory (occurring prior to subsequent doses). Delayed and anticipatory symptoms are more difficult to control than acute symptoms and require different management.

Patients vary in their susceptibility to drug-induced nausea and vomiting; those affected more often include women, patients under 50 years of age, anxious patients, and those who experience motion sickness. Susceptibility also increases with repeated exposure to the cytotoxic drug.

Drugs may be divided according to their emetogenic potential and some examples are given below, but the symptoms vary according to the dose, to other drugs administered and to the individual’s susceptibility to emetogenic stimuli.

Mildly emetogenic treatment—fluorouracil, etoposide, methotrexate (less than 100 mg/m^2, low dose in children), the vinca alkaloids, and abdominal radiotherapy.

Moderately emetogenic treatment—the taxanes, doxorubicin hydrochloride, intermediate and low doses of cyclophosphamide, mitoxantrone, and high doses of methotrexate (0.1–1.2 g/m^2).

Highly emetogenic treatment—cisplatin p. 768, dacarbazine p. 751, and high doses of cyclophosphamide.

Prevention of acute symptoms
For patients at low risk of emesis, pretreatment with dexamethasone p. 581 or lorazepam p. 412 may be used.

For patients at high risk of emesis, a 5HT3-receptor antagonist, usually given by mouth in combination with dexamethasone p. 581 and the neurokinin receptor antagonist aprepitant p. 351 is effective.

Prevention of delayed symptoms
For delayed symptoms associated with moderately emetogenic chemotherapy, a combination of dexamethasone and 5HT3-receptor antagonist is effective; for highly emetogenic chemotherapy, a combination of dexamethasone and aprepitant is effective. Metoclopramide hydrochloride p. 347 is also licensed for delayed chemotherapy-induced nausea and vomiting.
Prevention of anticipatory symptoms
Good symptom control is the best way to prevent anticipatory symptoms. Lorazepam can be helpful for its amnesic, sedative, and anxiolytic effects.

Treatment for cytotoxic-induced side effects

Anthracycline side-effects
Anthracycline-induced cardiotoxicity
The anthracycline cytotoxic drugs are associated with dose-related, cumulative, and potentially life-threatening cardiotoxic side-effects.

Anthracycline extravasation
Local guidelines for the management of extravasation should be followed or specialist advice sought. See further information on the prevention and management of extravasation injury.

Chemotherapy-induced mucositis and myelosuppression
Folinic acid p. 781 (given as calcium folinate) is used to counteract the folate-antagonist action of methotrexate p. 762 and thus speed recovery from methotrexate-induced mucositis or myelosuppression (‘folinic acid rescue’). Folinic acid is also used in the management of methotrexate overdose, together with other measures to maintain fluid and electrolyte balance, and to manage possible renal failure.

Folinic acid does not counteract the antibacterial activity of folate antagonists such as trimethoprim p. 462. When folinic acid and fluorouracil p. 761 are used together in metastatic colorectal cancer the response-rate improves compared to that with fluorouracil alone.

The calcium salt of levofolinic acid p. 782, a single isomer of folinic acid, is also used for rescue therapy following methotrexate administration, for cases of methotrexate overdose, and for use with fluorouracil for colorectal cancer. The dose of calcium levofolinate is generally half that of calcium folinate.

The disodium salts of folinic acid and levofolinic acid are also used for rescue therapy following methotrexate therapy, and for use with fluorouracil for colorectal cancer.

Urothelial toxicity
Haemorrhagic cystitis is a common manifestation of urothelial toxicity which occurs with the oxazaphosphorines, cyclophosphamide p. 750 and ifosfamide p. 751; it is caused by the metabolite acrolein. Mesna p. 783 reacts specifically with this metabolite in the urinary tract, preventing toxicity. Mesna is used routinely (preferably by mouth) in patients receiving ifosfamide, and in patients receiving cyclophosphamide p. 750 by the intravenous route at a high dose (e.g. more than 2 g) or in those who experienced urothelial toxicity when given cyclophosphamide previously.

Anthracycines and other cytotoxic antibiotics
Drugs in this group are widely used. Many cytotoxic antibiotics act as radiomimetics and simultaneous use of radiotherapy should be avoided because it may markedly increased toxicity. Daunorubicin p. 754, doxorubicin hydrochloride p. 754, epirubicin hydrochloride p. 756 and idarubicin hydrochloride p. 756 are anthracycline antibiotics. Mitoxantrone p. 778 is an anthracycline derivative.

Doxorubicin hydrochloride is available as both conventional and liposomal formulations. The different formulations vary in their licensed indications, pharmacokinetics, dosage and administration, and are not interchangeable. Conventional doxorubicin hydrochloride is used to treat the acute leukaemias, Hodgkin’s and non-Hodgkin’s lymphomas, paediatric malignancies, and some solid tumours including breast cancer.

Epirubicin hydrochloride is structurally related to doxorubicin hydrochloride and clinical trials suggest that it is as effective in the treatment of breast cancer.

Idarubicin hydrochloride has general properties similar to those of doxorubicin hydrochloride; it is mostly used in the treatment of haematological malignancies.

Daunorubicin also has general properties similar to those of doxorubicin hydrochloride.

Mitoxantrone is structurally related to doxorubicin hydrochloride.

Pixantrone p. 779 is licensed as monotherapy for the treatment of refractory or multiply relapsed aggressive non-Hodgkin B-cell lymphomas, although the benefits of using it as a fifth-line or greater chemotherapy in refractory patients has not been established.

Bleomycin p. 766 is given intravenously or intramuscularly to treat metastatic germ cell cancer and, in some regimens, non-Hodgkin’s lymphoma.

Dactinomycin is principally used to treat paediatric cancers. Its side-effects are similar to those of doxorubicin, except that cardiac toxicity is not a problem.

Mitomycin p. 767 is given intravenously to treat upper gastrointestinal and breast cancers and by bladder instillation for superficial bladder tumours. It causes delayed bone marrow toxicity and therefore it is usually administered at 6-weekly intervals.

Vinpca alkaloids
The vinca alkaloids, vincristine sulfate p. 773, vinorelbine sulfate p. 773, and vindesine sulfate p. 774, are used to treat a variety of cancers including leukaemias, lymphomas, and some solid tumours (e.g. breast and lung cancer). Vinorelbine p. 775 is a semi-synthetic vinca alkaloid. See also, role of vinorelbine in the treatment of breast cancer.

Antimetabolites
Antimetabolites are incorporated into new nuclear material or combine irreversibly with cellular enzymes, preventing normal cellular division.

Alkyating drugs
Extensive experience is available with these drugs, which are among the most widely used in cancer chemotherapy. They act by damaging DNA, thus interfering with cell replication.

Cyclophosphamide p. 750 is used mainly in combination with other agents for treating a wide range of malignancies, including some leukaemias, lymphomas, and solid tumours. It is given by mouth or intravenously; it is inactive until metabolised by the liver.

Ifosfamide p. 751 is related to cyclophosphamide and is given intravenously.

Melphalan p. 752 is licensed for the treatment of multiple myeloma, polycythaemia vera, childhood neuroblastoma, advanced ovarian adenocarcinoma, and advanced breast cancer. However, in practice, melphalan is rarely used for ovarian adenocarcinoma; it is no longer used for advanced breast cancer. Melphalan is also licensed for regional arterial perfusion in localised malignant melanoma of the extremities and localised soft-tissue sarcoma of the extremities.

Lomustine p. 752 is a lipid-soluble nitrosourea and the drug is given at intervals of 4 to 6 weeks.

Carmustine p. 749 has similar activity to lomustine; it is given to patients with multiple myeloma, non-Hodgkin’s lymphomas, and brain tumours. Carmustine implants are licensed for intracranial use in adults for the treatment of recurrent glioblastoma multiforme as an adjunct to surgery. Carmustine implants are also licensed for high-grade malignant glioma as adjunctive treatment to surgery and radiotherapy.
Extramustine phosphate p. 751 is a combination of an oestrogen and chloromethine used predominantly in prostate cancer. It is given by mouth and has both an antimitotic effect and (by reducing testosterone concentration) a hormonal effect.

Mitobronitol is occasionally used to treat chronic myeloid leukaemia; it is available on a named-patient basis from specialist importing companies.

**ALKYLATING AGENTS**

**Bendamustine hydrochloride**

**INDICATIONS AND DOSE**

Treatment of chronic lymphocytic leukaemia | Treatment of non-Hodgkin's lymphoma | Treatment of multiple myeloma

**BY INTRAVENOUS INFUSION**

- **CONTRA-INDICATIONS** Jaundice, low leucocyte count, low platelet count, major surgery less than 30 days before start of treatment, severe bone marrow suppression

- **CAUTIONS** Avoid in Acute porphyrias p. 864 - cardiac disorders—monitor serum potassium and ECG

- **INTERACTIONS** → Appendix 1 (bendamustine).

- **SIDE-EFFECTS**
  - **Common or very common** Aplasia, bone-marrow suppression, extravasation, hyperuricaemia, male sterility, nausea, oral mucositis, premature menopause, secondary malignancy, Stevens-Johnson syndrome
  
  - **Very rare** Anticholinergic syndrome, diarrhoea, dysphagia, encephalopathy, multiple organ failure, myocardial infarction, neurological disorders, paraesthesia, peripheral neuropathy, phlebitis, pulmonary fibrosis, tachycardia, taste disturbance

  - **Frequency not known** Alopecia, bone-marrow suppression, drowsiness, exacerbation, hyperuricaemia, increased risk of neutropenic sepsis, increased risk of skin toxicities, increased risk of thrombocytopenia, peripheral neuropathy, pulmonary fibrosis, rash, secondary malignancy, Stevens-Johnson syndrome

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Secondary malignancy: Prolonged use of alkylating drugs, particularly when combined with extensive irradiation, is associated with a marked increase in the incidence of acute non-lymphocytic leukaemia.

- **CONCEPTION AND CONTRACEPTION** Effective contraception is required during treatment in men or women, and for 6 months after treatment in men.

- **PREGNANCY** Avoid (teratogenic and mutagenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

- **BREAST FEEDING** Discontinue breast-feeding.

- **HEPATIC IMPAIRMENT** Consider a 30% dose reduction in moderate impairment. Avoid in severe impairment.

- **RENAL IMPAIRMENT** No information available on use in patients with creatinine clearance less than 10 mL/minute.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE technology appraisals (TAs)** Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (February 2011) NICE TA216

  Bendamustine is recommended as an option for the treatment of chronic lymphocytic leukaemia in patients for whom fludarabine combination chemotherapy is not appropriate. www.nice.org.uk/TA216

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (March 2011) that bendamustine (Levact®) is accepted for restricted use within NHS Scotland for the treatment of chronic lymphocytic leukaemia in patients for whom fludarabine combination chemotherapy is not appropriate.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

  - **Powder for solution for infusion**
    - Levact (Napp Pharmaceuticals Ltd)
      - Bendamustine hydrochloride 25 mg: Levact 25 mg powder for concentrate for solution for infusion vials | 5 vial [POM] £347.26 (Hospital only)
      - Bendamustine hydrochloride 100 mg: Levact 100 mg powder for concentrate for solution for infusion vials | 5 vial [POM] £1,379.04 (Hospital only)

  - Important safety information
    - RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES, see p. 745

  - **CAUTIONS** Avoid in Acute porphyrias p. 864 - high dose (antiepileptic prophylaxis required) - history of seizures (antiepileptic prophylaxis required) - ineffective once in blast crisis phase - previous progenitor cell transplant (increased risk of hepatic veno-occlusive disease) - previous radiation therapy (increased risk of hepatic veno-occlusive disease) - risk of second malignancy - three or more cycles of chemotherapy (increased risk of hepatic veno-occlusive disease)

  - **INTERACTIONS** → Appendix 1 (busulfan).

  - **SIDE-EFFECTS**
    - **GENERAL SIDE-EFFECTS**
      - **Common or very common** Cardiac tamponade in thalassaemia, hepatic fibrosis, hepatic veno-occlusive disease, hepatotoxicity, hyperbilirubinaemia, jaundice, pneumonia, skin hyperpigmentation
      - **Rare** Aplastic anaemia, seizures, visual disturbances
      - **Very rare** Gynaecomastia, myasthenia gravis
      - **Frequency not known** Alopecia, bone-marrow suppression, hyperuricaemia, irreversible bone-marrow aplasia, lung toxicity, male sterility, nausea, oral mucositis, premature menopause, secondary malignancy, thrombocytopenia, tumour lysis syndrome, vomiting

- **SPECIFIC SIDE-EFFECTS**
  - With intravenous use extravasation

  - **SIDE-EFFECTS, FURTHER INFORMATION**
    - Lung toxicity: Discontinue if lung toxicity develops.
Carmustine

INDICATIONS AND DOSE
Multiple myeloma | Non-Hodgkin's lymphomas | Brain tumours
BY INTRAVENOUS INFUSION
Adult: (consult product literature)

Recurrence glioblastoma multiforme as an adjunct to surgery | High-grade malignant glioma as an adjunctive treatment to surgery and radiotherapy
BY INTRAVESIONAL IMPLANTATION
Adult: (consult product literature)

Cautions
Avoid in acute porphyrias p. 864

Interactions
Appendix 1 (carmustine).

Side-effects
general side-effects
Alopecia | bone-marrow suppression (delayed) | hyperuricaemia | irritable to tissues | male sterility | nausea | oral mucositis | premature menopause | secondary malignancy | thromboembolism | tumour lysis syndrome | vomiting

specific side-effects
With intravenous use pulmonary fibrosis (delayed) | renal damage (cumulative)

SIDE-EFFECTS, FURTHER INFORMATION
Secondary malignancy: Prolonged use of alkylating drugs, particularly when combined with extensive irradiation, is associated with a marked increase in the incidence of acute non-lymphocytic leukaemia.

CONCEPTION AND CONTRACEPTION
Manufacturer advises effective contraception during treatment in men or women.

Chlorambucil

INDICATIONS AND DOSE
Some lymphomas and chronic leukaemias (used either alone or in combination therapy)
BY MOUTH
Adult: (consult local protocol)

Cautions
Avoid in acute porphyrias p. 864 | children with nephrotic syndrome (increased seizure risk) | history of epilepsy (increased seizure risk)

Side-effects
Uncommon: Skin rash
Very rare: Male sterility (in prepubertal and pubertal males)
Frequency not known: Alopecia | bone-marrow suppression | hyperuricaemia | nausea | oral mucositis | premature menopause | secondary malignancy | Stevens-Johnson syndrome | thromboembolism | toxic epidermal necrolysis | tumour lysis syndrome | vomiting

SIDE-EFFECTS, FURTHER INFORMATION
Secondary malignancy: Prolonged use of alkylating drugs, particularly when combined with extensive irradiation, is associated with a marked increase in the incidence of acute non-lymphocytic leukaemia.

Skin reactions
If a rash occurs further chlorambucil is contra-indicated and cyclophosphamide is substituted.

CONCEPTION AND CONTRACEPTION
Manufacturer advises effective contraception during treatment in men or women.

Pregnancy
Avoid. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

Breast Feeding
Discontinue breast-feeding.

National funding/access decisions
NICE technology appraisals (TAs)
Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma (June 2007) NICE TA121
Carmustine implants are an option for the treatment of newly diagnosed high-grade (Grade 3 or 4) glioma only for patients in whom at least 90% of the tumour has been resected. Carmustine implants should only be used within specialist centres. www.nice.org.uk/TA121

Medicinal forms
There can be variation in the licensing of different medicines containing the same drug.

Implant
Gliadel (Eisai Ltd)
Carmustine 7.7 mg Gliadel 7.7 mg implant | 8 device (PMS £520.00 (Hospital only))

Important safety information
Risks of incorrect dosing of oral anti-cancer medicines, see p. 745
patients who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them, only if:
- bendamustine-based therapy is not suitable and
- the manufacturer provides obinutuzumab with the discount agreed in the patient access scheme.
Patients currently receiving obinutuzumab that is not recommended according to the above criteria should have the option to continue treatment until they and their clinician consider it appropriate to stop. www.nice.org.uk/TA343

Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia
(June 2015) NICE TA344
Ofatumumab in combination with chlorambucil is an option for untreated chronic lymphocytic leukaemia only if:
- the person is ineligible for fludarabine-based therapy and
- bendamustine is not suitable and
- the manufacturer provides ofatumumab with the discount agreed in the patient access scheme.
Patients currently receiving ofatumumab that is not recommended according to the above criteria should have the option to continue treatment until they and their clinician consider it appropriate to stop. www.nice.org.uk/TA344

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet
- CHLORAMBUCIL (Non-proprietary)
  Chlorambucil 2 mg Chlorambucil 2mg tablets | 25 tablet | PAY £60.51 DT price = £60.51

Cyclophosphamide

INDICATIONS AND DOSE
Rheumatoid arthritis with severe systemic manifestations
BY MOUTH
- Adult: 1–1.5 mg/kg daily
Severe systemic rheumatoid arthritis | Other connective tissue diseases (especially with active vasculitis)
BY INTRAVENOUS INJECTION
- Adult: 0.5–1 g every 2 weeks, then reduced to 0.5–1 g every 1 month, frequency adjusted according to clinical response and haematological monitoring. To be given with prophylactic mesna
Used, mainly in combination with other agents for treating a wide range of malignancies, including some leukaemias, lymphomas, and solid tumours
BY MOUTH OR BY INTRAVENOUS INFUSION
- Adult: (consult local protocol)

UNLICENSED USE
Not licensed for rheumatoid arthritis with severe systemic manifestations.

Important safety information
RISKS OF INCORRECT DOsing OF ORAL ANti-CANCer MEDICINES, see p. 745

CONTRA-INDICATIONS
Haemorrhagic cystitis

CAUTIONS
Avoid in Acute porphyrrias p. 864 | diabetes mellitus | previous or concurrent mediastinal irradiation—risk of cardiotoxicity

INTERACTIONS
- Appendix 1 (cyclophosphamide).

SIDE-EFFECTS
GENERAL SIDE-EFFECTS
- Common or very common: Anorexia | cardiotoxicity at high doses | disturbances of carbohydrate metabolism | inappropriate secretion of anti-diuretic hormone | interstitial pulmonary fibrosis | pancreatitis | pigmentation of nails | pigmentation of palms | pigmentation of soles | urothelial toxicity
- Rare: Hepatotoxicity | renal dysfunction
- Frequency not known: Alopecia | bone–marrow suppression | haemorrhagic cystitis | hyperuricaemia | male sterility | nausea | oral mucositis | premature menopause | secondary malignancy | thromboembolism | tumour lysis syndrome | vomiting

SPECIFIC SIDE-EFFECTS
- With intravenous use: extravasation

SIDE-EFFECTS, FURTHER INFORMATION
Haemorrhagic cystitis
A urinary metabolite of cyclophosphamide, acrolein, can cause haemorrhagic cystitis; this is a rare but serious complication; increased fluid intake for 24–48 hours after intravenous injection, can prevent this complication. When high-dose therapy (e.g. more than 2 g intravenously) is used or when the patient is considered to be at high risk of cystitis (e.g. because of pelvic irradiation), mesna (given initially intravenously then by mouth) can also help prevent cystitis.

Secondary malignancy
Prolonged use of alkylating drugs, particularly when combined with extensive irradiation, is associated with a marked increase in the incidence of acute non-lymphocytic leukaemia.

CONCEPTION AND CONCEPTION
Manufacturer advises effective contraception during and for at least 3 months after treatment in men or women.

PREGNANCY
Avoid. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

BREAST FEEDING
Discontinue breast-feeding during and for 36 hours after stopping treatment.

HEPATIC IMPAIRMENT
Reduce dose—consult local treatment protocol for details.

RENAL IMPAIRMENT
Reduce dose if serum creatinine concentration greater than 120 micromol/litre.

DIRECTIONS FOR ADMINISTRATION
For intravenous infusion (cyclophosphamide injection; Baxter) give via drip tubing in Glucose 5% or Sodium chloride 0.9%; reconstitute 500 mg with 25 mL sodium chloride 0.9%; reconstitute 1 g with 50 mL sodium chloride 0.9%.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, solution for injection, oral suspension, solution for infusion, oral solution

Tablet
CAUTIONARY AND ADVISORY LABELS
25, 27
- CYCLOPHOSPHAMIDE (Non-proprietary)
  Cyclophosphamide (as Cyclophosphamide monohydrate)
  50 mg Cyclophosphamide 50mg tablets | 100 tablet | NICE £139.00 DT price = £139.00

Powder for solution for injection
- CYCLOPHOSPHAMIDE (Non-proprietary)
  Cyclophosphamide (as Cyclophosphamide monohydrate)
  500 mg Cyclophosphamide 500mg powder for solution for injection vials | 1 vial | £9.66-£9.95
  Cyclophosphamide (as Cyclophosphamide monohydrate) 1 gram Cyclophosphamide 1g powder for solution for injection vials | 1 vial | £10.66-£11.47
  Cyclophosphamide (as Cyclophosphamide monohydrate) 2 gram Cyclophosphamide 2g powder for solution for injection vials | 1 vial | NICE no price available

BNF 70
Dacarbazine

INDICATIONS AND DOSE
Metastatic melanoma | Soft tissue sarcomas (combination therapy) | Hodgkin’s disease (combination therapy)

BY INTRAVENOUS INFUSION OR BY INTRAVENOUS INJECTION
Adult: (consult local protocol)

● CAUTIONS
Caution in handling—irritant to tissues

● INTERACTIONS
Appendix 1 (dacarbazine).

● SIDE-EFFECTS

▶ Rare Irritant to skin - irritant to tissues - liver necrosis due to hepatic vein thrombosis
▶ Frequency not known Alopecia - bone-marrow suppression - extravasation - hyperuricaemia - myelosuppression - oral mucositis - severe nausea - severe vomiting - tumour lysis syndrome - vomiting

CONCEPTION AND CONTRACEPTION
Ensure effective contraception during and for at least 6 months after treatment in men or women.

● PREGNANCY
Avoid (carcinogenic and teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

● BREAST FEEDING
Discontinue breast-feeding.

● HEPATIC IMPAIRMENT
Dose reduction may be required in combined renal and hepatic impairment. Avoid in severe impairment.

● RENAL IMPAIRMENT
Dose reduction may be required in combined renal and hepatic impairment. Avoid in severe impairment.

PRESCRIBING AND DISPENSING INFORMATION
Dacarbazine is a component of a commonly used combination for Hodgkin’s disease (ABVD—doxorubicin [previously Adriamycin®], bleomycin, vinblastine, and dacarbazine).

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Powder for solution for injection

Dacarbazine (as Dacarbazine citrate) 100 mg Dacarbazine 100mg powder for solution for injection vials | 10 vial 

Dacarbazine (as Dacarbazine citrate) 200 mg Dacarbazine 200mg powder for solution for injection vials | 10 vial 

Powder for solution for infusion

Dacarbazine (as Dacarbazine citrate) 500 mg Dacarbazine 500mg powder for solution for infusion vials | 1 vial

Dacarbazine (as Dacarbazine citrate) 1 gram Dacarbazine 1g powder for solution for infusion vials | 1 vial

Estramustine phosphate

INDICATIONS AND DOSE
Prostate cancer

BY MOUTH
Adult: Initially 560–840 mg daily in divided doses; maintenance 140–1400 mg daily in divided doses

Important safety information
RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES, see p. 745.

CONTRA-INDICATIONS
Peptic ulceration - severe cardiovascular disease - thromboembolic disorders.

CAUTIONS
Avoid in Acute porphyrias p. 864 - cardiovascular disease - cerebrovascular disease - conditions which might be aggravated by fluid retention (such as epilepsy or migraine) - congestive heart failure - diabetes - hypercalcaemia - hypertension

INTERACTIONS
Appendix 1 (estramustine).

SIDE-EFFECTS

▶ Rare Angioedema

SIDE-EFFECTS, FURTHER INFORMATION
Secondary malignancy Prolonged use of alkylating drugs, particularly when combined with extensive irradiation, is associated with a marked increase in the incidence of acute non-lymphocytic leukaemia.

CONCEPTION AND CONTRACEPTION
Men should use effective contraceptive methods during treatment.

HEPATIC IMPAIRMENT
Manufacturer advises caution. Avoid in severe impairment. In hepatic impairment, manufacturer advises regular liver function tests.

RENAL IMPAIRMENT
Manufacturer advises caution.

DIRECTIONS FOR ADMINISTRATION
Each dose should be taken not less than 1 hour before or 2 hours after meals and should not be taken with products containing calcium, magnesium or aluminium, including dairy products and antacid medication.

PATIENT AND CARER ADVICE
Patients should be given advice on how to administer estramustine capsules.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS 5, 23

Estracyt (Pfizer Ltd)

Estramustine phosphate (as Estramustine sodium phosphate) 140 mg Estracyt 140mg capsules | 100 capsule 

Ifosfamide

INDICATIONS AND DOSE
Malignant disease

BY INTRAVENOUS INFUSION
Adult: (consult local protocol)

CONTRA-INDICATIONS
Acute infection - urinary-tract infection - urinary-tract obstruction - urothelial damage

CAUTIONS
Avoid in Acute porphyrias p. 864 - diabetes mellitus

INTERACTIONS
Appendix 1 (ifosfamide).

SIDE-EFFECTS

▶ Common or very common Confusion - disorientation - drowsiness - psychosis - renal toxicity (may lead to tubular dysfunction, Fanconi’s syndrome, or diabetes insipidus) - restlessness - uraemic toxicity
▶ Uncommon Severe encephalopathy
▶ Rare Anaemia - constipation - convulsions - diarrhoea
▶ Very rare Jaundice - syndrome of inappropriate antidiuretic hormone secretion - thrombophlebitis
▶ Frequency not known Acute pancreatitis - alopecia - arthralgias - bone-marrow suppression - extravasation - heart failure - hyperuricaemia - male sterility - nausea - oral mucositis - premature menopause - secondary malignancy - thromboembolism - tumour lysis syndrome - vomiting
**Lomustine**

**Drug Action** Lomustine is a lipid-soluble nitrosourea.

**Indications and Dose**

**Hodgkin’s disease resistant to conventional therapy**

- **By mouth**
  - Adult: 120–130 mg/m² every 6–8 weeks, dose is for when lomustine is used alone

**Malignant melanoma**

- Certain solid tumours

**By mouth**

- Adult: 60–130 mg/m² daily for 14 days, then reduced to 2–6 mg once weekly

**Localised malignant melanoma of the extremities and localised soft tissue sarcoma of the extremities**

- Adult: 6–10 mg/kg daily for 5–7 days, then reduced to 2–4 mg/kg daily until satisfactory response

**Immunosuppressed patients**

- Adult: 40 mg capsules (melphalan)

**Melphalan**

**Indications and Dose**

- Multiple myeloma

**By Mouth**

- Adult: 150 micrograms/kg daily for 4 days, dose to be repeated every 5 weeks

**By intravenous injection or by intravenous infusion**

- Adult: (consult product literature)

**Polyctyemia vera**

**By mouth**

- Adult: Initially 6–10 mg daily for 5–7 days

**Localised malignant melanoma of the extremities and localised soft tissue sarcoma of the extremities**

- By regional arterial perfusion

- Adult: (consult local protocol)

**Important safety information**

- **Risks of incorrect dosing of oral anti-cancer medicines**, see p. 745

**Caution** Avoid in Acute porphyrias, see p. 864

**Interactions** → Appendix 1 (melphalan).

**Side-effects**

- **General side-effects**

  - Rare: Interstitial pneumonitis, life threatening pulmonary fibrosis

  - **Frequency not known**

    - Alopecia, bone-marrow suppression, haematuria, male sterility, nausea, oral mucositis, permanent bone marrow damage (with prolonged use), premature menopause, secondary malignancy, thrombocytopaenia, tumour lysis syndrome, vomiting

- **Specific side-effects**

  - With intravenous use: extravasation

**Side-effects, further information**

- Prolonged use of alkylating drugs, particularly when combined with extensive irradiation, is associated with a marked increase in the incidence of acute non-lymphocytic leukaemia.

- **Conception and contraception** Manufacturer advises adequate contraception during treatment in men or women.

- **Pregnancy** Avoid. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

- **Breastfeeding** Discontinue breast-feeding.

- **Renal impairment** Reduce dose initially (consult product literature).

- **Monitoring requirements** Monitor full blood count before and throughout treatment.

**Medicinal forms**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule

  **Capsule**

  - **Lomustine (non-proprietary)**

    - Lomustine 40 mg: Lomustine 40 mg capsules | 20 capsule pack £67.60

- **Prescribing and dispensing information** The brand name CCNU® has been used for lomustine capsules.

**Urothelial toxicity** Mesna is routinely given with ifosfamide to reduce urothelial toxicity.

**Secondary malignancy** Prolonged use of alkylating drugs, particularly when combined with extensive irradiation, is associated with a marked increase in the incidence of acute non-lymphocytic leukaemia.

**Conception and contraception** Manufacturer advises adequate contraception during and for at least 6 months after treatment in men or women.

**Pregnancy** Avoid. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

**Breastfeeding** Discontinue breast-feeding.

**Renal Impairment** Avoid in severe impairment.

**Consequences and contraception** Manufacturer advises adequate contraception during treatment in men or women.

**Pregnancy** Avoid. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

**Breastfeeding** Discontinue breast-feeding.

**Renal Impairment** Reduce dose initially (consult product literature).

**Monitoring requirements** Monitor full blood count before and throughout treatment.

**Medicinal forms**

- There can be variation in the licensing of different medicines containing the same drug.
**Indications and Dose**

Newly diagnosed glioblastoma multiforme in adults (in combination with radiotherapy) and subsequently as monotherapy | Second-line treatment of malignant glioma in adults

**By Mouth**

- Adult: (consult product literature)

**Important Safety Information**

**Risks of Incorrect Dosing of Oral Anti-Cancer Medicines**, see p. 745

**Cautions**

- Pneumocystis jirovecii pneumonia—consult product literature for monitoring and prophylaxis requirements

**Interactions**

- Appendix 1 (temozolomide).

**Side-Effects**

- Alopecia, bone-marrow suppression, hyperuricaemia, nausea, oral mucositis, thromboembolism, tumour lysis syndrome, vomiting

**Side-Effects, Further Information**

For further information on side-effects consult product literature.

**Conception and Contraception**

Manufacturer advises adequate contraception during treatment. Men should avoid fathering a child during and for at least 6 months after treatment.

**Pregnancy**

Avoid (teratogenic and embryotoxic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

**Breast Feeding**

Discontinue breast-feeding.

**Hepatic Impairment**

Use with caution in severe impairment—no information available.

**Renal Impairment**

Manufacturer advises caution—no information available.

**Monitoring Requirements**

- Monitor liver function before treatment initiation, after each treatment cycle and midway through 42-day treatment cycles—consider the balance of benefits and risks of treatment if results are abnormal at any point (fetal liver injury reported).
- Monitor for myelodysplastic syndrome.
- Monitor for secondary malignancies.

**NICE Technology Appraisals (TAs)**

- Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma (June 2007) NICE TA121

**Thiotepa**

**Indications and Dose**

Conditioning treatment before haematopoietic stem cell transplantation in the treatment of haematological disease or solid tumours, in combination with other chemotherapy by intravenous infusion

- Adult: (consult local protocol)

**Cautions**

- Avoid in Acute porphyrias p. 864

**Interactions**

- Appendix 1 (thiotepa).

**Side-Effects**

- Alopecia, bone-marrow suppression, extravasation, hyperuricaemia, male sterility, nausea, oral mucositis, premature menopause—secondary malignancy, thromboembolism, tumour lysis syndrome, vomiting

**Side-Effects, Further Information**

Secondary malignancy—Prolonged use of alkylating drugs, particularly when combined with extensive irradiation, is associated with a marked increase in the incidence of acute non-lymphocytic leukaemia.

**Pregnancy**

Avoid (teratogenic and embryotoxic in animals). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

**Breast Feeding**

Discontinue breast-feeding.

**NICE Technology Appraisals (TAs)**

- Thiotepa (Tepadina) is not recommended for use within NHS Scotland in combination with other chemotherapy as conditioning treatment in adults or children with haematological diseases, or solid tumours prior to haematopoietic stem cell transplantation.

**Medicinal Forms**

There can be variation in the licensing of different medicines containing the same drug.
Daunorubicin

INDICATIONS AND DOSE
Acute myelogenous leukaemia | Acute lymphocytic leukaemia

BY INTRAVENOUS INFUSION
Adult: (consult local protocol)
Advanced AIDS-related Kaposi’s sarcoma (liposomal formulation only)

BY INTRAPERITONEAL INSTILLATION
Adult: (consult product literature)

CONTRA-INDICATIONS
Myocardial insufficiency | previous treatment with maximum cumulative doses of daunorubicin or other anthracycline | recent myocardial infarction | severe arrhythmia

Thiotepa 15 mg Thiotepa 15mg powder for concentrate for solution for infusion vials | 1 vial (£70) no price available
Thiotepa 100 mg Thiotepa 100mg powder for concentrate for solution for infusion vials | 1 vial (£70) no price available

Treosulfan

INDICATIONS AND DOSE
Ovarian cancer
BY MOUTH OR BY INTRAVENOUS INJECTION OR BY INTRAPERITONEAL INSTILLATION
Adult: (consult product literature)

SIDE-EFFECTS
Common or very common
Skin pigmentation

RARE
Allergic alveolitis | haemorrhagic cystitis | pulmonary fibrosis

Frequency not known
Alopecia | bone-marrow suppression | extravasation of intravenous drugs | hyperuricaemia | nausea | oral mucositis | thromboembolism | tumour lysis syndrome | vomiting

SIDE-EFFECTS, FURTHER INFORMATION
Secondary malignancy | prolonged use of alkylating drugs, particularly when combined with extensive irradiation, is associated with a marked increase in the incidence of acute non-lymphocytic leukaemia.

PREGNANCY
Avoid. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

BREAST FEEDING
Avoid. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Capsule
CAUTIONARY AND ADVISORY LABELS 25
Treosulfan (Non-proprietary)
Treosulfan 250 mg | 100 capsule (£20) £622.10

Powder for solution for injection
Treosulfan 1 gram | 1 g powder for solution for injection vials | 5 vial (£20) £256.35
Treosulfan 5 gram | 5 g powder for solution for injection vials | 5 vial (£20) £990.64

ANTHRACYCLINES

Doxorubicin hydrochloride

INDICATIONS AND DOSE
Acute leukaemia | Hodgkin’s lymphoma | Non-Hodgkin’s lymphoma | Some solid tumours including breast cancer

BY INTRAVENOUS INJECTION
Adult: (consult product literature)
Some papillary bladder tumours (bladder instillation) | Recurrent superficial bladder tumours (bladder instillation) | Transitional cell carcinoma (bladder instillation) | Carcinoma in situ (bladder instillation)

BY INTRAPERITONEAL INSTILLATION
Adult: (consult product literature)
CAELYX®
For AIDS-related Kaposi’s sarcoma in patients with low CD4 count and extensive mucocutaneous or visceral disease | Advanced ovarian cancer when platinum-based chemotherapy has failed | Progressive multiple myeloma (in combination with bortezomib) in patients who have received at least one prior therapy and who have undergone or are unsuitable for bone-marrow transplantation | Monotherapy for metastatic breast cancer in patients with increased cardiac risk

BY INTRAVENOUS INFUSION
▶ Adult: (consult product literature)

MYOCET®
For use with cyclophosphamide for metastatic breast cancer
▶ Adult: (consult product literature)

● CONTRA-INDICATIONS Consult product literature
● CAUTIONS Cardiac disease · caution in handling—irritant to tissues · consult product literature · elderly · hypertension · previous myocardial irradiation
● INTERACTIONS → Appendix 1 (doxorubicin). Caution is necessary with concomitant use of cardiotonic drugs, or drugs that reduce cardiac contractility. Concomitant use with trastuzumab is associated with cardiotoxicity. The use of anthracyclines even after stopping trastuzumab can increase the risk of cardiotoxicity and if possible should be avoided for up to 24 weeks. If trastuzumab needs to be used, cardiac function should be monitored closely.

SIDE-EFFECTS
● Common or very common Dehydration · diarrhoea · red colouration of the urine
● Uncommon Supraventricular tachycardia (related to drug administration)
● Frequency not known Alopecia · bone-marrow suppression · cardiomyopathy (with higher cumulative doses) · consult product literature · extravasation · heart failure (potentially fatal) · hyperuricaemia · nausea · oral mucositis · renal damage · thromboembolism · tumour lysis syndrome · vomiting

SIDE-EFFECTS, FURTHER INFORMATION
Extravasation Extravasation can cause severe tissue necrosis. Cardiomyopathy Higher cumulative doses are associated with cardiomyopathy and it is usual to limit total cumulative doses to 450 mg/m² because symptomatic and potentially fatal heart failure is common above this dose. Cardiotoxic Some evidence suggests that weekly low-dose administration may be less cardiotoxic.

Liposomal formulations Liposomal formulations of doxorubicin may reduce the incidence of cardiotoxicity and lower the potential for local necrosis, but infusion reactions, sometimes severe, may occur. Hand-foot syndrome (painful, macular reddening skin eruptions) occurs commonly with liposomal doxorubicin and may be dose limiting. It can occur after 2–3 treatment cycles and may be prevented by cooling hands and feet and avoiding socks, gloves, or tight-fitting footwear for 4–7 days after treatment. Elevated bilirubin concentration Doxorubicin is largely excreted in the bile and an elevated bilirubin concentration is an indication for reducing the dose.

CONCEPTION AND CONTRACEPTION Manufacturer advises effective contraception during and for at least 6 months after treatment in men or women.

PREGNANCY Avoid (teratogenic and toxic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

BREAST FEEDING Discontinue breast-feeding.

● HEPATIC IMPAIRMENT Reduce dose according to bilirubin concentration—consult product literature or local treatment protocol for details. Avoid in severe impairment.

● RENAL IMPAIRMENT Consult product literature in severe impairment.

● MONITORING REQUIREMENTS Patients should be assessed before treatment, by echocardiography. Cardiac monitoring during treatment may assist in determining safe dosage.

● DIRECTIONS FOR ADMINISTRATION Conventional doxorubicin is given by injection into a fast-running infusion, commonly at 21-day intervals.

● PRESCRIBING AND DISPENSING INFORMATION Doxorubicin is available as both conventional and liposomal formulations. The different formulations vary in their licensed indications, pharmacokinetics, dosage and administration, and are not interchangeable.

● NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)
▶ Paclitaxel, pegylated liposomal doxorubicin, and topotecan for second-line or subsequent treatment of advanced ovarian cancer (May 2005) NICE TA91 Paclitaxel, combined with a platinum compound (carboplatin or cisplatin), is an option for advanced cancer that relapses 6 months or more after completing initial platinum-based chemotherapy. Paclitaxel alone is an option for advanced ovarian cancer that does not respond to, or relapses within 6 months of completing initial platinum-based chemotherapy. Pegylated liposomal doxorubicin is an option for advanced ovarian cancer that does not respond to, or relapses within 12 months of completing initial platinum-based chemotherapy. Paclitaxel alone or pegylated liposomal doxorubicin are options for advanced ovarian cancer in patients who are allergic to platinum compounds. Topotecan alone is an option only for advanced ovarian cancer that does not respond to, or relapses within 6 months of completing initial platinum-based chemotherapy or in those allergic to platinum compounds and for whom paclitaxel alone or pegylated liposomal doxorubicin are inappropriate.

www.nice.org.uk/TA91

● MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for infusion

Solution for injection
▶ DOXORUBICIN HYDROCHLORIDE (Non-proprietary)
Doxorubicin hydrochloride 2 mg per 1 ml Doxorubicin 10mg/5ml solution for injection vials | 1 vial (£5.55) (Hospital only) Doxorubicin 50mg/25ml solution for injection Cytosafe vials | 1 vial (£2.00) Doxorubicin 50mg/25ml solution for infusion vials | 1 vial (£4.30) £10.00 Doxorubicin 10mg/5ml solution for injection Cytosafe vials | 1 vial (£2.00) £20.00 Doxorubicin 10mg/ml solution for injection Cytosafe vials | 1 vial (£2.00) £20.00 Doxorubicin 50mg/25ml solution for infusion vials | 1 vial (£2.00) £40.00 Doxorubicin 50mg/25ml solution for injection Cytosafe vials | 1 vial (£2.00) £80.00 Doxorubicin 10mg/ml solution for injection Cytosafe vials | 1 vial (£2.00) £160.00 Doxorubicin 50mg/25ml solution for infusion vials | 1 vial (£2.00) £20.00 Doxorubicin 50mg/ml solution for injection Cytosafe vials | 1 vial (£2.00) £40.00 Doxorubicin 10mg/ml solution for infusion Cytosafe vials | 1 vial (£2.00) £80.00 Doxorubicin 50mg/ml solution for injection Cytosafe vials | 1 vial (£2.00) £160.00 Doxorubicin 10mg/ml solution for infusion Cytosafe vials | 1 vial (£2.00) £80.00 Doxorubicin 50mg/ml solution for injection Cytosafe vials | 1 vial (£2.00) £160.00 Doxorubicin 10mg/ml solution for infusion Cytosafe vials | 1 vial (£2.00) £80.00 Doxorubicin 50mg/ml solution for injection Cytosafe vials | 1 vial (£2.00) £160.00 Doxorubicin 50mg/ml solution for infusion Cytosafe vials | 1 vial (£2.00) £80.00 Doxorubicin 50mg/ml solution for injection Cytosafe vials | 1 vial (£2.00) £160.00 Doxorubicin 50mg/ml solution for infusion Cytosafe vials | 1 vial (£2.00) £80.00 Doxorubicin 50mg/ml solution for injection Cytosafe vials | 1 vial (£2.00) £160.00 Doxorubicin 50mg/ml solution for infusion Cytosafe vials | 1 vial (£2.00) £80.00 Doxorubicin 50mg/ml solution for injection Cytosafe vials | 1 vial (£2.00) £160.00

Powder for solution for injection
▶ Doxorubicin (medac UK)
Doxorubicin hydrochloride 10 mg Doxorubicin 10mg powder for solution for injection vials | 10 vial (£12.80)
Doxorubicin hydrochloride 50 mg Doxorubicin 50mg powder for solution for injection vials | 10 vial (£31.40)

Solution for infusion
▶ DOXORUBICIN HYDROCHLORIDE (Non-proprietary)
Doxorubicin hydrochloride 2 mg per 1 ml Doxorubicin 200mg/100ml solution for injection Cytosafe vials | 1 vial (£412.00)
Epirubicin hydrochloride

**INDICATIONS AND DOSE**
Treatment of breast cancer | Treatment and prophylaxis of certain forms of superficial bladder cancer

**BY INTRAVENOUS INFUSION OR BY INTRAVESICAL INSTILLATION**

- **Adult:** (consult product literature or local protocols)

  - **CONTRA-INDICATIONS**
    - Bladder inflammation or contraction (when used as a bladder instillation) - catheterisation difficulties (when used as a bladder instillation) - haematuria (when used as a bladder instillation) - invasive tumours penetrating the bladder (when used as a bladder instillation) - myocardiopathy - previous treatment with maximum cumulative doses of epirubicin or other anthracycline - recent myocardial infarction - severe arrhythmia - severe myocardial insufficiency - unstable angina - urinary tract infections (when used as a bladder instillation)

  - **CAUTIONS**
    - Caution in handling—irritant to tissues

  - **INTERACTIONS**
    - Appendix 1 (epirubicin).

  Caution is necessary with concomitant use of cardiotoxic drugs, or drugs that reduce cardiac contractility. Concomitant use with trastuzumab is associated with cardiotoxicity. The use of anthracyclines even after stopping trastuzumab can increase the risk of cardiotoxicity and if possible should be avoided for up to 24 weeks. If trastuzumab needs to be used, cardiac function should be monitored closely.

  - **SIDE-EFFECTS**
    - Alopecia - bone-marrow suppression - cardiotoxicity - extravasation - hyperpigmentation of nails - hyperpigmentation of oral mucosa - hyperpigmentation of skin - hyperuricaemia - nausea - oral mucositis - red colouration of the urine - thromboembolism - tumour lysis syndrome - vomiting

  **SIDE-EFFECTS, FURTHER INFORMATION**

  **Cardiotoxicity**
  A maximum cumulative dose of 0.9–1 g/m² is recommended to help avoid cardiotoxicity.

  - **PREGNANCY**
    - Avoid (carcinogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

  - **BREAST FEEDING**
    - Discontinue breast-feeding.

  - **HEPATIC IMPAIRMENT**
    - Reduce dose according to bilirubin concentration—consult local treatment protocol for details. Avoid in severe impairment.

  - **RENAL IMPAIRMENT**
    - Dose reduction may be necessary in severe impairment.

  - **MEDICINAL FORMS**
    - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, solution for infusion

**Solution for injection**

- **EPIRUBICIN HYDROCHLORIDE (Non-proprietary)**
  - Epirubicin hydrochloride 2 mg per 1 ml
    - Epirubicin 10mg/5ml solution for injection vials | 1 vial (Pos) £122.24
    - Epirubicin 50mg/25ml solution for injection vials | 1 vial (Pos) £110.88

- **Pharmorubicin (Pfizer Ltd)**
  - Epirubicin hydrochloride 2 mg per 1 ml
    - Pharmorubicin 50mg/25ml solution for injection Cytosafe vials | 1 vial (Pos) £110.19
    - Pharmorubicin 10mg/5ml solution for injection Cytosafe vials | 1 vial (Pos) £121.24

**Solution for infusion**

- **EPIRUBICIN HYDROCHLORIDE (Non-proprietary)**
  - Epirubicin hydrochloride 2 mg per 1 ml
    - Epirubicin 200mg/100ml solution for infusion vials | 1 vial (Pos) £1386.16

- **Pharmorubicin (Pfizer Ltd)**
  - Epirubicin hydrochloride 2 mg per 1 ml
    - Pharmorubicin 200mg/100ml solution for infusion Cytosafe vials | 1 vial (Pos) £1386.16

**Idarubicin hydrochloride**

**INDICATIONS AND DOSE**

- **Acute non-lymphocytic leukaemias monotherapy**
  - **BY MOUTH**
    - Adult: 30 mg/m² daily for 3 days; maximum 400 mg/m² per course

- **Acute non-lymphocytic leukaemia in combination therapy**
  - **BY MOUTH**
    - Adult: 15–30 mg/m² daily for 3 days; maximum 400 mg/m² per course

- **Advanced breast cancer after failure of first-line chemotherapy (not including anthracyclines)—monotherapy**
  - **BY INTRAVENOUS INJECTION**
    - Adult: 45 mg/m² for 1 dose, repeat treatment every 3–4 weeks, alternatively 15 mg/m² daily for 3 consecutive days, repeat treatment every 3–4 weeks; maximum 400 mg/m² per course

- **Acute leukaemia | Advanced breast cancer after failure of first-line chemotherapy (not including anthracyclines)**
  - **BY INTRAVENOUS INJECTION**
    - Adult: (consult product literature)

**Important safety information**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES,** see p. 745

- **CONTRA-INDICATIONS**
  - Previous treatment with maximum cumulative dose of idarubicin or other anthracycline - recent myocardial infarction - severe arrhythmias - severe myocardial insufficiency

- **CAUTIONS**
  - Caution in handling—irritant to tissues

- **INTERACTIONS**
  - Appendix 1 (idarubicin).

  Concomitant use with trastuzumab is associated with cardiotoxicity. The use of anthracyclines even after stopping trastuzumab can increase the risk of cardiotoxicity and if possible should be avoided for up to 24 weeks. If trastuzumab needs to be used, cardiac function should be monitored closely.

  **SIDE-EFFECTS**

  **GENERAL SIDE-EFFECTS**

  - Common or very common
    - Abdominal pain - cardiac disorders - diarrhoea - haemorrhage - rash - red pigmentation of the urine

  - Uncommon
    - Nail hyperpigmentation - skin hyperpigmentation
Cytotoxic responsive malignancy 757

- Frequency not known  
  Alopecia · bone-marrow suppression · hyperuricaemia · nausea · oral mucositis · thromboembolism · tumour lysis syndrome · vomiting

**SPECIFIC SIDE-EFFECTS**

- With intravenous use extravasation
- **PREGNANCY** Avoid (teratogenic and toxic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746:
- **BREAST FEEDING** Discontinue breast-feeding.
- **HEPATIC IMPAIRMENT** Reduce dose according to serum bilirubin concentration. Avoid in severe impairment.
- **RENAL IMPAIRMENT** Reduce dose. Avoid in severe impairment.
- **CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception during and for 3 months after treatment in men or women.

**MEDICINAL FORMS**

- **INDICATIONS AND DOSE**
  - **BY MOUTH**
  - **BY INJECTION**
  - **CAPSULE**
  
  **Capsule**
  
  **Capecitabine (Celgene Ltd)**
  
  Capecitabine is metabolised to fluorouracil.

- **Solution for injection**

  **Solution for injection**
  
  **Zavedos (Pfizer Ltd)**
  
  There can be variation in the licensing of different medicines containing the same drug.

**ANTIMETABOLITES**

Azacitidine

- **DRUG ACTION** Azacitidine is a pyrimidine analogue.

**INDICATIONS AND DOSE**

- **Treatment of intermediate-2 and high-risk myelodysplastic syndromes, chronic myelomonocytic leukaemia, and acute myeloid leukaemia, in adults who are not eligible for haemopoietic stem cell transplantation**

  **BY SUBCUTANEOUS INJECTION**
  
  - Adult: (consult local protocol)

- **CONTRA-INDICATIONS** Advanced malignant hepatic tumour

- **CAUTIONS** History of severe congestive heart failure · unstable cardiac disease (consider cardiopulmonary assessment before and during treatment) · unstable pulmonary disease (consider cardiopulmonary assessment before and during treatment)

- **SIDE-EFFECTS**

  - **Common or very common** Abdominal pain · anorexia · anxiety · arthralgia · cerebral haemorrhage · constipation · diarrhoea · dizziness · drowsiness · dyspepsia · dyspnoea · gastro-intestinal disturbances · haematuria · haemorrhage · headache · hypertension · hypokalaemia · hypotension · injection-site reactions · insomnia · myalgia · pneumonia · rash

  - **Uncommon** Anaphylactic reactions · hypersensitivity reactions

- **Frequency not known** Alopecia · bone-marrow suppression · extravasation · hepatic coma · hepatic failure · hyperuricaemia · nausea · oral mucositis · renal failure · thromboembolism · tumour lysis syndrome · vomiting

**Capecitabine**

- **DRUG ACTION** Capecitabine is metabolised to fluorouracil.

**INDICATIONS AND DOSE**

- **Stage III colon cancer, adjuvant following surgery (monotherapy)**
  
  **BY MOUTH**
  
  - Adult: 1.25 g/m² twice daily for 14 days, subsequent courses repeated after a 7-day interval, recommended duration of treatment is 6 months, adjust dose according to tolerability—consult product literature

- **Stage III colon cancer, adjuvant following surgery (combination therapy)**

  **BY MOUTH**
  
  - Adult: 0.8–1 g/m² twice daily for 14 days, subsequent courses repeated after a 7-day interval, recommended duration of treatment is 6 months, adjust dose according to tolerability—consult product literature

**Metastatic colorectal cancer (monotherapy)**

**BY MOUTH**

- Adult: 1.25 g/m² twice daily for 14 days, subsequent courses repeated after a 7-day interval, adjust dose according to tolerability—consult product literature (continued)
Malignant disease

Metastatic colorectal cancer (combination therapy)

**BY MOUTH**
- Adult: 0.8–1 g/m² twice daily for 14 days, subsequent courses repeated after a 7-day interval, adjust dose according to tolerability—consult product literature

Advanced gastric cancer (first-line treatment in combination with a platinum based regimen)

**BY MOUTH**
- Adult: 0.8–1 g/m² twice daily for 14 days, subsequent courses repeated after a 7-day interval, alternatively 625 mg/m² twice daily given continuously, adjust dose according to tolerability—consult product literature

Locally advanced or metastatic breast cancer (second-line treatment as monotherapy after failure of a taxane and anthracycline regimen or where further anthracycline treatment is not indicated) Locally advanced or metastatic breast cancer (second-line treatment, in combination with docetaxel, where previous therapy included an anthracycline)

**BY MOUTH**
- Adult: 1.25 g/m² twice daily for 14 days, subsequent courses repeated after a 7-day interval, adjust dose according to tolerability—consult product literature

- **CONTRA-INDICATIONS** Dihydropyrimidine dehydrogenase deficiency
- **CAUTIONS** Diabetes mellitus · diarrhoea or dehydration—consult product literature for guidance on dose modification and treatment interruption · electrolyte disturbances · history of angina pectoris · history of arrhythmias · history of significant cardiovascular disease · nervous system disease
- **INTERACTIONS** → Appendix 1 (capecitabine).
- **SIDE-EFFECTS** Alopecia · bone-marrow suppression · hyperuricaemia · nausea · oral mucositis · thromboembolism · tumour lysis syndrome · vomiting
- **SIDE-EFFECTS, FURTHER INFORMATION** For further information on side-effects, consult product literature
- **PREGNANCY** Avoid (teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.
- **BREAST FEEDING** Discontinue breast-feeding.
- **HEPATIC IMPAIRMENT** Manufacturer advises monitor liver function in mild to moderate impairment—consult product literature for guidance on treatment interruption; avoid in severe impairment.
- **RENAL IMPAIRMENT** Reduce starting dose of 1.25 g/m² to 75% if creatinine clearance 30–50 mL/minute. Avoid if creatinine clearance less than 30 mL/minute.
- **MONITORING REQUIREMENTS**
  - Severe skin reactions Monitor for symptoms of severe skin reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis)—permanently discontinue treatment immediately if symptoms occur.
  - Hand-foot syndrome Monitor for symptoms of hand-foot syndrome—interrupt treatment if significant syndrome occurs and refer to product literature.
  - Monitor plasma-calcium concentration.
  - Monitor for eye disorders (including keratitis and corneal disorders).
- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE technology appraisals (TAs)**
    - Capecitabine and tegafur for uracil for metastatic colorectal cancer (May 2003) NICE TA61
    - Capecitabine or tegafur with uracil [now discontinued] (in combination with folic acid) is an option for the first-line treatment of metastatic colorectal cancer. www.nice.org.uk/TA61

- **Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes’ C) colon cancer (April 2006) NICE TA100**
  - Capecitabine alone or oxaliplatin combined with fluorouracil and folinic acid are options for adjuvant treatment following surgery for stage III (Dukes’ C) colon cancer. www.nice.org.uk/TA100

- **Capecitabine for the treatment of advanced gastric cancer (July 2010) NICE TA191**
  - Capecitabine in combination with a platinum-based regimen is recommended for the first-line treatment of inoperable advanced gastric cancer. www.nice.org.uk/TA191

- **Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer (December 2010) NICE TA212**
  - Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine is not recommended for the treatment of metastatic colorectal cancer. www.nice.org.uk/TA212

- **Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer (August 2012) NICE TA263**
  - Bevacizumab in combinations with capecitabine is not recommended within its marketing authorisation for the first-line treatment of metastatic breast cancer, that is, when treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate, or when taxanes or anthracyclines have been used as part of adjuvant treatment in the previous 12 months. www.nice.org.uk/TA263

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS** 21

- **CAPECITABINE (Non-proprietary)**
  - Capecitabine 150 mg Capcitabine 150mg tablets | 60 tablet £46.02 (Hospital only) | 60 tablet £39.99
  - Capecitabine 300 mg Capcitabine 300mg tablets | 120 tablet £205.99 (Hospital only) | 120 tablet £185.00

- **Xeloda** (Roche Products Ltd)
  - Capecitabine 150 mg Xeloda 150mg tablets | 60 tablet £40.02
  - Capecitabine 500 mg Xeloda 500mg tablets | 120 tablet £265.55 (Hospital only) | 120 tablet £265.00

**Cladribine**

**INDICATIONS AND DOSE**

**LITAK®**

- **Hairy cell leukaemia**
  - **BY SUBCUTANEOUS INJECTION**
    - Adult: (consult product literature or local protocols)
  - **LEUSTAT®**
    - **B-cell chronic lymphocytic leukaemia in patients who have failed to respond to standard regimens containing an alkylating agent** Hairy cell leukaemia
  - **BY INTRAVENOUS INFUSION**
    - Adult: (consult product literature or local protocols)

- **CAUTIONS** Use irradiated blood only

- **CAUTIONS, FURTHER INFORMATION**
  - Immunosuppressive effect of cladribine Cladribine has a potent and prolonged immunosuppressive effect. Patients treated with cladribine are more prone to serious bacterial, opportunistic fungal, and viral infections, and prophylactic therapy is recommended in those at risk. To prevent potentially fatal transfusion-related graft-versus-host reaction, only irradiated blood products should be
administered. Prescribers should consult specialist literature when using highly immunosuppressive drugs.

- **INTERACTIONS** → Appendix 1 (cladribine).
- **SIDE-EFFECTS** Abdominal pain, acute renal failure (with high doses), alopecia, anxiety, arthralgia, athrosis, bone-marrow suppression, chills, constipation, cough, diarrhoea, dizziness, dyspnoea, extravasation, flatulence, haemolytic anaemia, headache, hyperuricaemia, insomnia, malaise, myalgia, nausea, oedema, oral mucositis, pruritus, purpura, rash, severe myelosuppression (with neutropenia, anaemia and thrombocytopenia), severe neurotoxicity (with high doses), sweating, thrush, tachycardia, thromboembolism, tumour lysis syndrome, vomiting.

**CONCEPTION AND CONTRACEPTION** Manufacturer advises caution for men who should not father children during and for 6 months after treatment.

- **PREGNANCY** Avoid (teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.
- **BREAST FEEDING** Discontinue breast-feeding.
- **HEPATIC IMPAIRMENT** Regular monitoring recommended in hepatic impairment.
- **RENAL IMPAIRMENT** Regular monitoring recommended in renal impairment.
- **DIRECTIONS FOR ADMINISTRATION** Litak® for subcutaneous use only—no dilution required.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Litak (Lipomed GmbH)
  - Cladribine 2 mg per 1 ml Litak 10 mg/5 ml solution for injection vials | 1 vial £165.00 (Hospital only) | 5 vials £820.00 (Hospital only)

**Solution for infusion**

- Leustat (Janssen-Cilag Ltd)
  - Cladribine 1 mg per 1 ml Leustat 10 mg/10 ml solution for infusion vials | 1 vial £156.70

**Cytarabine**

**DRUG ACTION** Cytarabine acts by interfering with pyrimidine synthesis.

**INDICATIONS AND DOSE**

Induction of remission of acute myeloblastic leukaemia

- **BY INTRAVENOUS INFUSION OR BY INTRAVENOUS INJECTION OR BY SUBCUTANEOUS INJECTION**
  - Adult: (consult local protocol)
  - Lymphomatous meningitis
    - BY INTRATHECAL INJECTION
      - Adult: (consult local protocol)

**Important safety information**

Not all cytarabine preparations can be given by intrathecal injection—consult product literature.

**INTERACTIONS** → Appendix 1 (cytarabine).

**SIDE-EFFECTS** Alopecia, bone-marrow suppression, extravasation, hyperuricaemia, nausea, oral mucositis, thromboembolism, tumour lysis syndrome, vomiting.

- **PREGNANCY** Avoid (teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.
- **BREAST FEEDING** Discontinue breast-feeding.
- **HEPATIC IMPAIRMENT** Reduce dose—consult product literature.
- **MONITORING REQUIREMENTS** Cytarabine is a potent myelosuppressant and requires careful haematological monitoring.

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (July 2007) that liposomal cytarabine suspension (DepoCyt®) is not recommended for use within NHS Scotland for the intrathecal treatment of lymphomatous meningitis.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

**Solution for injection**

- Cytarabine (Non-proprietary)
  - Cytarabine 20 mg per 1 ml Cytarabine 500 mg/25 ml solution for injection vials | 1 vial £135.00
  - Cytarabine 100 mg/5 ml solution for injection vials | 5 vials £20.98–£30.00

- Cytarabine 100 mg per 1 ml Cytarabine 500 mg/5 ml solution for injection vials | 5 vials £100.00
  - Cytarabine 100 mg/1 ml solution for injection vials | 5 vials £30.00

- Cytarabine 2 g/20 ml solution for injection vials | 1 vial £73.00

**Suspension for Injection**

- DepoCyt (Napp Pharmaceuticals Ltd)
  - Cytarabine 10 mg per 1 ml DepoCyt 50 mg/5 ml suspension for injection vials | 1 vial no price available (Hospital only)
Decitabine

**DRUG ACTION** Decitabine is a pyrimidine analogue.

**INDICATIONS AND DOSE**
Treatment of newly diagnosed acute myeloid leukaemia in patients over 65 years of age who are not candidates for standard induction chemotherapy

- **BY INTRAVENOUS INFUSION**
  - Elderly: (consult local protocol)

- **CAUTIONS**
  - History of severe congestive heart failure - history of unstable cardiac disease
  - **INTERACTIONS** → Appendix 1 (decitabine).

- **SIDE-EFFECTS**
  - **Common or very common** Diarrhoea - epistaxis - headache
  - **Uncommon** Acute febrile neutrophilic dermatosis
  - **Frequency not known** Alopecia - bone-marrow suppression - extravasation - hyperuricaemia - nausea - oral mucositis - thromboembolism - tumour lysis syndrome - vomiting

- **PREGNANCY** Avoid (teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

- **BREAST FEEDING** Discontinue breast-feeding.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution - no information available.

- **RENAL IMPAIRMENT** Manufacturer advises caution if creatinine clearance less than 30 mL/minute - no information available.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

- **Powder for solution for infusion**
  - **ELECTROLYTES:** May contain Potassium, sodium
  - **Dacogen** (Janssen-Cilag Ltd)
    - Decitabine 50 mg Dacogen 50mg powder for concentrate for solution for infusion vials (1 vial; £170.86)

Fludarabine phosphate

**INDICATIONS AND DOSE**
Initial treatment of advanced B-cell chronic lymphocytic leukaemia (CLL) or after first line treatment in patients with sufficient bone-marrow reserves

- **BY MOUTH**
  - Adult: 40 mg/m² for 5 days every 28 days, usually given for 6 cycles
  - **BY INTRAVENOUS INJECTION** or **BY INTRAVENOUS INFUSION**
  - Adult: (consult product literature)

**Important safety information**
**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES,** see p. 745.

- **CONTRA-INDICATIONS** Haemolytic anaemia

- **CAUTIONS** Increased susceptibility to skin cancer - worsening of existing skin cancer

**CAUTIONS, FURTHER INFORMATION**
**Immunosuppression** Fludarabine has a potent and prolonged immunosuppressive effect. Patients treated with fludarabine are more prone to serious bacterial, opportunistic fungal, and viral infections, and prophylactic therapy is recommended in those at risk. To prevent potentially fatal transfusion-related graft-versus-host reaction, only irradiated blood products should be administered. Prescribers should consult specialist literature when using highly immunosuppressive drugs. Co-trimoxazole is used to prevent pneumocytis infection.

- **INTERACTIONS** → Appendix 1 (fludarabine).

- **SIDE-EFFECTS**
  - **Common or very common** Acute myeloid leukaemia - anorexia - chills - cough - diarrhoea - fever - immunosupression - malaise - myelodysplastic syndrome - myelosuppression (may be cumulative) - oedema - peripheral neuropathy - pneumonia - rash - visual disturbances - weakness
  - **Uncommon** Autoimmune disorder - confusion - fibrosis - haemorrhage - immune-mediated haemolytic anaemia - neutropenia - pneumonitis - pulmonary toxicity - thrombocytopenia
  - **Rare** Agitation - arthralgia - blindness - coma - heart failure - optic neuropathy - seizures - skin cancer - Stevens-Johnson syndrome - toxic epidermal necrolysis
  - **Frequency not known** Alopecia - bone-marrow suppression - extravasation - haemorrhagic cystitis - hyperuricaemia - nausea - oral mucositis - thromboembolism - tumour lysis syndrome - vomiting

**CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception during and for at least 6 months after treatment in men or women.

- **PREGNANCY** Avoid (embryotoxic and teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

- **BREAST FEEDING** Discontinue breast-feeding.

- **RENAL IMPAIRMENT** Reduce dose by up to 50% if creatinine clearance 30–70 mL/minute. Avoid if creatinine clearance less than 30 mL/minute.

- **MONITORING REQUIREMENTS**
  - Monitor for signs of haemolysis.
  - Monitor for neurological toxicity.
  - Assess creatinine clearance in patients over 65 years before treatment initiation.

- **DIRECTIONS FOR ADMINISTRATION** Concentrate for intravenous injection or infusion must be diluted before administration (consult product literature).

- **NATIONAL FUNDING/ACCESS DECISIONS**

  **NICE technology appraisals (TAs)**
  - **Fludarabine for the treatment of B-cell chronic lymphocytic leukaemia (September 2001) NICE TA29**
    - Oral fludarabine is recommended for the second-line treatment of B-cell chronic lymphocytic leukaemia in patients who have either failed, or are intolerant of, first line chemotherapy, and who would otherwise have received combination chemotherapy of either:
      - cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)
      - cyclophosphamide, doxorubicin and prednisolone (CAP)
    - or
      - cyclophosphamide, vincristine and prednisolone (CVP)
    - Intravenous fludarabine should only be used when oral fludarabine is contra-indicated. www.nice.org.uk/TA29
  - **Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia (February 2007) NICE TA119**
    - Fludarabine monotherapy is not recommended for the first-line treatment of chronic lymphocytic leukaemia. www.nice.org.uk/TA119

**Scottish Medicines Consortium (SMC) Decisions**
The **Scottish Medicines Consortium** has advised (October 2006) that fludarabine is accepted for restricted use for the treatment of B-cell chronic lymphocytic leukaemia (CLL) in patients with sufficient bone marrow reserves. First-line treatment should only be initiated in patients with advanced disease, Rai stages III/IV (Binet stage C), or Rai stages I/II (Binet stage A/B) where the patient has disease-related symptoms or evidence of progressive disease.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.
Fluorouracil

INDICATIONS AND DOSE
Treatment of some solid tumours including gastro-intestinal tract cancers and breast cancer in combination with folic acid in advanced colorectal cancer.

BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION OR BY INTRA-ARTERIAL INFUSION

Adult: (consult product literature)

• INTERACTIONS → Appendix 1 (fluorouracil).

• SIDE-EFFECTS
  • Rare Cerebellar syndrome
  • Frequency not known Alopecia, bone-marrow suppression, desquamative hand-foot syndrome (on prolonged infusion), extravasation, hyperuricaemia, mucositis, myelosuppression, nausea, oral mucositis, thromboembolism, tumour lysis syndrome, vomiting

• PREGNANCY
  Avoid (teratogenic). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

• BREAST FEEDING Discontinue breast-feeding.

• HEPATIC IMPAIRMENT Manufacturer advises caution.

• HANDLING AND STORAGE Caution in handling—irritant to tissues.

• MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

• FLUOROURACIL (Non-proprietary)
  Fluorouracil (as Fluorouracil sodium) 25 mg per 1 ml
  Fluorouracil 250mg/25ml solution for injection via 1 vial (Pom) £6.40 | 10 vial (Pom) £64.00 Fluorouracil 250mg/10ml solution for injection via 5 vial (Pom) £20.00–£24.00
  Fluorouracil 500mg/20ml solution for injection via 1 vial (Pom) £12.80

Fluorouracil 500mg/10ml solution for injection via 1 vial (Pom) £3.20

Solution for infusion

• FLUOROURACIL (Non-proprietary)
  Fluorouracil (as Fluorouracil sodium) 25 mg per 1 ml
  Fluorouracil 50mg/ml solution for infusion via 1 vial (Pom) £4.78
  Fluorouracil 5mg/50ml solution for infusion via 1 vial (Pom) £6.20

Fluorouracil 5mg/ml solution for infusion via 1 vial (Pom) £64.00 Fluorouracil 2.5g/50ml solution for infusion via 1 vial (Pom) £82.00

Fluorouracil (as Fluorouracil sodium) 50 mg per 1 ml
  Fluorouracil 5g/100ml solution for infusion via 1 vial (Pom) £64.00 Fluorouracil 2.5g/50ml solution for infusion via 1 vial (Pom) £82.00

Gemcitabine

INDICATIONS AND DOSE
First-line treatment for locally advanced or metastatic non-small cell lung cancer (as monotherapy in elderly patients and in palliative treatment; otherwise in combination with cisplatin). Treatment of locally advanced or metastatic pancreatic cancer. Treatment of advanced or metastatic bladder cancer (in combination with cisplatin). Treatment of locally advanced or metastatic epithelial ovarian cancer which has relapsed after a recurrence-free interval of at least 6 months following previous platinum-based therapy (in combination with carboplatin). Treatment of metastatic breast cancer which has relapsed after previous chemotherapy including an anthracycline (in combination with paclitaxel).

BY INTRAVENOUS INFUSION

Adult: (consult local protocol)

• INTERACTIONS → Appendix 1 (gemcitabine).

• SIDE-EFFECTS
  • Rare Haemolytic uraemic syndrome
  • Frequency not known Alopecia, bone-marrow suppression, extravasation, hyperuricaemia, influenza-like symptoms, myelosuppression, mucositis, myelosuppression, nausea, oral mucositis, thromboembolism, tumour lysis syndrome, vomiting

• CONCEPTION AND CONTRACEPTION Manufacturer advises effective contraception during treatment. Men must avoid fathering a child during and for 6 months after treatment.

• PREGNANCY Avoid (teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

• BREAST FEEDING Discontinue breast-feeding.

• HEPATIC IMPAIRMENT Manufacturer advises caution.

• RENAL IMPAIRMENT Manufacturer advises caution.

• NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

Gemcitabine is an option for first-line chemotherapy for patients with advanced or metastatic adenocarcinoma of the pancreas and a Karnofsky score of at least 50 [Karnofsky score is a measure of the ability to perform ordinary tasks].

Gemcitabine is not recommended for patients who can have potentially curative surgery. There is insufficient evidence about its use for second-line treatment of pancreatic adenocarcinoma. www.nice.org.uk/TA25

Gemcitabine, in combination with paclitaxel, is an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate. www.nice.org.uk/TA116

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (November 2006) that gemcitabine is accepted for restricted use for the treatment of metastatic breast cancer, which has relapsed following previous chemotherapy including an anthracycline (unless contra-indicated).

• MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.
Solution for infusion

- **GEMCITABINE (Non-proprietary)**
  - Gemcetabine (as Gemcetabine hydrochloride)
    - **200 mg** Gemcetabine 200mg/5.3ml concentrate for solution for infusion vials | 1 vial [RSP] £25.00 (Hospital only) | 1 vial [POM] £32.00
    - Gemcetabine 200mg/2ml concentrate for solution for infusion vials | 1 vial [POM] no price available
    - Gemcetabine (as Gemcetabine hydrochloride) 1 gram Gemcetabine 1g/26.3ml concentrate for solution for infusion vials | 1 vial [POM] £125.00 (Hospital only) | 1 vial [POM] £162.00
    - Gemcetabine 1g/10ml concentrate for solution for infusion vials | 1 vial [POM] no price available
    - Gemcetabine (as Gemcetabine hydrochloride) 2 gram Gemcetabine 2g/20ml concentrate for solution for infusion vials | 1 vial [POM] no price available
    - Gemcetabine 2g/52.6ml concentrate for solution for infusion vials | 1 vial [POM] £250.00 (Hospital only)

Powder for solution for infusion

- **GEMCITABINE (Non-proprietary)**
  - Gemcetabine (as Gemcetabine hydrochloride)
    - **200 mg** Gemcetabine 200mg powder for solution for infusion vials | 1 vial [POM] £32.00–£32.55 (Hospital only) | 1 vial [PO] £32.00
    - Gemcetabine (as Gemcetabine hydrochloride) 1 gram Gemcetabine 1g powder for solution for infusion vials | 1 vial [PO] £162.00–£162.76 (Hospital only) | 1 vial [POM] £162.00
    - Gemcetabine (as Gemcetabine hydrochloride) 1.5 gram Gemcetabine 1.5g powder for solution for infusion vials | 1 vial [PO] £231.93
    - Gemcetabine (as Gemcetabine hydrochloride) 2 gram Gemcetabine 2g powder for solution for infusion vials | 1 vial [PO] £324.00 (Hospital only) | 1 vial [POM] £324.00
  - **Gemzar**
    - Gemzar (Eli Lilly and Company Ltd)
      - Gemcetabine (as Gemcetabine hydrochloride) 200 mg Gemzar 200mg powder for solution for infusion vials | 1 vial [PO] £32.55 (Hospital only)
      - Gemcetabine (as Gemcetabine hydrochloride) 1 gram Gemzar 1g powder for solution for infusion vials | 1 vial [PO] £162.76 (Hospital only)

Mercaptopurine (6-Mercaptopurine)

**INDICATIONS AND DOSE**

Severe acute Crohn’s disease | Maintenance of remission of Crohn’s disease | Ulcerative colitis

**BY MOUTH**

- Adult: 1–1.5 mg/kg daily, some patients may respond to lower doses

Acute leukaemias | Chronic myeloid leukaemia

**BY MOUTH USING TABLETS**

- Adult: Initially 2.5 mg/kg daily, adjusted according to response, alternatively initially 50–75 mg/m² daily, adjusted according to response

**BY MOUTH USING ORAL SUSPENSION**

- Adult: Initially 25–75 mg/m² daily, adjusted according to response

**Dose equivalence and conversion**

Mercaptopurine tablets and Xaluprine™ oral suspension are not bioequivalent, haematological monitoring is advised when switching formulations.

**UNLICENSED USE**

Not licensed for use in severe ulcerative colitis and Crohn’s disease.

**Important safety information**

Risks of incorrect dosing of oral anti-cancer medicines, see p. 745

**CONTRA-INDICATIONS**

Absent thiopurine methyltransferase activity

**CAUTIONS**

Reduced thiopurine methyltransferase activity

**CAUTIONS, FURTHER INFORMATION**

Thiopurine methyltransferase

The enzyme thiopurine methyltransferase (TPMT) metabolises thiopurine drugs (azathioprine, mercaptopurine, tioguanine); the risk of myelosuppression is increased in patients with reduced activity of the enzyme, particularly for the few individuals in whom TPMT activity is undetectable. Patients with absent TPMT activity should not receive thiopurine drugs; those with reduced TPMT activity may be treated under specialist supervision.

**INTERACTIONS**

Appendix 1 (mercaptopurine).

**SIDE-EFFECTS**

- Rare: Pancreatitis - transient oligospermia
- Very rare: Intestinal ulceration - lymphoma
- Frequency not known: Alopecia - anorexia - bone-marrow suppression - hepatotoxicity - hyperuricaemia - nausea - oral mucositis - thromboembolism - tumour lysis syndrome - vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

Gastro-intestinal side-effects

Tioguanine has a lower incidence of gastrointestinal side-effects than mercaptopurine.

- PREGNANCY: Avoid (teratogenic). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.
- BREAST FEEDING: Discontinue breast-feeding.
- HEPATIC IMPAIRMENT: May need dose reduction.
- RENAL IMPAIRMENT: Reduce dose.
- PRE-TREATMENT SCREENING: Consider measuring thiopurine methyltransferase (TPMT) activity before starting mercaptopurine therapy.
- MONITORING REQUIREMENTS: Monitor liver function.
- PRESCRIBING AND DISPENSING INFORMATION: Flavours of oral liquid formulations may include raspberry.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, tablet, capsule.

**Tablet**

- **MERCAPTOPURINE (Non-proprietary)**
  - Mercaptopurine 50 mg Mercaptopurine 50mg tablets | 25 tablet [POM] £5.45 DT price = £5.04
  - Mercaptopurine 20 mg per 1 ml Xaluprine 20mg/ml oral suspension | 100 ml [POM] £17.00

**Methotrexate**

**DRUG ACTION**

Methotrexate inhibits the enzyme dihydrofolate reductase, essential for the synthesis of purines and pyrimidines.

**INDICATIONS AND DOSE**

Severe Crohn’s disease

**BY INTRAMUSCULAR INJECTION**

- Adult: Initially 25 mg once weekly until remission induced; maintenance 15 mg once weekly

Maintenance of remission of severe Crohn’s disease

**BY MOUTH**

- Adult: 10–25 mg once weekly

Moderate to severe active rheumatoid arthritis

**BY MOUTH**

- Adult: 7.5 mg once weekly, adjusted according to response; maximum 20 mg per week
Severe active rheumatoid arthritis
BY INTRavenous INJECTION OR BY INTRAMUScular INJECTION OR BY SUBCUTANeous INJECTION
▶ Adult: Initially 7.5 mg once weekly, then increased in steps of 2.5 mg once weekly, adjusted according to response; maximum 25 mg per week

Neoplastic diseases
BY INTRavenous INJECTION OR BY INTRATHecal INJECTION OR BY INTRASpinal INJECTION OR BY INTRAMUScular INJECTION OR BY INTRAVenous INFUSION OR BY MOUTH
▶ Adult: (consult product literature)

Severe psoriasis unresponsive to conventional therapy (specialist use only)
BY MOUTH OR BY INTRAMUScular INJECTION OR BY INTRavenous INJECTION OR BY SUBCUTANeous INJECTION
▶ Initially 2.5–10 mg once weekly, then increased in steps of 2.5–5 mg, adjusted according to response, dose to be adjusted at intervals of at least 1 week; usual dose 7.5–15 mg once weekly, stop treatment if inadequate response after 3 months at the optimum dose; maximum 30 mg per week

● UNLICENSED USE Not licensed for use in severe Crohn’s disease.

Important safety information
Note that the dose is a weekly dose. To avoid error with low-dose methotrexate, it is recommended that:
● the patient is carefully advised of the dose and frequency and the reason for taking methotrexate and any other prescribed medicine (e.g. folic acid);
● only one strength of methotrexate tablet (usually 2.5 mg) is prescribed and dispensed;
● the prescription and the dispensing label clearly show the dose and frequency of methotrexate administration;
● the patient is warned to report immediately the onset of any feature of blood disorders (e.g. sore throat, bruising, and mouth ulcers), liver toxicity (e.g. nausea, vomiting, abdominal discomfort, and dark urine), and respiratory effects (e.g. shortness of breath).

● CONTRA-INDICATIONS Active infection (in non-malignant conditions) - ascites - immunodeficiency syndromes (in non-malignant conditions) - significant pleural effusion

● CAUTIONS Acute porphyrias p. 864 - diarrhoea - extreme caution in blood disorders (avoid if severe) - peptic ulceration - photosensitivity — psoriasis lesions aggravated by UV radiation (skin ulceration reported) - risk of accumulation in pleural effusion or ascites—drain before treatment - ulcerative colitis - ulcerative stomatitis

CONTRA-INDICATIONS, FURTHER INFORMATION
Blood count Bone marrow suppression can occur abruptly; factors likely to increase toxicity include advanced age, renal impairment, and concomitant use with another anti-folate drug (e.g. trimethoprim). A clinically significant drop in white cell count or platelet count calls for immediate withdrawal of methotrexate and introduction of supportive therapy.
Liver toxicity Liver cirrhosis reported. Treatment should not be started or should be discontinued if any abnormality of liver function tests or liver biopsy is present or develops during therapy. Abnormalities can return to normal within 2 weeks after which treatment may be recommenced if judged appropriate.
Pulmonary toxicity Pulmonary toxicity may be a special problem in rheumatoid arthritis (patient to seek medical attention if dyspnoea, cough or fever); monitor for symptoms at each visit—discontinue if pneumonitis suspected.

Gastro-intestinal toxicity Withdraw treatment if stomatitis develops—may be first sign of gastro-intestinal toxicity.

● INTERACTIONS ▶ Appendix 1 (methotrexate).

If aspirin or other NSAIDs are given concurrently the dose of methotrexate should be carefully monitored.

● SIDE-EFFECTS
▶ Rare Pneumonitis

SIDE-EFFECTS, FURTHER INFORMATION
In patients taking methotrexate for non-malignant conditions who experience side-effects, folic acid given on a different day from the methotrexate, may help to reduce the frequency of such side-effects. Withdraw treatment if stomatitis develops—may be first sign of gastro-intestinal toxicity. Treatment with folic acid (as calcium folinate) may be required in acute toxicity.

● CONCEPTION AND CONTRACEPTION Effective contraception required during and for at least 3 months after treatment in men or women.

● PREGNANCY Avoid (teratogenic; fertility may be reduced during therapy but this may be reversible).

● BREAST FEEDING Discontinue breast-feeding—present in milk.

● HEPATIC IMPAIRMENT When used for malignancy, avoid in severe hepatic impairment—consult local treatment protocol for details. Avoid with hepatic impairment in non-malignant conditions—dose-related toxicity.

● RENAL IMPAIRMENT Reduce dose. Risk of nephrotoxicity at high doses. Avoid in severe impairment.

● PRE-TREATMENT SCREENING Exclude pregnancy before treatment. Patients should have full blood count and renal and liver function tests before starting treatment.

● MONITORING REQUIREMENTS
▶ In view of reports of blood dyscrasias (including fatalities) and liver cirrhosis with low-dose methotrexate patients should:
  ● have full blood count and renal and liver function tests repeated every 1–2 weeks until therapy stabilised, thereafter patients should be monitored every 2–3 months
  ● be advised to report all symptoms and signs suggestive of infection, especially sore throat
  ● Local protocols for frequency of monitoring may vary.
  ● Treatment with folic acid (as calcium folinate) may be required in acute toxicity.

● PRESCRIBING AND DISPENSING INFORMATION Folic acid following methotrexate administration helps to prevent methotrexate-induced mucositis and myelosuppression.

● PATIENT AND CARER ADVICE Methotrexate treatment booklets. Methotrexate treatment booklets should be issued where appropriate.
In England, Wales, and Northern Ireland, they are available for purchase from:
3M Security Print and Systems Limited
Gorse Street, Chadderton
Oldham OL9 9QH
Tel: 0845 610 1112
GP practices can obtain supplies through their Local Area Team stores. NHS Hospitals can order supplies from
www.nhsforms.co.uk or by emailing nhsforms@mhm.com.
In Scotland, treatment booklets can be obtained by
emailing stockorders.dppas@theapsgroup.com or by fax on 0131 629 9967.
These booklets include advice for adults taking oral methotrexate for inflammatory conditions, and a section for recording results of blood tests and dosage information.
Patients should be advised to avoid self-medication with over-the-counter aspirin or ibuprofen. Patients should be counselled on the dose, treatment booklet, and the use of NSAIDs. Patients and their carers should be warned to report immediately the onset of any feature of blood disorders (e.g. sore throat, bruising, and mouth ulcers), liver toxicity (e.g. nausea, vomiting, abdominal discomfort and dark urine), and respiratory effects (e.g. shortness of breath).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, oral suspension, oral solution

**Tablet**

- **METHOTREXATE (Non-proprietary)**
  - Methotrexate 2.5 mg: Methotrexate 2.5mg tablets | 24 tablet (P) £13.75 | 28 tablet (P) £13.82 DT price = £2.80 | 100 tablet (P) £14.19
  - Methotrexate 10 mg: Methotrexate 10mg tablets | 100 tablet (P) £57.21 DT price = £35.15
- **Maxtrex (Pfizer Ltd)**
  - Methotrexate 2.5 mg: Maxtrex 2.5mg tablets | 24 tablet (P) £2.39 | 100 tablet (P) £9.96
  - Methotrexate 10 mg: Maxtrex 10mg tablets | 100 tablet (P) £45.16 DT price = £35.15

**Solution for injection**

- **METHOTREXATE (Non-proprietary)**
  - Methotrexate (as Methotrexate sodium) 2.5 mg per 1 ml Methotrexate 5mg/2ml solution for injection vials | 5 vial (P) £30.00 £36.00
  - Methotrexate (as Methotrexate sodium) 25 mg per 1 ml Methotrexate 1g/40ml solution for injection vials | 1 vial (P) £43.68 (Hospital only) | 1 vial (P) £44.57 £67.50
  - Methotrexate 500mg/20ml solution for injection vials | 1 vial (P) £8.88 (Hospital only) | 1 vial (P) £25.07 £48.00
  - Methotrexate 50mg/2ml solution for injection vials | 1 vial (P) £4.49 (Hospital only) | 1 vial (P) £3.00 | 5 vial (P) £35.00
  - Methotrexate 200mg/8ml solution for injection vials | 1 vial (P) £10.02
  - Methotrexate (as Methotrexate sodium) 100 mg per 1 ml Methotrexate 1g/10ml solution for injection vials | 1 vial (P) £85.00
  - **Metoject PEN (medac UK)**
    - Methotrexate 50 mg per 1 ml Metoject PEN 30mg/0.6ml solution for injection pre-filled pen | 1 pre-filled disposable injection (P) £18.95 Metoject PEN 22.5mg/0.45ml solution for injection pre-filled pen | 1 pre-filled disposable injection (P) £18.45 Metoject PEN 12.5mg/0.25ml solution for injection pre-filled pen | 1 pre-filled disposable injection (P) £16.50 Metoject PEN 20mg/0.4ml solution for injection pre-filled pen | 1 pre-filled disposable injection (P) £17.84 Metoject PEN 17.5mg/0.35ml solution for injection pre-filled pen | 1 pre-filled disposable injection (P) £17.50 Metoject PEN 7.5mg/0.15ml solution for injection pre-filled pen | 1 pre-filled disposable injection (P) £14.85 Metoject PEN 10mg/0.2ml solution for injection pre-filled pen | 1 pre-filled disposable injection (P) £15.29 Metoject PEN 27.5mg/0.55ml solution for injection pre-filled pen | 1 pre-filled disposable injection (P) £18.89 Metoject PEN 25mg/0.5ml solution for injection pre-filled pen | 1 pre-filled disposable injection (P) £18.48 Metoject PEN 15mg/0.3ml solution for injection pre-filled pen | 1 pre-filled disposable injection (P) £16.57

**Solution for infusion**

- **METHOTREXATE (Non-proprietary)**
  - Methotrexate (as Methotrexate sodium) 25 mg per 1 ml Methotrexate 5g/200ml solution for infusion vials | 1 vial (P) £200.57
  - Methotrexate (as Methotrexate sodium) 100 mg per 1 ml Methotrexate 5g/50ml solution for infusion vials | 1 vial (P) £400.00

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**Nelarabine**

**INDICATIONS AND DOSE**

T-cell acute lymphoblastic leukaemia and T-cell lymphoblastic lymphoma in patients who have relapsed or who are refractory after receiving at least two previous regimes

BY INTRAVENOUS INFUSION

- **Adults:** (consult local protocol)
  - **CAUTIONS**
    - Previous or concurrent craniospinal irradiation
    - Frequency not known
    - Neurotoxicity
    - Female patients
  - **SIDE-EFFECTS**
    - Common or very common
    - Neurotoxicity (discontinue)
    - Frequency not known
    - Abdominal pain, - anaemia, - nausea
    - Electrolyte disturbances
    - Fatigue
    - Headache
    - Hypothyroidism
    - Hypotension
    - Muscle weakness
    - Myalgia
    - Oedema
    - Oral mucositis
    - Parasthesia
    - Peripheral neurological disorders
    - Pleural effusion
    - Pyrexia
    - Seizures
    - Taste disturbance
    - Thromboembolism
    - Tremor
    - Tumour lysis syndrome
    - Vomiting
  - **PREGNANCY**
    - Avoid (toxicity in animal studies).
    - See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.
  - **BREAST FEEDING**
    - Discontinue breast-feeding.
  - **MONITORING REQUIREMENTS**
    - Neurotoxicity
    - Close monitoring for neurological events is strongly recommended—discontinue if neurotoxicity occurs.
  - **PATIENT AND CARER ADVICE**
    - Drowsiness may affect
    - Close monitoring for neurological events is
    - Neurotoxicity (discontinue)
    - Frequency not known
    - Abdominal pain, - anaemia, - nausea
    - Electrolyte disturbances
    - Fatigue
    - Headache
    - Hypothyroidism
    - Hypotension
    - Muscle weakness
    - Myalgia
    - Oedema
    - Oral mucositis
    - Parasthesia
    - Peripheral neurological disorders
    - Pleural effusion
    - Pyrexia
    - Seizures
    - Taste disturbance
    - Thromboembolism
    - Tremor
    - Tumour lysis syndrome
    - Vomiting
  - **CONCEPTION AND CONCEPTION**
    - Manufacturer advises effective contraception during and for at least 3 months after treatment in men and women.

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (March 2008) that the use of nelarabine (Atriance®) within NHS Scotland is restricted to bridging treatment before stem cell transplantation.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- **NELARABINE (Novartis Pharmaceuticals UK Ltd)**
  - Nelarabine 5 mg per 1 ml
    - Atriance 250mg/50ml solution for infusion vials | 6 vial (P) £1,332.00

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**Malignant disease**
Pemetrexed

- **DRUG ACTION** Pemetrexed inhibits thymidylate transferase and other folate-dependent enzymes.

**INDICATIONS AND DOSE**

Treatment of unresectable malignant pleural mesothelioma which has not previously been treated with chemotherapy (in combination with cisplatin) | First-line treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology (in combination with cisplatin) | Second-line treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology (monotherapy) | Maintenance treatment in locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology that has not progressed immediately following platinum-based chemotherapy (monotherapy)

**BY INTRAVENOUS INFUSION**

- **CAUTIONS** Diabetes - history of cardiovascular disease - prophylactic folic acid supplementation required (consult product literature) - prophylactic vitamin B12 supplementation required (consult product literature)

- **INTERACTIONS** → Appendix 1 (pemetrexed).
  
  - Caution with concomitant nephrotoxic drugs including non-steroidal anti-inflammatory drugs (consult product literature).
  
  - **SIDE-EFFECTS**
    
    - Common or very common Conjunctivitis - dehydration - gastro-intestinal disturbances - increased lacrimation - neuropathy - oedema - skin disorders
    
    - Uncommon Arrhythmias - colitis - interstitial pneumonia
    
    - Rare Acute renal failure - hepatitis - peripheral ischaemia
    
    - **Frequency not known** Alopecia - bone-marrow suppression - extravasation - hyperuricaemia - nausea - oral mucositis - Stevens-Johnson syndrome - thromboembolism - toxic epidermal necrolysis - tumour lysis syndrome - vomiting

- **CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception during treatment. Men must avoid fathering a child during and for 6 months after treatment.

- **PREGNANCY** Avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

- **BREAST FEEDING** Discontinue breast-feeding.

- **RENAL IMPAIRMENT** Manufacturer advises avoid if creatinine clearance less than 45 mL/minute—no information available.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  - **NICE technology appraisals (TAs)**

    - Pemetrexed for the treatment of non-small cell lung cancer (August 2007) NICE TA124
    
      Pemetrexed is not recommended for the treatment of locally advanced or metastatic non-small cell lung cancer which has previously been treated with chemotherapy.

    - Pemetrexed for the treatment of malignant pleural mesothelioma (January 2008) NICE TA135
    
      Pemetrexed is an option for the treatment of malignant pleural mesothelioma only in patients who have a WHO performance status of 0 or 1 [WHO performance status is a measure of the ability to perform ordinary tasks], who are considered to have advanced disease and for whom surgical resection is considered inappropriate.

    - Pemetrexed for the first-line treatment of non-small cell lung cancer (September 2009) NICE TA181
    
      Pemetrexed, in combination with cisplatin, is an option for the first-line treatment of locally advanced or metastatic non-small cell lung cancer only if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma. www.nice.org.uk/TA181

- **Pemetrexed for the treatment of non-small cell lung cancer** (June 2010) NICE TA190

  Pemetrexed is an option for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology that has not progressed immediately following combination therapy of a platinum compound with either gemcitabine, paclitaxel, or docetaxel. www.nice.org.uk/TA190

- **Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer** (April 2014) NICE TA309

  Pemetrexed is not recommended for the maintenance treatment of locally advanced or metastatic non-squamous non-small-cell lung cancer in patients whose disease has not progressed immediately following induction therapy with pemetrexed and cisplatin.

  www.nice.org.uk/TA309

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (August 2008) that pemetrexed (Alimta®) is accepted for restricted use within NHS Scotland as monotherapy for the second-line treatment of locally advanced or metastatic non-small cell lung cancer without predominantly squamous cell histology; it is restricted for use in patients with good performance status who would otherwise be eligible for docetaxel treatment.

The Scottish Medicines Consortium has advised (January 2010) that pemetrexed (Alimta®) is accepted for restricted use within NHS Scotland in combination with cisplatin for the first-line treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology; it is restricted to patients in whom the histology of the tumour has been confirmed as adenocarcinoma or large cell carcinoma.

The Scottish Medicines Consortium has advised (July 2005) that pemetrexed (Alimta®) in combination with cisplatin is accepted for restricted use within NHS Scotland for previously untreated patients with stage III/IV unresectable malignant pleural mesothelioma.

- **MEDICINAL FORMS**

  - There can be variation in the licensing of different medicines containing the same drug.

  - **Powder for solution for infusion**

    - **ELECTROLYTES:** May contain Sodium

    - **Alimta (Eli Lilly and Company Ltd)**

      Pemetrexed (as Pemetrexed disodium) 100 mg Alimta 100mg powder for concentrate for solution for infusion vials | 1 vial £35.00 (Hospital only)

      Pemetrexed (as Pemetrexed disodium) 500 mg Alimta 500mg powder for concentrate for solution for infusion vials | 1 vial £170.00 (Hospital only)

**Tegafur with gimeracil and oteracil**

- **DRUG ACTION** Tegafur is a prodrug of fluorouracil. Gimeracil inhibits the degradation of fluorouracil and oteracil decreases the activity of fluorouracil in normal gastrointestinal mucosa.
**INDICATIONS AND DOSE**

Treatment of advanced gastric cancer when used in combination with cisplatin

**BY MOUTH**

- Adult: (consult local protocol)

**Important safety information**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**, see p. 745

- **CONTRA-INDICATIONS**
  - Dihydropyrimidine dehydrogenase deficiency
- **INTERACTIONS** → Appendix 1 (tegafur).
- **SIDE-EFFECTS**
  - Alopecia · bone-marrow suppression · hyperuricaemia · nausea · neuropathy · ocular toxicity · oral mucositis · thromboembolism · tumour lysis syndrome · vomiting
- **CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception during and for up to 6 months after treatment.
- **PREGNANCY** Avoid. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.
- **BREAST FEEDING** Discontinue breast-feeding.
- **RENA L IMPAIRMENT** Reduce dose if creatinine clearance 30–50 mL/minute—consult product literature. Manufacturer advises avoid if creatinine clearance less than 30 mL/minute.
- **NATIONAL FUNDING/ACCESS DECISIONS**

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (August 2012) that tegafur with gimeracil and oteracil (Teysuno®) is accepted for restricted use within NHS Scotland for the treatment of advanced gastric cancer, when given in combination with cisplatin, in patients who are unsuitable for an anthracycline, fluorouracil and platinum triplet first-line regimen.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

**CAUTIONARY AND ADVISORY LABELS 23**

- **Teyusu** (Nordic Pharma Ltd)
  - Gimeracil 4.35 mg, Oteracil (as Oteracil potassium) 11.8 mg, Tegafur 15 mg; Teyusu 15mg/4.35mg/11.8mg capsules | 126 capsule [P32] £279.72
  - Gimeracil 5.8 mg, Oteracil (as Oteracil potassium) 15.8 mg, Tegafur 20 mg; Teyusu 20mg/5.8mg/15.8mg capsules | 84 capsule [P32] £248.40

**Antineoplastic Antibiotics**

**Bleomycin**

**INDICATIONS AND DOSE**

Squamous cell carcinoma | Metastatic germ cell cancer | Non-Hodgkin’s lymphoma

**BY INTRAVENOUS INJECTION OR BY LOCAL INFILTRATION OR BY INTRA-ARTERIAL INFUSION OR BY INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INFUSION**

- Adult: (consult product literature or local protocols)

- **CAUTIONS** Caution in handling—irritant to tissues
- **INTERACTIONS** → Appendix 1 (bleomycin).
- **SIDE-EFFECTS**
  - Common or very common Dermatological toxicity · mucositis
  - Frequency not known Alopecia · chills (after drug administration) · extravasation · fever (after drug administration) · hypersensitivity reactions · hyperuricaemia · increased pigmentation particularly affecting the flexures and subcutaneous sclerotic plaques · less bone marrow suppression · nausea · oral mucositis · progressive pulmonary fibrosis (dose-related) · pulmonary
toxicity - Raynaud’s phenomenon - thromboembolism - tumour lysis syndrome - vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

**Hypersensitivity reactions**

Hypersensitivity reactions manifest by chills and fevers commonly occur a few hours after drug administration and may be prevented by simultaneous administration of a corticosteroid, for example hydrocortisone intravenously.

**Progressive pulmonary fibrosis**

This is dose-related, occurring more commonly at cumulative doses greater than 300 000 units and in the elderly. Basal lung crepitations or suspicious chest X-ray changes are an indication to stop therapy with this drug.

**Respiratory failure**

Patients who have received extensive treatment with bleomycin (e.g. cumulative dose more than 100 000 units) may be at risk of developing respiratory failure if a general anaesthetic is given with high inspired oxygen concentrations. Anaesthetists should be warned of this.

**PREGNANCY**

Avoid (teratogenic and carcinogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

**BREAST FEEDING**

Discontinue breast feeding.

**RENAL IMPAIRMENT**

Reduce dose by half if serum creatinine 177–354 micromol/litre; reduce dose further if serum-creatinine greater than 354 micromol/litre.

**PRESCRIBING AND DISPENSING INFORMATION**

To conform to the European Pharmacopoeia vials previously labelled as containing ‘15 units’ of bleomycin are now labelled as containing 15 000 units. The amount of bleomycin in the vial has not changed.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**

- **Bleo-Kyowa (Prostrakan Ltd)**
  - Bleomycin (as Bleomycin sulfate) 15000 unit: £190.00

**Mitomycin**

**INDICATIONS AND DOSE**

**Recurrent superficial bladder tumours (bladder instillation)**

- **BY INTRAVESICAL INSTILLATION**
  - Adult: (consult product literature or local protocols)

**Upper gastro-intestinal cancers**

**Breast cancers**

- **BY INTRAVENTOUS INJECTION**
  - Adult: (consult product literature or local protocols)

**CAUTIONS**

Caution in handling—irritant to tissues

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**

Alopecia - bone marrow damage - bone-marrow suppression - hyperuricaemia - lung fibrosis - nausea - oral mucositis - renal damage - thromboembolism - tumour lysis syndrome - vomiting

**SPECIFIC SIDE-EFFECTS**

- With intravenous use extravasation

**SIDE-EFFECTS, FURTHER INFORMATION**

**Bone-marrow toxicity**

Mitomycin is usually administered at 6-weekly intervals because it causes delayed bone-marrow toxicity. Prolonged use may result in a permanent effect.

**PREGNANCY**

Avoid (teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

**BREAST FEEDING**

Discontinue breast-feeding.

**Carboplatin**

**INDICATIONS AND DOSE**

Treatment of advanced ovarian cancer and lung cancer (particularly the small cell type)

**BY INTRAVENOUS INFUSION**

- **Adult**: The dose of carboplatin is determined according to renal function rather than body surface area (consult product literature)

**INTERACTIONS**

- **Appendix 1 (platinum compounds)**

**SIDE-EFFECTS**

Alopecia - bone-marrow suppression - extravasation - hyperuricaemia - myelosuppression - nausea - nausea - nephrotoxicity - neurotoxicity - oral mucositis - ototoxicity - thromboembolism - tumour lysis syndrome - vomiting - vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

Carboplatin is better tolerated than cisplatin; nausea and vomiting are reduced in severity and nephrotoxicity, neurotoxicity, and otoxicity are much less of a problem than with cisplatin. It is, however, more myelosuppressive than cisplatin.

**PREGNANCY**

Avoid (teratogenic and embryotoxic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

**BREAST FEEDING**

Discontinue breast-feeding.

**RENAL IMPAIRMENT**

Reduce dose. Avoid if creatinine clearance less than 20 mL/minute. Monitor haematological parameters in renal impairment. Monitor renal function in renal impairment.

**PRESCRIBING AND DISPENSING INFORMATION**

Carboplatin can be given in an outpatient setting.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- **CARBOPLATIN (Non-proprietary)**
  - Carboplatin 10 mg per 1 ml: Carboplatin 50mg/5ml concentrate for solution for infusion vials | 1 vial £22.04 (Hospital only) | 1 vial £20.00 Carboplatin 150mg/15ml concentrate for solution for infusion vials | 1 vial £56.92 (Hospital only) | 1 vial £50.00 Carboplatin 600mg/60ml concentrate for solution for infusion vials | 1 vial £260.00 Carboplatin 600mg/60ml solution for infusion vials | 1 vial £260.00 Carboplatin 450mg/45ml concentrate for solution for infusion vials | 1 vial £168.85 (Hospital only) | 1 vial £160.00 Carboplatin 450mg/45ml solution for infusion vials | 1 vial £179.48 Carboplatin 150mg/15ml solution for infusion vials | 1 vial £65.83 Carboplatin 50mg/5ml solution for infusion vials | 1 vial £22.86
Cisplatin

INDICATIONS AND DOSE
Treatment of testicular, lung, cervical, bladder, head and neck, and ovarian cancer (alone or in combination) by intravenous infusion
- Adult: (consult product literature)

- CAUTIONS
- CAUTIONS, FURTHER INFORMATION
  Hydration Cisplatin requires intensive intravenous hydration and treatment may be complicated by severe nausea and vomiting.
- INTERACTIONS → Appendix 1 (platinum compounds).
- SIDE-EFFECTS Alopecia, bone-marrow suppression, extravasation, hyperuricaemia, hypomagnesaemia, myelosuppression, nephrotoxicity, oral mucositis, ototoxicity, peripheral neuropathy, severe nausea, severe vomiting, thromboembolism, tumour lysis syndrome
- CONCEPTION AND CONTRACEPTION Manufacturer advises effective contraception during and for at least 6 months after treatment in men or women.
- PREGNANCY Avoid (teratogenic and toxic in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.
- BREAST FEEDING Discontinue breast-feeding.
- RENAL IMPAIRMENT Avoid if possible—nephrotoxic.
- MONITORING REQUIREMENTS
  - Nephrotoxicity Monitoring of renal function is essential.
  - Monitor full blood count.
  - Monitor audiometry.
  - Monitor plasma electrolytes.
- DIRECTIONS FOR ADMINISTRATION Cisplatin is increasingly given in a day care setting.

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.
- Solution for infusion
  - CISPLATIN (Non-proprietary)
    Cisplatin 1 mg per 1 ml Cisplatin 50mg/50ml concentrate for solution for infusion vials | 1 vial (hospital only) no price available
    Cisplatin 100mg/100ml solution for infusion vials | 1 vial (hospital only) £50.22 (Hospital only) | 1 vial (hospital) £52.93-£55.64 Cisplatin 10mg/10ml solution for infusion vials | 1 vial (hospital) £5.90 (Hospital only) | 1 vial (hospital) £5.90 Cisplatin 50mg/50ml solution for infusion vials | 1 vial (hospital) £25.37 (Hospital only) | 1 vial (hospital) £26.74-£28.11 Cisplatin 100mg/100ml concentrate for solution for infusion vials | 1 vial (hospital) no price available Cisplatin 100mg/100ml concentrate for solution for infusion vials | 1 vial (hospital) no price available

Oxaliplatin

INDICATIONS AND DOSE
Treatment of metastatic colorectal cancer (in combination with fluorouracil and folinic acid) | Treatment of colon cancer after resection of the primary tumour (adjuvant treatment) by intravenous infusion
- Adult: (consult product literature)

- CONTRA-INDICATIONS Peripheral neuropathy with functional impairment
- INTERACTIONS → Appendix 1 (platinum compounds).
- SIDE-EFFECTS Alopecia, bone-marrow suppression, extravasation, gastro-intestinal disturbances, hyperuricaemia, myelosuppression, nausea, neurotoxicity (dose limiting), ototoxicity, posterior reversible encephalopathy syndrome (associated with oxaliplatin combination chemotherapy) - sensory peripheral neuropathy (dose limiting), thromboembolism, transient vision loss (reversible on discontinuation), tumour lysis syndrome, vomiting

SIDE-EFFECTS, FURTHER INFORMATION
Respiratory symptoms If unexplained respiratory symptoms occur, oxaliplatin should be discontinued until investigations exclude interstitial lung disease and pulmonary fibrosis.
- CONCEPTION AND CONTRACEPTION Effective contraception required during and for 4 months after treatment in women and 6 months after treatment in men.
- PREGNANCY Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.
- BREAST FEEDING Discontinue breast-feeding.
- RENAL IMPAIRMENT Reduce dose in mild to moderate impairment (consult product literature). Avoid if creatinine clearance less than 30 mL/minute.
- NATIONAL FUNDING/ACCESS DECISIONS
  NICE technology appraisals (TAs)
  - Irinotecan, oxaliplatin, and raltitrexed for advanced colorectal cancer (August 2005) NICE TA93
    A combination of fluorouracil and folinic acid with either irinotecan or oxaliplatin are options for first-line treatment for advanced colorectal cancer. Irinotecan alone or fluorouracil and folinic acid with oxaliplatin are options for patients who require further treatment subsequently. www.nice.org.uk/TA93
  - Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes’ C) colon cancer (April 2006) NICE TA100
    Capecitabine alone or oxaliplatin combined with fluorouracil and folinic acid are options for adjuvant treatment following surgery for stage III (Dukes’ C) colon cancer. www.nice.org.uk/TA100

- MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.
- Solution for infusion
  - OXALIPLATIN (Non-proprietary)
    Oxaliplatin 5 mg per 1 ml Oxaliplatin 100mg/20ml concentrate for solution for infusion vials | 1 vial (hospital) £33.00 (Hospital only) | 1 vial (hospital) £33.15 Oxaliplatin 50mg/10ml concentrate for solution for infusion vials | 1 vial (hospital) £5.90 Oxaliplatin 20mg/100ml concentrate for solution for infusion vials | 1 vial (hospital) £25.37 Oxaliplatin 100mg/100ml concentrate for solution for infusion vials | 1 vial (hospital) £26.74-£28.11 Oxaliplatin 200mg/40ml concentrate for solution for infusion vials | 1 vial (hospital) no price available
  - OXALIPLATIN (Non-proprietary)
    Oxaliplatin 50 mg Oxaliplatin 50mg powder for solution for infusion vials | 1 vial (hospital) £15.00-£15.67 Oxaliplatin 100 mg Oxaliplatin 100mg powder for solution for infusion vials | 1 vial (hospital) £29.90-£31.30

RETINOID AND RELATED DRUGS

Bexarotene

- DRUG ACTION Bexarotene is an agonist at the retinoid X receptor, which is involved in the regulation of cell differentiation and proliferation. Bexarotene can cause regression of cutaneous T-cell lymphoma.
Tretinoin

**INDICATIONS AND DOSE**
Induction of remission in acute promyeloctic leukaemia (used in previously untreated patients as well as in those who have relapsed after standard chemotherapy or who are refractory to it)

**BY MOUTH**
- Adult: 45 mg/m² daily in 2 divided doses maximum duration of treatment is 90 days, consult product literature for details of concomitant chemotherapy

**CAUTIONS**
- Increased risk of thromboembolism during first month of treatment

**INTERACTIONS**
- Appendix 1 (retinoids).

**SIDE-EFFECTS**

**SIDE-EFFECTS, FURTHER INFORMATION**
**Retinoic acid syndrome**
Fever, dyspnoea, acute respiratory distress, pulmonary infiltrates, pleural effusion, hyperleucocytosis, hypotension, oedema, weight gain, hepatic, renal and multi-organ failure requires immediate treatment—consult product literature.

**CONCEPTION AND CONTRACEPTION**
Exclude pregnancy before starting treatment. Effective contraception must be used for at least 1 month before oral treatment, during treatment and for at least 1 month after stopping (oral progestogen-only contraceptives not considered effective).

**PREGNANCY**
Teratogenic. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

**BREAST FEEDING**
Avoid (discontinue breast-feeding).

**HEPATIC IMPAIRMENT**
Reduce dose to 25 mg/m².

**RENAL IMPAIRMENT**
Reduce dose to 25 mg/m².

**MONITORING REQUIREMENTS**
Monitor haematological and coagulation profile, liver function, serum calcium and plasma lipids before and during treatment.

**PRESCRIBING AND DISPENSING INFORMATION**
Tretinoin is the acid form of vitamin A.
For further information on side-effects, consult product literature.

- **CONCEPTION AND CONTRACEPTION** Ensure effective contraception during treatment (women) and for up to 6 months after treatment (men).
- **PREGNANCY** See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.
- **BREAST FEEDING** Discontinue breast-feeding.
- **HEPATIC IMPAIRMENT** Avoid.
- **RENAL IMPAIRMENT** Use with caution if creatinine clearance less than 50 mL/minute.
- **MONITORING REQUIREMENTS** Monitor electrolytes—correct dehydration.

- **DIRECTIONS FOR ADMINISTRATION** Intravenous infusion

- **HEPATIC IMPAIRMENT** Reduce dose according to liver enzymes (consult product literature). Avoid in severe impairment.
- **RENAL IMPAIRMENT** Monitor liver function in hepatic impairment.
- **BREAST FEEDING** Discontinue breast-feeding.
- **CONCEPTION AND CONTRACEPTION** Effective contraception for men and women during treatment, and for at least 6 months after stopping treatment in men.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE technology appraisals (TAs)**
    - Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen (May 2012) NICE TA255
      - Cabazitaxel in combination with prednisone or prednisolone is not recommended for the treatment of hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.
      - Patients currently receiving cabazitaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen should have the option to continue treatment until they and their clinicians consider it appropriate to stop. www.nice.org.uk/TA255

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Solution for infusion**
    - **EXCIPIENTS:** May contain Ethanol
      - **Jevtana (Sanofi)**
        - Cabazitaxel 40 mg per vial JEVTA 60mg/1.5ml concentrate and solvent for solution for infusion vials | 1 vial (£90.00) £3,696.00 (Hospital only)

**Docetaxel**

**INDICATIONS AND DOSE**

Adjuvant treatment of operable node-positive and operable node-negative breast cancer (in combination with doxorubicin and cyclophosphamide) | Initial chemotherapy of locally advanced or metastatic breast cancer (with doxorubicin) | Locally advanced or metastatic breast cancer where cytotoxic chemotherapy with an anthracycline or an alkylating drug has failed (monotherapy) | Locally advanced or metastatic breast cancer where cytotoxic chemotherapy with an anthracycline has failed (with capcitabine) | Initial chemotherapy of metastatic breast cancer which overexpresses human epidermal growth factor-2 (with trastuzumab) | Locally advanced or metastatic non-small cell lung cancer (with cisplatin) | Hormone-resistant metastatic prostate cancer (in combination with prednisone or prednisolone) | Initial treatment of metastatic gastric adenocarcinoma, including adenocarcinoma of the gastro-esophageal junction (with cisplatin and fluorouracil) | Induction treatment of locally advanced squamous cell carcinoma of the head and neck (with cisplatin and fluorouracil)

- **BY INTRAVENOUS INFUSION**
  - **Adult:** (consult product literature or local protocols)

- **CAUTIONS**
  - Avoid in Acute porphyrias p. 864 - consult product literature
- **INTERACTIONS**
  - **Appendix 1 (docetaxel).**
- **SIDE-EFFECTS**
  - Alopecia | bone-marrow suppression | cytoid macular oedema | extravasation | fatal respiratory disorders | gastro-intestinal toxicity | heart failure | hypersensitivity reactions | hyperuricaemia | nausea | oral mucositis | peripheral neurotoxicity | persistent fluid retention (commonly as leg oedema that worsens during treatment) can be resistant to treatment | severe skin reactions | thromboembolism | tumour lysis syndrome | vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

Hypersensitivity reactions and fluid retention | Pretreatment with dexamethasone by mouth is recommended for reducing fluid retention and hypersensitivity reactions (consult product literature). Consult product literature for monitoring and management of side effects.

- **CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception for men and women during treatment, and for at least 6 months after stopping treatment in men.
- **PREGNANCY** Avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.
- **BREAST FEEDING** Discontinue breast-feeding.
- **HEPATIC IMPAIRMENT** Reduce dose according to liver enzymes (consult product literature). Avoid in severe impairment. Monitor liver function in hepatic impairment.
- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE technology appraisals (TAs)**
    - Docetaxel for the treatment of hormone-refractory metastatic prostate cancer (June 2006) NICE TA101
      - Docetaxel is an option for hormone-refractory metastatic prostate cancer and a Karnofsky score of at least 60% [Karnofsky score is a measure of the ability to perform ordinary tasks]. www.nice.org.uk/TA101
    - Docetaxel for the adjuvant treatment of early node-positive breast cancer (September 2006) NICE TA109
      - Docetaxel, when given concurrently with doxorubicin and cyclophosphamide (TAC regimen), is recommended as an option for the adjuvant treatment of women with early node-positive breast cancer. www.nice.org.uk/TA109
  - **Scottish Medicines Consortium (SMC) Decisions**
    - The Scottish Medicines Consortium has advised that docetaxel (Taxotere®) in combination with cisplatin and fluorouracil is accepted for restricted use within NHS Scotland for the induction treatment of patients with unresectable (May 2007) and resectable (June 2008) locally advanced squamous cell carcinoma of the head and neck.

- **MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Solution for infusion**
  - **EXCIPIENTS:** May contain Ethanol
  - **DOCETAXEL (Non-proprietary)**
    - Docetaxel 10 mg per vial Docetaxel 80mg/8ml concentrate for solution for infusion vials | 1 vial (£53.47) £3,257.75 (Hospital only)
    - Docetaxel 16 mg per vial Docetaxel 160mg/16ml concentrate for solution for infusion vials | 1 vial (£166.75) (£1,063.50) (Hospital only)
    - Docetaxel 20 mg per vial Docetaxel 200mg/20ml concentrate for solution for infusion vials | 1 vial (£362.75) (£2,478.00) (Hospital only)
    - Docetaxel 20 mg per vial Docetaxel 80mg/4ml concentrate for solution for infusion vials | 1 vial (£53.47) £90.00
    - Docetaxel 140mg/7ml concentrate for solution for infusion vials:
      - 1 vial (£90.00) Docetaxel 20mg/1ml concentrate for solution for infusion vials | 1 vial (£160.00)
Paclitaxel

**Drug Action** Paclitaxel is a member of the taxane group of drugs.

**Indications and Dose**
- Treatment of ovarian cancer (advanced or residual disease following laparotomy) in combination with cisplatin (conventional paclitaxel only).
- Treatment of metastatic ovarian cancer where platinum-containing therapy has failed (conventional paclitaxel only).
- Treatment of locally advanced or metastatic breast cancer (in combination with other cytotoxics or alone if other cytotoxics have failed or are inappropriate) (conventional paclitaxel only).
- Adjunct treatment of node-positive breast cancer following treatment with anthracycline and cyclophosphamide (conventional paclitaxel only).
- Treatment of non-small cell lung cancer (in combination with cisplatin) when surgery or radiotherapy not appropriate (conventional paclitaxel only).
- Treatment of advanced AIDS-related Kaposi’s sarcoma where liposomal anthracycline therapy has failed (conventional paclitaxel only).
- First-line treatment of metastatic adenocarcinoma of the pancreas (in combination with gemcitabine) (conventional paclitaxel only).
- Monotherapy of metastatic breast cancer when first-line treatment has failed and standard, anthracycline-containing therapy is not indicated (albumin-bound paclitaxel only).
- In combination with gemcitabine for the first-line treatment of metastatic adenocarcinoma of the pancreas (albumin-bound paclitaxel only).

**By Intravenous Infusion**
- Adult: (consult product literature or local protocols)

**Cautions** Avoid in Acute porphyrias p. 864. Consult product literature—patients aged over 75 years with metastatic adenocarcinoma of the pancreas.

**Interactions** Appendix 1 (paclitaxel).

**Side-Effects**
- Common or very common: Arrhythmia, arthralgia, febrile neutropenia, gastro-intestinal disorders, myalgia, peripheral neuropathy, sensory neuropathy, tachycardia.
- Rare: Bradycardia, cardiac arrest, congestive heart failure, left ventricular dysfunction.
- Frequency not known: Alopecia, arthralgias (nearly always asymptomatic), asymptomatic hypotension, bone marrow suppression, bradycardia, cardiac conduction defects, extravasation, hypersensitivity reactions, hyperuricaemia, muscle pain, myelosuppression, nausea, neutropenia, oral mucositis, pneumonitis, Stevens-Johnson syndrome, thromboembolism, toxic epidermal necrolysis, tumour lysis syndrome, vomiting.

**Side-Effects, Further Information**

**Hypersensitivity Reactions** Routine premedication with a corticosteroid, an antihistamine and a histamine H1-receptor antagonist is recommended to prevent severe hypersensitivity reactions; hypersensitivity reactions may occur rarely despite premedication.

**Conception and Contraception** Ensure effective contraception during and for at least 6 months after treatment in men or women.

**Pregnancy** Avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

**Breast Feeding** Discontinue breast-feeding.

**Hepatic Impairment** Avoid in severe impairment.

**Monitoring Requirements**
- Cardiac monitoring should be undertaken, particularly if patients have underlying cardiac disease or previous exposure to anthracyclines.
- Patients should be monitored for signs and symptoms of pneumonitis and sepsis.

**Prescribing and Dispensing Information** Paclitaxel is available as both conventional and albumin-bound formulations. The different formulations vary in their licensed indications, pharmacokinetics, dosage and administration, and are not interchangeable. Prescribers should specify the brand to be dispensed.

**National Funding/Access Decisions**

**NICE Technology Appraisals (TAs)**
- Paclitaxel for ovarian cancer (January 2003) NICE TA55
  *Either* paclitaxel in combination with a platinum compound (cisplatin or carboplatin) or a platinum compound alone are alternatives for the first-line treatment of ovarian cancer (usually following surgery).
  *www.nice.org.uk/TA55*.
- Paclitaxel, pegylated liposomal doxorubicin, and topotecan for second-line or subsequent treatment of advanced ovarian cancer (May 2005) NICE TA91
  *Paclitaxel*, combined with a platinum compound (carboplatin or cisplatin), is an option for advanced cancer that relapses 6 months or more after completing initial platinum-based chemotherapy. Paclitaxel alone is an option for advanced ovarian cancer that does not respond to, or relapses within 6 months of completing initial platinum-based chemotherapy.
  *Paclitaxel* alone is an option for advanced ovarian cancer in patients who are allergic to platinum compounds. *www.nice.org.uk/TA91*.
- Paclitaxel for the adjuvant treatment of early node-positive breast cancer (September 2006) NICE TA108
  *Paclitaxel*, within its licensed indication, is *not* recommended for the adjuvant treatment of women with early node-positive breast cancer. *www.nice.org.uk/TA108*.

**Medicinal Forms**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for Infusion**

**Exciipients:** May contain Polyoxyl castor oils

**Paclitaxel** (Non-proprietary)
- Paclitaxel 6 mg per 1 ml Paclitaxel 150mg/25ml concentrate for solution for infusion vials | 1 vial ( Hosp) £300.52, £301.52 (Hospital only) | 1 vial ( Hosp) £105.84
  *Paclitaxel* 100mg/16.7ml concentrate for solution for infusion vials | 1 vial ( Hosp) £303.65-£374.00 (Hospital only) | 1 vial ( Hosp) £117.21
  *Paclitaxel* 300mg/50ml concentrate for solution for infusion vials | 1 vial ( Hosp) £861.52-£1,122.00 (Hospital only) | 1 vial ( Hosp) £951.63

**Powder for Suspension for Infusion**

**Electrolytes:** May contain Sodium

**Abraxane** (Celgene Ltd)
- Abraxane albumin 100 mg Abraxane 100mg powder for suspension for infusion vials | 1 vial ( Hosp) £246.00 (Hospital only)

**Cytotoxic Responsive Malignancy 771**
TOPOISOMERASE I INHIBITORS

Irinotecan hydrochloride

• **DRUG ACTION** Irinotecan inhibits topoisomerase I, an enzyme involved in DNA replication.

**INDICATIONS AND DOSE**

Metastatic colorectal cancer in combination with fluorouracil and folinic acid or as monotherapy when treatment containing fluorouracil has failed.

- First-line treatment of metastatic carcinoma of the colon or rectum (in combination with fluorouracil, folinic acid and bevacizumab).
- First-line treatment of metastatic colorectal carcinoma (in combination with capecitabine with or without bevacizumab).

**BY INTRAVENOUS INFUSION**

- Adult: (consult product literature or local protocols)

- **CONTRA-INDICATIONS** Bowel obstruction - chronic inflammatory bowel disease

- **CAUTIONS** Raised plasma-bilirubin concentration - risk factors for cardiac disease

- **INTERACTIONS** → Appendix 1 (irinotecan).

- **SIDE-EFFECTS**
  - Uncommon Interstitial pulmonary disease
  - Frequency not known Acute cholinergic syndrome (with early diarrhoea) and delayed diarrhoea (consult product literature) - alopecia - anorexia - asthenia - bone-marrow suppression - extravasation - gastro-intestinal effects (delayed diarrhoea requiring prompt treatment may follow irinotecan treatment) - hyperuricaemia - myelosuppression (dose limiting) - nausea - oral mucositis - thromboembolism - tumour lysis syndrome - vomiting

- **CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception during and for up to 1 month after treatment in women and up to 3 months after treatment in men.

- **PREGNANCY** Avoid (teratogenic and toxic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

- **BREAST FEEDING** Discontinue breast-feeding.

- **HEPATIC IMPAIRMENT** Avoid if plasma-bilirubin concentration greater than 3 times upper limit of normal range. Monitor closely for neutropenia if plasma-bilirubin concentration 1.5–3 times upper limit of normal range (consult product literature).

- **RENAL IMPAIRMENT** Manufacturer advises avoid—no information available.

- **MONITORING REQUIREMENTS** Monitor respiratory function.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Paclitaxel, pegylated liposomal doxorubicin, and topotecan for second-line or subsequent treatment of advanced ovarian cancer (May 2005) NICE TA91

Topotecan alone is an option only for advanced ovarian cancer that does not respond to, or relapses within 6 months of completing initial platinum-based chemotherapy or in those allergic to platinum compounds and for whom paclitaxel alone or pegylated liposomal doxorubicin are inappropriate. www.nice.org.uk/TA91

- Topotecan for the treatment of recurrent and stage IVB cervical cancer (October 2009) NICE TA183

Topotecan in combination with cisplatin is recommended as a treatment option for recurrent or stage IVB cervical cancer in patients who have not previously received cisplatin. www.nice.org.uk/TA183

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- **IRINOTECAN HYDROCHLORIDE (Non-proprietary)**
  - Irinotecan hydrochloride trihydrate 20 mg per 1 ml  
  - E001.25–E000.00 (Hospital only) Irinotecan 40mg/2ml concentrate for solution for infusion vials | 1 vial (PFS) £50.35
  - E390.00 (Hospital only) | 1 vial (PFS) £53.00
  - Irinotecan 100mg/5ml concentrate for solution for infusion vials | 1 vial (PFS) £53.00 (Hospital only) Campto 40mg/2ml concentrate for solution for infusion vials | 1 vial (PFS) £123.50
  - Campto (Pfizer Ltd)

- **TOPOTECAN HYDROCHLORIDE (Non-proprietary)**
  - Camptosar 100mg/5ml concentrate for solution for infusion vials | 1 vial (PFS) £130.00 (Hospital only) Campto 40mg/2ml concentrate for solution for infusion vials | 1 vial (PFS) £390.00 (Hospital only)

**Topotecan**

• **DRUG ACTION** Topotecan inhibits topoisomerase I, an enzyme involved in DNA replication.

**INDICATIONS AND DOSE**

Metastatic ovarian cancer when first-line or subsequent treatment has failed.

- Treatment of recurrent carcinoma of the cervix, after radiotherapy, and for patients with stage IVB cervical cancer (in combination with cisplatin)

**BY INTRAVENOUS INFUSION**

- Adult: (consult product literature or local protocols)

Relapsed small-cell lung cancer when retreatment with the first-line regimen is considered inappropriate.

**BY INTRAVENOUS INFUSION OR BY MOUTH**

- Adult: (consult product literature or local protocols)

**Important safety information**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**, see p. 745

- **SIDE-EFFECTS** Alopecia - anorexia - asthenia - bone-marrow suppression - extravasation - gastro-intestinal effects - hyperuricaemia - myelosuppression (dose-limiting) - nausea - oral mucositis - thromboembolism - tumour lysis syndrome - vomiting

- **PREGNANCY** Avoid (teratogenicity and fetal loss in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

- **BREAST FEEDING** Discontinue breast-feeding.

- **HEPATIC IMPAIRMENT** Avoid in severe impairment.

- **RENAL IMPAIRMENT** Reduce dose. Avoid infusion if creatinine clearance less than 20 mL/minute. Avoid oral route if creatinine clearance less than 60 mL/minute.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Paclitaxel, pegylated liposomal doxorubicin, and topotecan for second-line or subsequent treatment of advanced ovarian cancer (May 2005) NICE TA91

- Topotecan for the treatment of recurrent and stage IVB cervical cancer (October 2009) NICE TA183

Topotecan in combination with cisplatin is recommended as a treatment option for recurrent or stage IVB cervical cancer in patients who have not previously received cisplatin. www.nice.org.uk/TA183
Topotecan for the treatment of relapsed small-cell lung cancer (November 2009) NICE TA184

Oral topotecan is recommended as an option for treatment in patients with relapsed small-cell lung cancer only if re-treatment with the first-line regimen is not considered appropriate, and the combination of cyclophosphamide, doxorubicin and vincristine is contra-indicated. Intravenous topotecan is not recommended for people with relapsed small-cell lung cancer.

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (November 2007) that topotecan (Hycamtin®) is accepted for restricted use in combination with cisplatin for treatment of recurrent carcinoma of the cervix after radiotherapy and for stage IVB disease; it is restricted to patients who have not previously received cisplatin treatment.

The Scottish Medicines Consortium has advised (March 2009) that use of topotecan capsules within NHS Scotland is restricted to patients in whom standard intravenous chemotherapy is inappropriate and who would otherwise receive best supportive care.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS 25

Hycamtin® (Novartis Pharmaceuticals UK Ltd)

Topotecan (as Topotecan hydrochloride) 250 microgram Hycamtin 0.25mg capsules | 10 capsule £75.00

Topotecan (as Topotecan hydrochloride) 1 mg Hycamtin 1mg capsules | 10 capsule £90.00

Solution for infusion

TOPOTECAN (Non-proprietary)

Topotecan (as Topotecan hydrochloride) 1 mg per 1 ml Topotecan 4mg/4ml concentrate for solution for infusion vials | 1 vial £261.56 (hospital only) | 1 vial £250 no price available | 5 vial £1,453.10 (hospital only) | 5 vial £1,453.10 Topotecan 1mg/1ml concentrate for solution for infusion vials | 1 vial £87.88 (hospital only) | 1 vial £87.88 (hospital only) | 5 vial £488.25 (hospital only) | 5 vial £488.25

Powder for solution for infusion

Hycamtin® (Novartis Pharmaceuticals UK Ltd)

Topotecan (as Topotecan hydrochloride) 1 mg Hycamtin 1mg powder for concentrate for solution for infusion vials | 1 vial £97.65

Topotecan (as Topotecan hydrochloride) 4 mg Hycamtin 4mg powder for concentrate for solution for infusion vials | 1 vial £348.76

Brands may include Potactasol

VINKA ALKALOIDS

Vinblastine sulfate

INDICATIONS AND DOSE

Variety of cancers including leukaemias, lymphomas, and some solid tumours (e.g. breast and lung cancer)

Adults: (consult product literature)

Important safety information

Vinblastine is for intravenous administration only. Inadvertent intrathecal administration can cause severe neurotoxicity, which is usually fatal.

The National Patient Safety Agency has advised (August 2008) that adult and teenage patients treated in an adult or adolescent unit should receive their vinca alkaloid dose in a 50 mL minibag. Teenagers and children treated in a child unit may receive their vinca alkaloid dose in a syringe.

CONTRA-INDICATIONS

CONTRA-INDICATIONS, FURTHER INFORMATION

Intrathecal injection contra-indicated.

CAUTIONS

Caution in handling—irritant to tissues

INTERACTIONS

Appendix 1 (vinblastine).

SIDE-EFFECTS

Abdominal pain, alopecia, autonomic neuropathy, constipation, hyperuricaemia, loss of deep tendon reflexes, motor weakness, myelosuppression (dose-limiting), nausea, neurotoxicity, oral mucositis, ototoxicity, peripheral neuropathy, peripheral paraesthesia, severe bronchospasm following administration (more commonly when used in combination with mitomycin-C), severe local irritation (care must be taken to avoid extravasation), thromboembolism, tumour lysis syndrome, vomiting.

SIDE-EFFECTS, FURTHER INFORMATION

Neurotoxicity, usually as peripheral or autonomic neuropathy, occurs with all vinca alkaloids; it occurs less often with vinblastine than with vincristine.

Patients with neurotoxicity commonly have peripheral paraesthesia, loss of deep tendon reflexes, abdominal pain, and constipation; ototoxicity has been reported. If symptoms of neurotoxicity are severe, doses should be reduced. Motor weakness can also occur and dose reduction or discontinuation of therapy may be appropriate if motor weakness increases. Recovery from neurotoxic effects is usually slow but complete.

PREGNANCY

Avoid (limited experience suggests fetal harm; teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

BREAST FEEDING

Discontinue breast-feeding.

HEPATIC IMPAIRMENT

Dose reduction may be necessary—consult local treatment protocol for details.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

VINBLASTINE SULFATE (Non-proprietary)

Vinblastine sulfate 1 mg per 1 ml Vinblastine 10mg/10ml solution for injection vials | 5 vial £85.00

Vincristine sulfate

INDICATIONS AND DOSE

Variety of cancers including leukaemias, lymphomas, and some solid tumours (e.g. breast and lung cancer)

Adult: (consult local protocol)
Malignant disease

SIDE-EFFECTS
- Rare: Diarrhoea - inappropriate secretion of antidiuretic hormone - intestinal necrosis - paralytic ileus - seizures - urinary retention
- Frequency not known: Abdominal pain - alopecia - autonomic neuropathy - constipation - extravasation - eye disorders - hyperuricaemia - loss of deep tendon reflexes - motor weakness - muscle wasting - myelosuppression (negligible) - nausea - neurotoxicity - oral mucositis - otoxicity - peripheral neuropathy - peripheral paraesthesia - severe bronchospasm following administration (more commonly when used in combination with mitomycin-C) - severe local irritation (care must be taken to avoid extravasation) - thromboembolism - tumour lysis syndrome - vomiting

INTERACTIONS
- Neuromuscular disease
- Some solid tumours (e.g. breast and lung cancer)
- Cytotoxic drugs, p. 746.

MEDICINAL FORMS
- Vincristine sulfate (Non-proprietary)
  - Solution for injection
- Vinflunine
  - Powder for solution for injection

HEPATIC IMPAIRMENT
Dose reduction may be necessary.

BREAST FEEDING
Discontinue breast-feeding.

SIDE-EFFECTS, FURTHER INFORMATION
- Neurotoxicity: Neurotoxicity, usually as peripheral or autonomic neuropathy, occurs with all vinca alkaloids and is a limiting side-effect of vincristine. Patients with neurotoxicity commonly have peripheral paraesthesia, loss of deep tendon reflexes, abdominal pain, and constipation; otoxicity has been reported. If symptoms of neurotoxicity are severe, doses should be reduced. Motor weakness can also occur and dose reduction or discontinuation of therapy may be appropriate if motor weakness increases. Recovery from neurotoxic effects is usually slow but complete.

PREGNANCY
Avoid (teratogenicity and fetal loss in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

SIDE-EFFECTS
- Alopecia - autonomic neuropathy - bone-marrow suppression - extravasation - hyperuricaemia - irritant to tissues - myelosuppression (dose-limiting) - nausea - neurotoxicity - oral mucositis - peripheral neuropathy - severe bronchospasm following administration (more commonly when used in combination with mitomycin-C) - severe local irritation (if extravasated) - thromboembolism - tumour lysis syndrome - vomiting

SIDES EFFECTS, FURTHER INFORMATION
- Neurotoxicity: Neurotoxicity, usually as peripheral or autonomic neuropathy; it occurs less often with vindesine than with vincristine. Patients with neurotoxicity commonly have peripheral paraesthesia, loss of deep tendon reflexes, abdominal pain, and constipation; otoxicity has been reported. If symptoms of neurotoxicity are severe, doses should be reduced. Motor weakness can also occur and increasing motor weakness calls for dose reduction or discontinuation. Recovery from neurotoxic effects is usually slow but complete.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Powder for solution for injection
- Eldisine (Genus Pharmaceuticals Ltd)
  - Vinflunine sulfate 5 mg. Eldisine 5mg powder for solution for injection vials | 1 vial [POD] £78.30 (Hospital only)

Vinflunine

INDICATIONS AND DOSE
Treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a platinum-containing regimen (monotherapy)
- Adult: (consult local protocol)

Important safety information
Vinflunine injections are for intravenous administration only. Inadvertent intrathecal administration can cause severe neurotoxicity, which is usually fatal. The National Patient Safety Agency has advised (August 2008) that adult and teenage patients treated in an adult or adolescent unit should receive their vinca alkaloid dose in a 50 mL minibag. Teenagers and children treated in a child unit may receive their vinca alkaloid dose in a syringe.

CONTRA-INDICATIONS
- Contra-indications, further information
- Intrathecal injection contra-indicated.

CAUTIONS
- Cardiovascular disease - QT-interval prolongation (avoid hypokalaemia)

INTERACTIONS
- Appendix 1 (vinflunine).

SIDE-EFFECTS
- Common or very common: Anorexia - cutaneous reactions - dehydration - diarrhoea - dyspepsia - fatigue - hypertension - hypotension - insomnia - oedema - sweating - tachycardia - thrombosis
- Uncommon: Increased weight - myocardial infarction - renal failure
BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION

Adult: (consult product literature)

Important safety information
Vinorelbine injections are for intravenous administration only. Inadvertent intrathecal administration can cause severe neurotoxicity, which is usually fatal. The National Patient Safety Agency has advised (August 2008) that adult and teenage patients treated in an adult or adolescent unit should receive their vinca alkaloid dose in a 50 mL minibag. Teenagers and children treated in a child unit may receive their vinca alkaloid dose in a syringe.

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES, see p. 745

CONTRA-INDICATIONS

With oral use concurrent radiotherapy if treating the liver - long-term oxygen therapy - previous significant surgical resection of small bowel - previous significant surgical resection of stomach

CONTRA-INDICATIONS, FURTHER INFORMATION

Intrathecal injection contra-indicated.

CAUTIONS

Caution in handling - irritant to tissues - ischaemic heart disease

INTERACTIONS ➔ Appendix 1 (vinorelbine).

SIDE-EFFECTS

Rare Pancreatitis

Frequency not known Alopecia - autonomic neuropathy - extravasation - hyperuricaemia - inappropriate anti-diuretic hormone secretion - myelosuppression (dose-limiting) - nausea - neurotoxicity - oral mucositis - peripheral neuropathy - QT-interval prolongation - severe bronchospasm following administration (more commonly when used in combination with mitomycin-C) - severe local irritation (if extravasated) - thromboembolism - tumour lysis syndrome - vomiting

SIDE-EFFECTS, FURTHER INFORMATION

Neurotoxicity Neurotoxicity, usually as peripheral or autonomic neuropathy, occurs with all vinca alkaloids; it is a limiting side-effect of vincristine. Patients with neurotoxicity commonly have peripheral paraesthesia, loss of deep tendon reflexes, abdominal pain, and constipation; ototoxicity has been reported. If symptoms of neurotoxicity are severe, doses should be reduced. Motor weakness can also occur and dose reduction or discontinuation of therapy may be appropriate if motor weakness increases. Recovery from neurotoxic effects is usually slow but complete.

CONCEPTION AND CONTRACEPTION

Manufacturer advises effective contraception during and for up to 3 months after treatment.

PREGNANCY

Avoid unless essential - teratogenicity and embryotoxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

BREAST FEEDING

Discontinue breast-feeding.

HEPATIC IMPAIRMENT

Reduce dose - consult product literature.

RENAL IMPAIRMENT

Reduce dose if creatinine clearance less than 60 mL/minute - consult product literature.

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract (January 2013) NICE TA272

Vinflunine is not recommended for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract that has progressed after treatment with platinum-based chemotherapy. www.nice.org.uk/Ta272

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for infusion

Javlor (Pierre Fabre Ltd)

Vinflunine (as Vinflunine ditartrate) 25 mg per 1 mL

Javlor 250mg/10ml concentrate for solution for infusion | 1 vial (PSt) £1.062.50

Javlor 50mg/2ml concentrate for solution for infusion | 1 vial (PSt) £212.50

Vinorelbine

DRUG ACTION

Vinorelbine is a semi-synthetic vinca alkaloid.

INDICATIONS AND DOSE

Advanced breast cancer | Advanced non-small cell lung cancer

BY MOUTH

Adult: 60 mg/m² once weekly for 3 weeks, then increased if tolerated to 80 mg/m² once weekly (max. 160 mg once weekly)

CONTRA-INDICATIONS

Manufacturer advises effective contraception during and for 3 months after treatment; men must avoid fathering a child during and for at least 3 months after treatment.

PREGNANCY

Avoid unless essential (teratogenicity, and fetal loss in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

BREAST FEEDING

Discontinue breast-feeding.

HEPATIC IMPAIRMENT

Reduce oral dose in moderate impairment. Avoid oral use in severe impairment. Reduce intravenous dose in severe impairment.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS 21, 25

Navelbine (Pierre Fabre Ltd)

Vinorelbine (as Vinorelbine tartrate) 20 mg

Navelbine 20mg capsules | 1 capsule (PSt) £43.98 (Hospital only)
776 Malignant disease

Vinorelbine (as Vinorelbine tartrate) 30 mg Navelbine 30mg capsules | 1 capsule (PO) £65.98 (Hospital only)
Vinorelbine (as Vinorelbine tartrate) 80 mg Navelbine 80mg capsules | 1 capsule (PO) £175.92 (Hospital only)
Solution for infusion
> VINORELBINE (Non-proprietary)
Vinorelbine (as Vinorelbine tartrate) 10 mg per 1 ml Vinorelbine 50mg/5ml concentrate for solution for infusion vials | 1 vial (PO) £139.00 | 10 vial (PO) £1,539.80 Vinorelbine 10mg/1ml concentrate for solution for infusion vials | 1 vial (PO) £29.00 | 10 vial (PO) £292.50
> Navelbine (Pierre Fabre Ltd) Vinorelbine (as Vinorelbine tartrate) 10 mg per 1 ml Navelbine 10mg/1ml concentrate for solution for infusion vials | 10 vial (PO) £297.45 (Hospital only) Navelbine 50mg/5ml concentrate for solution for infusion vials | 10 vial (PO) £1,395.79 (Hospital only)

OTHER CYTOTOXIC DRUGS

Arsenic trioxide

INDICATIONS AND DOSE
Acute promyelocytic leukaemia in patients who have relapsed or failed to respond to previous treatment with a retinoid and chemotherapy

BY INTRAVENOUS INFUSION
> Adult: (consult local protocol)

> CAUTIONS Hypokalaemia (correct before treatment) - hypomagnesaemia (correct before treatment) - previous treatment with anthracyclines (increased risk of QT interval prolongation)

> INTERACTIONS → Appendix 1 (arsenic trioxide).

Avoid concomitant administration with drugs causing QT interval prolongation.

SIDE-EFFECTS
> Common or very common Atrial fibrillation - atrial flutter - diarrhoea - fatigue - haemorrhage - hyperglycaemia - hypokalaemia - myalgia - nausea - oral mucositis - thromboembolism - tumour lysis syndrome - vomiting

SIDE-EFFECTS, FURTHER INFORMATION

Leucocyte activation syndrome
Signs and symptoms of leucocyte activation syndrome include unexplained fever, dyspnoea, weight gain, pulmonary infiltrates, pleural or pericardial effusions, with or without leucocytosis—treat with high dose corticosteroids, consult product literature.

CONCEPTION AND CONTRACEPTION
Manufacturer advises effective contraception during treatment in men and women.

PREGNANCY
Avoid (teratogenic and embryotoxic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

BREAST FEEDING
Discontinue breast-feeding.

HEPATIC IMPAIRMENT
Manufacturer advises caution—limited information available.

RENAI IMPAIRMENT
Manufacturer advises caution—limited information available.

MONITORING REQUIREMENTS
ECG required before and during treatment—consult product literature.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Solution for infusion
> Trisenox (Teva UK Ltd)
Arsenic trioxide 1 mg per 1 ml Trisenox 10mg/10ml concentrate for solution for infusion ampoules | 10 ampoule (PO) £2,920.00 (Hospital only)

Crisantaspase

DRUG ACTION
Crisantaspase is the enzyme asparaginase produced by Erwinia chrysanthemi.

INDICATIONS AND DOSE
Acute lymphoblastic leukaemia

BY Intramuscular injection OR BY SUBCUTANEOUS INJECTION OR BY INTRAVENOUS INJECTION
> Adult: (consult product literature)

> CONTRA-INDICATIONS
History of pancreatitis related to asparaginase therapy

SIDE-EFFECTS
> Common or very common Coagulation disorders - confusion - convulsions - diarrhoea - dizziness - drowsiness - headache - lethargy - liver dysfunction - neurotoxicity - pancreatitis

> Uncommon
Anaphylaxis - changes in blood lipids - hyperglycaemia

> Rare
CNS depression

> Very rare
Abdominal pain - hypertension - myalgia

> Frequency not known
Alopecia - bone-marrow suppression - extravasation - hyperuricaemia - nausea - oral mucositis - thromboembolism - tumour lysis syndrome - vomiting

PREGNANCY
Avoid. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

BREAST FEEDING
Discontinue breast-feeding.

DIRECTIONS FOR ADMINISTRATION
Facilities for the management of anaphylaxis should be available.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Powder for solution for injection
> Erwinase (EUSA Pharma Ltd)
Crisantaspase 10000 unit Erwinase 10,000 unit powder for solution for injection vials | 5 vial (PO) £3,065.00

Eribulin

INDICATIONS AND DOSE
Treatment of locally advanced or metastatic breast cancer when the disease has progressed after treatment with at least 1 chemotherapy regimen for advanced disease

BY INTRAVENOUS INJECTION
> Adult: Give on day 1 and day 8 of a 21-day cycle, previous therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless the patient is unsuitable for these treatments (consult local protocol)

> CONTRA-INDICATIONS
Congenital long QT syndrome

> CAUTIONS
Bradyarrhythmias (increased susceptibility to QT-interval prolongation) - congestive heart failure (increased susceptibility to QT-interval prolongation) - electrolyte disturbances (increased susceptibility to QT-interval prolongation) - susceptibility to QT-interval prolongation

INTERACTIONS → Appendix 1 (eribulin).

Caution with concomitant use of drugs that prolong QT-interval.

SIDE-EFFECTS
Alopecia - bone-marrow suppression - extravasation - hyperuricaemia - myelosuppression -
nausea·oral mucositis·peripheral neuropathy·QT-interval prolongation·thromboembolism·tumour lysis syndrome·vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**
For further information on side effects, consult product literature.

- **CONCEPTION AND CONTRACEPTION** Ensure effective contraception during and for up to 3 months after treatment in men or women.
- **PREGNANCY** Avoid unless essential (teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.
- **BREAST FEEDING** Discontinue breast-feeding.
- **HEPATIC IMPAIRMENT** Reduce dose.
- **Renal impairment** Consider dose reduction if creatinine clearance less than 40 mL/minute.
- **MONITORING REQUIREMENTS**
  - Monitor for signs of peripheral neuropathy—severe peripheral neurotoxicity requires treatment delay or dose reduction (consult product literature).
  - ECG monitoring recommended in patients prescribed concomitant use of drugs that prolong the QT-interval or who are susceptible to QT-interval prolongation.
  - Monitor electrolytes periodically.
- **NATIONAL FUNDING/ACCESS DECISIONS**
- **SIDE-EFFECTS** Alopecia·bone marrow suppression·hyperuricaemia·irritant to tissues·nausea·oral mucositis (more common if given with doxorubicin)·thromboembolism·tumour lysis syndrome·vomiting
- **PREGNANCY** Avoid (teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.
- **BREAST FEEDING** Discontinue breast-feeding.
- **HEPATIC IMPAIRMENT** Avoid in severe impairment.

**RENAL IMPAIRMENT** Consider dose reduction—consult local treatment protocol for details.

**DIRECTIONS FOR ADMINISTRATION** Etoposide may be given orally or by slow intravenous infusion, the oral dose being double the intravenous dose. A preparation containing etoposide phosphate can be given by intravenous injection or infusion. Etoposide is usually given daily for 3–5 days and courses should not be repeated more frequently than at intervals of 21 days.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

- **CAUTIONARY AND ADVISORY LABELS 23**
  - Veneposide (Bristol-Myers Squibb Pharmaceuticals Ltd)
  - Etoposide 50 µg/Vepesid 50mg capsules | 20 capsule [P36] £39.82
  - Etoposide 100 µg/Vepesid 100mg capsules | 10 capsule [P36] £87.23

**Powder for solution for injection**

- Etopophos (Bristol-Myers Squibb Pharmaceuticals Ltd)
  - Etoposide (as etoposide phosphate) 100 mg
  - Etoposide 100mg powder for solution for injection vials | 10 vial [P40] £261.68

**Solution for infusion**

- ETOPOSIDE (Non-proprietary)
  - Etoposide 20 mg per 1 ml

**Hydroxycarbamide**

*(Hydroxyurea)*

**INDICATIONS AND DOSE**
Treatment of chronic myeloid leukaemia | Treatment of cancer of the cervix in conjunction with radiotherapy | Polycythaemia

**BY MOUTH**

- Adult: 20–30 mg/kg daily, alternatively 80 mg/kg every 3 days

**Sickle-cell disease—consult with a specialist centre**

- Adult: Initially 15 mg/kg daily, increased in steps of 2.5–5 mg/kg daily every 12 weeks according to response; usual dose 15–30 mg/kg daily; maximum 35 mg/kg per day

**IEC monitoring recommended in patients prescribed concomitant use of drugs that prolong the QT-interval or who are susceptible to QT-interval prolongation.**

**Medical safety information**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**, see p. 745

- **CAUTIONS** Leg ulcers (review treatment if cutaneous vasculitic ulcerations develop).
- **INTERACTIONS** → Appendix 1 (hydroxycarbamide).
- **SIDE-EFFECTS**
  - Common or very common Headache·myelosuppression·skin reactions
  - Rare Amenorrhoea (in sickle-cell disease)·fever (in sickle-cell disease)
  - Frequency not known Alopecia·bleeding (in sickle-cell disease)·bone marrow suppression·dizziness·hyperuricaemia·hypomagnesaemia (in sickle-cell disease)·nausea·oral mucositis·rash·reduced sperm count and activity·skin cancers (particularly in elderly patients)·thromboembolism·tumour lysis syndrome·vomiting
- **CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception before and during treatment.

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**Etoposide**

**INDICATIONS AND DOSE**
Small cell carcinoma of the bronchus, the lymphomas and testicular cancer

**BY MOUTH**

- Adult: 120–240 mg/m² daily for 5 days

**BY INTRAVENOUS INFUSION**

- Adult: (consult product literature)

**Important safety information**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**, see p. 745

**INTERACTIONS** → Appendix 1 (etoposide).

**SIDE-EFFECTS**

- Alopecia·bone marrow suppression·hyperuricaemia·irritant to tissues·nausea·oral mucositis (more common if given with doxorubicin)·thromboembolism·tumour lysis syndrome·vomiting

**PREGNANCY** Avoid (teratogenic in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

**BREAST FEEDING** Discontinue breast-feeding.

**HEPATIC IMPAIRMENT** Avoid in severe impairment.
Mitotane

**DRUG ACTION** Mitotane selectively inhibits the activity of the adrenal cortex, necessitating corticosteroid replacement therapy.

**INDICATIONS AND DOSE** Symptomatic treatment of advanced or inoperable adrenocortical carcinoma

**BY MOUTH**
- Adult: Initially 2–3 g daily in 2–3 divided doses adjusted according to plasma-concentration monitoring. In severe illness initial dose can be increased up to 6 g daily, reduce dose or interrupt treatment if signs of toxicity, discontinue if inadequate response after 3 months

Important safety information

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES, see p. 745

**CAUTIONS** Avoid in Acute porphyrias p. 864 • risk of accumulation in overweight patients

**INTERACTIONS** → Appendix 1 (mitotane).

**SIDE-EFFECTS**
- Common or very common Anaemia • anorexia • asthenia • ataxia • cognitive impairment • confusion • diarrhoea • dizziness • drowsiness • endocrine side effects • epigastric discomfort • gastro-intestinal disturbances • gynaecomastia • headache • hypercholesterolaemia • hypertriglyceridaemia • hypogonadism • leucopenia • liver disorders • movement disorder • myasthenia • nausea • neuropathy • neurotoxicity • parasthesia • prolonged bleeding time • rash • thrombocytopenia • thyroid disorders • vomiting
- Rare Flushing • haematuria • haemorrhagic cystitis • hypersalivation • hypertension • hypouricaemia • ocular disorders • postural hypotension • proteinuria • pyrexia • visual disturbances
- Frequency not known Alopecia • bone-marrow suppression • hyperuricaemia • nausea • oral mucositis • thromboembolism • tumour lysis syndrome • vomiting

**PREGNANCY** Manufacturer advises avoid. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

**BREAST FEEDING** Discontinue breast-feeding.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment. Avoid in severe impairment. In mild to moderate hepatic impairment, monitoring of plasma-mitotane concentration is recommended.

**RENAI IMPAIRMENT** Manufacturer advises caution in mild to moderate impairment. Avoid in severe impairment. In mild to moderate renal impairment, monitoring of plasma-mitotane concentration is recommended.

**MONITORING REQUIREMENTS**
- Plasma-mitotane concentration for optimum response
- Monitor plasma-mitotane concentration—consult product literature.

**PRESCRIBING AND DISPENSING INFORMATION** Corticosteroid replacement therapy Corticosteroid replacement therapy is necessary with treatment with mitotane. The dose of glucocorticoid should be increased in case of shock, trauma, or infection.

**PATIENT AND CARER ADVICE** Central nervous system toxicity may affect performance of skilled tasks (e.g. driving). Patients should be warned to contact doctor immediately if injury, infection, or illness occurs (because of risk of acute adrenal insufficiency).

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension, capsule

**Tablet**
- SIKLOS (Nordic Pharma Ltd)
  - Hydroxyurea 100 mg | 60 tablet [PO]
  - Hydroxyurea 1 gram | 30 tablet [PO]
- HYDROXYCARBAMIDE (non-proprietary)
  - Hydroxyurea 500 mg | 100 capsule [PO]
  - Hydroxyurea 1000 mg | 30 capsule [PO]
  - Hydroxyurea 1500 mg | 30 capsule [PO]

**Capsule**
- HYDROXYCARBAMIDE (non-proprietary)
  - Hydroxyurea 500 mg | 100 capsule [PO]

**INDICATIONS AND DOSE** Metastatic breast cancer • Non-Hodgkin’s lymphoma • Adult acute non-lymphocytic leukaemia • Non-resectable primary hepatocellular carcinoma

**BY INTRAVENOUS INFUSION**
- Adult: (consult local protocol)
Cytotoxic responsive malignancy 779

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.
  - Powder for solution for injection
    - Nipent (Hospital UK Ltd)
    - Pentostatin 10 mg Nipent 10mg powder for solution for injection vials | 1 vial £786.78 (Hospital only)

Pixantrone

**INDICATIONS AND DOSE**
- Treatment of refractory or multiply relapsed aggressive non-Hodgkin B-cell lymphomas (monotherapy)
- **BY INTRAVENOUS INFUSION**
  - Adult: (consult product literature)

**CONTRA-INDICATIONS**
- Active severe infection - risk factors for severe infection

**CAUTIONS**
- Active cardiovascular disease - cardiac risk factors - caution in handling - irritant to tissues - concurrent radiotherapy to the mediastinal area - history of cardiovascular disease - previous radiotherapy to the mediastinal area - previous therapy with anthracyclines - previous therapy with anthracenediones

**INTERACTIONS**
- Caution with concurrent use of cardiotoxic drugs.
- Increased risk of cardiotoxicity. Contra-indicated with concurrent immunisation with live virus vaccines.

**SIDE-EFFECTS**
- Common or very common: Abdominal pain - abnormal liver function tests - biochemical disturbances - bone pain - cardiac disorders - cardiac toxicity (during or following treatment) - chromaturia - conjunctivitis - constipation - cough - diarrhoea - drowsiness - dry mouth - dyspepsia - dyspnnea - electrolyte disturbances - haematuria - headache - hypotension - infection - loss of appetite - malaise - nail disorder - oedema - pallor - paraesthesia - proteinuria - pruritus - pyrexia - severe myelosuppression - skin discoloration - tachycardia - taste disturbances - vein discoloration - weight loss


- Frequency not known: Alopecia - bone-marrow suppression - extravasation - hyperuricaemia - nausea - oral mucositis - photosensitivity - thromboembolism - tumour lysis syndrome - vomiting

**CONCEPTION AND CONTRACEPTION**
- Ensure effective contraception during and for at least 6 months after treatment in men or women.

**PREGNANCY**
- Manufacturer advises avoid - toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

**BREAST FEEDING**
- Manufacturer advises avoid - no information available.

**HEPATIC IMPAIRMENT**
- No information available - manufacturer advises caution in mild to moderate impairment. Avoid in severe impairment.

**RENAL IMPAIRMENT**
- No information available - manufacturer advises caution.

**MONITORING REQUIREMENTS**
- Baseline investigations should include a full blood count, assessment of cardiac function measured by left ventricular ejection fraction, and measurement of serum concentrations of total bilirubin and total creatinine.

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**Pentostatin**

**INDICATIONS AND DOSE**
- Hairy cell leukaemia (initiated in specialist centres)
- **BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION**
  - Adult: To be given on alternate weeks (consult product literature)

**INTERACTIONS**
- Appendix 1 (pentostatin)

**SIDE-EFFECTS**
- Alopecia - bone-marrow suppression - extravasation - hyperuricaemia - immunosuppression - myelosuppression - nausea - neurotoxicity (withhold or discontinue) - oral mucositis - severe rash (withhold treatment) - thromboembolism - tumour lysis syndrome - vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**
- Pentostatin can cause myelosuppression, immunosuppression, and a number of other side-effects that may be severe. Treatment should be withheld in patients who develop a severe rash, and withheld or discontinued in patients showing signs of neurotoxicity.

**CONCEPTION AND CONTRACEPTION**
- Manufacturer advises that men should not father children during and for 6 months after treatment.

**PREGNANCY**
- Avoid (teratogenic in animal studies).

**BREAST FEEDING**
- Discontinue breast-feeding.

**HEPATIC IMPAIRMENT**
- Limited information available.

**RENAL IMPAIRMENT**
- Avoid if creatinine clearance less than 60 ml/minute.

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**Solution for infusion**
- Mitoxantrone (as Mitoxantrone hydrochloride) 2 mg per 1 ml Mitoxantrone 20mg/10ml concentrate for solution for infusion vials | 1 vial £121.85
- Mitoxantrone (Baxter Healthcare Ltd) Mitoxantrone (as Mitoxantrone hydrochloride) 2 mg per 1 ml Onkotrone 20mg/10ml solution for infusion vials | 1 vial no price available
- Onkotrone 25mg/12.5ml solution for infusion vials | 1 vial no price available

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**Medicinal forms**
- There can be variation in the licensing of different medicines containing the same drug.

**SIDE-EFFECTS, FURTHER INFORMATION**
- Cardiotoxicity Cardiac examinations are recommended after a cumulative dose of 160 mg/m².

**CONCEPTION AND CONTRACEPTION**
- Manufacturer advises effective contraception during and for at least 6 months after treatment in men or women.

**PREGNANCY**
- Avoid. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

**BREAST FEEDING**
- Discontinue breast-feeding.

**HEPATIC IMPAIRMENT**
- Use with caution — consult local treatment protocol.

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**RENAL IMPAIRMENT**
- If trastuzumab needs to be used, cardiac function should be monitored closely.

**SIDE-EFFECTS**

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**SIDE-EFFECTS, FURTHER INFORMATION**
- Heart failure - electrocardiographic abnormalities - ventricular ejection fraction, and measurement of serum concentrations of total bilirubin and total creatinine.

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**INTERACTIONS**
- Concomitant use of cardiotoxic drugs - increased risk of cardiotoxicity. Contra-indicated with concurrent immunisation with live virus vaccines.

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**SIDE-EFFECTS**
- Common or very common: Abnormal liver function tests - biochemical disturbances - bone pain - cardiac disorders - cardiotoxicity (during or following treatment) - chromaturia - conjunctivitis - constipation - cough - diarrhoea - drowsiness - dry mouth - dyspepsia - dyspnnea - electrolyte disturbances - haematuria - headache - hypotension - infection - loss of appetite - malaise - nail disorder - oedema - pallor - paraesthesia - proteinuria - pruritus - pyrexia - severe myelosuppression - skin discoloration - tachycardia - taste disturbances - vein discoloration - weight loss

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**UNCOMMON**

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**FREQUENCY NOT KNOWN**
- Alopecia - bone-marrow suppression - extravasation - hyperuricaemia - nausea - oral mucositis - photosensitivity - thromboembolism - tumour lysis syndrome - vomiting

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**CONCEPTION AND CONTRACEPTION**
- Ensure effective contraception during and for at least 6 months after treatment in men or women.

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**PREGNANCY**
- Manufacturer advises avoid - toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

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**BREAST FEEDING**
- Manufacturer advises avoid - no information available.

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**HEPATIC IMPAIRMENT**
- No information available - manufacturer advises caution in mild to moderate impairment. Avoid in severe impairment.

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**RENAL IMPAIRMENT**
- No information available - manufacturer advises caution.

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**MONITORING REQUIREMENTS**
- Baseline investigations should include a full blood count, assessment of cardiac function measured by left ventricular ejection fraction, and measurement of serum concentrations of total bilirubin and total creatinine.
Malignant disease

- Full blood count and cardiac function should be monitored throughout treatment.
- **PATIENT AND CARER ADVICE**
  Photosensitivity
  Photosensitivity is a theoretical risk and patients should be advised to follow sun protection strategies.
- **NATIONAL FUNDING/ACCESS DECISIONS**
  **NICE technology appraisals (TAs)**
  - Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin’s B-cell lymphoma (February 2014) NICE TA306
  Pixantrone monotherapy is recommended as an option for treating adults with multiply relapsed or refractory aggressive non-Hodgkin’s B-cell lymphoma in patients:
  - who have previously been treated with rituximab and
  - who are receiving third- or fourth-line treatment and
  - if the manufacturer provides pixantrone with the discount agreed in the patient access scheme. www.nice.org.uk/TA306

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

- **Powder for solution for infusion**
  - ELECTROLYTES: May contain Sodium
  - Pixuvri (CTI Life Sciences Ltd) ▼
  - Pixantrone (as Pixantrone dimaleate) 29 mg
  - powder for concentrate for solution for infusion vials | 1 vial | no price available

**Procarbazine**
- **DRUG ACTION**
  Procarbazine is a mild monoamine-oxidase inhibitor.

- **INDICATIONS AND DOSE**
  Hodgkin’s lymphoma
  - Adult: (consult local protocol)

- **SIDE-EFFECTS**
  - Common or very common
  - Loss of appetite
  - Frequency not known
  - Alopecia • bone-marrow suppression • hypersensitivity rash (discontinue treatment) • hyperuricaemia • jaundice • myelosuppression • nausea • oral mucositis • thromboembolism • tumour lysis syndrome • vomiting
  - **PREGNANCY**
  - Avoid (teratogenic in animal studies and isolated reports in humans). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.
  - **BREAST FEEDING**
  - Discontinue breast-feeding.
  - **HEPATIC IMPAIRMENT**
  - Caution in mild to moderate impairment. Avoid in severe impairment.
  - **RENAI IMPAIRMENT**
  - Caution in mild to moderate impairment. Avoid in severe impairment.

**Raltitrexed**
- **DRUG ACTION**
  Raltitrexed is a thymidylate synthase inhibitor.

- **INDICATIONS AND DOSE**
  Palliation of advanced colorectal cancer when fluorouracil and folinic acid cannot be used
  - BY INTRAVENOUS INFUSION
  - Adult: (consult local protocol)

- **INTERACTIONS**
  - Appendix 1 (raltitrexed).

- **SIDE-EFFECTS**
  - Alopecia • bone-marrow suppression • extravasation • gastro-intestinal effects • hyperuricaemia • myelosuppression • nausea • oral mucositis • thromboembolism • tumour lysis syndrome • vomiting
  - **CONCEPTION AND CONTRACEPTION**
  - Ensure effective contraception during and for at least 6 months after treatment in men or women.

- **PREGNANCY**
  - See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

- **BREAST FEEDING**
  - Discontinue breast-feeding.

- **HEPATIC IMPAIRMENT**
  - Caution in mild to moderate impairment. Avoid in severe impairment.

- **RENAI IMPAIRMENT**
  - Reduce dose and increase dosing interval if creatinine clearance less than 65 mL/minute (consult product literature). Avoid if creatinine clearance less than 25 mL/minute.

**NATIONAL FUNDING/ACCESS DECISIONS**
- **NICE technology appraisals (TAs)**
  - Irinotecan, oxaliplatin, and raltitrexed for advanced colorectal cancer (August 2005) NICE TA93
  - Raltitrexed is not recommended for the treatment of advanced colorectal cancer. Its use should be confined to clinical studies. www.nice.org.uk/TA93

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

- **Powder for solution for infusion**
  - Tomudex (Hospira UK Ltd)
  - Raltitrexed 2 mg
  - Tomudex 2mg powder for solution for infusion vials | 1 vial | £175.00

**Trabectedin**
- **INDICATIONS AND DOSE**
  Treatment of advanced soft tissue sarcoma when treatment with anthracyclines and ifosfamide has failed or is contra-indicated
  - Treatment of relapsed platinum-sensitive ovarian cancer (in combination with pegylated liposomal doxorubicin)
  - BY INTRAVENOUS INFUSION
  - Adult: (consult product literature or local protocols)

- **SIDE-EFFECTS**
  - Common or very common
  - Loss of appetite
  - Frequency not known
  - Alopecia • bone-marrow suppression • hypersensitivity rash (discontinue treatment) • hyperuricaemia • jaundice • myelosuppression • nausea • oral mucositis • thromboembolism • tumour lysis syndrome • vomiting
  - **PREGNANCY**
  - Avoid (teratogenic in animal studies and isolated reports in humans). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.
  - **BREAST FEEDING**
  - Discontinue breast-feeding.
  - **HEPATIC IMPAIRMENT**
  - Caution in mild to moderate impairment. Avoid in severe impairment.
  - **RENAI IMPAIRMENT**
  - Caution in mild to moderate impairment. Avoid in severe impairment.

- **CONTRA-INDICATIONS**
  - Elevated creatine phosphokinase (consult product literature).

- **INTERACTIONS**
  - Caution in concomitant use with hepatotoxic drugs (avoid alcohol).
Trabectedin for the treatment of relapsed ovarian cancer

- Rare Hepatic failure (fatal cases reported)
- Frequency not known Abdominal pain, alopecia, anorexia, arthralgia, anemia, back pain, bone-marrow suppression, constipation, cough, dehydration, diarrhea, dizziness, dyspepsia, dyspnea, extravasation, fatigue, flushing, headache, hepatobiliary disorders, hyperuricaemia, hypokalaemia, hypotension, increased blood creatine kinase, insomnia, myalgia, nausea, oedema, oral mucositis, paraesthesia, peripheral neuropathy, pyrexia, taste disturbance, thromboembolism, tumour lysis syndrome, vomiting

Side-effects, further information
A corticosteroid, such as dexamethasone by intravenous infusion, must be given 30 minutes before therapy for its antiemetic and hepatoprotective effects (consult product literature).

- Conception and contraception Effective contraception recommended during and for at least 3 months after treatment in women and during and for at least 5 months after treatment in men.
- Pregnancy See Pregnancy and reproductive function in Cytotoxic drugs, p. 746.
- Breast feeding Manufacturer advises avoid breastfeeding during and for 3 months after treatment.
- Renal impairment Avoid monotherapy if creatinine clearance less than 30 mL/minute. Avoid combination regimens if creatinine clearance less than 60 mL/minute.

Monitoring requirements
- Specific haematological, renal and hepatic parameters must be monitored and within certain ranges prior to starting treatment and repeated weekly during the first 2 cycles and at least once between treatments in subsequent cycles—consult product literature for full details.
- Monitor for signs and symptoms of rhabdomyolysis (including myelotoxicity, severe liver function disorder, renal failure, muscle weakness or pain)—monitor creatine phosphokinase closely and discontinue treatment (consult product literature).

National funding/access decisions
- NICE technology appraisals (TAs)
  - Trabectedin for the treatment of advanced soft tissue sarcoma (February 2010) NICE TA185
    Trabectedin is an option for advanced soft tissue sarcoma when treatment with anthracyclines and ifosfamide has failed, is inappropriate or is not tolerated. The cost of trabectedin for treatment after the fifth cycle is met by the manufacturer. www.nice.org.uk/TA185
  - Trabectedin for the treatment of relapsed ovarian cancer (April 2011) NICE TA222
    Trabectedin in combination with pegylated liposomal doxorubicin is not recommended for the treatment of relapsed platinum-sensitive ovarian cancer. www.nice.org.uk/TA222

Medicinal forms
- There can be variation in the licensing of different medicines containing the same drug.

Powder for solution for infusion
- Yondelis (Pharma Mar, S.A.)
  - Trabectedin 250 microgram Yondelis 0.25 mg powder for concentrate for solution for infusion vials [1 vial] no price available (Hospital only)
  - Trabectedin 1 mg Yondelis 1 mg powder for concentrate for solution for infusion vials [1 vial] no price available (Hospital only)

2.3 Cytotoxic drug-induced side effects

Folates

Folinic acid

Indications and dose
Prevention of methotrexate-induced adverse effects
- By Intramuscular injection or by intravenous infusion
  - Adult: 15 mg every 6 hours for 24 hours, to be started usually 12–24 hours after start of methotrexate infusion, dose may be continued by mouth, consult local treatment protocol for further information

Suspected methotrexate overdosage
- By Intravenous injection or by Intravenous infusion
  - Adult: Initial dose equal to or exceeding dose of methotrexate, to be given at a maximum rate of 160 mg/minute, consult poisons information centres for advice on continuing management

Adjunct to fluorouracil in colorectal cancer
- By slow intravenous injection
  - Adult: (consult product literature)

Sodiofolin®
As an antidote to methotrexate
- By Intravenous infusion or by Intravenous injection
  - Adult: (consult product literature)

Adjunct to fluorouracil in colorectal cancer
- By Intravenous injection or by Intravenous infusion
  - Adult: (consult product literature)

Contra-indications
Intrathecal injection

- Caution Not indicated for pernicious anaemia or other megaloblastic anaemias caused by vitamin B12 deficiency
- Avoid simultaneous administration of methotrexate

- Interactions
  - Appendix 1 (folates).

- Side-effects
  - Rare Agitation (after high doses) - depression (after high doses) - insomnia (after high doses) - pyrexia (after parenteral use)

- Pregnancy
  - Not known to be harmful; benefit outweighs risk.

- Breast feeding
  - Presence in milk unknown but benefit outweighs risk.

National funding/access decisions
- NICE technology appraisals (TAs)
  - Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer (December 2010) NICE TA212
    Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine is not recommended for the treatment of metastatic colorectal cancer. www.nice.org.uk/TA212

Medicinal forms
- There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
- Folinic acid (as Calcium folinate) 3 mg per 1 ml Calcium folinate 3mg/1ml solution for injection ampoules [5 ampoule] £30.00–£36.00
- Folinic acid (as Calcium folinate) 7.5 mg per 1 ml Calcium folinate 15mg/2ml solution for injection ampoules [5 ampoule] £38.99–£38.00
- Folinic acid (as Calcium folinate) 10 mg per 1 ml Calcium folinate 50mg/5ml solution for injection ampoules [1 vial] £18.44 (Hospital)
Levofolic acid

**DRUG ACTION** Levofolic acid is an isomer of folinic acid.

### INDICATIONS AND DOSE

**Prevention of methotrexate-induced adverse effects**

**BY INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INJECTION**

- Adult: Usual dose 7.5 mg every 6 hours for 10 doses, usually started 12–24 hours after beginning of methotrexate infusion

**Suspected methotrexate overdosage**

- Adult: Initial dose at least 50% of the dose of methotrexate, intravenous infusion to be administered at a maximum rate of 150 mg/minute, consult poisons information centres for advice on continuing management

**Adjunct to fluorouracil in colorectal cancer**

- Adult: (consult product literature)

### CONTRA-INDICATIONS

- Intrathecal injection

### CAUTIONS

- Not indicated for pernicious anaemia or other megaloblastic anaemias caused by vitamin B<sub>12</sub> deficiency
- Avoid simultaneous administration of methotrexate

### INTERACTIONS

- Appendix 1 (folates).

### SIDE-EFFECTS

- Rare
  - Agitation (after high doses)
  - Depression (after high doses)
  - Insomnia (after high doses)
  - Pyrexia (after parenteral use)

- PREGNANCY
  - Not known to be harmful; benefit outweighs risk.

- BREAST FEEDING
  - Presence in milk unknown but benefit outweighs risk.

### MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug.

#### Solution for injection

- **Isovorin** (Pfizer Ltd)
  - Levofolic acid (as Calcium levofolinate) 10 mg per 1 ml
  - Isovorin 75mg/15.5ml solution for injection vials | 1 vial (£11.62)
  - Isovorin 25mg/2.5ml solution for injection vials | 1 vial (£8.13)

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**IRON CHELATORS**

**Dexrazoxane**

**INDICATIONS AND DOSE**

**CARDIOXANE®**

Prevention of chronic cumulative cardiotoxicity caused by doxorubicin or epirubicin treatment in advanced or metastatic breast cancer patients who have received a prior cumulative dose of 300 mg/m<sup>2</sup> of doxorubicin or a prior cumulative dose of 540 mg/m<sup>2</sup> of epirubicin when further anthracycline treatment is required

**BY INTRAVENOUS INFUSION**

- Adult: Administer 10 times the doxorubicin-equivalent dose or 10 times the epirubicin-equivalent dose, dose to be given 30 minutes before anthracycline administration

**Savene®**

Anthracycline extravasation

**BY INTRAVENOUS INFUSION**

- Adult: Initially 1 g/m<sup>2</sup> daily (max. per dose 2 g) for 2 days, then 500 mg/m<sup>2</sup> for 1 day, first dose to be given as soon as possible and within 6 hours after injury

### CONTRA-INDICATIONS

- Children

### CAUTIONS

- Myelosuppression (effects may be additive to those of chemotherapy)

**CARDIOXANE®**

Manufacturer advises caution in patients with heart failure—no information available

Manufacturer advises caution in patients with myocardial infarction in previous 12 months—no information available

Manufacturer advises caution in patients with symptomatic valvular heart disease—no information available

Manufacturer advises caution in patients with uncontrolled angina—no information available

### INTERACTIONS

- Appendix 1 (dexrazoxane)

### SIDE-EFFECTS

**CARDIOXANE®**

- **Common or very common**
  - Anorexia
  - Astenia
  - Diarrhoea
  - Dizziness
  - Dry mouth
  - Dyspnoea
  - Erythema
  - Infection
  - Malaise
  - Nausea
  - Oedema
  - Paraesthesia
  - Peripheral neuropathy
  - Stomatitis
  - Syncope
  - Vomiting

- **Uncommon**
  - Abdominal pain
  - Acute myeloid leukaemia
  - Constipation
  - Cough
  - Dyspepsia
  - Headache
  - Lymphoedema
  - Nail disorder
  - Reduced ejection fraction
  - Tachycardia
  - Thrombocytopenia
  - Thromboembolism

**Savene®**

- **Common or very common**
  - Alopecia
  - Anaemia
  - Bleeding disorders
  - Blood disorders
  - Cough
  - DIARRHOEA
  - Dizziness
  - Dry mouth
  - Dyspnoea
  - Erythema
  - Fatigue
  - Headache
  - Hypersensitivity reactions
  - Leucopenia
  - Mucositis
  - Nausea
  - Oedema
  - Peripheral neuropathy
  - Peripheral oedema
  - Pruritus
  - Pyrexia
  - Stomatitis
  - Syncope
  - Thrombocytopenia
  - Tremor
  - Vaginal haemorrhage
  - Vomiting

**Uncommon**

- Drowsiness
- Myalgia
- Thromboembolism

**Common or very common**

- Alopecia
- Anaemia
- Blood disorders
- Bleeding disorders
- Blood disorders
- Cough
- DIARRHOEA
- Dizziness
- Dry mouth
- Dyspnoea
- Erythema
- Fatigue
- Headache
- Hypersensitivity reactions
- Leucopenia
- Mucositis
- Nausea
- Oedema
- Peripheral neuropathy
- Peripheral oedema
- Pruritus
- Pyrexia
- Stomatitis
- Syncope
- Thrombocytopenia
- Tremor
- Vaginal haemorrhage
- Vomiting

### CONCEPTION AND CONTRACEPTION

Ensure effective contraception during and for at least 3 months after treatment in men and women.

### PREGNANCY

Avoid unless essential (toxicity in animal studies).

### BREAST FEEDING

Discontinue breast-feeding.
Hypertension associated with cytotoxic drugs

### Palifermin

**DRUG ACTION** Palifermin is a human keratinocyte growth factor.

**INDICATIONS AND DOSE**

Management of oral mucositis in patients with haematological malignancies receiving myeloblastic radiochemotherapy with autologous haematopoietic stem-cell support

**BY INTRAVENOUS INJECTION**

- Adult: 60 micrograms/kg once daily for 3 doses (third dose given 24–48 hours before myeloblastic therapy) then 3 further doses at least 24 hours after myeloblastic therapy, and more than 4 days after most recent palifermin injection, starting on the same day as (but after) stem-cell infusion

**SIDE-EFFECTS**

- Arthralgia
- Discoloration of the tongue
- Erythema
- Fever
- Oedema
- Oral paraesthesia
- Pruritus
- Rash
- Skin hyperpigmentation
- Taste disturbance
- Thickening of the tongue

**PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk—毒性 in animal studies.

**MEDICAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Powder for solution for injection**
  - Kepivance (Swedish Orphan Biovitrum Ltd)
  - Palifermin 6.25 mg Kepivance 6.25 mg powder for solution for injection vials | 6 vial (£9.265.44)

### UROPROTECTIVE DRUGS

#### Mesna

**INDICATIONS AND DOSE**

Cytotoxic induced urothelial toxicity

**BY MOUTH OR BY INTRAVENOUS INJECTION**

- Adult: Dose to be calculated according to oxazaphosphorine (cyclophosphamide or ifosfamide) treatment (consult product literature)

**SIDE-EFFECTS**

- Common or very common Colic, depression, diarrhoea, fatigue, headache, hypotension, irritability, joint pains, limb pains, nausea, rash, tachycardia, vomiting

**ALLERGY AND CROSS-SENSITIVITY** Contraindicated if history of hypersensitivity to thiol-containing compounds.

**PREGNANCY** Not known to be harmful. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

**EFFECT ON LABORATORY TESTS** False positive urinary ketones. False positive or false negative urinary erythrocytes.

**DIRECTIONS FOR ADMINISTRATION** For oral administration of the injection, contents of ampoule are taken in a flavoured drink such as orange juice or cola which may be stored in a refrigerator for up to 24 hours in a sealed container.

**MEDICAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

- **Tablet**
  - MESNA (Non-proprietary)
    - Mesna 400 mg Mesna 400 mg tablets | 10 tablet (£134.30–£134.40)
    - Mesna 600 mg Mesna 600 mg tablets | 10 tablet (£190.60)

**Solution for injection**

- MESNA (Non-proprietary)
  - Mesna 100 mg per 1 ml Mesna 1g/10ml solution for injection ampoules | 15 ampoule (£41.15 Mesna 400mg/4ml solution for injection ampoules | 15 ampoule (£201.15)

2.4 Hyperuricaemia associated with cytotoxic drugs

Drugs used for Hyperuricaemia associated with cytotoxic drugs not listed below; Allopurinol, p. 905
Malignant disease

URATE OXIDASES

Rasburicase

**INDICATIONS AND DOSE**
Prophylaxis and treatment of acute hyperuricaemia, before and during initiation of chemotherapy, in patients with haematological malignancy and high tumour burden at risk of rapid lysis

**BY INTRAVENOUS INFUSION**
- Adult: 200 micrograms/kg once daily for up to 7 days according to plasma-uric acid concentration

- CONTRA-INDICATIONS G6PD deficiency
- CAUTIONS Atopic allergies
- SIDE-EFFECTS Fever
- Uncommon Anaphylaxis - bronchospasm - diarrhoea - haemolytic anaemia - headache - hypersensitivity reactions - methaemoglobinaemia - nausea - rash - vomiting
- PREGNANCY Manufacturer advises avoid — no information available.
- BREAST FEEDING Manufacturer advises avoid — no information available.
- MONITORING REQUIREMENTS Monitor closely for hypersensitivity.
- EFFECT ON LABORATORY TESTS May interfere with test for uric acid—consult product literature.
- DIRECTIONS FOR ADMINISTRATION For intravenous infusion (Fasturtec®), give intermittently in Sodium chloride 0.9%; reconstitute with solvent provided; gently swirl vial without shaking to dissolve; dilute requisite dose to 50 mL with infusion fluid and give over 30 minutes.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

- Powder and solvent for solution for infusion
  - Rasburicase 1.5 mg Fasturtec 1.5 mg powder and solvent for solution for infusion vials | 3 vial (Pack) £208.39 (Hospital only)
  - Rasburicase 7.5 mg Fasturtec 7.5 mg powder and solvent for solution for infusion vials | 1 vial (Pack) £289.44 (Hospital only)

2.5 Hormone responsive malignancy

**Hormones, malignant disease**

Hormonal manipulation has an important role in the treatment of breast, prostate, and endometrial cancer, and a more marginal role in the treatment of hypernephroma. These treatments are not curative, but may provide excellent palliation of symptoms in selected patients, sometimes for a period of years. Tumour response, and treatment toxicity should be carefully monitored and treatment changed if progression occurs or side-effects exceed benefit.

**Oestrogens**
Diethylstilbestrol p. 788 is sometimes used to treat prostate cancer, but it is not usually used first-line because of its side-effects. It is occasionally used in postmenopausal women with breast cancer. Ethinylestradiol p. 655 is the most potent oestrogen available; unlike other oestrogens it is only slowly metabolised in the liver.

**Progestogens**
Progestogens have a role in the treatment of endometrial cancer; their use in breast cancer and renal cell cancer has declined. Progestogens are now rarely used to treat prostate cancer. Medroxyprogesterone acetate p. 695 or megestrol acetate p. 788 are usually chosen and can be given orally; high-dose or parenteral treatment cannot be recommended.

**Androgens**
Testosterone esters have largely been superseded by other drugs for breast cancer.

**Hormone Antagonists**

**Breast Cancer**
The management of patients with breast cancer involves surgery, radiotherapy, drug therapy, or a combination of these. For operable breast cancer, treatment before surgery (neoadjuvant therapy) reduces the size of the tumour and facilitates breast-conserving surgery; hormone antagonist therapy (e.g. letrozole) is chosen for steroid hormone-receptor-positive breast cancer and chemotherapy for steroid hormone-receptor-negative tumours or for younger women.

**Early breast cancer**
All women should be considered for adjuvant therapy following surgical removal of the tumour. Adjuvant therapy is used to eradicate the micrometastases that cause relapses. Choice of adjuvant treatment is determined by the risk of recurrence, steroid hormone-receptor status of the primary tumour, and menopausal status.

Adjuvant therapy comprises cytotoxic chemotherapy and hormone-antagonist therapy. Women with steroid hormone-receptor-positive breast cancer are considered for hormone-antagonist therapy (preceded by cytotoxic chemotherapy if necessary) whilst women with steroid hormone-receptor-negative breast cancer should be considered for cytotoxic chemotherapy.

Aromatase inhibitors act predominantly by blocking the conversion of androgens to oestrogens in the peripheral tissues. They do not inhibit ovarian oestrogen synthesis and should not be used in premenopausal women. Anastrozole p. 792 and letrozole p. 793 are non-steroidal aromatase inhibitors; exemestane p. 792 is a steroidal aromatase inhibitor. Aromatase inhibitors are usually prescribed as initial adjuvant therapy in postmenopausal women with oestrogen-receptor-positive tumours; tamoxifen p. 751, an oestrogen-receptor antagonist, is used if an aromatase inhibitor is not appropriate. Adjuvant hormone antagonist therapy should generally be continued for 5 years following removal of the tumour. In postmenopausal women considered for extended adjuvant therapy, 5 years of tamoxifen is followed by letrozole for a further 2–3 years. Trastuzumab p. 743 is licensed for use in early breast cancer which overexpresses human epidermal growth factor-2 (HER2) in women who have received surgery, chemotherapy and radiotherapy (as appropriate).

Premenopausal women with oestrogen-receptor-positive breast cancer who decline chemotherapy may benefit from treatment with goserelin or ovarian ablation.

**Advanced breast cancer**
Treatment of advanced breast cancer depends on the patient’s drug history and an assessment of disease severity. Aromatase inhibitors, such as anastrozole or letrozole, are the preferred treatment in postmenopausal women with oestrogen-receptor-positive advanced breast cancer, a long disease-free interval following treatment for early breast cancer, and disease limited to bone or soft tissues; tamoxifen can be used if aromatase inhibitors are not suitable. Progestogens, such as medroxyprogesterone acetate p. 695, may be used after aromatase inhibitors and tamoxifen in postmenopausal women.
Tamoxifen should be considered for pre- and perimenopausal women with oestrogen-receptor-positive breast cancer not previously treated with tamoxifen. Ovarian suppression is used in pre- and perimenopausal women who have had disease progression despite treatment with tamoxifen. The gonadorelin analogue goserelin is licensed for advanced breast cancer in pre- and perimenopausal women suitable for hormone manipulation.

Trastuzumab emtansine p. 744 can be used alone for treating HER2-positive, unresectable, locally advanced breast cancer previously treated with trastuzumab and a taxane, or when there is disease recurrence during or following adjuvant therapy.

Cytotoxic chemotherapy is indicated for advanced steroid hormone-receptor-negative tumours and for aggressive disease, particularly when metastases involve visceral sites (e.g. the liver) or if the disease-free interval following treatment for early breast cancer is short.

Cytotoxic drugs used in breast cancer
An anthracycline combined with fluorouracil p. 761 and cyclophosphamide p. 750, and sometimes also with methotrexate p. 762 is effective. Cyclophosphamide, methotrexate, and fluorouracil can be useful if an anthracycline is inappropriate (e.g. in cardiac disease).

Metastatic disease
The choice of chemotherapy regimen will be influenced by whether the patient has previously received adjuvant treatment and the presence of any co-morbidity.

For women who have not previously received chemotherapy, an anthracycline (such as doxorubicin hydrochloride p. 754 or epirubicin hydrochloride p. 756) alone or in combination with another cytotoxic drug is the standard initial therapy for metastatic breast disease.

Patients with anthracycline-refractory or resistant disease should be considered for treatment with a taxane either alone or in combination with trastuzumab p. 743 if they have tumours that overexpress HER2. Other cytotoxic drugs with activity against breast cancer include capetitabine p. 757, mitoxantrone p. 778, mitomycin p. 767, and vinorelbine p. 775. Trastuzumab p. 743 alone or in combination with trastuzumab p. 743 if they have tumours that overexpress HER2. Trastuzumab emtansine can be used as monotherapy in HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane, or when there is a disease recurrence during or following adjuvant therapy.

The use of bisphosphonates in patients with metastatic breast cancer may reduce pain and prevent skeletal complications of bone metastases.

Gonadorelin analogues and gonadotrophin-releasing hormone antagonists
Metastatic cancer of the prostate usually responds to hormonal treatment aimed at androgen depletion. Standard treatments include bilateral subcapsular orchidectomy or use of a gonadorelin analogue (buserelin p. 631, goserelin p. 632, leuporelacte p. 633, or triptorelin p. 635). The gonadotrophin-releasing hormone antagonist, degarelix p. 787, is also available. Response in most patients lasts for 12 to 18 months. No entirely satisfactory therapy exists for disease progression despite this treatment (hormone-refractory prostate cancer), but occasional patients respond to other hormone manipulation e.g. with an anti-androgen. Bone disease can often be palliated with irradiation or, if widespread, with strontium ranelate p. 626 or prednisolone p. 585.

Gonadorelin analogues
Gonadorelin analogues are as effective as orchidectomy or diethylstilbestrol p. 788 but are expensive and require parenteral administration, at least initially. They cause initial stimulation then depression of luteinising hormone release by the pituitary.

Gonadorelin analogues are also used in women for breast cancer and other indications. The gonadorelin analogues cause side-effects similar to the menopause in women and orchidectomy in men.

Anti-androgens
Cyproterone acetate p. 662, flutamide p. 787 and bicalutamide p. 786 are anti-androgens that inhibit the tumour ‘flare’ which may occur after commencing gonadorelin analogue administration. Cyproterone acetate and flutamide are also licensed for use alone in patients with metastatic prostate cancer refractory to gonadorelin analogue therapy. Bicalutamide is used for prostate cancer either alone or as an adjunct to other therapy, according to the clinical circumstances.

Abiraterone acetate p. 786 (in combination with prednisone p. 586 or prednisolone p. 585) and enzalutamide p. 787 are licensed for metastatic castration-resistant prostate cancer in patients whose disease has progressed during or after treatment with a docetaxel-containing chemotherapy regimen. Abiraterone acetate p. 786 and enzalutamide p. 787 are also used to treat metastatic castration-resistant prostate cancer in patients who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated. Medical castration with a luteinising hormone-releasing hormone analogue should be continued during treatment in patients not surgically castrated.

Gonadotrophin-releasing hormone antagonists
Degarelix p. 787 is a gonadotrophin-releasing hormone antagonist used to treat advanced hormone-dependent prostate cancer. It does not induce a testosterone surge or tumour ‘flare’, therefore anti-androgen therapy is not required.

Somatostatin analogues
Lanreotide p. 789, octreotide p. 789 and pasireotide p. 790 are analogues of the hypothalamic release-inhibiting hormone somatostatin. Lanreotide and octreotide are indicated for the relief of symptoms associated with neuroendocrine (particularly carcinoid) tumours and acromegaly. Additionally, lanreotide is licensed for the treatment of thyroid tumours and octreotide is also licensed for the prevention of complications following pancreatic surgery. Lanreotide (Somatuline Autogel®) is also licensed for the treatment of unresectable locally advanced or metastatic gastroenteropancreatic neuroendocrine tumours of midgut, pancreatic or unknown origin where hindgut sites of origin have been excluded. Octreotide long-acting depot injection is licensed for treatment of advanced neuroendocrine tumours of the midgut, or treatment where primary origin is not known but non-midgut sites of origin have been excluded. Octreotide may also be valuable in reducing vomiting in palliative care and in stopping variceal bleeding [unlicensed indication]—see also vasopressin p. 576 and terlipressin acetate p. 77. Pasireotide is licensed for the treatment of Cushing’s disease when surgery has failed or is inappropriate.
Abiraterone acetate

**INDICATIONS AND DOSE**

Metastatic castration-resistant prostate cancer in patients whose disease has progressed during or after treatment with a docetaxel-containing chemotherapy regimen (in combination with prednisone or prednisolone). Metastatic castration-resistant prostate cancer in patients who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated (in combination with prednisone or prednisolone).

**CAUTIONS**

- Diabetes (increased risk of hyperglycaemia—monitor blood sugar frequently) · history of cardiovascular disease
- Concomitant use of drugs known to be associated with myopathy or rhabdomyolysis.

**SIDE-EFFECTS**

- **Common or very common** Angina · arthralgia · atrial fibrillation · diarrhoea · dyspepsia · fractures · haematuria · heart failure · hepatotoxicity · hypertension · hypertriglyceridaemia · hypokalaemia · peripheral oedema · rash · sepsis · tachycardia · urinary tract infection
- **Uncommon** Adrenal insufficiency · myopathy · rhabdomyolysis
- **Rare** Allergic alveolitis

**CONCEPTION AND CONTRACEPTION**

Men should use condoms if their partner is pregnant, and use condoms in combination with another effective contraceptive method if their partner is of child-bearing potential—sexuality in animal studies.

**HEPATIC IMPAIRMENT**

Use with caution in moderate impairment and only if benefit clearly outweighs risk. Avoid in severe impairment.

**РЕNAL IMPAIRMENT**

Use with caution in severe impairment—no information available.

**MONITORING REQUIREMENTS**

- Monitor blood pressure, serum potassium concentration, and fluid balance before treatment, and at least monthly during treatment—consult product literature for details of restarting treatment at a lower dose and discontinue permanently if 20 times the upper limit.

**NATIONAL FUNDING/ACCESS DECISIONS**

- Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen (June 2012) *NICE TA259*
Enzalutamide

INDICATIONS AND DOSE
Metastatic castration-resistant prostate cancer in patients whose disease has progressed during or after docetaxel therapy

BY MOUTH
- Adult: 160 mg once daily, for dose adjustments due to side-effects, consult product literature

CAUTIONS
- Alcoholism - bradycardia - brain injury - brain metastases - brain tumours - history of QT-interval prolongation - history or risk of seizure - recent cardiovascular disease - risk factors for QT-interval prolongation - stroke - uncontrolled hypertension

INTERACTIONS
- Appendix 1 (enzalutamide)
- Avoid concomitant use of drugs that prolong QT interval.

SIDE-EFFECTS
- Common or very common Anxiety - cognitive disorder - dry skin - falls - fractures - headache - hot flush - hypertension - memory impairment - neutropenia - pruritus - visual hallucinations
- Uncommon Leucopenia - seizure
- CONCEPTION AND CONTRACEPTION Men should use condoms during treatment and for 3 months after stopping treatment if their partner is pregnant, and use condoms in combination with another effective contraceptive method if their partner is of child-bearing potential—vulnerability to QT-interval prolongation.

HEPATIC IMPAIRMENT
- Manufacturer advises caution in moderate impairment. Avoid in severe impairment.

RENAL IMPAIRMENT
- Caution in severe impairment—no information available.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.

Capsule
- CAUTIONARY AND ADVISORY LABELS 25
- Xtandi (Astellas Pharma Ltd)
  - Enzalutamide 40 mg | 112 capsule
  - £2,734.67

Hormone responsive malignancy 787

Flutamide

INDICATIONS AND DOSE
Advanced prostate cancer

BY MOUTH
- Adult: 250 mg 3 times a day

CAUTIONS
- Avoid excessive alcohol consumption - avoid in Acute porphyrias p. 864 - cardiac disease (oedema reported)

INTERACTIONS
- Appendix 1 (flutamide)

SIDE-EFFECTS

HEPATIC IMPAIRMENT
- Use with caution (hepatotoxic).

MONITORING REQUIREMENTS
- Liver function tests, monthly for first 4 months, periodically thereafter and at the first sign or symptom of liver disorder (e.g. pruritus, dark urine, persistent anorexia, jaundice, abdominal pain, unexplained influenza-like symptoms).

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.

Tablet
- FLUTAMIDE (Non-proprietary)
  - Flutamide 250 mg | 84 tablet
  - £98.58 DT price = £74.84

GONADOTROPHIN-RELEASING HORMONE ANTAGONISTS

Degarelix

INDICATIONS AND DOSE
Advanced hormone-dependent prostate cancer

BY SUBCUTANEOUS INJECTION
- Adult: Initially 240 mg, to be administered as 2 injections of 120 mg, then 80 mg every 28 days, dose to be administered into the abdominal region

CAUTIONS
- Diabetes - susceptibility to QT-interval prolongation

INTERACTIONS
- Avoid concomitant use of drugs that prolong QT interval.

SIDE-EFFECTS
- Common or very common Asthenia - dizziness - drowsiness - headache - hot flushes - influenza-like symptoms - injection-site reactions - insomnia - nausea - night sweats - sweating - weight gain

HEPATIC IMPAIRMENT
- Manufacturer advises caution in severe impairment—no information available.

RENAL IMPAIRMENT
- Manufacturer advises caution in severe impairment—no information available.

MONITORING REQUIREMENTS
- Monitor bone density.
Malignant disease

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

*Powder and solvent for solution for injection*
- **Firmagon** (Ferring Pharmaceuticals Ltd) 80 mg – 1 vile
- **Degarelix** (as Degarelix acetate) 120 mg – 2 vile

**INDICATIONS AND DOSE**

- **Breast cancer in postmenopausal women**
  - **BY MOUTH**
    - Adult: 10–20 mg daily

- **Prostate cancer**
  - **BY MOUTH**
    - Adult: 1–3 mg daily

**CAUTIONS**
Cardiovascular disease

**SIDE-EFFECTS**
Arterial thrombosis · bone pain (in breast cancer) · feminising effects in men · fluid retention · gynaecomastia · hypercalcaemia (in breast cancer) · impotence · jaundice · nausea · sodium retention with oedema · thromboembolism · venous thrombosis · withdrawal bleeding

**PREGNANCY**
In first trimester, high doses associated with vaginal carcinoma, urogenital abnormalities, and reduced fertility in fetal offspring. Increased risk of hypospadias in male offspring.

**HEPATIC IMPAIRMENT**
Avoid. Avoid in active liver disease including disorders of hepatic excretion (e.g. Dubin-Johnson or Rotor syndromes), infective hepatitis (until liver function returns to normal), and liver tumours.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

*Tablet*
- **DIETHYLSTILBESTROL (Non-proprietary)**
  - Diethylstilbestrol 1 mg – 28 tablet
  - Diethylstilbestrol 5 mg – 28 tablet

**INDICATIONS AND DOSE**

- **Breast cancer in postmenopausal women**
  - **BY MOUTH**
    - Adult: 10–20 mg daily

- **Prostate cancer**
  - **BY MOUTH**
    - Adult: 1–3 mg daily

**MEGESTROL ACETATE**

**INDICATIONS AND DOSE**

- **Treatment of breast cancer**
  - **BY MOUTH**
    - Adult: 160 mg once daily

**CONTRA-INDICATIONS**
Acute porphyrias p. 864 · breast cancer (unless progestogens are being used in the management of this condition) · genital cancer (unless progestogens are being used in the management of this condition) · history during pregnancy of idiopathic jaundice · history during pregnancy of pempigoid gestationis · history during pregnancy of severe pruritus · history of liver tumours · severe arterial disease · undiagnosed vaginal bleeding

**CAUTIONS**
Asthma · cardiodysfunction · conditions that may worsen with fluid retention · diabetes (progestogens can decrease glucose tolerance—monitor patient closely) · epilepsy · history of depression · hypertension · migraine · susceptibility to thromboembolism (particular caution with high dose)

**INTERACTIONS**
Appendix 1 (progestogens).

**SIDE-EFFECTS**
Acne · adrenal insufficiency · alopecia · anaphylactoid reactions · asthenia · bloating · breast tenderness · carpal tunnel syndrome · change in libido · constipation · Cushing’s syndrome · depression · diarrhoea · dizziness · drowsiness · fluid retention · headache · hirsutism · indigestion · insomnia · jaundice · loss of vision during treatment (discontinue treatment if papilloedema or retinal vascular lesions) · menstrual disturbances · nausea · premenstrual-like syndrome · pruritus · rash · skin reactions · tumour flare (with or without hypercalcaemia) · urinary frequency · urticaria · vomiting · weight change · weight gain

**PREGNANCY**
 Avoid. Reversible feminisation of male fetuses reported in animal studies. Risk of hypospadias in male fetuses and masculinisation of female fetuses.

**BREAST FEEDING**
Discontinue breast-feeding.

**HEPATIC IMPAIRMENT**
Manufacturer advises caution in severe impairment.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, tablet, capsule

*Tablet*
- **Megace** (Bristol-Myers Squibb Pharmaceuticals Ltd) 160 mg – 30 tablet

**DIETHYLSTILBESTROL (Non-proprietary)**

**Somatostatin analogues**

**CAUTIONS**
Diabetes mellitus (antidiabetic requirements may be reduced) · insulinoma (increased depth and duration of hyperglycaemia may occur—observe patients and monitor blood glucose levels when initiating treatment and changing doses) · may cause growth hormone-secreting pituitary tumour expansion during treatment (causing serious complications)

**SIDE-EFFECTS**
Rare Pancreatitis (shortly after administration)

**FREQUENCY NOT KNOWN**
Abdominal pain · anorexia · bloating · diarrhoea · flatulence · gallstones (after long-term treatment) · gastro-intestinal disturbances · hyperglycaemia (with chronic administration) · hypoglycaemia · impaired postprandial glucose tolerance (with chronic administration) · irritation at the injection site · nausea · pain at the injection site · steatorrhoea · vomiting

**MONITORING REQUIREMENTS**
Monitor for signs of tumour expansion (e.g. visual field defects).

**DIRECTIONS FOR ADMINISTRATION**
Injection sites should be rotated.
### Lanreotide

**INDICATIONS AND DOSE**

**SOMATULINE AUTOGEL®**

- **Acromegaly (if somatostatin analogue not given previously)**
  - Adult: Initially 60 mg every 28 days, adjusted according to response, (consult product literature), for patients treated previously with somatostatin analogue, consult product literature for initial dose, dose to be given in the gluteal region

- **Neuroendocrine (particularly carcinoid) tumours**
  - Adult: Initially 60–120 mg every 28 days, adjusted according to response, dose to be given in the gluteal region

- **Unresectable locally advanced or metastatic gastroenteropancreatic neuroendocrine tumours of midgut, pancreatic or unknown origin where hindgut sites of origin have been excluded**
  - Adult: 120 mg every 28 days

- **SOMATULINE LA®**
  - **Acromegaly and neuroendocrine (particularly carcinoid) tumours**
    - Adult: Initially 30 mg every 14 days, increased to 30 mg every 7–10 days, adjusted according to response
  - **Thyroid tumours**
    - Adult: Initially 30 mg every 14 days, increased to 30 mg every 10 days, adjusted according to response

- **CAUTIONS**
  - Cardiac disorders (including bradycardia) - patients with carcinoid tumours—exclude the presence of an obstructive intestinal tumour before treatment
  - **INTERACTIONS** → Appendix 1 (lanreotide).
  - **SIDE-EFFECTS**
    - Common or very common: Alopecia, biliary dilatation, bradycardia, constipation, dizziness, dyspepsia, headache, lethargy, malaise, musculoskeletal pain, myalgia, raised bilirubin
    - Uncommon: Hot flushes, insomnia
    - Rare: Hypothyroidism
  - **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.
  - **BREAST FEEDING** Manufacturer advises caution—no information available.
  - **MONITORING REQUIREMENTS** Monitor for hypothyroidism when clinically indicated.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

#### Solution for injection

- **Somatuline Autogel** (Ipsen Ltd)
  - **Lanreotide** (as Lanreotide acetate) 120 mg per 1 ml Somatuline Autogel 60mg/0.5ml solution for injection pre-filled syringes with safety system | 1 pre-filled disposable injection £55.00
  - **Lanreotide** (as Lanreotide acetate) 180 mg per 1 ml Somatuline Autogel 90mg/0.5ml solution for injection pre-filled syringes with safety system | 1 pre-filled disposable injection £73.00

- **Powder and solvent for suspension for injection**
  - **Somatuline LA** (Ipsen Ltd)
    - **Lanreotide** (as Lanreotide acetate) 30 mg Somatuline LA 30mg powder and solvent for suspension for injection vials | 1 vial £32.00

### Octreotide

**INDICATIONS AND DOSE**

- **Symptoms associated with carcinoid tumours with features of carcinoid syndrome, VIPomas, glucagonomas**
  - **BY SUBCUTANEOUS INJECTION**
    - Adult: Initially 50 micrograms 1–2 times a day, adjusted according to response to 200 micrograms 3 times a day, higher doses may be required exceptionally; maintenance doses are variable; in carcinoid tumours, discontinue after 1 week if no effect; if rapid response required, initial dose may be given by intravenous injection (with ECG monitoring)
  - **Acromegaly, short-term treatment before pituitary surgery or long-term treatment in those inadequately controlled by other treatment or until radiotherapy becomes fully effective**
    - Adult: 100–200 micrograms 3 times a day, if no improvement within 3 months
  - **Prevention of complications following pancreatic surgery**
    - **BY SUBCUTANEOUS INJECTION**
      - Adult: (consult product literature)
  - **Test dose before use of depot preparation**
    - **BY SUBCUTANEOUS INJECTION**
      - Adult: Test dose 50–100 micrograms for 1 dose, test dose should be given if subcutaneous octreotide not previously given
  - **Acromegaly | Neuroendocrine (particularly carcinoid) tumour adequately controlled by subcutaneous octreotide**
    - **BY DEEP INTRAMUSCULAR INJECTION USING DEPOT INJECTION**
      - Adult: 20 mg every 4 weeks then adjusted according to response to 50 micrograms per day, to be administered into the gluteal muscle, for acromegaly, start depot 1 day after the last dose of subcutaneous octreotide, for neuroendocrine tumours, continue subcutaneous octreotide for 2 weeks after first dose of depot octreotide
  - **Advanced neuroendocrine tumours of the midgut, or tumours of unknown primary origin where non-midgut sites of origin have been excluded**
    - **BY DEEP INTRAMUSCULAR INJECTION USING DEPOT INJECTION**
      - Adult: 30 mg every 4 weeks
  - **Reduce intestinal secretions in palliative care**
    - **Reduce vomiting due to bowel obstruction in palliative care**
      - **BY CONTINUOUS SUBCUTANEOUS INFUSION**
        - Adult: 0.25–0.5 mg/24 hours (max. per dose 0.75 mg/24 hours), occasionally doses higher than the maximum are sometimes required

- **INTERACTIONS** → Appendix 1 (octreotide).
- **SIDE-EFFECTS**
  - Alopecia, arthrythmias, biliary colic (associated with abrupt withdrawal of subcutaneous octreotide), bradycardia, dehydration, dizziness, dyspepsia, headache, hepatitis, pancreatitis (associated with abrupt withdrawal of subcutaneous octreotide), rash

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - **Gastro-intestinal side-effects** Administering non-depot injections of octreotide between meals and at bedtime may reduce gastro-intestinal side-effects.

- **CONCEPTION AND CONTRACEPTION** Effective contraception required during treatment.
- **PREGNANCY** Possible effect on fetal growth; manufacturer advises use only if potential benefit outweighs risk.
- **BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.
Hepatic impairment

Adjustment of maintenance dose of non-depot preparations may be necessary in patients with liver cirrhosis.

Monitoring requirements

- With intravenous use ECG monitoring required with intravenous administration.
- Monitor thyroid function on long-term therapy.
- Monitor liver function.

Treatment cessation

Avoid abrupt withdrawal of short-acting subcutaneous octreotide (associated with biliary colic and pancreatitis).

Directions for administration

For intravenous infusion, dilute with Sodium Chloride 0.9% to a concentration of 10–50%.

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

**Octreotide (Non-proprietary)**

Octreotide (as Octreotide acetate) 50 microgram per 1 ml

Octreotide 50micrograms/1ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (Pasireotide) €10.65

Octreotide 50micrograms/1ml solution for injection ampoules | 5 ampoule (Pasireotide) €9.74–€18.60 Octreotide 50micrograms/1ml solution for injection vials | 5 vial (Pasireotide) €14.37–€22.00

Octreotide (as Octreotide acetate) 100 microgram per 1 ml

Octreotide 100micrograms/1ml solution for injection ampoules | 5 ampoule (Octreotide) €18.61–€32.65 Octreotide 100micrograms/1ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (Octreotide) €28.90 Octreotide 100micrograms/1ml solution for injection vials | 5 vial (Octreotide) €27.97–€32.65

Octreotide (as Octreotide acetate) 200 microgram per 1 ml

Octreotide 1mg/5ml solution for injection vials | 1 vial (Octreotide) €65.00–€69.66

Octreotide (as Octreotide acetate) 500 microgram per 1 ml

Octreotide 500micrograms/1ml solution for injection vials | 5 vial (Octreotide) €135.47–€158.25 Octreotide 500micrograms/1ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (Octreotide) €135.47–€149.00

Sandostatin (Novartis Pharmaceuticals UK Ltd)

Octreotide (as Octreotide acetate) 50 microgram per 1 ml

Octreotide 50micrograms/1ml solution for injection ampoules | 5 ampoule (Sandostatin) €14.87

Octreotide (as Octreotide acetate) 100 microgram per 1 ml

Octreotide 100micrograms/1ml solution for injection ampoules | 5 ampoule (Sandostatin) €27.97

Octreotide (as Octreotide acetate) 200 microgram per 1 ml

Sandostatin 1mg/5ml solution for injection vials | 1 vial (Sandostatin) €55.73

Octreotide (as Octreotide acetate) 500 microgram per 1 ml

Sandostatin 500micrograms/1ml solution for injection ampoules | 5 ampoule (Sandostatin) €135.47

Powder and solvent for suspension for injection

Sandostatin LAR (Novartis Pharmaceuticals UK Ltd)

Octreotide (as Octreotide acetate) 10 mg Sandostatin LAR 10mg powder and solvent for suspension for injection vials | 1 vial (Sandostatin) €469.84

Octreotide (as Octreotide acetate) 20 mg Sandostatin LAR 20mg powder and solvent for suspension for injection vials | 1 vial (Sandostatin) €776.05

Octreotide (as Octreotide acetate) 30 mg Sandostatin LAR 30mg powder and solvent for suspension for injection vials | 1 vial (Sandostatin) €993.44

Pasireotide

Indications and dose

Cushing’s disease when surgery has failed or is inappropriate

By subcutaneous injection

- Adult: Initially 600 micrograms twice daily for 2 months, then increased if necessary to 900 micrograms twice daily, consider discontinuation if no response within 2 months, for dose adjustment due to side effects—consult product literature

Caution

Cardiac disorders (including bradycardia) - susceptibility to QT-interval prolongation (including electrolyte disturbances)

Interactions

Caution with concomitant use of drugs that prolong QT interval.

Side-effects


Pregnancy

Avoid—toxicity in animal studies.

Breast feeding

Avoid—present in milk in animal studies.

Hepatic impairment

Reduce initial dose to 300 micrograms twice daily (increased if necessary after 2 months to max. 600 micrograms twice daily) in moderate impairment. Avoid in severe impairment.

Monitoring requirements

- Monitor liver function before treatment and after 1, 2, 4, 8, and 12 weeks of treatment.
- QT-interval prolongation Monitor ECG and electrolytes in patients susceptible to QT-prolongation before treatment, after one week, and periodically thereafter.
- Diabetes mellitus In diabetic patients, assess glycaemic status before treatment, weekly for the first 2–3 months of treatment, periodically thereafter, and 3 months after treatment is complete.

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

- Signifor (Novartis Pharmaceuticals UK Ltd) ▲ Pasireotide (as Pasireotide disparetate) 300 microgram per 1 ml Signifor 0.3mg/1ml solution for injection ampoules | 60 ampoule (Signifor) €2,800.00 Pasireotide (as Pasireotide disparetate) 600 microgram per 1 ml Signifor 0.6mg/1ml solution for injection ampoules | 60 ampoule (Signifor) €3,240.00 Pasireotide (as Pasireotide disparetate) 900 microgram per 1 ml Signifor 0.9mg/1ml solution for injection ampoules | 60 ampoule (Signifor) €3,240.00

2.6 Hormone responsive breast cancer

Anti-oestrogens

Fulvestrant

Indications and dose

Treatment of oestrogen-receptor-positive metastatic or locally advanced breast cancer in postmenopausal women in whom disease progresses or relapses while on, or after, other anti-oestrogen therapy

By deep intramuscular injection

- Adult: 500 mg every 2 weeks for the first 3 doses, then 500 mg every 1 month, to be administered into the buttock

- Side-effects

Common or very common Anorexia - asthenia - back pain - diarrhoea - headache - hot flushes - hypersensitivity reactions - injection-site reactions - nausea - rash - urinary-tract infections - venous thromboembolism - vomiting
Tamoxifen

**DRUG ACTION** An anti-oestrogen which induces gonadotrophin release by occupying oestrogen receptors in the hypothalamus, thereby interfering with feedback mechanisms; chorionic gonadotrophin is sometimes used in the hypothalamus, thereby interfering with feedback mechanisms; chorionic gonadotrophin release by occupying oestrogen receptors

**INDICATIONS AND DOSE**

**Pre- and perimenopausal women with oestrogen-receptor-positive breast cancer not previously treated with tamoxifen**

**BY MOUTH**

- **Adult:** 20 mg daily

**Anovulatory infertility**

- **Adult:** Initially 20 mg daily on days 2, 3, 4 and 5 of cycle, if necessary the daily dose may be increased to 40 mg then 80 mg for subsequent courses; if cycles irregular, start initial course on any day, with subsequent course starting 45 days later or on day 2 of cycle if menstruation occurs

**CONTRA-INDICATIONS** Treatment of infertility contra-indicated if personal or family history of idiopathic venous thromboembolism or genetic predisposition to thromboembolism

**CAUTIONS** Porphyria

**INTERACTIONS** → Appendix 1 (tamoxifen).

**SIDE-EFFECTS**

- Rare Angioedema · bullous pemphigoid · cholestasis · fatty liver · hepatitis · hypersensitivity reactions · hypertriglyceridaemia · interstitial pneumonitis · neutropenia · Stevens-Johnson syndrome

- Frequency not known Alopecia · anaemia · catarracts · corneal changes · decreased platelet counts · endometrial changes · gastrointestinal disturbances · headache · hot flushes · hypercalcaemia if bony metastases · increased risk of thromboembolic events, especially when used with cytotoxics · leucopenia · light-headiness · liver enzyme changes · occasional cystic ovarian swellings in premenopausal women · occasionally oedema · pancreatitis · pruritus vulvae · rashes · retinopathy · suppression of menstruation in some premenopausal women · thrombocytopenia · thromboembolic events · tumour flare · uterine fibroids · vaginal bleeding · vaginal discharge · visual disturbances

**SIDE-EFFECTS, FURTHER INFORMATION**

**Endometrial changes** Increased endometrial changes, including hyperplasia, polyps, cancer, and uterine sarcoma reported; prompt investigation required if abnormal vaginal bleeding including menstrual irregularities, vaginal discharge, and pelvic pain or pressure in those receiving (or who have received) tamoxifen.

**Risk of thromboembolism** Tamoxifen can increase the risk of thromboembolism particularly during and immediately after major surgery or periods of immobility (consider interrupting treatment to initiate anticoagulant measures).

**CONCEPTION AND CONTRACEPTION** Unless being used in the treatment of female infertility, effective contraception must be used during treatment and for 2 months after stopping. Patients being treated for infertility should be warned that there is a risk of multiple pregnancy (rarely more than twins).

**PREGNANCY** Avoid—possible effects on fetal development.

**BREAST FEEDING** Suppresses lactation. Avoid unless potential benefit outweighs risk.

**PATIENT AND CARER ADVICE**

Endometrial changes Patients should be informed of the risk of endometrial cancer and told to report relevant symptoms promptly. Thromboembolism Patients should be made aware of the symptoms of thromboembolism and advised to report sudden breathlessness and any pain in the calf of one leg.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Faslodex (AstraZeneca UK Ltd)

  Fulvestrant 50 mg per ml

  Faslodex 250mg/5ml solution for injection pre-filled syringes | 2 pre-filled disposable injection £52.41

**CONTRA-INDICATIONS**

- Breast cancer (hormone responsive)

**INDICATIONS AND DOSE**

Hormone-dependent metastatic breast cancer in postmenopausal women

**BY MOUTH**

- **Adult:** 60 mg daily

**CONTRA-INDICATIONS** Bradycardia · electrolyte disturbances (particularly uncorrected hypokalaemia) · endometrial hyperplasia · heart failure with reduced left-ventricular ejection fraction · history of arrhythmias · QT prolongation

**CAUTIONS** Avoid in Acute porphyrias p. 864 · history of severe thromboembolic disease

**INTERACTIONS** → Appendix 1 (toremifene).
Avoid concomitant administration of drugs that prolong QT interval.

- **SIDE-EFFECTS**
  - **Common or very common** Depression, dizziness, fatigue, hot flushes, nausea, oedema, rash, sweating, vaginal bleeding, vaginal discharge, vomiting
  - **Uncommon** Anorexia, constipation, dyspnoea, endometrial hypertrophy, headache, increased weight, insomnia, thromboembolic events
  - **Very rare** Alopecia, jaundice, transient corneal opacity
  - **Frequency not known** Hypercalcaemia (especially if bone metastases and usually at beginning of treatment)

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Endometrial changes: Increased endometrial changes, including hyperplasia, polyps, and cancer reported. Abnormal vaginal bleeding including menstrual irregularities, vaginal discharge, and symptoms such as pelvic pain or pressure should be promptly investigated.

- **PREGNANCY** Avoid.
- **BREAST FEEDING** Avoid.
- **HEPATIC IMPAIRMENT** Elimination decreased in hepatic impairment—avoid if severe.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  | Tablet | Anastrozole 1 mg | Anastrozole 1 mg tablets | 28 tablet | £68.56 DT price = £1.98
  | Tablet | Arimidex (AstraZeneca UK Ltd) | Anastrozole 1 mg | Anastrozole 1 mg tablets | 28 tablet | £68.56 DT price = £1.98

- **Exemestane**

  | INDICATIONS AND DOSE | Adjuvant treatment of oestrogen-receptor-positive early breast cancer in postmenopausal women following 2–3 years of tamoxifen therapy | Advanced breast cancer in postmenopausal women in whom anti-oestrogen therapy has failed
  | BY MOUTH | Adult: 25 mg daily

  | CONTRA-INDICATIONS | Not indicated for premenopausal women
  | INTERACTIONS | Appendix 1 (exemestane).
  | SIDE-EFFECTS | Common or very common: Abdominal pain, alopecia, anorexia, constipation, depression, dizziness, dyspepsia, fatigue, headache, hot flushes, insomnia, nausea, rash, sweating, vomiting
  | CONTRA-INDICATIONS | Not for premenopausal women
  | CAUTIONS | Susceptibility to osteoporosis
  | SIDE-EFFECTS | Very rare: Allergic reactions, anaphylaxis, angioedema
  | Frequency not known | Anorexia, arthralgia, arthritis, asthenia, bone fractures, bone pain, cutaneous vasculitis, diarrhoea, drowsiness, hair thinning, headache, hot flushes, nausea, rash, slight increases in total cholesterol levels, Stevens–Johnson syndrome, vaginal bleeding, vaginal dryness, vomiting
  | PREGNANCY | Avoid.
  | BREAST FEEDING | Avoid.
  | HEPATIC IMPAIRMENT | Avoid.
  | RENAL IMPAIRMENT | Avoid if moderate to severe impairment.
  | NATIONAL FUNDING/ACCESS DECISIONS | The Scottish Medicines Consortium (SMC) Decisions
  | Scottish Medicines Consortium (SMC) Decisions | The Scottish Medicines Consortium has advised (October 2005) that exemestane (Aromasin®) is accepted for restricted use within NHS Scotland as an adjuvant treatment in postmenopausal women with oestrogen-receptor-positive invasive early breast cancer, following 2–3 years of initial adjuvant tamoxifen therapy.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  | Tablet | Exemestane (Non-proprietary) | Exemestane 25 mg | Exemestane 25 mg tablets | 30 tablet | £88.80 DT price = £22.48
  | Tablet | Aromasin (Pfizer Ltd) | Exemestane 25 mg | Aromasin 25 mg tablets | 30 tablet | £88.80 DT price = £22.48

- **Osteoporosis** Assess bone mineral density before treatment and at regular intervals.
- **PATIENT AND CARER ADVICE** Asthenia and drowsiness may initially affect ability to drive or operate machinery.
### Letrozole

**INDICATIONS AND DOSE**

- **First-line treatment in postmenopausal women with hormone-dependent advanced breast cancer**
- **Adjuvant treatment of oestrogen-receptor-positive invasive early breast cancer in postmenopausal women**
- **Advanced breast cancer in postmenopausal women (naturally or artificially induced menopause)** in whom other anti-oestrogen therapy has failed
- **Extended adjuvant treatment of hormone-dependent invasive breast cancer in postmenopausal women who have received standard adjuvant tamoxifen therapy for 5 years**
- **Neo-adjuvant treatment in postmenopausal women with localised hormone-receptor-positive, human epidermal growth factor-2 negative breast cancer where chemotherapy is not suitable and surgery not yet indicated**

**BY MOUTH**

- **Adult**
  - 2.5 mg daily

**CONTRA-INDICATIONS** Not indicated for premenopausal women

**CAUTIONS** Susceptibility to osteoporosis

**SIDE-EFFECTS**

- **Common or very common**
  - Abdominal pain
  - Alopecia
  - Anorexia
  - Appetite increase
  - Arthralgia
  - Bone fracture
  - Constipation
  - Depression
  - Diarrhoea
  - Dizziness
  - Dry skin
  - Dyspepsia
  - Fatigue
  - Headache
  - Hot flushes
  - Hypercholesterolaemia
  - Hypertension
  - Increased sweating
  - Musculoskeletal pain
  - Nausea
  - Osteoporosis
  - Peripheral oedema
  - Rash
  - Vaginal bleeding
  - Vomiting
  - Weight changes

- **Uncommon**
  - Anxiety
  - Arthritis
  - Blurred vision
  - Breast pain
  - Cardiac events
  - Cataract
  - Cerebrovascular events
  - Cough
  - Dysaesthesia
  - Dyspnoea
  - Eye irritation
  - General oedema
  - Insomnia
  - Leucopenia
  - Memory impairment
  - Mucosal dryness
  - Palpitation
  - Pruritus
  - Pyrexia
  - Stomatitis
  - Tachycardia
  - Taste disturbance
  - Thrombophlebitis
  - Tumour pain
  - Urinary frequency
  - Urinary-tract infection
  - Urticaria
  - Vaginal discharge

- **Rare**
  - Arterial thrombosis
  - Pulmonary embolism

**FREQUENCY NOT KNOWN**

- Hepatitis
- Toxic epidermal necrolysis

**CONCEPTION AND CONTRACEPTION**

Manufacturer advises effective contraception required until postmenopausal status fully established (return of ovarian function reported in postmenopausal women).

**PREGNANCY**

Avoid (isolated cases of birth defects reported).

**BREAST FEEDING**

Manufacturer advises avoid.

**HEPATIC IMPAIRMENT**

Manufacturer advises caution in severe impairment.

**RENAL IMPAIRMENT**

Manufacturer advises caution if creatinine clearance less than 10 mL/minute.

**MONITORING REQUIREMENTS**

- Osteoporosis: Assess bone mineral density before treatment and at regular intervals.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Tablet**
  - LETROZOLE (Non-proprietary)
  - Letrozole 2.5 mg tablets: 14 tablet (30) £49.90
  - DT price = £2.26
  - 28 tablet (30) £84.86
  - Femara (Novartis Pharmaceuticals UK Ltd)
  - Letrozole 2.5 mg: Femara 2.5 mg tablets: 30 tablet (30) £90.92

### 2.7 Immunotherapy responsive malignancy

**IMMUNOMODULATING DRUGS**

**Mifamurtide**

**INDICATIONS AND DOSE**

- Treatment of high-grade, resectable, non-metastatic osteosarcoma after complete surgical resection (in combination with chemotherapy)

**BY INTRAVENOUS INFUSION**

- **Adult**
  - Infusion to be given over 1 hour (consult product literature or local protocols)

**UNLICENSED USE**

- Not licensed for use in patients over 30 years of age at initial diagnosis.

**CAUTIONS**

- Asthma—consider prophylactic bronchodilator therapy
c- chronic obstructive pulmonary disease—consider prophylactic bronchodilator therapy
- History of autoimmune disease
- History of collagen disease
- History of inflammatory disease

**INTERACTIONS**

- Appendix 1 (mifamurtide)

**SIDE-EFFECTS**

- Abdominal pain
- Alopecia
- Anaemia
- Anorexia
- Anxiety
- Blurred vision
- Confusion
- Constipation
- Cough
- Depression
- Diarrhoea
- Dizziness
- Dyspepsia
- Fatigue
- Headache
- Hot flushes
- Hypertension
- Insomnia
- Leucopenia
- Memory impairment
- Mucosal dryness
- Palpitation
- Pruritus
- Pyrexia
- Stomatitis
- Tachycardia
- Taste disturbance
- Thrombophlebitis
- Tumour pain
- Urinary frequency
- Urinary-tract infection
- Urticaria
- Vascular discharge

**FREQUENCY NOT KNOWN**

- Hepatitis
- Toxic epidermal necrolysis

**CONCEPTION AND CONTRACEPTION**

Effective contraception required.

**PREGNANCY**

Avoid.

**BREAST FEEDING**

Avoid—no information available.

**HEPATIC IMPAIRMENT**

Use with caution—no information available.

**RENAL IMPAIRMENT**

Use with caution—no information available.

**MONITORING REQUIREMENTS**

- Monitor renal function, hepatic function and clotting parameters.
- Monitor patients with history of venous thrombosis, vasculitis, or unstable cardiovascular disorders for persistent or worsening symptoms during administration—consult product literature.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Mifamurtide for the treatment of osteosarcoma (October 2011) NICE TA235

Mifamurtide in combination with postoperative multi-agent chemotherapy is recommended (within its licensed indication), as an option for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection in children, adolescents and young adults and when mifamurtide is made available at a reduced cost to the NHS under the patient access scheme. www.nice.org.uk/TA235

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.
Histamine dihydrochloride

**INDICATIONS AND DOSE**
Maintenance therapy, in combination with aldesleukin, in patients with acute myeloid leukaemia in first remission

- **Adult:** consult product literature

**CONTRA-INDICATIONS**
Consult product literature for information about histamine dihydrochloride contra-indications.

**INTERACTIONS**
Appendix 1 (histamine).

**SIDE-EFFECTS**
Consult product literature for side effects.

**CONCEPTION AND CONTRACEPTION**
Ensure effective contraception during treatment in men and women.

**PREGNANCY**
Manufacturer advises avoid—no information available.

**BREAST FEEDING**
Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT**
Increased risk of tachycardia and hypotension in moderate to severe impairment.

**RENAL IMPAIRMENT**
Increased risk of hypotension in severe impairment.

**NATIONAL FUNDING/ACCESS DECISIONS**
Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (December 2010) that histamine dihydrochloride (Ceplene®) is not recommended for use within NHS Scotland.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- Ceplene (Meda Pharmaceuticals Ltd)
- Histamine dihydrochloride 1 mg per 1 ml solution for injection vials 14 vial (POM) £1,181.32

**IMMUNOTHERAPIES**

**Bacillus calmette-guérin**

**DRUG ACTION**
Bacillus Calmette-Guérin is a live attenuated strain derived from Mycobacterium bovis.

**INDICATIONS AND DOSE**
Bladder instillation for the treatment of primary or recurrent bladder carcinoma and for the prevention of recurrence following transurethral resection

- **Adult:** consult product literature

**CONTRA-INDICATIONS**
Fever of unknown origin - HIV infection - impaired immune response - severe haematuria - tuberculosis - urinary-tract infection

**CAUTIONS**
Bladder injury (delay administration until mucosal damage healed) - traumatic catheterisation (delay administration until mucosal damage healed) - urethral injury (delay administration until mucosal damage healed)

**SIDE-EFFECTS**
- Rare: Arthralgia - bladder contracture - hypersensitivity reactions - orchitis - rash - renal abscess - transient urethral obstruction
- **Frequency not known:** Cystitis - dysuria - fever - haematuria - influenza-like syndrome - malaise - ocular symptoms - systemic BCG infection (with fatalities)—consult product literature - urinary frequency

**PREGNANCY**
Avoid.

**BREAST FEEDING**
Avoid.

**PRE-TREATMENT SCREENING**
Screen for active tuberculosis (contra-indicated if tuberculosis confirmed).

**INTERFERONS**
**Interferon alfa**

**INDICATIONS AND DOSE**

- **INTRONA® PEN**
  - Chronic myelogenous leukaemia (as monotherapy or in combination with cytarabine)
  - Hairy cell leukaemia
  - Follicular lymphoma
  - Lymph or liver metastases of carcinoid tumour
  - Chronic hepatitis B
  - Chronic hepatitis C
  - Adjunct to surgery in malignant melanoma
  - Maintenance of remission in multiple myeloma

- **INTRONA® VIALS**
  - Chronic myelogenous leukaemia (as monotherapy or in combination with cytarabine)
  - Hairy cell leukaemia
  - Follicular lymphoma
  - Lymph or liver metastases of carcinoid tumour
  - Chronic hepatitis B
  - Chronic hepatitis C
  - Adjunct to surgery in malignant melanoma
  - Maintenance of remission in multiple myeloma

- **ROFERON-A®**
  - Chronic myelogenous leukaemia
  - Hairy cell leukaemia
  - Chronic hepatitis B
  - Chronic hepatitis C
  - Adjunct to surgery in malignant melanoma
  - AIDS-related Kaposi’s sarcoma
  - Advanced renal cell carcinoma
  - Progressive cutaneous T-cell lymphoma
  - Follicular non-Hodgkin’s lymphoma

**CONTRA-INDICATIONS**
Avoid injections containing benzyl alcohol in neonates

**CONTRA-INDICATIONS, FURTHER INFORMATION**
For contra-indications consult product literature and local treatment protocol.

**CAUTIONS**
For cautions consult product literature and local treatment protocol.

**INTERACTIONS**
Appendix 1 (interferons).
Interferon gamma-1b (Immune interferon)

INDICATIONS AND DOSE
To reduce the frequency of serious infection in chronic granulomatous disease

BY SUBCUTANEOUS INJECTION
Adult: 50 micrograms/m\(^2\) 3 times a week

To reduce the frequency of serious infection in severe malignant osteoporosis

BY SUBCUTANEOUS INJECTION
Adult: 50 micrograms/m\(^2\) 3 times a week

CAUTIONS
Arrhythmias - cardiac disease - congestive heart failure - ischaemia - seizure disorders (including seizures associated with fever)

INTERACTIONS
Appendix 1 (interferons).
Avoid simultaneous administration of foreign proteins including immunological products (risk of exaggerated immune response).

SIDE-EFFECTS
Common or very common Abdominal pain - arthralgia - chills - depression - diarrhoea - fatigue - fever - headache - injection-site reactions - myalgia - nausea - rash - vomiting

Rare Confusion - systemic lupus erythematosus

Frequency not known Neutropenia - proteinuria - raised liver enzymes - thrombocytopenia

CONCEPTION AND CONTRACEPTION
Effective contraception required during treatment—consult product literature.

PREGNANCY
Manufacturers recommend avoid unless potential benefit outweighs risk (toxicity in animal studies).

BREAST FEEDING
Manufacturers advise avoid—no information available.

HEPATIC IMPAIRMENT
Manufacturer advises caution in severe impairment—risk of accumulation.

RENAI IMPAIRMENT
Manufacturer advises caution in severe impairment—risk of accumulation.

MONITORING REQUIREMENTS
Monitor before and during treatment: haematological tests (including full blood count, differential white cell count, and platelet count), blood chemistry tests (including renal and liver function tests) and urinalysis.

MEDICAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
EXCIPIENTS: May contain Benzyl alcohol

Interferon alfa-2b 10 mega u per ml Introna 10 million units/1ml solution for injection vials | 1 vial (Plast) no price available

Interferon alfa-2b 15 mega u per ml Introna 15 million units/1ml solution for injection multidose vials | 1 vial (Plast) £103.94

Interferon alfa-2b 25 mega u per ml Introna 25 million units/1ml solution for injection multidose pens | 1 pre-filled disposable injection (Plast) £74.83

Interferon alfa-2b 50 mega u per ml Introna 60 million units/1ml solution for injection multidose pens | 1 pre-filled disposable injection (Plast) £249.45

Interferon alfa-2b 6 mega u per ml Roferon-A 3 million units/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (Plast) £14.20

Interferon alfa-2b 9 mega u per ml Roferon-A 4.5 million units/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (Plast) £21.29

Interferon alfa-2b 12 mega u per ml Roferon-A 6 million units/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (Plast) £28.37

Interferon alfa-2b 18 mega u per ml Roferon-A 9 million units/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (Plast) £42.57

Interferon alfa-2b 50 mega u per ml Roferon-A 150 million units/1ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (Plast) £749.45

Interferon alfa-2b (Roche Products Ltd)

Interferon alfa-2a 6 mega u per ml Roferon-A 3 million units/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (Plast) £14.20

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Interferon alfa-2a 50 mega u per ml Roferon-A 60 million units/1ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (Plast) £249.45

Interferon gamma-1b (immune interferon)

INDICATIONS AND DOSE
To reduce the frequency of serious infection in chronic granulomatous disease

BY SUBCUTANEOUS INJECTION
Adult: 50 micrograms/m\(^2\) 3 times a week

To reduce the frequency of serious infection in severe malignant osteoporosis

BY SUBCUTANEOUS INJECTION
Adult: 50 micrograms/m\(^2\) 3 times a week

CAUTIONS
Arrhythmias - cardiac disease - congestive heart failure - ischaemia - seizure disorders (including seizures associated with fever)

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Appendix 1 (interferons).
Avoid simultaneous administration of foreign proteins including immunological products (risk of exaggerated immune response).

SIDE-EFFECTS
Common or very common Abdominal pain - arthralgia - chills - depression - diarrhoea - fatigue - fever - headache - injection-site reactions - myalgia - nausea - rash - vomiting

Rare Confusion - systemic lupus erythematosus

Frequency not known Neutropenia - proteinuria - raised liver enzymes - thrombocytopenia

CONCEPTION AND CONTRACEPTION
Effective contraception required during treatment—consult product literature.

PREGNANCY
Manufacturers recommend avoid unless potential benefit outweighs risk (toxicity in animal studies).

BREAST FEEDING
Manufacturers advise avoid—no information available.

HEPATIC IMPAIRMENT
Manufacturer advises caution in severe impairment—risk of accumulation.

RENAI IMPAIRMENT
Manufacturer advises caution in severe impairment—risk of accumulation.

MONITORING REQUIREMENTS
Monitor before and during treatment: haematological tests (including full blood count, differential white cell count, and platelet count), blood chemistry tests (including renal and liver function tests) and urinalysis.

MEDICAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
EXCIPIENTS: May contain Benzyl alcohol

Interferon alfa-2b 10 mega u per ml Introna 10 million units/1ml solution for injection vials | 1 vial (Plast) no price available

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Roferon-A (Roche Products Ltd)
INTERLEUKINS

Aldesleukin

**DRUG ACTION** Aldesleukin produces tumour shrinkage in a small proportion of patients, but it has not been shown to increase survival.

**INDICATIONS AND DOSE**

Metastatic renal cell carcinoma (specialist use only)

- **BY SUBCUTANEOUS INJECTION OR BY INTRAVENOUS INFUSION**
  - Adult: (consult product literature)

**UNLICENSED USE** Aldesleukin is not licensed for use in patients in whom all three of the following prognostic factors are present: performance status of Eastern Cooperative Oncology Group of 1 or greater, more than one organ with metastatic disease sites, and a period of less than 24 months between initial diagnosis of primary tumour and date of evaluation of treatment.

**CONTRA-INDICATIONS** Consult product literature for information about aldesleukin contra-indications.

**CAUTIONS** Consult product literature for information about aldesleukin cautions.

**INTERACTIONS**

- **SIDE-EFFECTS**
  - Common or very common Bone-marrow toxicity - CNS toxicity - hepatic toxicity - renal toxicity - thyroid toxicity
  - Frequency not known Alopecia - bone-marrow suppression - extravasation - hyperuricaemia - nausea - oral mucositis - thromboembolism - tumour lysis syndrome - vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

Also consult product literature.

- **CONCEPTION AND CONTRACEPTION** Ensure effective contraception during treatment in men and women.

- **PREGNANCY** Use only if potential benefit outweighs risk (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

- **BREAST FEEDING** Discontinue breast-feeding.

- **DIRECTIONS FOR ADMINISTRATION**
  - Aldesleukin is now rarely given by intravenous infusion because of an increased risk of capillary leak syndrome, which can cause pulmonary oedema and hypotension.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**

- **Proleukin** (Novartis Pharmaceuticals UK Ltd)
  - *Aldesleukin 18 mega u Proleukin 18 million unit powder for solution for injection vials | 1 vial £112.00 | 10 vial £1,036.00*

THALIDIOMIDE AND RELATED ANOLOGUES

Lenalidomide

**DRUG ACTION** Lenalidomide is an immunomodulating drug with anti-neoplastic, anti-angiogenic, and pro-erythropoietic properties.

**INDICATIONS AND DOSE**

Multiple myeloma (newly diagnosed) in patients not eligible for transplant, given in combination with dexamethasone until disease progression

- **BY MOUTH**
  - Adult: 25 mg once daily for 21 consecutive days of repeated 28-day cycles, for doses of dexamethasone, and dose adjustments due to side-effects, consult product literature

Multiple myeloma in patients who have received at least one prior therapy, given in combination with dexamethasone

- **BY MOUTH**
  - Adult: 10 mg once daily for 21 consecutive days of repeated 28-day cycles, for doses of dexamethasone, and dose adjustments due to side-effects, consult product literature

**CAUTIONS**

- High tumour burden—risk of tumour lysis syndrome
- Patients with risk factors for myocardial infarction

**CAUTIONS, FURTHER INFORMATION**

Thromboembolism Risk factors for thromboembolism (such as smoking, hypertension, hyperlipidaemia) should be minimised and thromboprophylaxis should be considered in patients with multiple risk factors.

**Second primary malignancy** Patients should be carefully evaluated before and during treatment with lenalidomide using routine cancer screening for occurrence of second primary malignancy and treatment should be instituted as indicated.

**INTERACTIONS**

- **SIDE-EFFECTS**

- **Uncommon** Acquired Fanconi syndrome - angioedema - blindness - cataract - clotting disorders - colitis - haemolysis - hepatic failure - ischaemia - secondary malignancies

- **Rare** Stevens-Johnson syndrome - toxic epidermal necrolysis - tumour lysis syndrome
> Frequency not known Cholestatic hepatitis - cytolytic hepatitis - interstitial pneumonitis - leukocytoclastic vasculitis - pancreatitis - toxic hepatitis

**SIDE-EFFECTS, FURTHER INFORMATION**

**Rash** If rash occurs, treatment should be discontinued and only restarted following appropriate clinical evaluation. Discontinue permanently if angioedema, exfoliative or bullous rash, or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected. For information on side effects consult product literature.

**CONCEPTION AND CONTRACEPTION** For women of child-bearing potential, pregnancy must be excluded before starting treatment with lenalidomide (perform pregnancy test on initiation or within 3 days prior to initiation). Women must practise effective contraception at least 1 month before, during, and for at least 1 month after treatment, including during dose interruptions (oral combined hormonal contraceptives and copper-releasing intra-uterine devices not recommended) and men should use condoms during treatment, during dose interruption, and for at least 1 week after stopping if their partner is pregnant or is of childbearing potential and not using effective contraception. Patients, prescribers and pharmacists must comply with pregnancy prevention measures as specified in the manufacturer’s Pregnancy Prevention Programme.

**PREGNANCY Important: teratogenic risk** Lenalidomide is structurally related to thalidomide and there is a risk of teratogenesis.

**BREAST FEEDING** Discontinue breast-feeding—no information available.

**RENAL IMPAIRMENT** Reduce dose in moderate to severe impairment—consult product literature.

**MONITORING REQUIREMENTS**
- Monitor full blood count (including differential white cell count, platelet count, haemoglobin, and haematocrit) and liver function before treatment, then every week for the first 8 weeks, then monthly thereafter (reduce dose or interrupt treatment if neutropenia, thrombocytopenia or impaired liver function develop—consult product literature).
- Monitor for arterial or venous thromboembolism (if thromboembolic event occurs, discontinue lenalidomide and treat with standard anticoagulation therapy; lenalidomide may be restarted with continued anticoagulation therapy once thromboembolic event resolved—consult product literature).
- Monitor for renal impairment.
- Monitor for signs and symptoms of peripheral neuropathy.
- Monitor visual ability regularly (risk of cataract).
- Hepatic disorders Liver function should be monitored particularly when there is history of, or concurrent viral liver infection, or when lenalidomide is combined with drugs known to be associated with liver dysfunction (e.g. paracetamol).

**PRESCRIBING AND DISPENSING INFORMATION** Patient, prescriber, and supplying pharmacy must comply with a pregnancy prevention programme. Every prescription must be accompanied by a completed Prescription Authorisation Form.

**PATIENT AND CARER ADVICE** Patient counselling is advised for lenalidomide capsules (pregnancy and contraception). Thromboembolism Patients and their carers should be made aware of the symptoms of thromboembolism and advised to report sudden breathlessness, chest pain, or swelling of a limb.

Neutropenia and thrombocytopenia Patients and their carers should be made aware of the symptoms of neutropenia and advised to seek medical advice if symptoms suggestive of neutropenia (such as fever, sore throat) or of thrombocytopenia (such as bleeding) develop.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**
- **Lenalidomide for the treatment of multiple myeloma (June 2009) NICE TA171** Lenalidomide in combination with dexamethasone is an option for the treatment of multiple myeloma in patients who have received two or more prior therapies. The drug cost of lenalidomide will be met by the manufacturer for patients who remain on treatment for more than 26 cycles. [www.nice.org.uk/TA171](http://www.nice.org.uk/TA171)
- **Lenalidomide for treating myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality (September 2014) NICE TA322** Lenalidomide is recommended as an option, within its marketing authorisation, for treating transfusion-dependent anaemia caused by low or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate, with the following condition:
  - the drug cost of lenalidomide (excluding any related costs) for people who remain on treatment for more than 26 cycles (each of 28 days; normally a period of 2 years) will be met by the company. [www.nice.org.uk/TA322](http://www.nice.org.uk/TA322)

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (April 2010) that lenalidomide, in combination with dexamethasone, is accepted for restricted use within NHS Scotland for patients with multiple myeloma who have received at least two prior therapies and (March 2014) for those who have received prior treatment with bortezomib and for whom thalidomide has not been tolerated or is contra-indicated.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

**CAUTIONARY AND ADVISORY LABELS 25**

<table>
<thead>
<tr>
<th>Druggist</th>
<th>Revlimid (Celgene Ltd)</th>
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<tbody>
<tr>
<td>Lenalidomide 2.5 mg</td>
<td>Revlimid 2.5mg capsules</td>
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<tr>
<td>Lenalidomide 25 mg</td>
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</table>

**Pomalidomide**

**DRUG ACTION** Pomalidomide is structurally related to thalidomide and has immunomodulatory properties and direct anti-myeloma tumoricidal activity.

**INDICATIONS AND DOSE**

Treatment of relapsed or refractory multiple myeloma in patients who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and who have had disease progression during the last treatment (in combination with dexamethasone) **BY MOUTH**

- Adult: 4 mg once daily for 21 consecutive days of repeated 28-day cycles, for doses of dexamethasone and dose adjustment due to side effects—consult product literature
Thalidomide

**Drug action** Thalidomide has immunomodulatory and anti-inflammatory activity.

**Indications and Dose**
First-line treatment for untreated multiple myeloma, in patients aged 65 years and over, or for those not eligible for high-dose chemotherapy (for example, patients with significant co-morbidity such as cardiac risk factors) in combination with melphalan and prednisolone

**By Mouth**
Adult: 200 mg once daily for 6–8 weeks, maximum 12 cycles, dose to be taken at bedtime

**Caution** High tumour burden—risk of tumour lysis syndrome

**Caution, Further Information**
Thromboembolism Risk factors for thromboembolism (such as smoking, hypertension, hyperlipidaemia) should be minimised. Thromboprophylaxis is recommended for at least the first 5 months of treatment, especially in patients with additional thrombotic risk factors.

**Second primary malignancy** Patients should be carefully evaluated before and during treatment with thalidomide using routine cancer screening for occurrence of second primary malignancy and treatment should be instituted as indicated.

**Peripheral neuropathy** Patients with pre-existing peripheral neuropathy should not be treated with thalidomide unless the potential clinical benefits outweigh the risk.

**Prescribing and Dispensing Information**
Patient, prescriber, and supplying pharmacy must comply with a pregnancy prevention programme. Every prescription must be accompanied by a completed Prescription Authorisation Form.

**Patient and carer advice** Patients and their carers should be made aware of the symptoms of thromboembolism and advised to report sudden breathlessness, chest pain, or swelling of a limb. Patients and their carers should be made aware of the symptoms of neutropenia and advised to seek medical advice if symptoms suggestive of neutropenia (such as fever, sore throat) or of thrombocytopenia (such as bleeding) develop. Patient counselling is advised for pomalidomide capsules (pregnancy and contraception).

**National Funding/Access Decisions**
NICE technology appraisals (TAs)

- Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib (March 2015) NICE TA338 Pomalidomide, in combination with dexamethasone, is not recommended for the treatment of relapsed and refractory multiple myeloma in adults who have had at least 2 previous treatments, including lenalidomide and bortezomib, and whose disease has progressed on the last therapy. <www.nice.org.uk/TA338

**Medicinal Forms**
There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

- Cautionary and Advisory Labels 3, 25
- Excipients: May contain Propylene glycol

<table>
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INTERACTIONS Use caution with concomitant drugs that increase the risk of peripheral neuropathy or thromboembolism.

SIDE-EFFECTS

Common or very common Anaemia • asthenia • bradycardia • cardiac failure • confusion • constipation • deep vein thrombosis • depression • dizziiness • drowsiness • dry mouth • dysaesthesia • dyspepsia • dyspnoea • interstitial lung disease • leucopenia • lymphopenia • neutropenia • paraesthesia • peripheral neuropathy • peripheral oedema • pneumonia • pulmonary embolism • pyrexia • skin reactions • Stevens-Johnson syndrome • syncope • thrombocytopenia • tremor • vomiting

Frequency not known Atrial fibrillation • atroventricular block • cerebrovascular events • convulsions • gastro-intestinal haemorrhage • gastro-intestinal perforation • hearing loss • hepatic disorders • hypothyroidism • intestinal obstruction • menstrual disorders • myocardial infarction • renal failure • second primary malignancy • sexual dysfunction • toxic epidermal necrolysis • worsening of Parkinson’s disease symptoms

PATIENT AND CARER ADVICE

Patients and their carers should be made aware of the symptoms of thromboembolism and advised to report sudden breathlessness, chest pain, or swelling of a limb. Patients and their carers should be made aware of the symptoms of neutropenia and advised to seek medical advice if symptoms suggestive of neutropenia (such as fever, sore throat) or of thrombocytopenia (such as bleeding) develop. Patients and their carers should be advised to seek medical advice if symptoms of peripheral neuropathy such as paraesthesia, abnormal coordination, or weakness develop. Patient counselling advised for thalidomide capsules (pregnancy and contraception).

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

Bortezomib and thalidomide for the first-line treatment of multiple myeloma (July 2011) NICE TA228

Thalidomide in combination with an alkylating drug and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate. www.nice.org.uk/TA228

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension, tablet

Tablet

Talidex (Alan Pharmaceuticals)

Thalidomide 25 mg Talidex 25mg tablets | 30 tablet £485.00

Capsule

CAUTIONARY AND ADVISORY LABELS 2

THALIDOMIDE (Non-proprietary)

Thalidomide Celgene 50mg capsules | 28 capsule | £29.48

PHOTOREACTORS

Porfimer sodium

Drug action

Porfimer sodium accumulates in malignant tissue and is activated by laser light to produce a cytotoxic effect.

INDICATIONS AND DOSE

Photodynamic therapy of non-small cell lung cancer and obstructing oesophageal cancer

BY SLOW INTRAVENOUS INJECTION

Adult: (consult product literature)

CONTRA-INDICATIONS

Acute porphyria p. 864 • broncho-oesophageal fistula • tracheo-oesophageal fistula

SIDE-EFFECTS

Alopecia • bone-marrow suppression • constipation • extravasation • hyperuricaemia • nausea • oral mucositis • photosensitivity (sunscreens offer no protection) • thromboembolism • tumour lysis syndrome • vomiting

PREGNANCY

Manufacturer advises avoid unless essential.

BREAST FEEDING

No information available—manufacturer advises avoid.

HEPATIC IMPAIRMENT

Avoid in severe impairment.

PATIENT AND CARER ADVICE

Photosensitivity Avoid exposure of skin and eyes to direct sunlight or bright indoor light for at least 30 days.

PHOTOSENSITISERS

8 Photodynamic therapy responsive malignancy

2.8 Photodynamic therapy responsive malignancy

Photodynamic therapy of non-small cell lung cancer and obstructing oesophageal cancer

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Photosensitivity Avoid exposure of skin and eyes to direct sunlight or bright indoor light for at least 30 days.
800 Malignant disease

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Powder for solution for injection
- Photofrin (Axcan Pharma Inc)
  Porfimer sodium 15 mg Photofrin 15 mg powder for solution for injection vials | 1 vial (P) no price available (Hospital only)
- Photofrin 75 mg Photofrin 75 mg powder for solution for injection vials | 1 vial (P) no price available (Hospital only)

Side-effects
- Suppression
- Thromboembolism
- Nausea
- Vomiting
- Hyperpigmentation
- Alopecia

INTERACTIONS
- Concomitant photosensitising treatment
- Acute porphyrias
- Myelodysplastic syndromes
- Hepatic impairment
- Renal impairment
- Pregnancy and reproductive function
- Contraception advised

CONTRA-INDICATIONS
- Acute porphyrias
- Myelodysplastic syndromes
- Severe hepatic or renal impairment
- Pregnancy

CONCEPTION AND CONTRACEPTION
- Manufacturer advises avoid pregnancy for at least 3 months after treatment.

BY SLOW INTRAVENOUS INJECTION
- Adult: (consult product literature)

INDICATIONS AND DOSE
Photodynamic therapy of advanced head and neck squamous cell carcinoma refractory to, or unsuitable for, other treatments

PRESCRIBING AND DISPENSING INFORMATION
- No information available

HEDGEHOG PATHWAY INHIBITORS

Vismodegib

DRUG ACTION
Vismodegib is a hedgehog pathway inhibitor.

INDICATIONS AND DOSE
Symptomatic metastatic basal cell carcinoma
Locally advanced basal cell carcinoma not appropriate for surgery or radiotherapy

BY MOUTH
- Adult: 150 mg once daily

Important safety information
Risks of incorrect dosing of oral anti-cancer medicines, see p. 745

INTERACTIONS
- Appendix 1 (vismodegib)

SIDE-EFFECTS
- Common or very common
  - Abdominal pain
  - Abnormal hair growth
  - Alopecia
  - Anemia
  - Arthralgia
  - Ataxia
  - Decreased appetite
  - Dehydration
  - Diarrhea
  - Dyspepsia
  - Hyperpigmentation
  - Hyponatremia
  - Hyperuricaemia
  - Mucositis
  - Muscle spasms
  - Musculoskeletal pain
  - Nausea
  - Pruritus
  - Rash
  - Taste disturbances
  - Vomiting
  - Weight loss

CONCEPTION AND CONTRACEPTION
For women of childbearing potential, pregnancy must be excluded before initiation of treatment, and monthly during treatment. Women must use two contraceptive methods (including one highly effective method and one barrier method) during treatment and for 24 months after the final dose of vismodegib. Men must use a condom during treatment and for 2 months after the final dose.

PREGNANCY
- Important: teratogenic risk—may cause severe birth defects and embryo-fetal death.

BREAST FEEDING
- Avoid during treatment and for 24 months after final dose.

HEPATIC IMPAIRMENT
- No information available—manufacturer advises caution in moderate to severe impairment.

RENAL IMPAIRMENT
- No information available—manufacturer advises caution in severe impairment.

PRESCRIBING AND DISPENSING INFORMATION
Prescribers and pharmacists must comply with prescribing and dispensing restrictions as specified in the manufacturer’s Pregnancy Prevention Programme, and ensure that the patient fully acknowledges the programme’s pregnancy prevention measures—consult product literature for further information.

PATIENT AND CARER ADVICE
Counselling on pregnancy and contraception advised. Patients must comply with the manufacturer’s pregnancy prevention programme.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Capsule
- Cautionary and advisory labels 25
  - Erihide (Roche Products Ltd)
  - Vismodegib 150 mg Vismodegib 150 mg capsules | 28 capsule (P)
  - £6,285.00 (Hospital only)

Temoporfin

DRUG ACTION
Temoporfin accumulates in malignant tissue and is activated by laser light to produce a cytotoxic effect.

INDICATIONS AND DOSE
Photodynamic therapy of advanced head and neck squamous cell carcinoma refractory to, or unsuitable for, other treatments

PRESCRIBING AND DISPENSING INFORMATION
- No information available

CONTRA-INDICATIONS
- Acute porphyrias
- Myelodysplastic syndromes
- Severe hepatic or renal impairment
- Pregnancy

CONCEPTION AND CONTRACEPTION
- Manufacturer advises avoid pregnancy for at least 3 months after treatment.

BY SLOW INTRAVENOUS INJECTION
- Adult: (consult product literature)
TARGETED THERAPY RESPONSIVE MALIGNANCY 801

PROTEASOME INHIBITORS

Bortezomib

**DRUG ACTION** Bortezomib is a proteasome inhibitor.

**INDICATIONS AND DOSE**

Treatment of multiple myeloma that has progressed despite the use of at least one therapy, and where the patient has already had, or is unable to have, haematopoietic stem cell transplantation (either as monotherapy, or in combination with pegylated liposomal doxorubicin or dexamethasone) | Treatment of previously untreated multiple myeloma in patients who are not eligible for high-dose chemotherapy with haematopoietic stem cell transplantation (in combination with melphalan and prednisolone) | Induction treatment of previously untreated multiple myeloma in patients who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation (in combination with dexamethasone, or with dexamethasone and thalidomide) | BY INTRAVENOUS INJECTION OR BY SUBCUTANEOUS INJECTION

- **Adult:** (consult local protocol)

<table>
<thead>
<tr>
<th>Important safety information</th>
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<tbody>
<tr>
<td>Bortezomib injection is for intravenous or subcutaneous administration only. Inadvertent intrathecal administration with fatal outcome has been reported.</td>
</tr>
</tbody>
</table>

**CONTRA-INDICATIONS** Acute diffuse infiltrative pulmonary disease - pericardial disease

**CAUTIONS** Amyloidosis - cardiovascular disease - consider antiviral prophylaxis for herpes zoster infection - dehydration - history of syncope - pulmonary disease (discontinue if interstitial lung disease develops) - risk factors for seizures - risk of neuropathy - consult product literature

**INTERACTIONS** | Appendix 1 (bortezomib).

Caution with concurrent use of medication which may cause hypotension.

**SIDE-EFFECTS**

- **Common or very common** Constipation (cases of ileus reported) - decreased appetite - diarrhoea - dyspnoea - fatigue - headache - herpes zoster - hypotension - myalgia - paraesthesia - peripheral neuropathy - pyrexia - rash - reactivation of herpes zoster - sensory neuropathy

- **Uncommon** Acute diffuse infiltrative pulmonary disorders - heart failure - posterior reversible encephalopathy syndrome (discontinue treatment) - pulmonary hypertension - seizures

- **Rare** Autonomic neuropathy

- **Very rare** Progressive multifocal leucoencephalopathy

- **Frequency not known** Alopecia - bone-marrow suppression - extravasation - hyperuricaemia - nausea - oral mucositis - thromboembolism - tumour lysis syndrome - vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

For further information on side-effects, consult product literature.

**CONCEPTION AND CONTRACEPTION** Manufacturer advises effective contraception during and for 3 months after treatment in men or women.

**PREGNANCY** Toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

**BREAST FEEDING** Discontinue breast-feeding.

**HEPATIC IMPAIRMENT** Reduce dose in moderate to severe impairment—consult product literature.

**RENAL IMPAIRMENT** No information available for creatinine clearance less than 20 mL/minute/1.73 m².

**MONITORING REQUIREMENTS**

- Monitor blood-glucose concentration in patients on oral antidiabetics.

- Monitor for symptoms of progressive multifocal leucoencephalopathy (presenting as new or worsening neurological signs or symptoms)—discontinue treatment if diagnosed.

- Chest x-ray recommended before treatment to monitor for pulmonary disease—discontinue if interstitial lung disease develops.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- **Bortezomib monotherapy for relapsed multiple myeloma** (October 2007) NICE TA129

  Bortezomib monotherapy is an option for the treatment of progressive multiple myeloma in patients who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone-marrow transplantation, under the following circumstances:

  - the response to bortezomib is measured using serum M protein after a maximum of four cycles of treatment, and treatment is continued only in patients who have a reduction in serum M protein of 50% or more (where serum M protein is not measurable, an appropriate alternative biochemical measure of response should be used) and

  - the manufacturer rebates the full cost of bortezomib if there is an inadequate response (as defined above) after four cycles of treatment. [www.nice.org.uk/TA129](http://www.nice.org.uk/TA129)

- **Bortezomib and thalidomide for the first-line treatment of multiple myeloma** (July 2011) NICE TA228

Bortezomib in combination with an alkylating drug and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma if:

- high-dose chemotherapy with stem cell transplantation is considered inappropriate and

- the person is unable to tolerate or has contra-indications to thalidomide. [www.nice.org.uk/TA228](http://www.nice.org.uk/TA228)

- **Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation** (April 2014) NICE TA311

Bortezomib is recommended as an option within its marketing authorisation, in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adults with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation. [www.nice.org.uk/TA311](http://www.nice.org.uk/TA311)

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium, has advised (December 2013) that bortezomib (Velcade®) is accepted for restricted use within NHS Scotland in combination with dexamethasone and thalidomide for the induction treatment of adults with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation. [www.nice.org.uk/TA228](http://www.nice.org.uk/TA228)

**SCOTTISH MEDICINES CONSORTIUM (SMC) DECISIONS**

**Targeted therapy responsive malignancy 801**

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**

- **Velcade** (Janssen-Cilag Ltd)

  **Bortezomib 3.5 mg** Velcade 3.5mg powder for solution for injection vials | 1 vial (Exit) £762.38 (Hospital only)
PROTEIN KINASE INHIBITORS

Afatinib

**DRUG ACTION** Afatinib is a protein kinase inhibitor.

**INDICATIONS AND DOSE**
Treatment of locally advanced or metastatic non-small cell lung cancer with activating epidermal growth factor receptor (EGFR) mutations, in patients who have not previously been treated with EGFR tyrosine kinase inhibitor

BY MOUTH
- Adult: 40 mg once daily for 3 weeks, then increased if tolerated to 50 mg once daily, consult product literature for details on dosing and dose adjustment due to side effects

**CAUTIONS**
Cardiac risk factors - conditions which may affect left ventricular ejection fraction—consider cardiac monitoring, including assessment of left ventricular ejection fraction, at baseline and during treatment - diarrhoea—proactive management recommended (consult product literature) - exposure to sun (protect skin from exposure to sun) - history of keratitis - new pulmonary symptoms (including dyspnoea, cough, fever)—interrupt treatment until interstitial lung disease is excluded - severe dry eyes - signs and symptoms of keratitis—promptly refer to ophthalmologist for assessment - signs and symptoms of skin reaction—treat promptly and interrupt afatinib treatment if severe or if Stevens-Johnson syndrome suspected (consult product literature) - ulcerative keratitis - use of contact lenses - worsening pulmonary symptoms (including dyspnoea, cough, fever)—interrupt treatment until interstitial lung disease is excluded

**INTERACTIONS** → Appendix 1 (afatinib).

**SIDE-EFFECTS**
- **Common or very common** Acne - conjunctivitis - cystitis - decreased appetite - dehydration - diarrhoea - dry eyes - dry skin - dysgeusia - dyspepsia - epistaxis - hand-foot syndrome - hypokalaemia - muscle spasms - paronychia - pruritus - pyrexia - rash (see Cautions) - renal failure - rhinorhoea - weight loss
- **Uncommon** Interstitial lung disease - keratitis
- **Frequency not known** Alopecia - bone-marrow suppression - hyperuricaemia - nausea - oral mucositis - thromboembolism - tumour lysis syndrome - vomiting

**CONCEPTION AND CONTRACEPTION** Ensure effective contraception during and for at least one month after treatment in women of childbearing potential.

**PREGNANCY** Manufacturer advises avoid. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

**BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT** Monitor hepatic function regularly and consult product literature for dose adjustment in worsening liver function. Manufacturer advises avoid in severe hepatic impairment.

**RENAL IMPAIRMENT** Manufacturer advises avoid in severe renal impairment.

**DIRECTIONS FOR ADMINISTRATION** Tablets should be taken whole on an empty stomach. Food should not be consumed for at least 3 hours before and at least 1 hour after each dose. Giotrif® tablets may be dispersed in approximately 100 mL of noncarbonated water by stirring occasionally for up to 15 minutes (must not be crushed). The dispersion should be swallowed immediately, and the glass rinsed with the same volume of water which should also be swallowed. The dispersion can also be administered via a gastric tube.

**PATIENT AND CARER ADVICE** Ocular adverse reactions may affect performance of skilled tasks e.g. driving. Patient counselling advised (administration).

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**
- Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer (April 2014) NICE TA310

Afatinib is recommended as an option, within its marketing authorisation, for treating locally advanced or metastatic non-small-cell lung cancer in adults:
- whose tumour tests positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation, and
- who have not previously had an EGFR-TK inhibitor, and
- if the manufacturer provides afatinib with the discount agreed in the patient access scheme. www.nice.org.uk/TA310

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS 25</th>
<th>Giotrif (Boehringer Ingelheim Ltd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib 20 mg</td>
<td>Giotrif 20mg tablets</td>
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<tr>
<td>28 tablet</td>
<td>£2,023.28</td>
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<tr>
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Axitinib

**DRUG ACTION** Axitinib is a tyrosine kinase inhibitor.

**INDICATIONS AND DOSE**
Treatment of advanced renal cell carcinoma following failure of previous treatment with sunitinib or a cytokine (aldesleukin or interferon alfa)

BY MOUTH
- Adult: (consult product literature)

**CONTRA-INDICATIONS** Recent active gastro-intestinal bleeding - untreated brain metastases

**CAUTIONS** Hypertension (blood pressure should be well-controlled before starting and monitored during treatment)

**INTERACTIONS** → Appendix 1 (axitinib).

**SIDE-EFFECTS**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES, see p. 745**
Medicinal forms

Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment (February 2015)

- **NICE technology appraisals (TAs)**
  - Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment
    - **Inlyta (Pfizer Ltd)**
      - Axitinib 1 mg Inlyta 1mg tablets | 56 tablet £703.40 (Hospital only)
      - Axitinib 3 mg Inlyta 3mg tablets | 56 tablet £2,110.20 (Hospital only)
      - Axitinib 5 mg Inlyta 5mg tablets | 56 tablet £3,517.00 (Hospital only)
      - Axitinib 7 mg Inlyta 7mg tablets | 56 tablet £4,923.80 (Hospital only)

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**
  - **CAUTIONARY AND ADVISORY LABELS**
    - **Inlyta (Pfizer Ltd)**
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Bosutinib

**INDICATIONS AND DOSE**

- Treatment of chronic, accelerated and blast phase Philadelphia chromosome-positive chronic myeloid leukemia, in those previously treated with one or more tyrosine kinase inhibitors, and for whom imatinib, nilotinib and dasatinib are not clinically appropriate

- **Tablet**
  - **CAUTIONARY AND ADVISORY LABELS**
    - **Bosulif (Pfizer Ltd)**
      - Bosutinib 100 mg Bosulif 100mg tablets | 28 tablet £859.17 (Hospital only)
      - Bosutinib 500 mg Bosulif 500mg tablets | 28 tablet £3,436.67 (Hospital only)

- **CAUTIONS**
  - Cardiac disease
  - History of pancreatitis— withholding treatment if lipase elevated and abdominal symptoms occur
  - History of QT prolongation— monitor ECG and correct hypokalaemia and hypomagnesaemia before and during treatment

- **INTERACTIONS**
  - Appendix 1 (bosutinib).
  - Caution with concomitant use of drugs that prolong the QT interval (monitor ECG and correct hypokalaemia and hypomagnesaemia before and during treatment).

- **SIDE-EFFECTS**
  - Common or very common
    - Abdominal pain
    - Abnormal liver function
    - Acne
    - Arthralgia
    - Biochemical disturbances
    - Cough
    - Decreased appetite
    - Dehydration
    - Diarrhoea
    - Dizziness
    - Dysgeusia
    - Dyspnoea
    - Electrolyte disturbances
    - Gastritis
    - Headache
    - Hepatotoxicity
    - Infection
    - Malaise
    - Myalgia
    - Oedema
    - Pericarditis
    - Pleural effusion
    - Pleural effusion
    - Renal failure
    - Respiratory failure
    - Skin reaction
    - Stomatitis
    - Upper respiratory tract infection
    - Urticaria
    - Vomiting

- **有效性**
  - Effective

- **CONCEPTION AND CONTRACEPTION**
  - Effective contraception required during treatment in women.

- **PREGNANCY**
  - Avoid—toxicity in animal studies.

- **BREAST FEEDING**
  - Effective contraception required during treatment in women.

- **HEPATIC IMPAIRMENT**
  - Reduce starting dose in moderate impairment.
  - Avoid in severe impairment—no information available.

- **MONITORING REQUIREMENTS**
  - Monitor for thyroid dysfunction.
  - Monitor haemoglobin or haematocrit before and during treatment.
  - Monitor for proteinuria before and during treatment.
  - Monitor for symptoms of fistula.
  - Monitor for symptoms of gastrointestinal perforation.
  - Monitor hepatic function before and during treatment.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE technology appraisals (TAs)**
    - **Bosutinib for previously treated chronic myeloid leukaemia**
      - **(November 2013)** NICE TA299

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

- **Tablet**
  - **CAUTIONARY AND ADVISORY LABELS**
    - **Bosulif (Pfizer Ltd)**
      - Bosutinib 100 mg Bosulif 100mg tablets | 28 tablet £859.17 (Hospital only)
      - Bosutinib 500 mg Bosulif 500mg tablets | 28 tablet £3,436.67 (Hospital only)
Caboza	

**Drug Action** Cabozantinib is an inhibitor of several protein kinases.

**Indications and Dose**

Treatment of progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma

**By Mouth**

- Adult: 140 mg once daily, for dose adjustment or treatment interruption due to side effects, consult product literature (closely monitor for first 8 weeks of therapy).

**Important Safety Information**

**Risks of Incorrect Dosing of Oral Anti-Cancer Medicines**, see p. 745

**Contra-Indications** Reversible Posterior Leukoencephalopathy Syndrome

**Caution** Hypertension—discontinue treatment if uncontrolled despite medical intervention—palmar-plantar erythrodysesthesia syndrome—consider treatment interruption if severe and restart at a lower dose when resolved to grade 1. Patients at increased risk of fistulas—consult product literature. Patients at increased risk of gastrointestinal perforation—consult product literature. Patients at increased risk of gastro-intestinal perforation—consult product literature. Patients at risk of haemorrhage (including tumour involvement of the trachea or bronchi)—discontinue if symptoms develop. Patients at risk of thromboembolic events—consult product literature. Raynaud’s phenomenon—discontinue if symptoms develop. Risk of osteonecrosis of the jaw—susceptibility to QT-interval prolongation (e.g. cardiac disease, electrolyte disturbances, bradycardia, concomitant use of drugs that prolong the QT interval)—monitor ECG and electrolytes periodically.

**Caution, Further Information**

**Elective Surgery** Withhold treatment for at least 28 days before elective surgery and restart only if adequate wound healing—discontinue in patients with wound healing complications requiring medical intervention.

**Risk of Osteonecrosis of the Jaw** Discontinue treatment at least 28 days before elective invasive dental procedures—monitor for symptoms before and during treatment and discontinue if osteonecrosis develops.

**Interactions**

- Appendix 1 ( caboza	

Caution with concomitant use of drugs which increase the risk of osteonecrosis of the jaw e.g. bisphosphonates.

**Side-Effects**

- Common or very common: Abdominal pain; abnormal hair growth; abscess; acne; alopecia; anal fissure; anxiety; arthralgia; aspiration; atrial fibrillation; blurred vision; chelitis; chills; cholelithiasis; constipation; decreased appetite; dehydration; depression; diarrhoea; dizziness; dry skin; dysgeusia; dyspepsia; dysphagia; dysuria; erythema; face oedema; folliculitis; fungal infection; gastro-intestinal perforation; gastro-intestinal haemorrhage; glossodynia; haematuria; haemorrhoids; hair colour changes; headache; hyperbilirubinaemia; hyperkeratosis; hypertension; hypoaluminaemia; hypocalcaemia; hypokalaemia; hypophosphataemia; hypotension; hypothyroidism; impaired wound healing; lymphopenia; mucosal inflammation; muscle spasms; musculoskeletal chest pain; nausea; neutropenia; non-gastro-intestinal fistula; oophoronygael pain; osteonecrosis of jaw; pallor; palmar-plantar erythrodysesthesia syndrome; pancreatitis; paraesthesia; peripheral coldness; peripheral neuropathy; platelet disorders; pneumonia; proteinuria; pulmonary embolism; rash; respiratory tract haemorrhage; skin exfoliation; skin hypopigmentation; stomatitis; tinnitus; tremor; venous thrombosis; vomiting.

- Uncommon: Acute renal failure; amnorrhoea; angina; arterial thrombosis; aspergilloma; ataxia; atelectasis; cataract; conjunctivitis; cyst; delirium; facial pain; gastro-intestinal fistula; hepatic encephalopathy; hypocalcaemia; loss of consciousness; oesophagitis; pharyngeal oedema; pneumonitis; posterior reversible encephalopathy syndrome; rhododendroidysia; skin ulcer; speech disorder; supraventricular tachycardia; telangiectasia; transient ischaemic attack; vaginal haemorrhage.

- Frequency not known: Bone-marrow suppression; hyperuricemia; oral mucositis; thromboembolism; tumour lysis syndrome.

**Conception and Contraception** Patients and their sexual partners must use effective contraception (in addition to barrier method) during treatment and for at least 4 months after the last dose.

**Pregnancy** Manufacturer advises avoid unless potential benefit outweighs risk—tocotoxicity in animal studies. See also Pregnancy and reproductive function in Cytoxic drugs, p. 746.

**Breast Feeding** Manufacturer advises discontinue breast-feeding during treatment and for at least 4 months after the last dose.

**Hepatic Impairment** Manufacturer advises avoid.

**Renal Impairment** Manufacturer advises caution in renal impairment. Avoid in severe impairment.

**Monitoring Requirements** Monitor urine protein regularly and discontinue if nephrotic syndrome develops.

**Patient and Carer Advice**

Fatigue and weakness may affect performance of skilled tasks e.g. driving. Food should not be consumed for at least 2 hours before and at least 1 hour after each dose.

**Medicinal Forms**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

**Cautionary and Advisory Labels 25**

- Cometriq (Swedish Orphan Biovitrum Ltd)
- Cabozantinib (as Cabozantinib s-malate) 20 mg Cometriq 20 mg capsules | 7 capsule pack no price available | 21 capsule pack no price available | 84 capsule pack £4,800.00
- Cabozantinib (as Cabozantinib s-malate) 80 mg Cometriq 80 mg capsules | 7 capsule pack no price available | 21 capsule pack no price available | 112 capsule pack £4,800.00
- Cometriq (Swedish Orphan Biovitrum Ltd)
- Cometriq 20 mg capsules and Cometriq 80 mg capsules | 56 capsule pack £4,800.00 | 112 capsule pack £4,800.00

**Crizotinib**

**Drug Action** Crizotinib is a tyrosine kinase inhibitor.

**Indications and Dose**

Treatment of previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer

**By Mouth**

- Adult: 250 mg twice daily, for dose adjustments due to side-effect, consult product literature.

**Important Safety Information**

**Risks of Incorrect Dosing of Oral Anti-Cancer Medicines**, see p. 745

**Caution** History of diverticulitis (risk of gastro-intestinal perforation—discontinue treatment if
gastrointestinal perforation occurs) - metastases of gastrointestinal tract (risk of gastro-intestinal perforation—discontinue treatment if gastrointestinal perforation occurs) - patients with susceptibility to QT prolongation (including bradycardia, history of cardiac disease, concomitant use of drugs that prolong QT interval, and electrolyte disturbances)—periodic renal monitoring required - risk of gastro-intestinal perforation—discontinue treatment if gastrointestinal perforation occurs - vision disorders reported—consider full ophthalmological evaluation if vision disorder worsens or persists

**CAUTIONS, FURTHER INFORMATION**

**Hepatic impairment**

Avoid (toxicity in renal impairment). 

**Breast feeding**

Avoid (toxicity in breast feeding). 

**Pregnancy**

Avoid (toxicity in pregnancy). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

**Breast feeding**

Avoid—no information available.

**Hepatic impairment**

Manufacturer advises caution in mild to moderate impairment. Avoid in severe impairment.

**Renal impairment**

Reduce dose to 250 mg once daily in severe renal impairment not requiring peritoneal dialysis or hemodialysis, may be increased to 200 mg twice daily after at least 4 weeks, based on individual assessment of safety and tolerability.

**Monitoring requirements**

- Monitor liver function once a week during the first 2 months of treatment, then at least monthly thereafter and as clinically indicated.
- Monitor ECG and electrolytes (correct if abnormal) in all patients before starting treatment, then periodically and as clinically indicated thereafter.
- Monitor for signs and symptoms of treatment emergent bradycardia (including syncope, dizziness and hypotension)—monitor blood pressure and heart rate regularly.

**Patient and carer advice**

Counsel all patients on the early signs and symptoms of gastrointestinal perforation—advice to seek immediate medical attention.

**Driving and skilled tasks**

Symptomatic bradycardia (including syncope, dizziness and hypotension), vision disorder and fatigue may affect performance of skilled tasks (e.g. driving or operating machinery).

**National funding/access decisions**

**NICE technology appraisals (TAs)**

- Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene (September 2013) NICE TA296

Crizotinib is not recommended within its marketing authorisation, for treating adults with previously treated anaplastic-lymphoma-kinase-positive advanced non-small-cell lung cancer. www.nice.org.uk/TA296

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

CAUTIONARY AND ADVISORY LABELS 25

- Xalkori (Pfizer Ltd) Crizotinib 200 mg Xalkori 200 mg capsules | 60 capsule £4,689.00
- Crizotinib 250 mg Xalkori 250 mg capsules | 60 capsule £4,689.00

**Dabrafenib**

**Drug action**

Dabrafenib is a BRAF kinase inhibitor.

**Indications and dose**

Monotherapy for the treatment of unresectable or metastatic melanoma with BRAF V600 mutation by mouth

- Adult: 150 mg every 12 hours, for dose adjustments due to side effects consult product literature

**Important safety information**

Risks of incorrect dosing of oral anti-cancer medicines, see p. 745

**Contra-indications**

BRAF wild-type melanoma - long QT syndrome - uncorrectable electrolyte abnormalities (including magnesium)

**Caution**

Pyrexia (interrupt treatment if ≥38.5°C and assess for signs and symptoms of infection—consult product literature)

**Interactions**

Appendix 1 (dabrafenib). Contra-indicated with concomitant use of drugs that prolong the QT interval.

**Side-effects**

- Common or very common Acrochordon - arthralgia - basal cell carcinoma - chills - constipation - cough - cutaneous squamous cell carcinoma - decrease in left ventricular ejection fraction - decreased appetite - diarrhoea - dry skin - erythema - hand-foot syndrome - headache - hyperglycaemia - hyperkeratosis - hypophosphataemia - influenza-like symptoms - keratitis - malaise - myalgia - papilloma - pruritus - pyrexia - rash - skin lesions
- Less common or very common Acrochordon - arthralgia - basal cell carcinoma - chills - constipation - cough - cutaneous squamous cell carcinoma - decrease in left ventricular ejection fraction - decreased appetite - diarrhoea - dry skin - erythema - hand-foot syndrome - headache - hyperglycaemia - hyperkeratosis - hypophosphataemia - influenza-like symptoms - keratitis - malaise - myalgia - papilloma - pruritus - pyrexia - rash - skin lesions
- Rare Acrochordon - arthralgia - basal cell carcinoma - chills - constipation - cough - cutaneous squamous cell carcinoma - decrease in left ventricular ejection fraction - decreased appetite - diarrhoea - dry skin - erythema - hand-foot syndrome - headache - hyperglycaemia - hyperkeratosis - hypophosphataemia - influenza-like symptoms - keratitis - malaise - myalgia - papilloma - pruritus - pyrexia - rash - skin lesions

**Side-effects, further information**

Pancreatitis Promptly investigate signs and symptoms of pancreatitis—consult product literature.

**Conception and contraception**

Effective non-hormonal contraception required during and for one month after treatment in women of childbearing potential.
Malignant disease

**Dabrafenib for treating unresectable or metastatic BRAF**

- **PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.
- **BREAST FEEDING** Manufacturer advises avoid.
- **HEPATIC IMPAIRMENT** Manufacturer advises caution in moderate to severe impairment.
- **RENAL IMPAIRMENT** Manufacturer advises caution in severe impairment—no information available.
- **MONITORING REQUIREMENTS**
  - Assess for cutaneous squamous cell carcinoma and new primary melanoma before treatment, monthly during treatment, and for 6 months after discontinuation or until initiation of alternative treatment.
  - Assess and monitor for non-cutaneous secondary or recurrent malignancy before, during, and for 6 months after discontinuation or until initiation of alternative treatment—consult product literature.
  - Monitor serum creatinine and other signs of renal failure—consult product literature and interrupt dose as appropriate.
  - Monitor for ophthalmologic reactions including uveitis and iritis.
  - Monitor ECG and electrolytes (including magnesium) before and one month after treatment initiation and after each dose modification—consult product literature if abnormalities occur.
- **PATIENT AND CARER ADVICE** Ocular adverse reactions and fatigue may affect performance of skilled tasks e.g. driving.
- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **NICE technology appraisals (TAS)**
    - Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma (October 2014) NICE TA321 Dabrafenib is recommended, within its marketing authorisation, as an option for treating unresectable or metastatic BRAF V600 mutation-positive melanoma only if the manufacturer provides dabrafenib with the discount agreed in the patient access scheme. www.nice.org.uk/TA321
  - **Scottish Medicines Consortium (SMC) Decisions**
    - The Scottish Medicines Consortium has advised (February 2015) that dabrafenib (Tafinlar®) is accepted for restricted use within NHS Scotland for the treatment of unresectable or metastatic BRAF V600 mutation-positive melanoma in patients who have received no prior therapy.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.
- **Capsule**
  - CAUTIONARY AND ADVISORY LABELS 23, 25
  - **Tafinlar** (Novartis Pharmaceuticals UK Ltd)
    - Dabrafenib (as Dabrafenib mesilate) 50 mg Tafinlar 50mg capsules | 28 capsule (PO) £93.33. (Hospital only)
    - Dabrafenib (as Dabrafenib mesilate) 75 mg Tafinlar 75mg capsules | 28 capsule (PO) £1,400.00. (Hospital only)

**Dasatinib**
- **DRUG ACTION** Dasatinib is a tyrosine kinase inhibitor.

**INDICATIONS AND DOSE**

**Chronic phase chronic myeloid leukaemia (consult product literature for details)**
- **BY MOUTH**
  - Adult: 100 mg once daily, then increased if necessary up to 140 mg once daily

**Accelerated and blast phase chronic myeloid leukaemia**

- **BY MOUTH**
  - Adult: 140 mg once daily, then increased if necessary up to 180 mg once daily

**Important safety information**

**RISKS OF INCORRECT DOING OF ORAL ANTI-CANCER MEDICINES, see p. 745**

- **CAUTIONS** Risk of cardiac dysfunction (monitor closely) - susceptibility to QT-interval prolongation (correct hypokalaemia or hypomagnesaemia before starting treatment)
- **CAUTIONS, FURTHER INFORMATION**
  - **Pulmonary arterial hypertension** Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease before starting treatment; echocardiography should be performed at the start of treatment in patients with symptoms of cardiac disease and considered for patients with risk factors for cardiac or pulmonary disease. Treatment should be interrupted or the dose reduced in patients who develop dyspnoea or fatigue, while they are evaluated for common aetiologies (e.g. pleural effusion, pulmonary oedema, anaemia or lung infiltration); pulmonary arterial hypertension should be considered in the absence of these conditions, and if there is no improvement following dose reduction or interruption. If pulmonary arterial hypertension is confirmed, dasatinib should be permanently discontinued.

**INTERACTIONS** Appendix 1 (dasatinib).

**SIDE-EFFECTS**

- **Rare** Cor pulmonale - Frequency not known Alopecia - bone-marrow suppression - hyperuricaemia - interstitial lung disease - nausea - oral mucositis - thromboembolism - thrombosis - tumour lysis syndrome - vomiting

**CONCEPTION AND CONTRACEPTION** Effective contraception required during treatment.

**PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

**BREAST FEEDING** Discontinue breast-feeding.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in hepatic impairment.
**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Dasatinib, high dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance (January 2012) NICE TA241

Dasatinib is not recommended for the treatment of chronic, accelerated or blast-crisis phase CML in adults with imatinib intolerance or whose CML is resistant to treatment with standard-dose imatinib. www.nice.org.uk/TA241

- Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia (April 2012) NICE TA251

Dasatinib is not recommended for the first-line treatment of chronic phase Philadelphia-chromosome-positive CML. www.nice.org.uk/TA251

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**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (April 2007) that the use of dasatinib (Sprycel<sup>®</sup>) in NHS Scotland is restricted to patients in the chronic phase of chronic myeloid leukaemia.

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**ERLOTINIB**

**DRUG ACTION** Erlotinib is a tyrosine kinase inhibitor.

**INDICATIONS AND DOSE**

Treatment of locally advanced or metastatic non-small cell lung cancer after failure of previous chemotherapy | Monotherapy for maintenance treatment of locally advanced or metastatic non-small cell lung cancer with stable disease after four cycles of platinum-based chemotherapy

**BY MOUTH**

- Adult: 150 mg once daily

Treatment of metastatic pancreatic cancer (in combination with gemcitabine)

**BY MOUTH**

- Adult: 100 mg once daily

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**Important safety information**

**EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) INHIBITORS: SERIOUS CASES OF KERATITIS AND ULCERATIVE KERATITIS (MAY 2012)**

Keratitis and ulcerative keratitis have been reported following treatment with epidermal growth factor receptor (EGFR) inhibitors for cancer ( cetuximab, erlotinib, gefitinib and panitumumab). In rare cases, this has resulted in corneal perforation and blindness. Patients undergoing treatment with EGFR inhibitors who present with acute or worsening signs and symptoms suggestive of keratitis should be referred promptly to an ophthalmology specialist. Treatment should be interrupted or discontinued if ulcerative keratitis is diagnosed.
**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (May 2006) that erlotinib (Tarceva®) is accepted for restricted use within NHS Scotland for the treatment of locally advanced or metastatic non-small cell lung cancer, after failure of at least one chemotherapy regimen. Erlotinib is restricted to use in patients who would otherwise be eligible for treatment with docetaxel monotherapy. The Scottish Medicines Consortium has also advised (December 2011) that erlotinib (Tarceva®) is accepted for use within NHS Scotland for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) activating mutations.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

CAUTIONARY AND ADVISORY LABELS 23

- Erlotinib (as Erlotinib hydrochloride) 25 mg Tarceva 25mg tablets | 30 tablet pack £378.33
- Erlotinib (as Erlotinib hydrochloride) 100 mg Tarceva 100mg tablets | 30 tablet pack £1,134.14
- Erlotinib (as Erlotinib hydrochloride) 150 mg Tarceva 150mg tablets | 30 tablet pack £1,631.53

**Everolimus**

**DRUG ACTION**

Everolimus is a protein kinase inhibitor.

**INDICATIONS AND DOSE**

**VOTUBIA®**

Subependymal giant cell astrocytoma associated with tuberous sclerosis complex

BY MOUTH

- Adult: (consult product literature)

Renal angiomyolipoma associated with tuberous sclerosis complex

BY MOUTH

- Adult: (consult product literature)

**AFINITOR®**

Treatment of advanced renal cell carcinoma when the disease has progressed despite treatment with vascular endothelial growth factor-targeted therapy | Treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin | Treatment of hormone-receptor-positive, human epidermal growth factor-2 (HER-2) negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor

BY MOUTH

- Adult: 10 mg once daily

**Important safety information**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**, see p. 745

**CAUTIONS**

- History of bleeding disorders

**INTERACTIONS**

- Appendix 1 (everolimus).

Caution with concomitant use of drugs that increase risk of bleeding.

**SIDE-EFFECTS**

- Common or very common: Abdominal pain - anorexia - arthralgia - asthenia - chest pain - convulsions - dehydration - diarrhoea - dry mouth - dysphagia - electrolyte disturbance - epistaxis - eyelid oedema - fatigue - hand-foot syndrome - headache - hypercholesterolaemia - hyperglycaemia - hyperlipidaemia - hypertension - hypoglycaemia - increased susceptibility to aspergillosis - increased susceptibility to candidiasis - increased susceptibility to infections - increased susceptibility to pneumonitis - insomnia - interstitial lung disease - irritability - nail disorders - peripheral oedema - pneumonitis - renal failure - skin disorders - taste disturbance

- Uncommon: Aggression - agitation - congestive heart failure - flushing - impaired wound healing - rhabdomyolysis

- Frequency not known: Alopecia - bone-marrow suppression - haemorrhage - hepatitis B reactivation - hyperuricaemia - nausea - oral mucositis - thromboembolism - tumour lysis syndrome - vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

Reduce dose or discontinue if severe side-effects occur—consult product literature.

**CONCEPTION AND CONTRACEPTION**

Effective contraception must be used during and for up to 8 weeks after treatment.

**PREGNANCY**

Manufacturer advises avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

**BREAST FEEDING**

Manufacturer advises avoid.

**HEPATIC IMPAIRMENT**

Consult product literature.

**MONITORING REQUIREMENTS**

- Monitor blood-glucose concentration, serum-triglycerides and serum-cholesterol before treatment and periodically thereafter.

- Monitor renal function before treatment and periodically thereafter.

**DIRECTIONS FOR ADMINISTRATION**

**VOTUBIA®**

Tablets may be dispersed in approximately 30 mL of water by gently stirring, immediately before drinking. After solution has been swallowed, any residue must be re-dispersed in the same volume of water and swallowed.

**PATIENT AND CARER ADVICE**

Pneumonitis Non-infectious pneumonitis reported. Patients should be advised to seek urgent medical advice if new or worsening respiratory symptoms occur.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Everolimus for the second-line treatment of advanced renal cell carcinoma (April 2011) NICE TA219

Everolimus is not recommended for the second-line treatment of advanced renal cell carcinoma. [www.nice.org.uk/TA219](http://www.nice.org.uk/TA219)

- Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy (August 2013) NICE TA295

Everolimus, in combination with exemestane, is not recommended within its marketing authorisation for treating postmenopausal women with advanced human epidermal growth factor receptor 2 (HER2) negative hormone-receptor-positive breast cancer that has recurred or progressed following treatment with a non-steroidal aromatase inhibitor. [www.nice.org.uk/TA295](http://www.nice.org.uk/TA295)

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (April 2012) that everolimus (Afinitor®) is accepted for restricted use within NHS Scotland for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin (pNET) in adults with progressive disease.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.
**Gefitinib**

**DRUG ACTION** Gefitinib is a tyrosine kinase inhibitor.

**INDICATIONS AND DOSE**

Treatment of locally advanced or metastatic non-small cell lung cancer with activating mutations of epidermal growth factor receptor

**BY MOUTH**

- Adult: 250 mg once daily

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**Important safety information**

MHRA/CHM ADVICE: EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) INHIBITORS: SERIOUS CASES OF KERATITIS AND ULCERATIVE KERATITIS (MAY 2012)

Keratitis and ulcerative keratitis have been reported following treatment with epidermal growth factor receptor (EGFR) inhibitors for cancer (cetuximab, erlotinib, gefitinib and panitumumab). In rare cases, this has resulted in corneal perforation and blindness. Patients undergoing treatment with EGFR inhibitors who present with acute or worsening signs and symptoms suggestive of keratitis should be referred promptly to an ophthalmology specialist. Treatment should be interrupted or discontinued if ulcerative keratitis is diagnosed.

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**, see p. 745

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**INTERACTIONS** → Appendix 1 (gefitinib).

**SIDE-EFFECTS**

- **Common or very common** Acne, anorexia, asthenia, bleeperatitis, conjunctivitis, diarrhoea, dry eye, dry mouth, dry skin, epistaxis, haematuria, interstitial lung disease — discontinue if confirmed — nail disorder — proteinuria, pruritus, pyrexia, rash — skin reactions
- **Uncommon** Cornal erosion, pancreatitis
- **Rare** Hepatitis — toxic epidermal necrolysis
- **Frequency not known** Alopecia, bone-marrow suppression — hyperuricaemia — nausea — oral mucositis — thromboembolism — tumour lysis syndrome — vomiting

**PREGNANCY**

Manufacturer advises avoid unless essential — toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

**BREAST FEEDING** Discontinue breast-feeding.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in moderate to severe impairment due to cirrhosis.

**RENAL IMPAIRMENT** Manufacturer advises caution if creatinine clearance less than 20 mL/minute.

**MONITORING REQUIREMENTS**

- Monitor for worsening of dyspnoea, cough and fever — discontinue if interstitial lung disease confirmed.
- Monitor liver function — consider discontinuing if severe changes in liver function occur.

**NICE technology appraisals (TAs)**

- Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer (July 2010) NICE TA192

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**Ibrutinib**

**DRUG ACTION** Ibrutinib is a tyrosine kinase inhibitor.

**INDICATIONS AND DOSE**

Treatment of relapsed or refractory mantle cell lymphoma

**BY MOUTH**

- Adult: 560 mg once daily, for dose adjustments due to side effects consult product literature

**TREATMENT OF CHRONIC LYMPHOCYTIC LEUKAEMIA, IN PATIENTS WHO HAVE RECEIVED AT LEAST ONE PRIOR THERAPY, OR AS FIRST-LINE TREATMENT IN PATIENTS WITH 17p deletion or TP53 mutation who are unsuitable for chemo-immunotherapy**

**BY MOUTH**

- Adult: 420 mg once daily, for dose adjustments due to side effects consult product literature

**TREATMENT OF CHRONIC LYMPHOCYTIC LEUKAEMIA, IN PATIENTS WHO HAVE RECEIVED AT LEAST ONE PRIOR THERAPY, OR AS FIRST-LINE TREATMENT IN PATIENTS WITH 17p deletion or TP53 mutation who are unsuitable for chemo-immunotherapy (patients taking concomitant moderate or potent CYP3A4 inhibitors) | Treatment of relapsed or refractory mantle cell lymphoma (patients taking concomitant moderate or potent CYP3A4 inhibitors)**

**BY MOUTH**

- Adult: 140 mg once daily, for dose adjustments due to side effects consult product literature

**Dose adjustments due to interactions**

Reduce dose in patients taking concomitant potent CYP3A4 inhibitors (such as cobicistat, clarithromycin, darunavir boosted with ritonavir, indinavir, itraconazole, ketoconazole, ritonavir, saquinavir, telithromycin, and voriconazole) or moderate CYP3A4 inhibitors (such as amiodarone, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, dronedarone, erlotinib, fluconazole, fosamprenavir, imatinib, and verapamil); alternatively temporarily stop ibrutinib if the potent CYP3A4 inhibitor is only required for 7 days or less. Avoid concomitant use with these drugs unless unavoidable.

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**Important safety information**

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**, see p. 745

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**CAUTIONS** Family history of congenital short QT syndrome — increased risk of leukostasis, consider withholding treatment temporarily and monitor closely. Patients at risk from further shortening of QTc interval — personal history of congenital short QT syndrome — risk of haemorrhagic events — withhold ibrutinib treatment for at least 5 to 7 days before and after surgery depending on risk of bleeding.

**INTERACTIONS** → Appendix 1 (ibrutinib).

Avoid concomitant use of drugs that increase risk of bleeding.
810 Malignant disease

SIDE-EFFECTS

Common or very common

Arthralgia · atrial fibrillation · blurred vision · bruising · constipation · dehydration · diarrhoea · dizziness · dry mouth · epistaxis · haemorrhage · headache · musculoskeletal pain · peripheral oedema · petechiae · pyrexia · rash · respiratory tract infection · sepsis · sinusitis · skin infection · subdural haematoma · urinary tract infection

Uncommon

Leukostasis

Frequency not known

Alopecia · bone-marrow suppression · hyperuricaemia · nausea · oral mucositis · thromboembolism · tumour lysis syndrome · vomiting

CONCESSION AND CONTRACEPTION

Highly effective contraception (in addition to barrier method) required during and for one month after treatment.

PREGNANCY

Manufacturer advises avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

BREAST FEEDING

Manufacturer advises caution in breast feeding—no information available.

Hepatic impairment

Reduce dose to the following quantities in patients with hepatic impairment:

- Adult: 100 mg once daily
- Adult: 75 mg once daily

Renal impairment

Use in severe impairment only if benefit outweighs risk and with close monitoring for toxicity. Maintain hydration and monitor serum creatinine periodically in mild to moderate renal impairment.

MONITORING REQUIREMENTS

Monitor full blood count once a month.

Monitor for atrial fibrillation (increased risk in cardiac risk factors, acute infections and history of atrial fibrillation), monitor all patients periodically and complete ECG if arrhythmic symptoms or dyspnoea develop—consult product literature.

MEdICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Capsule

CAUTIONARY AND ADVISORY LABELS 25

- Imbruvica (janssen-Cilag Ltd)
- Idelalisib 150 mg

Zydelig 140 mg tablets | 90 capsule | 120 capsule

£4,599.00 | £6,132.00

Idelalisib

DRUG ACTION

Idelalisib is a protein kinase inhibitor.

INDICATIONS AND DOSE

Treatment of chronic lymphocytic leukaemia in patients who have received at least one previous therapy, or as first-line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemotherapy (in combination with rituximab)

Treatment of follicular lymphoma refractory to two lines of treatment (monotherapy)

BY MOUTH

- Adult: 150 mg twice daily, for dose adjustment due to side effects, consult product literature

Imatinib

DRUG ACTION

Imatinib is a tyrosine kinase inhibitor.

INDICATIONS AND DOSE

Treatment of chronic myeloid leukaemia in chronic phase after failure with interferon alfa

BY MOUTH

- Adult: 400 mg once daily, increased if necessary up to 800 mg daily in 2 divided doses

Treatment of chronic myeloid leukaemia in accelerated phase, or in blast crisis

BY MOUTH

- Adult: 600 mg once daily, then increased if necessary up to 800 mg daily in 2 divided doses

Treatment of newly diagnosed acute lymphoblastic leukaemia (in combination with other chemotherapy)

BY MOUTH

- Adult: 600 mg once daily

Important safety information

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES, see p. 745

CAUTIONS

Active hepatitis · diarrhoea—symptomatic management recommended (consult product literature)
Targeted therapy responsive malignancy 811

Treatment of c-kit (CD117)-positive unresectable or metastatic malignant gastro-intestinal stromal tumours (GIST) | Adjuvant treatment following resection of c-kit (CD117)-positive GIST, in patients at significant risk of relapse | Treatment of myelodysplastic/myeloproliferative diseases associated with platelet-derived growth factor receptor gene rearrangement

BY MOUTH

Adult: 400 mg once daily

Treatment of unresectable dermatofibrosarcoma protuberans | Recurrent or metastatic dermatofibrosarcoma protuberans, in patients who cannot have surgery

BY MOUTH

Adult: 800 mg daily in 2 divided doses

Treatment of advanced hypereosinophilic syndrome and chronic eosinophilic leukaemia

BY MOUTH

Adult: 100–400 mg once daily

Important safety information
RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES, see p. 745

- CAUTIONS Cardiac disease · history of renal failure · risk factors for heart failure
- INTERACTIONS → Appendix 1 (imidatinib).
- SIDE-EFFECTS
  - Common or very common Abdominal pain · appetite changes · arthralgia · ascites · conjunctivitis · constipation · cough · cramps · diarrhoea · dizziness · dry eyes · dry mouth · dry skin · dysphagia · epistaxis · fatigue · flatulence · flushing · gastro-oesophageal reflux · haemorrhage · headache · hypoesthesia · increased lacrimation · influenza-like symptoms · insomnia · oedema · paraesthesia · photosensitivity · pleural effusion · pruritus · pulmonary oedema · rash · sweating · taste disturbance · visual disturbances · weight changes
  - Uncommon Acute respiratory failure · anxiety · cold extremities · cough · depression · drowsiness · dysphagia · electrolyte disturbances · gastric ulceration · gout · gynaecomastia · haemoptoma · hearing loss · heart failure · hepatic dysfunction · hypertension · hypotension · impaired memory · irregular menstruation · menorrhagia · migraine · palpitation · pancreatitis · peripheral neuropathy · renal failure · sexual dysfunction · skin hyperpigmentation · syncope · tachycardia · tinnitus · tremor · urinary frequency · vertigo
  - Rare Angina · angioedema · arrhythmia · aseptic necrosis of bone · atrial fibrillation · cataract · confusion · convulsions · exfoliative dermatitis · gastro-intestinal perforation · glaucoma · haemolytic anaemia · hepatic failure · hepatic necrosis · increased intracranial pressure · inflammatory bowel disease · intestinal obstruction · myocardial infarction · myopathy · pulmonary fibrosis · pulmonary hypertension · rhabdomyolysis · Stevens-Johnson syndrome
  - Frequency not known Alopecia · bone-narrow suppression · drug rash with eosinophilia and systemic symptoms (DRESS) · growth retardation in children · hyperuricaemia · nausea · oral mucositis · thromboembolism · tumour lysis syndrome · vomiting
- CONCEPTION AND CONTRACEPTION Effective contraception required during treatment.
- PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk. See also Pregnancy and reproductive function in Cytoxic drugs, p. 746.
- BREAST FEEDING Discontinue breast-feeding.
- HEPATIC IMPAIRMENT Max. 400 mg daily; reduce dose further if not tolerated.

- RENAL IMPAIRMENT Maximum starting dose 400 mg daily if creatinine clearance less than 60 mL/minute; reduce dose further if not tolerated.
- MONITORING REQUIREMENTS
  - Monitor for gastrointestinal haemorrhage.
  - Monitor complete blood counts regularly.
  - Monitor for fluid retention.
  - Monitor liver function.
  - Monitor growth in children (may cause growth retardation).
- DIRECTIONS FOR ADMINISTRATION Tablets may be dispersed in water or apple juice.

PATIENT AND CARER ADVICE Patients or carers should be given advice on how to administer imatinib tablets.

NATIONAL FUNDING/ACCESS DECISIONS
NICE technology appraisals (TAs) NICE TA70

- Imatinib for chronic myeloid leukaemia (October 2003) Imatinib 400 mg daily is recommended as first-line treatment for Philadelphia-chromosome-positive chronic myeloid leukaemia in the chronic phase as an option for patients presenting in the accelerated phase or with blast crisis, provided that imatinib has not been used previously: www.nice.org.uk/TA70

- Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours (October 2004) NICE TA86 Imatinib 400 mg daily is recommended as first-line management of KIT (CD117)-positive unresectable or metastatic, or both, gastro-intestinal stromal tumours. Continued therapy is recommended only if a response to initial treatment [as defined by Southwest Oncology Group criteria available at www.nice.org.uk/TA86] is achieved within 12 weeks. Patients who have responded should be assessed at 12-week intervals. Discontinue if tumour ceases to respond. www.nice.org.uk/TA86

- Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours (November 2010) NICE TA209 Imatinib 600 mg daily or 800 mg daily is not recommended for unresectable or metastatic, or both, gastro-intestinal stromal tumours whose disease has progressed after treatment with imatinib 400 mg daily. www.nice.org.uk/TA209

- Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance (January 2012) NICE TA241 High-dose imatinib is not recommended for the treatment of chronic, accelerated or blast-crisis phase Philadelphia-chromosome-positive CML that is resistant to standard-dose imatinib. www.nice.org.uk/TA241


- Imatinib for the adjuvant treatment of gastro-intestinal stromal tumours (November 2014) NICE TA326 Imatinib is recommended as an option for adjuvant treatment of adult patients who are at high risk of relapse after surgery for KIT (CD117)-positive gastro-intestinal stromal tumours, as defined by the Miettinen 2006 criteria (based on tumour size, location, and mitotic rate), for up to 3 years. Patients currently receiving treatment initiated within the NHS with imatinib that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop. www.nice.org.uk/TA326
Malignant disease

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (March 2002) that imatinib (Glivec®) should be used for chronic myeloid leukaemia only under specialist supervision in accordance with British Society of Haematology guidelines (November 2001).

The Scottish Medicines Consortium has also advised (February 2012) that imatinib (Glivec®) is accepted for restricted use within NHS Scotland for the treatment of adult patients who are at significant risk of relapse following resection of a KIT (CD117) positive gastrointestinal stromal tumour (GIST) and who are at high risk of recurrence following complete resection (according to the Armed Forces Institute of Pathology (AFIP) risk criteria).

● MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 21.27

- Glivec (Novartis Pharmaceuticals UK Ltd)
- Imatinib (as imatinib mesilate) 100 mg Glivec 100mg tablets | 60 tablet £918.23
- Imatinib (as imatinib mesilate) 400 mg Glivec 400mg tablets | 30 tablet £1,836.48

Lapatinib

● DRUG ACTION Lapatinib is a tyrosine kinase inhibitor.

INDICATIONS AND DOSE

Treatment of advanced or metastatic breast cancer in patients with tumours that overexpress human epidermal growth factor receptor-2 (HER2) with hormone-receptor-negative disease who have had previous treatment with trastuzumab in combination with chemotherapy (in combination with trastuzumab)

BY MOUTH

- Adult: 1 g once daily

Treatment of advanced or metastatic breast cancer in patients with tumours that overexpress human epidermal growth factor receptor-2 (HER2), for patients who have had previous treatment with an anthracycline, a taxane, and trastuzumab (in combination with capecitabine)

BY MOUTH

- Adult: 1.25 g once daily

Treatment of advanced or metastatic breast cancer with tumours that overexpress human epidermal growth factor receptor-2 (HER2), for postmenopausal women with hormone-receptor-positive disease (in combination with an aromatase inhibitor)

BY MOUTH

- Adult: 1.5 g once daily

Important safety information

RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES, see p. 745

● CAUTIONS

Diarrhoea— withhold treatment if severe (consult product literature) - low gastric pH (reduced absorption) - susceptibility to QT-interval prolongation (including electrolyte disturbances)

● INTERACTIONS → Appendix 1 (lapatinib).

Caution with concomitant use of drugs that prolong QT-interval.

● SIDE-EFFECTS

- Common or very common Anorexia · cardiac failure (fatal cases reported) · decreased left ventricular ejection fraction · diarrhoea (treat promptly) · hepatotoxicity (discontinue permanently if severe) · hyperbilirubinemia · malaise · nail disorders · rash
- Uncommon Interstitial lung disease
- Frequency not known Alopecia · bone-marrow suppression · hyperuricaemia · nausea · oral mucositis · respiratory failure (including fatal cases) · thromboembolism · tumour lysis syndrome · vomiting
- PREGNANCY Avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746
- BREAST FEEDING Discontinue breast-feeding.
- HEPATIC IMPAIRMENT Caution in moderate to severe impairment—metabolism reduced.
- RENAL IMPAIRMENT Caution in severe impairment—no information available.

● MONITORING REQUIREMENTS

- Monitor left ventricular function.
- Monitor for pulmonary toxicity.
- Monitor liver function before treatment and at monthly intervals.

● DIRECTIONS FOR ADMINISTRATION Always take at the same time in relation to food: either one hour before or one hour after food.

● PATIENT AND CARER ADVICE Counselling advised (administration). Patients should be advised to report any unexpected changes in bowel habit.

● NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

- Lapatinib or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2 (June 2012) NICE TA257

Lapatinib or trastuzumab in combination with an aromatase inhibitor is not recommended for first-line treatment in postmenopausal women of metastatic hormone-receptor-positive breast cancer that overexpresses human epidermal growth factor receptor 2 (HER2).

Postmenopausal women currently receiving lapatinib or trastuzumab in combination with an aromatase inhibitor for this indication should have the option to continue treatment until they and their clinician consider it appropriate to stop. www.nice.org.uk/TA257

● MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

- Tyverb (Novartis Pharmaceuticals UK Ltd)
- Lapatinib ditosylate monohydrate 250 mg Tyverb 250mg tablets | 84 tablet £965.16 | 105 tablet £1,206.45

Nilotinib

● DRUG ACTION Nilotinib is a tyrosine kinase inhibitor.

INDICATIONS AND DOSE

Treatment of newly diagnosed chronic myeloid leukaemia in the chronic phase

BY MOUTH

- Adult: 300 mg twice daily
Targeted therapy responsive malignancy 813

Treatment of chronic and accelerated phase chronic myeloid leukaemia in patients who have resistance to or intolerance of previous therapy, including imatinib

BY MOUTH

Adult: 400 mg twice daily

Important safety information
RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES, see p. 745

• CAUTIONS History of pancreatitis • susceptibility to QT-interval prolongation (including electrolyte disturbances)
• INTERACTIONS Appendix 1 (nilotinib). Caution with concomitant use of drugs that prolong QT interval.
• SIDE-EFFECTS
  • Common or very common Abdominal pain • anorexia • arthralgia • asthenia • blood glucose changes • bone pain • constipation • cough • diarrhoea • dizziness • dry skin • dyspepsia • dysphonia • dyspnoea • erythema • fatigue • flatulence • flushing • headache • hyperhidrosis • hyperkalaemia • hypertension • hypomagnesaemia • insomnia • muscle spasm • oedema • palpitation • paraesthesia • pruritus • QT-interval prolongation • rash • urticaria • vertigo • weight changes
  • Uncommon Anxiety • arthrythmias • bradycardia • breast pain • cardiac failure • cardiac murmur • cardiomegaly • chest pain • conjunctivitis • coronary artery disease • decreased visual acuity • dehydration • depression • dry eyes • dry mouth • dysuria • ecchymosis • epistaxis • erectile dysfunction • gynaecomastia • haematomata • haemorrhage • hepatitis • hyperaesthesia • hypertensive crisis • hyperthyroidism • hypoaesthesia • hypocalcaemia • hypokalaemia • hypophaetaeemia • influenza-like symptoms • interstitial lung disease • melaena • migrane • pancreatitis • pericardial effusion • pleural effusion • tremor • urinary frequency
  • Frequency not known Alopecia • bone-marrow suppression • hyperuricaemia • nausea • oral mucositis • thromboembolism • tumour lysis syndrome • vomiting
• CONCEPTION AND CONTRACEPTION Effective contraception required during treatment.
• PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.
• BREAST FEEDING Manufacturer advises avoid—present in milk in animal studies.
• HEPATIC IMPAIRMENT Manufacturer advises caution.
• NATIONAL FUNDING/ACCESS DECISIONS
  • NICE technology appraisals (TAs)
    • Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance (January 2012) NICE TA241
    • Nilotinib is recommended for the treatment of chronic or accelerated phase Philadelphia–chromosome-positive chronic myeloid leukaemia (CML) in adults:
      • whose CML is resistant to treatment with standard dose imatinib, or
      • if the manufacturer makes nilotinib available with the discount agreed as part of the patient access scheme. www.nice.org.uk/TA241
    • Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia (April 2012) NICE TA251
    • Nilotinib is recommended as an option for the first-line treatment of adults with chronic phase Philadelphia-
chromosome-positive CML if the manufacturer makes nilotinib available with the discount agreed as part of the patient access scheme. www.nice.org.uk/TA251

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (February 2008) that nilotinib (Tasigna®) is accepted for restricted use within NHS Scotland for the treatment of chronic phase chronic myeloid leukaemia in adults resistant to or intolerant of at least one previous therapy, including imatinib, and (July 2011) for the treatment of adults with newly diagnosed chronic myeloid leukaemia in the chronic phase.

• MEDICINAL FORMS
  • There can be variation in the licensing of different medicines containing the same drug.
  • **Capsule**
  • CAUTIONARY AND ADVISORY LABELS 23, 25, 27
    • Tasigna (Novartis Pharmaceuticals UK Ltd)
      • Nilotinib (as Nilotinib hydrochloride monohydrate)
        • 150 mg Tasigna 150mg capsules | 312 capsule pack £2,432.85
        • Nilotinib (as Nilotinib hydrochloride monohydrate)
          • 200 mg Tasigna 200mg capsules | 112 capsule pack £2,432.85

Pazopanib

• DRUG ACTION Pazopanib is a tyrosine kinase inhibitor.

INDICATIONS AND DOSE

First-line treatment of advanced renal cell carcinoma

Treatment of advanced renal cell carcinoma in patients who have had previous treatment with cytokine therapy

BY MOUTH

Adult: 800 mg daily, adjust dose in steps of 200 mg according to tolerability; maximum 800 mg per day

Treatment of selective subtypes of advanced soft tissue sarcoma

BY MOUTH

Adult: (consult product literature)

Important safety information
RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES, see p. 745

• CONTRA-INDICATIONS Cerebral haemorrhage • clinically significant gastro-intestinal haemorrhage • haemoptysis in the past 6 months
• CAUTIONS Cardiac disease • increased risk of gastro-intestinal fistulae • increased risk of gastro-intestinal perforation • increased risk of haemorrhage • increased risk of thrombotic microangiopathy—permanently discontinue if symptoms develop • ischaemic stroke • myocardial infarction • risk of thrombotic events • susceptibility to QT-interval prolongation (including electrolyte disturbances) • transient ischaemic attack

CAUTIONS, FURTHER INFORMATION

Eelective surgery Discontinue treatment 7 days before elective surgery and restart only if adequate wound healing.

Blood pressure Blood pressure must be controlled before initiating treatment.

• INTERACTIONS Appendix 1 (pazopanib). Caution with concomitant use of drugs that prolong QT-interval.
• SIDE-EFFECTS
  • Common or very common Abdominal distension • abdominal pain • anorexia • blood disorders • blurred vision • chest pain • cough • dehydration • diarrhoea • dizziness • dry mouth • dry skin • dyspepsia • dyspnoea • epistaxis • flatulence • flushing • hair discoloration • headache • hepatic dysfunction • hiccups • hyperalbuminaemia •
hyperbilirubinaemia · hypertension · hypothyroidism · increased amylase · insomnia · malaise · muscle spasm · myalgia · nail disorders · oedema · paraesthesia · pneumothorax · proteinuria (discontinue if grade 4) · skin discoloration · skin reactions · sweating · taste disturbance · thrombocytopenia · venous thromboembolic events · voice changes · weight loss

- **Uncommon** Arthralgia · bradycardia · cardiac dysfunction · fistula · gastro-intestinal perforation · haemorrhage · hepatic failure · hypertensive crisis · hypomagnesaemia · menstrual disturbances · myocardial infarction · myocardial ischaemia · ophthalmoplegia · peripheral neuropathy · peritonitis · photosensitivity reactions · pulmonary embolism · QT-interval prolongation · stroke · transient ischaemic attack

- **Rare** Thrombotic microangiopathy
- **Frequency not known** Alopecia · bone-marrow suppression · hyperuricaemia · nausea · oral mucositis · thromboembolism · tumour lysis syndrome · vomiting

### Conception and Contraception
Effective contraception advised during treatment.

- **Pregnancy** Avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

- **Breast Feeding** Discontinue breast-feeding.

- **Hepatic Impairment** Reduce dose to 200 mg once daily in moderate impairment. Use with caution in mild to moderate impairment. Avoid in severe impairment.

- **Renal Impairment** Use with caution if creatinine clearance less than 30 mL/minute—no information available.

### Monitoring Requirements
- Monitor liver function before treatment and at weeks 3, 5, 7, and 9, then at months 3 and 4, and periodically thereafter as clinically indicated—consult product literature if elevated liver enzymes observed.
- Monitor blood pressure within 1 week of treatment initiation, then frequently throughout treatment (consider dose reduction or interruption if hypertension uncontrolled despite anti-hypertensive therapy; discontinue if blood pressure persistently elevated despite anti-hypertensive therapy and pazopanib dose reduction—consult product literature).
- Monitor for signs or symptoms of congestive heart failure—monitor left ventricular ejection fraction in patients at risk of heart failure before and during treatment.
- Monitor for proteinuria.
- Monitor thyroid function.
- Monitor for signs and symptoms of posterior reversible encephalopathy syndrome (including headache, hypertension, seizure, lethargy, confusion, visual and neurological disturbances)—permanently discontinue treatment if symptoms occur.

- **Patient and Carer Advice** Patients should be advised not to take antacids for at least 1 hour before or 2 hours after pazopanib.

### National Funding/Access Decisions

**NICE technology appraisals (TAs)**
- Pazopanib for the first-line treatment of advanced renal cell carcinoma (updated August 2013) NICE TA215

Pazopanib is recommended as a first-line treatment option for people with advanced renal cell carcinoma:
- who have not received prior cytokine therapy and have an Eastern Cooperative Oncology Group performance status of 0 or 1 and
- if the manufacturer provides pazopanib at the discounted price agreed under the patient access scheme. [www.nice.org.uk/TA215](http://www.nice.org.uk/TA215)

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### Scottish Medicines Consortium (SMC) Decisions

The **Scottish Medicines Consortium** (SMC) has advised (February 2011) that pazopanib (Votrient®) is accepted for restricted use within NHS Scotland for the first-line treatment of advanced renal cell carcinoma and (December 2012) is not recommended for use within NHS Scotland for the treatment of selective subtypes of advanced soft tissue sarcoma in patients who have received prior chemotherapy for metastatic disease, or who have progressed within 12 months after neoadjuvant therapy.

### Medicinal Forms
There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>£50.50</th>
<th>£121.00</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pazopanib</strong> (as Pazopanib hydrochloride) 200 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Votrient (Novartis Pharmaceuticals UK Ltd)</td>
<td>30 tablet</td>
<td>400 mg</td>
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</table>

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### Indications and Dose

**T**reatment of chronic, accelerated, or blast phase chronic myeloid leukaemia in patients who have the T315I mutation or who have resistance to or intolerance of dasatinib or nilotinib, and for whom subsequent treatment with imatinib is not clinically appropriate | Treatment of Philadelphia chromosome-positive acute lymphoblastic leukaemia in patients who have the T315I mutation or who have resistance to or intolerance of dasatinib, and for whom subsequent treatment with imatinib is not clinically appropriate

**By Mouth**
- Adult: 45 mg once daily, for dose adjustment due to side effects—consult product literature.

**Dose adjustments due to interactions**

Consider reducing the initial dose to 30 mg once daily with concomitant use of potent inhibitors of cytochrome P450 enzyme CYP3A4 (e.g. clarithromycin, indinavir, itraconazole, ritonavir, saquinavir, telithromycin or voriconazole).

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### Important Safety Information

**MHRA/CHM Advice: Ponatinib: Risk of Vascular Occlusive Events (November 2014)**

The benefits and risks of ponatinib have been reviewed by the European Medicines Agency’s Committee on Medicinal Products for Human Use, which has recommended that strengthened warnings should be added to the product information aimed at minimising the risk of blood clots and blockages in the arteries. The review concluded that available evidence shows that the risk of blood vessel blockage with ponatinib is likely to be dose-dependent. However, the data is insufficient to recommend reducing the dose of ponatinib, and there is a risk that a lower dose might not be as effective as the current dose in all patients and in long-term treatment. Therefore, no change has been made to the recommended starting dose.

Prescribers may wish to consider reducing the dose in patients with chronic phase chronic myeloid leukaemia who are responding well to treatment, and who might be at high risk of blood vessel blockage. Stop ponatinib if a complete response has not occurred within 3 months of treatment, and monitor patients for high blood pressure or signs of heart problems.
Regorafenib

- **Drug action**: Regorafenib is an inhibitor of several protein kinases.

**Indications and dose**

Treatment of metastatic colorectal cancer in patients who have previously been treated with, or who are unsuitable for standard treatment including fluoropyrimidine-based chemotherapy, a vascular endothelial growth factor inhibitor, and an epidermal growth factor receptor inhibitor.

**By mouth**

- Adult: 160 mg once daily for 21 consecutive days of repeated 28-day cycles, for dose adjustment due to side effects—consult product literature.

**Important safety information**

- **Risks of incorrect dosing of oral anti-cancer medicines, see p. 745**

- **Caution**: Ensure measures to prevent hand-foot skin reaction - Gilbert's syndrome—risk of hyperbilirubinemia - history of ischaemic heart disease—monitor for signs and symptoms of myocardial ischaemia and interrupt treatment if signs of ischaemia or infarction develop - hypertension—control blood pressure before treatment initiation and monitor as clinically indicated during treatment (review dose and consider treatment interruption if severe or persistent hypertension develops; discontinue treatment if hypertensive crisis occurs) - may impair wound healing— withhold treatment for major surgical procedures - predisposition to bleeding.

- **Interactions** → Appendix 1 (regorafenib). Caution in concomitant treatment with drugs that may increase the risk of bleeding (increased risk of haemorrhagic events).

- **Side-effects**
  - **Uncommon** Atrial flutter - cerebral artery stenosis - cerebral infarction - gastric haemorrhage - hepatotoxicity - jaundice - retinal vein occlusion - retinal vein thrombosis - visual impairment.
  - **Frequency not known** Alopecia - bone-marrow suppression - hyperuricaemia - nausea - oral mucositis - thromboembolism - tumour lysis syndrome - vomiting.

- **Conception and contraception** Ensure effective contraception during treatment in men and women; effectiveness of hormonal contraception unknown — alternative or additional methods of contraception should be used.

- **Pregnancy** Avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytopathic drugs, p. 746.

- **Breast feeding** Manufacturer advises discontinue breastfeeding—no information available.

- **Hepatic impairment** Manufacturer advises caution in severe impairment.

- **Renal impairment** No information available—manufacturer advises caution if creatinine clearance less than 50 mL/minute.

- **Monitoring requirements**
  - Monitor serum lipase every 2 weeks for the first 2 months and periodically thereafter for all patients— withhold treatment if lipase elevated and abdominal symptoms occur.
  - Monitor full blood count every 2 weeks for the first 3 months and then monthly thereafter or as clinically indicated.
  - Monitor liver function periodically.
  - Monitor for vascular occlusion or thromboembolism—interrupt treatment immediately if this occurs.

- **Medicinal forms** There can be variation in the licensing of different medicines containing the same drug.

Tablet

Cautionary and advisory labels 3, 25

- Iclusig (Ariad Pharma (UK) Ltd) ▼
  - Ponatinib (as Ponatinib hydrochloride) 15 mg Iclusig 15 mg tablets | 60 tablet (£5.00)
  - Ponatinib (as Ponatinib hydrochloride) 45 mg Iclusig 45 mg tablets | 30 tablet (£5.05)

**Malignant disease**
contraception during treatment and up to 8 weeks after last dose.

- **PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

- **BREAST FEEDING** Avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in moderate impairment. Avoid in severe impairment.

- **RENAL IMPAIRMENT** Caution in severe impairment—no information available.

- **BREAST FEEDING** Avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT** Reduce dose (consult product literature).

- **MONITORING REQUIREMENTS**
  - Monitor blood count and coagulation parameters and consider permanent discontinuation in event of severe bleeding.
  - Monitor hepatic function before treatment, then at least every two weeks for the first 2 months, then at least monthly thereafter and as clinically indicated—consult product literature if changes in liver function observed.
  - Monitor for signs and symptoms of posterior reversible encephalopathy syndrome (including seizure, headache, altered mental status, visual disturbances or cortical blindness, with or without hypertension)—discontinue treatment if symptoms occur.
  - Monitor biochemical, electrolyte and metabolic parameters during treatment; ensure measures to prevent hand-foot skin reaction—consult product literature if signs or symptoms develop.

- **DIRECTIONS FOR ADMINISTRATION** Tablets should be taken at the same time each day, swallowed whole with water after a light meal that contains less than 30% fat.

- **PATIENT AND CARER ADVICE** Counselling advised (administration).

- **INTERACTIONS** → Appendix 1 (ruxolitinib).

- **SIDE-EFFECTS**
  - **Common or very common** Dizziness, flatulence, headache, hypercholesterolaemia, weight gain
  - **Uncommon** Tuberculosis
  - **Frequency not known** Alopecia, bone-marrow suppression, hyperuricaemia, nausea, oral mucositis, progressive multifocal leucoencephalopathy, thromboembolism, tumour lysis syndrome, vomiting
  - **PREGNANCY** Avoid—toxicity in animal studies.

- **NEONATES** Caution in severe impairment—no information available.

- **PEDIATRIC USE** Caution in severe impairment—no information available.

- **GERIATRIC USE** Caution in severe impairment—no information available.

- **MONITORING REQUIREMENTS**
  - Monitor for infection during treatment.
  - Monitor for symptoms of progressive multifocal leucoencephalopathy (presenting as new or worsening neurological, cognitive or psychiatric signs or symptoms)—withhold treatment if suspected.

- **NATIONAL FUNDING/ACCESS DECISIONS**

- **RUXOLITINIB FOR DISEASE-RELATED SPLENOEGALY OR SYMPTOMS IN ADULTS WITH MYELOFIBROSIS**

  - **INDICATIONS AND DOSE**
    - Treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis.
    - **BY MOUTH**
      - **Adult:** (consult product literature or local protocols)

  - **SIDE-EFFECTS**
    - **Common or very common** Dizziness, flatulence, headache, hypercholesterolaemia, weight gain
    - **Uncommon** Tuberculosis
    - **Frequency not known** Alopecia, bone-marrow suppression, hyperuricaemia, nausea, oral mucositis, progressive multifocal leucoencephalopathy, thromboembolism, tumour lysis syndrome, vomiting
    - **PREGNANCY** Avoid—toxicity in animal studies.

- **BREAST FEEDING** Avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT** Reduce dose (consult product literature).

- **RENAL IMPAIRMENT** Reduce dose in severe impairment (consult product literature).

- **MONITORING REQUIREMENTS**
  - Monitor full blood count (including differential white cell count) before treatment, then every 2–4 weeks until dose stabilised, then as clinically indicated.
  - Monitor for infection during treatment.
  - Monitor for symptoms of progressive multifocal leucoencephalopathy (presenting as new or worsening neurological, cognitive or psychiatric signs or symptoms)—withhold treatment if suspected.

- **NATIONAL FUNDING/ACCESS DECISIONS**

- **RUXOLITINIB FOR DISEASE-RELATED SPLENOEGALY OR SYMPTOMS IN ADULTS WITH MYELOFIBROSIS**

  - **INDICATIONS AND DOSE**
    - Treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis.
    - **BY MOUTH**
      - **Adult:** (consult product literature or local protocols)

  - **SIDE-EFFECTS**
    - **Common or very common** Dizziness, flatulence, headache, hypercholesterolaemia, weight gain
    - **Uncommon** Tuberculosis
    - **Frequency not known** Alopecia, bone-marrow suppression, hyperuricaemia, nausea, oral mucositis, progressive multifocal leucoencephalopathy, thromboembolism, tumour lysis syndrome, vomiting
    - **PREGNANCY** Avoid—toxicity in animal studies.

- **BREAST FEEDING** Avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT** Reduce dose (consult product literature).

- **RENAL IMPAIRMENT** Reduce dose in severe impairment (consult product literature).

- **MONITORING REQUIREMENTS**
  - Monitor full blood count (including differential white cell count) before treatment, then every 2–4 weeks until dose stabilised, then as clinically indicated.
  - Monitor for infection during treatment.
  - Monitor for symptoms of progressive multifocal leucoencephalopathy (presenting as new or worsening neurological, cognitive or psychiatric signs or symptoms)—withhold treatment if suspected.

- **NATIONAL FUNDING/ACCESS DECISIONS**

- **RUXOLITINIB FOR DISEASE-RELATED SPLENOEGALY OR SYMPTOMS IN ADULTS WITH MYELOFIBROSIS**

  - **INDICATIONS AND DOSE**
    - Treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis.
    - **BY MOUTH**
      - **Adult:** (consult product literature or local protocols)

  - **SIDE-EFFECTS**
    - **Common or very common** Dizziness, flatulence, headache, hypercholesterolaemia, weight gain
    - **Uncommon** Tuberculosis
    - **Frequency not known** Alopecia, bone-marrow suppression, hyperuricaemia, nausea, oral mucositis, progressive multifocal leucoencephalopathy, thromboembolism, tumour lysis syndrome, vomiting
    - **PREGNANCY** Avoid—toxicity in animal studies.

- **BREAST FEEDING** Avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT** Reduce dose (consult product literature).

- **RENAL IMPAIRMENT** Reduce dose in severe impairment (consult product literature).

- **MONITORING REQUIREMENTS**
  - Monitor full blood count (including differential white cell count) before treatment, then every 2–4 weeks until dose stabilised, then as clinically indicated.
  - Monitor for infection during treatment.
  - Monitor for symptoms of progressive multifocal leucoencephalopathy (presenting as new or worsening neurological, cognitive or psychiatric signs or symptoms)—withhold treatment if suspected.

- **NATIONAL FUNDING/ACCESS DECISIONS**

- **RUXOLITINIB FOR DISEASE-RELATED SPLENOEGALY OR SYMPTOMS IN ADULTS WITH MYELOFIBROSIS**

  - **INDICATIONS AND DOSE**
    - Treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis.
    - **BY MOUTH**
      - **Adult:** (consult product literature or local protocols)

  - **SIDE-EFFECTS**
    - **Common or very common** Dizziness, flatulence, headache, hypercholesterolaemia, weight gain
    - **Uncommon** Tuberculosis
    - **Frequency not known** Alopecia, bone-marrow suppression, hyperuricaemia, nausea, oral mucositis, progressive multifocal leucoencephalopathy, thromboembolism, tumour lysis syndrome, vomiting
    - **PREGNANCY** Avoid—toxicity in animal studies.

- **BREAST FEEDING** Avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT** Reduce dose (consult product literature).

- **RENAL IMPAIRMENT** Reduce dose in severe impairment (consult product literature).

- **MONITORING REQUIREMENTS**
  - Monitor full blood count (including differential white cell count) before treatment, then every 2–4 weeks until dose stabilised, then as clinically indicated.
  - Monitor for infection during treatment.
  - Monitor for symptoms of progressive multifocal leucoencephalopathy (presenting as new or worsening neurological, cognitive or psychiatric signs or symptoms)—withhold treatment if suspected.

- **NATIONAL FUNDING/ACCESS DECISIONS**

- **RUXOLITINIB FOR DISEASE-RELATED SPLENOEGALY OR SYMPTOMS IN ADULTS WITH MYELOFIBROSIS**

  - **INDICATIONS AND DOSE**
    - Treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis.
    - **BY MOUTH**
      - **Adult:** (consult product literature or local protocols)

  - **SIDE-EFFECTS**
    - **Common or very common** Dizziness, flatulence, headache, hypercholesterolaemia, weight gain
    - **Uncommon** Tuberculosis
    - **Frequency not known** Alopecia, bone-marrow suppression, hyperuricaemia, nausea, oral mucositis, progressive multifocal leucoencephalopathy, thromboembolism, tumour lysis syndrome, vomiting
    - **PREGNANCY** Avoid—toxicity in animal studies.

- **BREAST FEEDING** Avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT** Reduce dose (consult product literature).

- **RENAL IMPAIRMENT** Reduce dose in severe impairment (consult product literature).

- **MONITORING REQUIREMENTS**
  - Monitor full blood count (including differential white cell count) before treatment, then every 2–4 weeks until dose stabilised, then as clinically indicated.
  - Monitor for infection during treatment.
  - Monitor for symptoms of progressive multifocal leucoencephalopathy (presenting as new or worsening neurological, cognitive or psychiatric signs or symptoms)—withhold treatment if suspected.
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Sunitinib

**DRUG ACTION** Sunitinib is a tyrosine kinase inhibitor.

**INDICATIONS AND DOSE**

- **Treatment of unresectable or metastatic malignant gastro-intestinal stromal tumours, after failure of imatinib**
  - **By mouth**
    - Adult: 50 mg once daily for 4 weeks, followed by a 2-week treatment-free period to complete 6-week cycle, adjusted in steps of 12.5 mg, doses adjusted according to tolerability; usual dose 25–75 mg daily

- **Treatment of unresectable or metastatic pancreatic neuroendocrine tumours**
  - **By mouth**
    - Adult: 37.5 mg once daily without treatment-free period; adjusted in steps of 12.5 mg, doses adjusted according to tolerability; maximum 50 mg per day

**Important safety information**

**RISK OF OSTEONECROSIS OF THE JAW (JANUARY 2011)**

Treatment with sunitinib may be a risk factor for the development of osteonecrosis of the jaw. Patients treated with sunitinib, who have previously received bisphosphonates, or are treated concurrently with bisphosphonates, may be particularly at risk. Dental examination and appropriate preventive dentistry should be considered before treatment with sunitinib. If possible, invasive dental procedures should be avoided in patients treated with sunitinib who have previously received, or who are currently receiving, intravenous bisphosphonates.

**RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**, see p. 745

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**CONCLUSIONS**

- **Cautions** Cardiovascular disease—discontinue if congestive heart failure develops; hypertension; increased risk of bleeding; susceptibility to QT-interval prolongation
- **Interactions** → Appendix 1 (sunitinib).
- **Side-effects**
  - **Common or very common** Acne, anorexia, arthralgia, asthenia, congestive heart failure, constipation, depression, dermatitis, desquamation, diarrhoea, dry skin, dysgeusia, dyspepsia, dysphagia, dysphonia, electrolyte disturbances, erectile dysfunction, exanthema, fatigue, fever, flushing, gastro-oesophageal reflux disease, haemorrhage, hand-foot skin reaction, hoarseness, hyperkeratosis, hypertension, hypophosphataemia, hypophosphatemia, keratoacanthoma, malaise, muscle spasms, myalgia, myocardial infarction, myocardial ischaemia, peripheral neuropathy, proteinuria, pruritus, rash, renal failure, rhinorrhoea, thyroid dysfunction, tinnitus
  - **Uncommon** Altered INR, altered prothrombin time, cholangitis, cholecystitis, dehydration, eczema, erythema multiforme, gastritis, gastrointestinal perforations, gynaecomastia, hypertensive crisis, interstitial lung disease-like events, pancreatitis, posterior reversible encephalopathy syndrome
  - **Rare** Hepatitis, leucocytoclastic vasculitis, nephrotic syndrome, QT-interval prolongation, rhabdomyolysis, Stevens-Johnson syndrome, toxic epidermal necrolysis
  - **Frequency not known** Alopecia, bone-marrow suppression, hyperuricaemia, nausea, oral mucositis, thromboembolism, tumour lysis syndrome, vomiting
- **Pregnancy** Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.
- **Breast Feeding** Discontinue breast-feeding.
- **Hepatic Impairment** Manufacturer advises caution in severe impairment—no information available.
- **Monitoring Requirements**
  - Consider periodic monitoring of ECG and electrolytes in patients susceptible to QT-interval prolongation.
  - Monitor blood pressure regularly and consider permanent discontinuation of sorafenib if resistant to antihypertensive therapy.
  - Monitor plasma-calcium concentration (increased risk of hypocalcaemia if history of hypoparathyroidism).
  - Monitor thyroid stimulating hormone in patients with differentiated thyroid carcinoma.
- **National Funding/Access Decisions**
- **NICE technology appraisals (TAs)**
  - Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced or metastatic renal cell carcinoma (August 2009) NICE TA178
  - Bevacizumab, sorafenib, and temsirolimus are not recommended as first-line treatments for people with advanced or metastatic renal cell carcinoma.
  - Sorafenib and sunitinib are not recommended as second-line treatments for people with advanced or metastatic renal cell carcinoma. [www.nice.org.uk/TA178](http://www.nice.org.uk/TA178)
  - Sorafenib for the treatment of advanced hepatocellular carcinoma (May 2010) NICE TA189
  - Sorafenib is not recommended for the treatment of advanced hepatocellular carcinoma in patients for whom surgical or locoregional therapies have failed or are unsuitable. [www.nice.org.uk/TA189](http://www.nice.org.uk/TA189)
  - **Medicinal Forms**
    - There can be variation in the licensing of different medicines containing the same drug.
  - **Tablet**
    - **Cautionary and Advisory Labels** 23
    - Nexavar (Bayer Plc)
      - Sorafenib (as Sorafenib tosylate) 200 mg Nexavar 200mg tablets 112 tablet [PoE £2,980.47](http://www.nice.org.uk/TA178)
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also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

**BREAST FEEDING** Discontinue breast-feeding.

**MONITORING REQUIREMENTS** Monitor for thyroid dysfunction.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Sunitinib for advanced or metastatic renal cell carcinoma (March 2009) NICE TA169
- Sunitinib is recommended as first-line treatment for advanced or metastatic renal cell carcinoma in patients who are suitable for immunotherapy and have an Eastern Cooperative Oncology Group performance status of 0 or 1. [www.nice.org.uk/TA169](http://www.nice.org.uk/TA169)
- Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced or metastatic renal cell carcinoma (August 2009) NICE TA178
- Sunitinib and sorafenib are not recommended as second-line treatments for people with advanced or metastatic renal cell carcinoma. [www.nice.org.uk/TA178](http://www.nice.org.uk/TA178)
- Sunitinib for the treatment of gastrointestinal stromal tumours (September 2009) NICE TA179
- Sunitinib is recommended as an option for treatment in patients with unresectable or metastatic gastrointestinal stromal tumours if imatinib treatment has failed because of resistance or intolerance, and the cost of sunitinib for the first treatment cycle is met by the manufacturer. [www.nice.org.uk/TA179](http://www.nice.org.uk/TA179)

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium (SMC) has advised (October 2009 and April 2011) that sunitinib (Suitent®) is accepted for restricted use within NHS Scotland for the treatment of unresectable or metastatic malignant gastro-intestinal stromal tumours after failure of imatinib and for unresectable or metastatic pancreatic neuroendocrine tumours.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

CAUTIONARY AND ADVISORY LABELS 14

- Sutent (Pfizer Ltd)
  - Sunitinib (as Sunitinib malate) 12.5 mg 28 capsules £784.70
  - Sunitinib (as Sunitinib malate) 25 mg 28 capsules £1,569.40
  - Sunitinib (as Sunitinib malate) 50 mg 28 capsules £3,138.80

**Torisel**

- Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced or metastatic renal cell carcinoma (August 2009) NICE TA178
- Bevacizumab, sorafenib, and temsirolimus are not recommended as first-line treatments for people with advanced or metastatic renal cell carcinoma. [www.nice.org.uk/TA178](http://www.nice.org.uk/TA178)

**Malignant disease**

**Temsroliimus**

**INDICATIONS AND DOSE**

First-line treatment of advanced renal cell carcinoma | Treatment of relapsed or refractory mantle cell lymphoma

**BY INTRAVENOUS INFUSION**

- Adult: (consult product literature or local protocols)

**INTERACTIONS**

Appendix 1 (temsroliimus).

- The main active metabolite of temsroliimus is sirolimus—see also interactions of sirolimus and consult product literature.

**SIDE-EFFECTS**

- Common or very common Abdominal pain, acne, anorexia, anxiety, arthralgia, asthenia, bowel perforation, chest pain, cough, depression, diarrhoea, dizziness, drowsiness, dysphagia, dyspnoea, epistaxis, eye disorders, folliculitis, gastrointestinal haemorrhage, hypercholesterolaemia, hyperglycaemia, hyperlipidaemia

- Uncommon Intracerebral bleeding

- Frequency not known Alopecia, bone-marrow suppression, extravasation, hypertension, nausea, oral mucositis, thrombocytopenia, tumour lysis syndrome, vomiting

**Hypersensitivity reactions**

- Hypersensitivity reactions, including some life-threatening and rare fatal reactions, are associated with temsroliimus therapy, usually during administration of the first dose. Symptoms include flushing, chest pain, dyspnoea, anphylaxis, loss of consciousness, and anaphylaxis. Where possible, patients should receive an intravenous dose of antihistamine 30 minutes before starting the temsroliimus infusion. The infusion may have to be stopped temporarily for the treatment of infusion-related effects—consult product literature for appropriate management. If adverse reactions are not managed with dose delays, a dose reduction should be considered—consult product literature.

**CONCEPTION AND CONTRACEPTION**

Ensure effective contraception during treatment in men and women.

**PREGNANCY**

Manufacturer advises avoid (toxicity in animal studies). See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

**BREAST FEEDING**

Manufacturer advises discontinue breast-feeding.

**HEPATIC IMPAIRMENT**

- In renal cell carcinoma, reduce dose in severe impairment (consult product literature). Use with caution. In mantle cell lymphoma, avoid in moderate or severe impairment.

**RENAL IMPAIRMENT**

Manufacturer advises caution in severe impairment—no information available.

**MONITORING REQUIREMENTS**

- Monitor respiratory function.
- Monitor blood lipids.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced or metastatic renal cell carcinoma (August 2009) NICE TA178
- Bevacizumab, sorafenib, and temsirolimus are not recommended as first-line treatments for people with advanced or metastatic renal cell carcinoma. [www.nice.org.uk/TA178](http://www.nice.org.uk/TA178)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

EXCipients: May contain Ethanol, propylene glycol

- Torisel (Pfizer Ltd)
  - Temsirolimus 25 mg per 1 ml Torisel 30mg/1.2ml concentrate for solution for infusion vials and diluent | 1 vial £620.00 (Hospital only)

- Temsirolimus 25 mg per 1 ml Torisel 30mg/1.2ml concentrate for solution for infusion vials and diluent | 1 vial £620.00 (Hospital only)
Targeted therapy responsive malignancy

Vandetanib

- **DRUG ACTION** Vandetanib is a tyrosine kinase inhibitor.

- **INDICATIONS AND DOSE** Treatment of aggressive and symptomatic medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease

  **BY MOUTH**
  - **Adult:** 300 mg once daily, for dose adjustment due to side effects—consult product literature

**Important safety information**

- **RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**, see p. 745

- **CONTRA-INDICATIONS** Congenital long QT syndrome · QT interval greater than 480 milliseconds

- **CAUTIONS** Brain metastases (intracranial haemorrhage reported) · electrolyte disturbances · history of torsades de pointes · hypertension · phototoxicity reactions reported (wear protective clothing and/or sunscreen) · susceptibility to QT-prolongation

- **INTERACTIONS** → Appendix 1 (vandetanib). Caution with concomitant use of drugs that prolong QT interval.

- **SIDE-EFFECTS**
  - **Common or very common** Abdominal pain · alopecia · anxiety · asthenia · balance disorders · blurred vision · cholelithiasis · colitis · conjunctivitis · constipation · corneal changes (including opacity) · corneal deposits · decreased appetite · dehydration · depression · diarrhoea · dizziness · dry eye · dry mouth · dysaesthesia · dyspepsia · dysphagia · dysuria · electrolyte disturbances · epistaxis · gastritis · gastrointestinal haemorrhage · glaucoma · haematuria · haemoptysis · halo vision · hand-foot syndrome · headache · hyperglycaemia · hypotension · hypothyroidism · insomnia · ischaemic cerebrovascular conditions · keratopathy · lethargy · loss of consciousness · micturition urgency · nephrolithiasis · oedema · pain · paraesthesia · photosensitivity · phototoxicity reactions · pneumonitis · poliomyelitis · proteinuria · pyrexia · QT-interval prolongation · taste disturbance · tremor
  - **Uncommon** Accommodation disorders · anuria · aspiration pneumonia · brain oedema · bullous dermatitis · cardiac arrest · cardiac conduction disorders · cardiac rate disorders · cardiac rhythm disorders · cataract · chromaturia · clonus · convulsions · erythema multiforme · faecal incontinence · heart failure · ileus · impaired healing · increased haemoglobin · interstitial lung disease (sometimes fatal) · intestinal perforation · pancreatitis · peritonitis · posterior reversible encephalopathy syndrome · respiratory failure · Stevens-Johnson syndrome · venous arthralgia
  - **Frequency not known** Alopecia · bone-marrow suppression · hyperuricaemia · nausea · oral mucositis · thromboembolism · tumour lysis syndrome · vomiting

- **CONCEPTION AND CONTRACEPTION** Effective contraception required during and for at least 4 months after treatment.

- **PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk. See also Pregnancy and reproductive function in Cytoxic drugs, p. 746.

- **BREAST FEEDING** Avoid—no information available.

- **HEPATIC IMPAIRMENT** Manufacturer advises avoid in severe impairment (serum bilirubin greater than 1.5 times the upper limit of normal).

- **RENAL IMPAIRMENT** Reduce dose to 200 mg if creatinine clearance 30–49 mL/minute. Avoid if creatinine clearance less than 30 mL/minute.

- **MONITORING REQUIREMENTS** Monitor ECG, serum potassium, calcium, magnesium and thyroid stimulating hormone before treatment, then 1, 3, 6 and 12 weeks after starting treatment and following dose adjustment or interruption, then every 3 months for at least 1 year.

- **DIRECTIONS FOR ADMINISTRATION** Tablets may be dispersed in half a glass of water by stirring until dispersed (approximately 10 minutes), immediately before drinking (do not crush). After solution has been swallowed, any residue must be re-dispersed in the same volume of water and swallowed. The solution can also be administered via nasogastric or gastrostomy tubes.

- **PATIENT AND CARER ADVICE** Alert card should be provided. Patients or carers should be given advice on how to administer vandetanib tablets.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**
  - Caprelsa (AstraZeneca UK Ltd) ▼
  - Vandetanib 100 mg Caprelsa 100mg tablets | 30 tablet | £2,500.00
  - Vandetanib 300 mg Caprelsa 300mg tablets | 30 tablet | £5,000.00

Vemurafenib

- **DRUG ACTION** Vemurafenib is a BRAF kinase inhibitor.

- **INDICATIONS AND DOSE** Monotherapy for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma

  **BY MOUTH**
  - **Adult:** 960 mg twice daily, for dose adjustment due to side effects—consult product literature

**Important safety information**

- **DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS SYNDROME)**

  DRESS syndrome has been reported in patients taking vemurafenib. DRESS syndrome starts with rash, fever, swollen glands, and increased white cell count, and it can affect the liver, kidneys and lungs; DRESS can also be fatal. Patients should be advised to stop taking vemurafenib and consult their doctor immediately if skin rash develops. Treatment with vemurafenib should not be restarted.

  **RISKS OF INCORRECT DOSING OF ORAL ANTI-CANCER MEDICINES**, see p. 745

- **CONTRA-INDICATIONS** Wild-type BRAF malignant melanoma

- **CAUTIONS** Electrolyte disturbances · prior or concurrent cancer associated with RAS mutation—increased risk of tumour progression · susceptibility to QT-prolongation

- **INTERACTIONS** → Appendix 1 (vemurafenib). Caution with concomitant use of drugs that prolong QT interval.

- **SIDE-EFFECTS**
  - **Common or very common** Actinic keratosis · alopecia · arthralgia · arthritis · asthenia · basal cell carcinoma · Bell’s palsy · constipation · cough · cutaneous squamous cell carcinoma · decreased appetite · diarrhoea · dizziness · dry skin · erythema · erythema nodosum · fatigue · folliculitis · hand-foot syndrome · headache · hyperkeratosis · keratosis pilaris · musculoskeletal pain · myalgia · new primary melanoma · pain in extremities ·
820 Malignant disease

peripheral oedema • photosensitivity reactions • pyrexia • QT-interval prolongation • seborrhoeic keratosis • skin papilloma • taste disturbance • uveitis

Uncommon Non-cutaneous squamous cell carcinoma • peripheral neuropathy • retinal vein occlusion • Stevens-Johnson syndrome • toxic epidermal necrolysis • vasculitis

Rare Progression of pre-existing NRAS mutated chronic myelomonocytic leukaemia

Frequency not known Alopecia • bone–marrow suppression • hypersensitivity reactions • hyperuricaemia • nausea • oral mucositis • thromboembolism • tumour lysis syndrome • vomiting

CONCEPTION AND CONTRACEPTION Effective contraception required during for at least 6 months after treatment.

PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

BREAST FEEDING Avoid—no information available.

HEPATIC IMPAIRMENT Manufacturer advises more frequent monitoring in moderate to severe hepatic impairment (including monthly ECG monitoring during first 3 months of treatment).

RENAI IMPAIRMENT Manufacturer advises caution in severe impairment.

MONITORING REQUIREMENTS

Monitor ECG and electrolytes before treatment, after one week before elective surgery and for at least 4 weeks after major surgery, or until wound fully healed - neutropenic infection - risk of fistula formation (discontinue if fistula develops) - risk of neutropenia - risk of thrombocytopenia

SIDE-EFFECTS

Common or very common Abdominal pain • anaphylaxis • apathy • decreased appetite • dehydration • diarrhoea • dysphonia • dyspnoea • fistula • haemorrhage (including nasal, rectal and gastro-intestinal) • haemorrhoids • hand-foot syndrome • headache • hypertension • infection - leucopenia • malaise • nasopharyngitis • neutropenia (including febrile neutropenia) • oropharyngeal pain • proctalgia • proteinuria • rhinorrhoea • sepsis • skin hyperpigmentation • stomatitis • thrombocytopenia • thromboembolic events (arterial and venous) • toothache • urinary tract infection • weight loss

Uncommon Gastro-intestinal perforation • impaired wound healing • nephrotic syndrome • posterior reversible encephalopathy syndrome • thrombotic microangiopathy

CONCEPTION AND CONTRACEPTION Exclude pregnancy before treatment. Effective contraception required during and for at least 6 months after treatment in men and women. Contraceptive advice should be given to men and women before therapy begins (and should cover the duration of contraception required after therapy has ended).

PREGNANCY Manufacturer advises avoid—toxicity in animal studies. See also Pregnancy and reproductive function in Cytotoxic drugs, p. 746.

BREAST FEEDING Manufacturer advises avoid—no information available.

HEPATIC IMPAIRMENT Caution in severe impairment—no information available.

RENAI IMPAIRMENT Caution in severe impairment—no information available.

MONITORING REQUIREMENTS

Monitor blood pressure at initiation and at least fortnightly during treatment (do not initiate treatment if pre-existing hypertension is uncontrolled)—consult

VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS

Afiblercept

DRUG ACTION Afiblercept is a recombinant fusion protein that acts as a soluble decoy receptor and binds to vascular endothelial growth factors A and B (VEGF-A, VEGF-B) and placental growth factor (PIGF). Afiblercept inhibits the activation of VEGF receptors and the proliferation of endothelial cells, thereby inhibiting the growth of new vessels that supply tumours with oxygen and nutrients.

INDICATIONS AND DOSE

In combination with irinotecan, fluorouracil and folinic acid (FOLFIRI) chemotherapy, in metastatic colorectal cancer that is resistant to, or has progressed after, an oxaliplatin-containing regimen

BY INTRAVENOUS INFUSION

Adult: (consult local protocol)

CONTRA-INDICATIONS Moderate or severe congestive heart failure • uncontrolled hypertension

CAUTIONS Febrile neutropenia • history of cardiovascular disease (may be exacerbated by hypertension) • increased risk of haemorrhage (including fatal events) • increased risk of hypertension • increased risk of thromboembolic events (consult product literature if event occurs) • may impair wound healing— withhold treatment for at least 4 weeks before elective surgery and for at least 4 weeks after major surgery, or until wound fully healed - neutropenic infection - risk of fistula formation (discontinue if fistula develops) - risk of neutropenia - risk of thrombocytopenia

DIRECTIONS FOR ADMINISTRATION Food may affect absorption (take at the same time with respect to food).

PATIENT AND CARER ADVICE Counselling advised (administration).

NICE technology appraisals (TAs)

Vemurafenib 240 mg

Tablet

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>25</th>
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<tbody>
<tr>
<td>− Zelboraf (Roche Products Ltd)</td>
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<tr>
<td>Vemurafenib 240 mg</td>
<td>Zelboraf 240mg tablets</td>
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</table>

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (November 2013) that vemurafenib (Zelboraf®) is accepted for restricted use within NHS Scotland as monotherapy for the first-line treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.
product literature if hypertension develops during treatment.

- Monitor for signs of gastro-intestinal perforation (discontinue if perforation develops).
- Monitor full blood count, including differential count and platelets at baseline and before each treatment cycle.
- Monitor for proteinuria before each treatment administration (consult product literature if symptoms develop).
- Monitor for signs and symptoms of diarrhoea and dehydration, particularly in elderly—consult product literature if severe diarrhoea occurs.
- Monitor for posterior reversible encephalopathy syndrome (presenting as seizures, altered mental status, nausea, vomiting, headache, or visual disturbance).

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy (March 2014) NICE TA307
  Aflibercept in combination with irinotecan and fluorouracil-based therapy is **not** recommended within its marketing authorisation for treating metastatic colorectal cancer that is resistant to or has progressed after an oxaliplatin-containing regimen. www.nice.org.uk/TA307

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- Zaltrap (Sanofi)
  - Aflibercept 25 mg per 1 ml Zaltrap 200mg/8ml concentrate for solution for infusion vials | 1 vial £391.30 (Hospital only)
  - Zaltrap 100mg/4ml concentrate for solution for infusion vials | 1 vial £295.65 (Hospital only)
Blood and blood-forming organs

1.1 Anaemias

Before initiating treatment for anaemia it is essential to determine which type is present. Iron salts may be harmful and result in iron overload if given alone to patients with anaemias other than those due to iron deficiency.

Sickle-cell disease

Sickle-cell disease is caused by a structural abnormality of haemoglobin resulting in deformed, less flexible red blood cells. Acute complications in the more severe forms include sickle-cell crisis, where infarction of the microvasculature and blood supply to organs results in severe pain. Sickle-cell crisis requires hospitalisation, intravenous fluids, analgesia and treatment of any concurrent infection. Chronic complications include skin ulceration, renal failure, and increased susceptibility to infection. Pneumococcal vaccine, haemophilus influenzae type b vaccine, an annual influenza vaccine and prophylactic penicillin reduce the risk of infection. Hepatitis B vaccine should be considered if the patient is not immune.

In most forms of sickle-cell disease, varying degrees of haemolytic anaemia are present accompanied by increased erythropoiesis; this may increase folate requirements and folate supplementation may be necessary.

Hydroxycarbamide p. 777 can reduce the frequency of crises and the need for blood transfusions in sickle-cell disease. The beneficial effects of hydroxycarbamide may not become evident for several months.

1.2 Anaemias, G6PD deficiency

Glucose 6-phosphate dehydrogenase (G6PD) deficiency is highly prevalent in individuals originating from most parts of Africa, from most parts of Asia, from Oceania, and from Southern Europe; it can also occur, rarely, in any other individuals. G6PD deficiency is more common in males than it is in females.

Individuals with G6PD deficiency are susceptible to developing acute haemolytic anaemia when they take a number of common drugs. They are also susceptible to developing acute haemolytic anaemia when they eat fava beans (broad beans, Vicia faba); this is termed favism and can be more severe in children or when the fresh fava beans are eaten raw.

When prescribing drugs for patients with G6PD deficiency, the following three points should be kept in mind:

- G6PD deficiency is genetically heterogeneous;
- susceptibility to the haemolytic risk from drugs varies;
Anaemias, hypoplastic, haemolytic, and renal

1.3 Anaemias, hypoplastic, haemolytic, and renal

Anaemias, hypoplastic, haemolytic, and renal

- Anabolic steroids, pyridoxine hydrochloride p. 882, antilymphocyte immunoglobulin, and various corticosteroids are used in hypoplastic and haemolytic anaemias.

Antilymphocyte immunoglobulin given intravenously through a central line over 12–18 hours each day for 5 days produces a response in about 50% of cases of acquired aplastic anaemia; the response rate may be increased when ciclosporin p. 717 is given as well. Severe reactions are common in the first 2 days and profound immunosuppression can occur; antilymphocyte immunoglobulin should be given under specialist supervision with appropriate resuscitation facilities. Alternatively, oxymetholone tablets (available from ‘special order’ manufacturers or specialist importing companies) can be used in aplastic anaemia for 3 to 6 months.

It is unlikely that dietary deprivation of pyridoxine hydrochloride produces clinically relevant haematological effects. However, certain forms of sideroblastic anaemia respond to pharmacological doses, possibly reflecting its role as a co-enzyme during haemoglobin synthesis. Pyridoxine hydrochloride is indicated in both idiopathic acquired and hereditary sideroblastic anaemias. Although complete cures have not been reported, some increase in haemoglobin can occur; the dose required is usually high. Reversible sideroblastic anaemias respond to treatment of the underlying cause but in pregnancy, haemolytic anaemias, and alcohol dependence, or during isoniazid treatment, pyridoxine hydrochloride is also indicated.

Corticosteroids have an important place in the management of haematological disorders. They include conditions with an autoimmune haemolytic anaemia, immune thrombocytopenias, and neutropenias, and major transfusion reactions. They are also used in chemotherapy schedules for many types of lymphoma, lymphoid leukemias, and paraproteinaemias, including multiple myeloma.

Erythropoietins

Epoetins (recombinant human erythropoietins) are used to treat the anaemia associated with erythropoietin deficiency in chronic renal failure, to increase the yield of autologous blood in normal individuals and to shorten the period of symptomatic anaemia in patients receiving cytotoxic chemotherapy.

Epoetin beta p. 828 is also used for the prevention of anaemia in preterm neonates of low birth-weight; only unpreserved formulations should be used in neonates because other preparations may contain benzyl alcohol. Darbepoetin alfa p. 825 is a hyperglycosylated derivative of epoetin; it has a longer half-life and can be administered less frequently than epoetin.

Methoxy polyethylene glycol-epoetin beta p. 824 is a continuous erythropoietin receptor activator that is licensed for the treatment of symptomatic anaemia associated with chronic kidney disease. It has a longer duration of action than epoetin.

ANDROSTAN DERIVATIVES

Oxymetholone

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<th>INDICATIONS AND DOSE</th>
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<tr>
<td>Aplastic anaemia</td>
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<td>BY MOUTH</td>
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<tr>
<td>Adult: 1–5 mg/kg daily for 3 to 6 months</td>
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- Oxymetholone (Non-proprietary)
  - Oxymetholone 50 mg (Oxymetholone 50mg capsules | 50 capsule [\text{E395.00 Schedule 4 (CD Anab)}]}

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Capsule

- **OXYMETHOLONE (Non-proprietary)**
CONTINUOUS ERYTHROPOIETIN RECEPTOR ACTIVATORS

**Methoxy polyethylene glycol-epoetin beta**

**INDICATIONS AND DOSE**

Symptomatic anaemia associated with chronic kidney disease in patients on dialysis and not currently treated with erythropoietins

**BY SUBCUTANEOUS INJECTION OR BY INTRAVENOUS INJECTION**

- **Adult:** Initially 600 nanograms/kg every 2 weeks, dose to be adjusted according to response at intervals of at least 4 weeks, maintenance dose of double the previous fortnightly dose may be given every 4 weeks, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks; or if haemoglobin concentration approaches or exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose.

Symptomatic anaemia associated with chronic kidney disease in patients not on dialysis and not currently treated with erythropoietins

**INITIALLY BY SUBCUTANEOUS INJECTION**

- **Adult:** Initially 1.2 micrograms/kg every 4 weeks, alternatively (by subcutaneous injection or by intravenous injection) initially 600 nanograms/kg every 2 weeks, dose to be adjusted according to response at intervals of at least 4 weeks, patients treated once every 2 weeks may be given maintenance dose of double the previous fortnightly dose every 4 weeks, subcutaneous route preferred in patients not on haemodialysis. Reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks; or if haemoglobin concentration approaches or exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose.

Symptomatic anaemia associated with chronic kidney disease in patients currently treated with erythropoietins

**BY SUBCUTANEOUS INJECTION OR BY INTRAVENOUS INJECTION**

- **Adult:** (consult product literature)

- **SIDE-EFFECTS** Hot flushes

- **PREGNANCY** No evidence of harm in animal studies—manufacturer advises caution.

- **BREAST FEEDING** Manufacturer advises use only if potential benefit outweighs risk—present in milk in animal studies.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Miracea** (Roche Products Ltd)
  - Methoxy polyethylene glycol-epoetin beta 100 microgram per 1 ml Miracea 30micrograms/0.3ml solution for injection pre-filled syringes | 1 pre-filled disposable injection | £44.05
  - Methoxy polyethylene glycol-epoetin beta 166.67 microgram per 1 ml Miracea 50micrograms/0.3ml solution for injection pre-filled syringes | 1 pre-filled disposable injection | £73.41
  - Methoxy polyethylene glycol-epoetin beta 250 microgram per 1 ml Miracea 75micrograms/0.3ml solution for injection pre-filled syringes | 1 pre-filled disposable injection | £110.11

**EPOETINS**

**Important safety information**

MHRA/CHM ADVICE (DECEMBER 2007) ERYTHROPOIETINS—HAEMOGLOBIN CONCENTRATION

Overcorrection of haemoglobin concentration in patients with chronic kidney disease may increase the risk of death and serious cardiovascular events, and in patients with cancer may increase the risk of thrombosis and related complications:

- patients should not be treated with erythropoietins for the licensed indications in chronic kidney disease or cancer in patients receiving chemotherapy unless symptoms of anaemia are present
- the haemoglobin concentration should be maintained within the range 10–12 g/100 mL
- haemoglobin concentrations higher than 12 g/100 mL should be avoided
- the aim of treatment is to relieve symptoms of anaemia, and in patients with chronic kidney disease to avoid the need for blood transfusion; the haemoglobin concentration should not be increased beyond that which provides adequate control of symptoms of anaemia (in some patients, this may be achieved at concentrations lower than the recommended range)

MHRA/CHM ADVICE (DECEMBER 2007 AND JULY 2008) ERYTHROPOIETINS—TUMOUR PROGRESSION AND SURVIVAL IN PATIENTS WITH CANCER

Clinical trial data show an unexplained excess mortality and increased risk of tumour progression in patients with anaemia associated with cancer who have been treated with erythropoietins. Many of these trials used erythropoietins outside of the licensed indications (i.e. overcorrected haemoglobin concentration or given to patients who have not received chemotherapy):

- erythropoietins licensed for the treatment of symptomatic anaemia associated with cancer, are licensed only for patients who are receiving chemotherapy
- the decision to use erythropoietins should be based on an assessment of the benefits and risks for individual patients; blood transfusion may be the preferred treatment for anaemia associated with cancer chemotherapy, particularly in those with a good cancer prognosis

**CONTRA-INDICATIONS** Patients unable to receive thromboprophylaxis - pure red cell aplasia following erythropoietin therapy - uncontrolled hypertension
Other factors, such as iron or folate deficiency, that contribute to the anaemia of chronic renal failure, such as iron or folate deficiency, before treatment. During dialysis (increase in unfractuated or low molecular weight heparin dose may be needed) - epilepsy - inadequately treated or poorly controlled blood pressure - interrupt treatment if blood pressure uncontrolled - ischaemic vascular disease - malignant disease - other inflammatory disease (can impair the response to erythropoietin) - risk of thrombosis may be increased when used for anaemia before orthopaedic surgery - avoid in cardiovascular disease including recent myocardial infarction or cerebrovascular accident - risk of thrombosis may be increased when used for anaemia in adults receiving cancer chemotherapy - sickle cell disease (lower target haemoglobin concentration may be appropriate) - sudden stabbing migraine-like pain (warning of a hypertensive crisis) - thrombocytosis (monitor platelet count for first 8 weeks)

**SIDE-EFFECTS**

- **Common or very common** Aggravation of hypertension (dose-dependent) - cardiovascular events - diarrhoea - dose-dependent increase in platelet count regressing during treatment (but thrombocytosis rarely) - headache - hypertensive crisis (in isolated patients with normal or low blood pressure) - increase in blood pressure (dose-dependent) - influenza-like symptoms (may be reduced if intravenous injection given over 5 minutes) - nausea - shunt thrombosis especially if tendency to hypotension or arteriovenous shunt complications - vomiting

- **Very rare** Sudden loss of efficacy because of pure red cell aplasia, particularly following subcutaneous administration in patients with chronic renal failure

- **Frequency not known** Anaphylaxis - angioedema - hyperkalaemia - hypersensitivity reactions - injection-site reactions - peripheral oedema - skin reactions

**SIDE-EFFECTS, FURTHER INFORMATION**

**Hypertensive crisis** In isolated patients with normal or low blood pressure, hypertensive crisis with encephalopathy-like symptoms and generalised tonic-clonic seizures requiring immediate medical attention has occurred with epoetin. Pure red cell aplasia There have been very rare reports of pure red cell aplasia in patients treated with erythropoietins. In patients who develop a lack of efficacy with erythropoietin therapy and with a diagnosis of pure red cell aplasia, treatment with erythropoietins must be discontinued and testing for erythropoietin antibodies considered. Patients who develop pure red cell aplasia should not be switched to another form of erythropoietin.

**MONITORING REQUIREMENTS**

- Monitor closely blood pressure, reticulocyte counts, haemoglobin, and electrolytes—interrupt treatment if blood pressure uncontrolled.
- Other factors, such as iron or folate deficiency, that contribute to the anaemia of chronic renal failure should be corrected before treatment and monitored during therapy. Supplemental iron may improve the response in resistant patients.

**Darbepoetin alfa**

**INDICATIONS AND DOSE**

Symptomatic anaemia associated with chronic renal failure in patients on dialysis

**BY SUBCUTANEOUS INJECTION OR BY INTRAVENOUS INJECTION**

- **Adult:** Initially 450 nanograms/kg once weekly, dose to be adjusted according to response by approximately 25% at intervals of at least 4 weeks, maintenance dose to be given once weekly or once every 2 weeks, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose, when changing route give same dose then adjust according to weekly or fortnightly haemoglobin measurements, adjust doses not more frequently than every 2 weeks during maintenance treatment

Symptomatic anaemia associated with chronic renal failure in patients not on dialysis

**BY SUBCUTANEOUS INJECTION**

- **Adult:** Initially 450 nanograms/kg once weekly, alternatively initially 750 nanograms/kg every 2 weeks, dose to be adjusted according to response by approximately 25% at intervals of at least 4 weeks, maintenance dose can be given once weekly, every 2 weeks, or once a month, subcutaneous route preferred in patients not on haemodialysis, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose, when changing route give same dose then adjust according to weekly or fortnightly haemoglobin measurements, adjust doses not more frequently than every 2 weeks during maintenance treatment

**BY INTRAVENOUS INJECTION**

- **Adult:** Initially 450 nanograms/kg once weekly, dose to be adjusted according to response by approximately 25% at intervals of at least 4 weeks, maintenance dose given once weekly, subcutaneous route preferred in patients not on haemodialysis, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose, when changing route give same dose then adjust according to weekly or fortnightly haemoglobin measurements, adjust doses not more frequently than every 2 weeks during maintenance treatment

Symptomatic anaemia in adults with non-myeloid malignancies receiving chemotherapy

**BY SUBCUTANEOUS INJECTION**

- **Adult:** Initially 6.75 micrograms/kg every 3 weeks, alternatively initially 2.25 micrograms/kg once weekly, if response inadequate after 9 weeks further treatment may not be effective; if adequate response obtained then reduce dose by 25–50%, reduce dose by approximately 25–50% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and restart at a dose approximately 25% lower than the previous dose. Discontinue approximately 4 weeks after ending chemotherapy

**SIDE-EFFECTS**

- Injection-site pain - oedema

**PREGNANCY** No evidence of harm in animal studies—manufacturer advises caution.
**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Epoetin alfa**
  - Darbepoetin alfa 25 microgram per 1 ml Aranesp
    - Darbepoetin alfa 40 microgram per 1 ml Aranesp
      - Darbepoetin alfa 100 microgram per 1 ml Aranesp
        - Darbepoetin alfa 200 microgram per 1 ml Aranesp
          - Darbepoetin alfa 500 microgram per 1 ml Aranesp
            - Darbepoetin alfa 1000 microgram per 1 ml Aranesp
              - Darbepoetin alfa 2500 microgram per 1 ml Aranesp

**Epoetin alfa**

**INDICATIONS AND DOSE**

EPREX® PRE-FILLED SYRINGES

Symptomatic anaemia associated with chronic renal failure in patients on haemodialysis

- **Adult:** Initially 50 units/kg twice weekly; maintenance 25–50 units/kg twice weekly, intravenous route preferred, intravenous injection to be given over 1–5 minutes, subcutaneous injection, maximum 1 ml per injection site, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose.

Symptomatic anaemia associated with chronic renal failure in adults on peritoneal dialysis

- **Adult:** Initially 50 units/kg twice weekly; maintenance 25–50 units/kg twice weekly, intravenous route preferred, intravenous injection to be given over 1–5 minutes, subcutaneous injection, maximum 1 ml per injection site, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose.

Severe symptomatic anaemia of renal origin in adults with renal insufficiency not yet on dialysis

- **Adult:** Initially 50 units/kg 3 times a week, increased in steps of 25 units/kg 3 times a week, increased according to response, dose to be increased at intervals of at least 4 weeks; maintenance 17–33 units/kg 3 times a week (max. per dose 200 units/kg 3 times a week), intravenous route preferred, intravenous injection to be given over 1–5 minutes, subcutaneous injection, maximum 1 ml per injection site, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose.

**Symptomatic anaemia in adults receiving cancer chemotherapy**

- **Adult:** Initially 150 units/kg 3 times a week, alternatively initially 450 units/kg once weekly, increased to 300 units/kg 3 times a week, increased if appropriate rise in haemoglobin (or reticulocyte count) not achieved after 4 weeks; discontinue if inadequate response after 4 weeks at higher dose, subcutaneous injection maximum 1 ml per injection site, reduce dose by approximately 25–50% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose.

**NICE technology appraisals (TAs)**

- Erythropoiesis-stimulating agents (epoetin and darbepoetin) are recommended, within their marketing authorisations, as options for treating anaemia in people with cancer who are having chemotherapy.

- Different erythropoiesis-stimulating agents are equally suitable, the product with the lowest acquisition cost for the course of treatment should be used. www.nice.org.uk/TA323

- Manufacturer advises caution.

- There can be variation in the licensing of different medicines.
to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose. Discontinue approximately 4 weeks after ending chemotherapy.

To increase yield of autologous blood (to avoid homologous blood) in predonation programme in moderate anaemia either when large volume of blood required or when sufficient blood cannot be saved for elective major surgery

BY INTRAVENOUS INJECTION

- Adult: 600 units/kg twice weekly for 3 weeks before surgery, consult product literature for details and advice on ensuring high iron stores, intravenous injection to be given over 1–5 minutes

Moderate anaemia (haemoglobin concentration 10–13 g/100 mL) before elective orthopaedic surgery in adults with expected moderate blood loss to reduce exposure to allogeneic blood transfusion or if autologous transfusion unavailable

BY SUBCUTANEOUS INJECTION

- Adult: 600 units/kg once weekly for 3 weeks before surgery and on day of surgery, alternatively 300 units/kg daily for 15 days starting 10 days before surgery, consult product literature for details, subcutaneous injection maximum 1 mL per injection site

BINOCRIT® PRE-FILLED SYRINGES

Symptomatic anaemia associated with chronic renal failure in patients on haemodialysis

BY INTRAVENOUS INJECTION

- Adult: Initially 50 units/kg 3 times a week, adjusted in steps of 25 units/kg 3 times a week, dose adjusted according to response at intervals of at least 4 weeks; maintenance 25–100 units/kg 3 times a week, intravenous injection to be given over 1–5 minutes, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose

Symptomatic anaemia associated with chronic renal failure in adults on peritoneal dialysis

BY INTRAVENOUS INJECTION

- Adult: Initially 50 units/kg twice weekly; maintenance 25–50 units/kg twice weekly, intravenous injection to be given over 1–5 minutes, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose

Severe symptomatic anaemia of renal origin in adults with renal insufficiency not yet on dialysis

BY INTRAVENOUS INJECTION

- Adult: Initially 50 units/kg 3 times a week, increased in steps of 25 units/kg 3 times a week, adjusted according to response, dose to be increased at intervals of at least 4 weeks; maintenance 17–33 units/kg 3 times a week (max. per dose 200 units/kg 3 times a week), intravenous injection to be given over 1–5 minutes, reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose

Symptomatic anaemia in adults receiving cancer chemotherapy

BY SUBCUTANEOUS INJECTION

- Adult: Initially 150 units/kg 3 times a week, alternatively initially 450 units/kg once weekly, increased to 300 units/kg 3 times a week, increased if appropriate rise in haemoglobin (or reticulocyte count) not achieved after 4 weeks; discontinue if inadequate response after 4 weeks at higher dose, subcutaneous injection maximum 1 mL per injection site, reduce dose by approximately 25–50% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose. Discontinue approximately 4 weeks after ending chemotherapy

To increase yield of autologous blood (to avoid homologous blood) in predonation programme in moderate anaemia either when large volume of blood required or when sufficient blood cannot be saved for elective major surgery

BY INTRAVENOUS INJECTION

- Adult: 600 units/kg twice weekly for 3 weeks before surgery, consult product literature for details and advice on ensuring high iron stores, intravenous injection to be given over 1–5 minutes

Moderate anaemia (haemoglobin concentration 10–13 g/100 mL) before elective orthopaedic surgery in adults with expected moderate blood loss to reduce exposure to allogeneic blood transfusion or if autologous transfusion unavailable

BY SUBCUTANEOUS INJECTION

- Adult: 600 units/kg once weekly for 3 weeks before surgery and on day of surgery, alternatively 300 units/kg daily for 15 days starting 10 days before surgery, consult product literature for details, subcutaneous injection maximum 1 mL per injection site

- Pregnancy
  No evidence of harm. Benefits probably outweigh risk of anaemia and of blood transfusion in pregnancy.

- Breast Feeding
  Unlikely to be present in milk. Minimal effect on infant.

- Hepatic Impairment
  Manufacturers advise caution in chronic hepatic failure.

- Prescribing and Dispensing Information
  Products containing epoetin alfa are not identical and although there should be no important differences in terms of safety and efficacy, when prescribing biological products it is good practice to use the brand name.

- National Funding/Access Decisions

Nice Technology Appraisals (TAs)

- Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer having chemotherapy (November 2014) Nice Ta323
  Erythropoiesis-stimulating agents (epoetin alfa, beta, theta and zeta, and darbepoetin alfa) are recommended, within their marketing authorisations, as options for treating anaemia in people with cancer who are having chemotherapy.
  If different erythropoiesis-stimulating agents are equally suitable, the product with the lowest acquisition cost for the course of treatment should be used. www.nice.org.uk/ Ta323

Blood and nutrition
Blood and blood-forming organs

Epoetin beta

INDICATIONS AND DOSE
Symptomatic anaemia associated with chronic renal failure

BY SUBCUTANEOUS INJECTION
- Adult: Initially 20 units/kg 3 times a week for 4 weeks, increased in steps of 20 units/kg 3 times a week, dose adjusted according to response at intervals of 4 weeks, total weekly dose may be divided into daily doses; maintenance, initially reduce dose by half, subsequent dose adjusted according to response at intervals of 1–2 weeks, total weekly maintenance dose may be given as a single dose or in 3 or 7 divided doses, subcutaneous route preferred in patients not on haemodialysis. Reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration approaches or exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose; maximum 720 units/kg per week.

BY INTRAVENOUS INJECTION
- Adult: Initially 40 units/kg 3 times a week for 4 weeks, then increased to 80 units/kg 3 times a week, then increased in steps of 20 units/kg 3 times a week if required, dose to be increased at intervals of 4 weeks; maintenance, initially reduce dose by half, subsequent dose adjusted according to response at intervals of 1–2 weeks, intravenous injection to be administered over 2 minutes, subcutaneous route preferred in patients not on haemodialysis. Reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration approaches or exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose; maximum 720 units/kg per week.

Syndromic anaemia in adults with non-myeloid malignancies receiving chemotherapy

BY SUBCUTANEOUS INJECTION
- Adult: Initially 450 units/kg once weekly for 4 weeks, dose to be given weekly as a single dose or in 3–7 divided doses, increase dose after 4 weeks (if a rise in haemoglobin of at least 1 g/100 mL not achieved), increased to 900 units/kg once weekly, dose to be given weekly as a single dose or in 3–7 divided doses, if adequate response obtained reduce dose by 25–50%, discontinue treatment if haemoglobin concentration does not increase by at least 1 g/100 mL after 8 weeks of therapy (response unlikely). Reduce dose by approximately 25–50% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose. Discontinue approximately 4 weeks after ending chemotherapy; maximum 60 000 units per week.

To increase yield of autologous blood (to avoid homologous blood) in predonation programme in moderate anaemia when blood-conserving procedures are insufficient or unavailable

BY INTRAVENOUS INJECTION OR BY SUBCUTANEOUS INJECTION
- Adult: (consult product literature)

PREGNANCY
No evidence of harm. Benefits probably outweigh risk of anaemia and of blood transfusion in pregnancy.

BREAST FEEDING
Unlikely to be present in milk. Minimal effect on infant.

HEPATIC IMPAIRMENT
Manufacturers advise caution in chronic hepatic failure.

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)
- Erythropoiesis-stimulating agents (epoetin and darboepoetin) for treating anaemia in people with cancer having chemotherapy (November 2014) NICE TA233 Erythropoiesis-stimulating agents (epoetin alfa, beta, theta and zeta, and darboepoetin alfa) are recommended, within their marketing authorisations, as options for treating anaemia in people with cancer who are having chemotherapy. If different erythropoiesis-stimulating agents are equally suitable, the product with the lowest acquisition cost for the course of treatment should be used. www.nice.org.uk/TA233

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
Solution for injection

EXCIPIENTS: May contain Phenylalanine

▶ Epoetin beta 1667 unit per 1 ml NeoRecormon 500units/0.3ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (Roche Products Ltd) £21.05
▶ Epoetin beta 6667 unit per 1 ml NeoRecormon 2,000units/0.3ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (Roche Products Ltd) £84.17
▶ Epoetin beta 10000 unit per 1 ml NeoRecormon 3,000units/0.3ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (Roche Products Ltd) £126.25
▶ Epoetin beta 13333 unit per 1 ml NeoRecormon 4,000units/0.3ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (Roche Products Ltd) £168.34
▶ Epoetin beta 6667 unit per 1 ml NeoRecormon 10,000units/0.6ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (Roche Products Ltd) £210.42
▶ NeoRecormon 5,000units/0.3ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (Roche Products Ltd) £420.85
▶ NeoRecormon 6,000units/0.3ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (Roche Products Ltd) £452.50
▶ Epoetin beta 20000 unit per 1 ml NeoRecormon 20,000units/0.6ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (Roche Products Ltd) £841.71
▶ Epoetin beta 33333 unit per 1 ml NeoRecormon 30,000units/0.6ml solution for injection pre-filled syringes | 4 pre-filled disposable injection (Roche Products Ltd) £841.71

Epoetin zeta

INDICATIONS AND DOSE
Symptomatic anaemia associated with chronic renal failure in patients on haemodialysis

▶ BY INTRAVENOUS INJECTION OR BY SUBCUTANEOUS INJECTION

Adult: Initially 50 units/kg 3 times a week, adjusted according to response, adjusted in steps of 25 units/kg 3 times a week, intravenous injection to be given over 1–5 minutes, if given by subcutaneous injection, a maximum of 1 mL can be given per injection site, avoid increasing haemoglobin concentration at a rate exceeding 2 g/100 mL over 4 weeks.

Symptomatic anaemia associated with chronic renal failure in adults on peritoneal dialysis

▶ BY INTRAVENOUS INJECTION OR BY SUBCUTANEOUS INJECTION

Adult: Initially 50 units/kg twice weekly; maintenance 25–50 units/kg twice weekly, intravenous injection to be given over 1–5 minutes, if given by subcutaneous injection, a maximum of 1 mL can be given per injection site, avoid increasing haemoglobin concentration at a rate exceeding 2 g/100 mL over 4 weeks.

Severe symptomatic anaemia of renal origin in adults with renal insufficiency not yet on dialysis

▶ BY INTRAVENOUS INJECTION OR BY SUBCUTANEOUS INJECTION

Adult: Initially 50 units/kg 3 times a week, adjusted according to response, adjusted in steps of 25 units/kg 3 times a week, dose to be increased at intervals of at least 4 weeks; maintenance 25–100 units/kg 3 times a week, intravenous injection to be given over 1–5 minutes, if given by subcutaneous injection, a maximum of 1 mL can be given per injection site, avoid increasing haemoglobin concentration at a rate exceeding 2 g/100 mL over 4 weeks.

Symptomatic anaemia in adults receiving cancer chemotherapy

▶ BY SUBCUTANEOUS INJECTION

Adult: Initially 150 units/kg 3 times a week, alternatively initially 450 units/kg once weekly, increased to 300 units/kg 3 times a week, only increase dose if appropriate rise in haemoglobin (or reticulocyte count) not achieved after 4 weeks; discontinue if inadequate response after 4 weeks at higher dose, maximum 1 mL per injection site, reduce dose by approximately 25–50% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose. Discontinue approximately 4 weeks after ending chemotherapy.

To increase yield of autologous blood (to avoid homologous blood) in predonation programme in moderate anaemia either when large volume of blood required or when sufficient blood cannot be saved for elective major surgery

▶ BY INTRAVENOUS INJECTION

Adult: 600 units/kg twice weekly for 3 weeks before surgery, intravenous injection to be given over 1–5 minutes, consult product literature for details and advice on ensuring high iron stores.

Moderate anaemia (haemoglobin concentration 10–13 g/100 mL) before elective orthopaedic surgery in adults with expected moderate blood loss to reduce exposure to allogeneic blood transfusion or if autologous transfusion unavailable

▶ BY SUBCUTANEOUS INJECTION

Adult: 600 units/kg every 1 week for 3 weeks before surgery and on day of surgery, alternatively 300 units/kg daily for 15 days starting 10 days before surgery, maximum 1 mL per injection site, consult product literature for details.

PREGNANCY
No evidence of harm. Benefits probably outweigh risk of anaemia and of blood transfusion in pregnancy.

BREAST FEEDING
Unlikely to be present in milk. Minimal effect on infant.

HEPATIC IMPAIRMENT
Manufacturers advise caution in chronic hepatic failure.

PRESCRIBING AND DISPENSING INFORMATION
Products containing epoetin zeta are not identical and although there should be no important differences in terms of safety and efficacy, when prescribing biological products it is good practice to use the brand name.

NATIONAL FUNDING/ACCESS DECISIONS
NICE technology appraisals (TAs)

▶ Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer having chemotherapy (November 2014) NICE TA323

Erythropoiesis-stimulating agents (epoetin alfa, beta, theta and zeta, and darbepoetin alfa) are recommended, within their marketing authorisations, as options for treating anaemia in people with cancer who are having chemotherapy.

If different erythropoiesis-stimulating agents are equally suitable, the product with the lowest acquisition cost for the course of treatment should be used. www.nice.org.uk/TA323

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

EXCIPIENTS: May contain Phenylalanine

▶ Retacrit ( Hospira UK Ltd)

Epoetin zeta 3333 unit per 1 ml Retacrit 2,000units/0.6ml solution for injection pre-filled syringes | 6 pre-filled disposable injection (Hospira UK Ltd) £67.88 (Hospital only)
**MONOCLONAL ANTIBODIES**

**Eculizumab**

- **DRUG ACTION** Eculizumab, a recombinant monoclonal antibody, inhibits terminal complement activation at the C5 protein and thereby reduces haemolysis and thrombotic microangiopathy.

**INDICATIONS AND DOSE**

Reduce haemolysis in paroxysmal nocturnal haemoglobinuria (PNH), in those with a history of blood transfusions (under expert supervision)

**BY INTRAVENOUS INFUSION**

- Adult: Initially 600 mg once weekly for 4 weeks, then increased to 900 mg once weekly for 1 week; maintenance 900 mg every 12–16 days

Reduce thrombotic microangiopathy in atypical haemolytic uraemic syndrome (aHUS) (specialist use only)

**BY INTRAVENOUS INFUSION**

- Adult: Initially 900 mg once weekly for 4 weeks, then increased to 1.2 g once weekly for 1 week; maintenance 1.2 g every 12–16 days

**CONTRA-INDICATIONS** Patients unvaccinated against Neisseria meningitidis - unresolved Neisseria meningitidis infection

**CAUTIONS** Active systemic infection

**CAUTIONS, FURTHER INFORMATION**

Meningococcal infection Vaccine against Neisseria meningitidis at least 2 weeks before treatment (tetravalent vaccine against serotypes A, C, W135 and Y recommended); revaccinate according to current medical guidelines. Patients receiving eculizumab less than 2 weeks after receiving meningococcal vaccine must be given prophylactic antibiotics until 2 weeks after vaccination. Advise patient to report promptly any signs of meningococcal infection. Other immunisations should also be up to date.

**SIDE-EFFECTS**

- **Common or very common** Alopecia - arthralgia - blood disorders - cough - dizziness - dysgeusia - dysuria - fatigue - gastro-intestinal disturbances - headache - infection (including meningococcal infection) - influenza-like symptoms - infusion-related reactions - leucopenia - myalgia - nasopharyngitis - oedema - paraesthesia - pruritus - rash - spontaneous erection - thrombocytopenia - vertigo


**CONCEPTION AND CONCEPTION** Manufacturer advises effective contraception during and for 5 months after treatment.

**PREGNANCY** No information available—use only if potential benefit outweighs risk. Human IgG antibodies known to cross placenta.

**BREAST FEEDING** No information available—manufacturer advises avoid breast-feeding during and for 5 months after treatment.

**MONITORING REQUIREMENTS**

- Monitor for 1 hour after infusion.
- For paroxysmal nocturnal haemoglobinuria, monitor for intravascular haemolysis (including serum-lactate dehydrogenase concentration) during treatment and for at least 8 weeks after discontinuation.
- For atypical haemolytic uraemic syndrome, monitor for thrombotic microangiopathy (measure platelet count, serum-lactate dehydrogenase concentration, and serum creatinine) during treatment and for at least 12 weeks after discontinuation.

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Soliris®), give intermittently in Glucose 5% or Sodium chloride 0.9%. Dilute requisite dose to a concentration of 5 mg/mL and mix gently; give over 25–45 minutes (infusion time may be increased to 2 hours if infusion-related reactions occur).

**PRESCRIBING AND DISPENSING INFORMATION** Consult product literature for details of supplemental doses with concomitant plasmapheresis, plasma exchange, or plasma infusion.

**PATIENT AND CARER ADVICE** A patient information card should be provided. Patient or carers should be advised to report promptly any signs of meningococcal infection.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

**ELECTROLYTES:** May contain Sodium

- Soliris (Alexion Pharma UK Ltd)

  Eculizumab 10 mg per 1 ml Soliris 300mg/30ml concentrate for solution for infusion vials | 1 vial (BNF) £3,120.00 (Hospital only)

### 1.4 Anaemias, iron deficiency

**Anaemias, iron-deficiency**

Treatment with an iron preparation is justified only in the presence of a demonstrable iron-deficiency state. Before starting treatment, it is important to exclude any serious underlying cause of the anaemia (e.g. gastric erosion, gastro-intestinal cancer).

Prophylaxis with an iron preparation may be appropriate in malabsorption, menorrhagia, pregnancy, after subtotal or total gastrectomy, in haemodialysis patients, and in the management of low birth-weight infants such as preterm neonates.

**Oral iron**

Iron salts should be given by mouth unless there are good reasons for using another route.

Ferrous salts show only marginal differences between one another in efficiency of absorption of iron. Haemoglobin regeneration rate is little affected by the type of salt used provided sufficient iron is given, and in most patients the
speed of response is not critical. Choice of preparation is thus usually decided by the incidence of side-effects and cost.

The oral dose of elemental iron for iron-deficiency anaemia should be 100 to 200 mg daily. It is customary to give this as dried ferrous sulfate; for prophylaxis of iron-deficiency anaemia, ferrous sulfate may be effective.

### Iron content of different iron salts

<table>
<thead>
<tr>
<th>Iron salt/amount</th>
<th>Content of ferrous iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous fumarate 200 mg</td>
<td>65 mg</td>
</tr>
<tr>
<td>Ferrous gluconate 300 mg</td>
<td>35 mg</td>
</tr>
<tr>
<td>Ferrous sulfate 300 mg</td>
<td>60 mg</td>
</tr>
<tr>
<td>Ferrous sulfate, dried 200 mg</td>
<td>65 mg</td>
</tr>
</tbody>
</table>

### Compound preparations

Preparations containing iron and folic acid p. 836 are used during pregnancy in women who are at high risk of developing iron and folic acid deficiency; they should be distinguished from those used for the prevention of neural tube defects in women planning a pregnancy.

It is important to note that the small doses of folic acid p. 836 contained in these preparations are inadequate for the treatment of megaloblastic anaemias.

Some oral preparations contain ascorbic acid p. 884 to aid absorption of the iron but the therapeutic advantage of such preparations is minimal and cost may be increased.

There is no justification for the inclusion of other ingredients, such as the B group of vitamins (except folic acid for pregnant women).

### Modified-release preparations

Modified-release preparations of iron are licensed for once-daily dosage, but have no therapeutic advantage and should not be used. These preparations are formulated to release iron gradually; the low incidence of side-effects may reflect the small amounts of iron available for absorption as the iron is carried past the first part of the duodenum into an area of the gut where absorption may be poor.

### Parenteral iron

Iron can be administered parenterally as iron dextran p. 832, iron sucrose p. 832, ferric carboxymaltose below, or iron isomaltoside 1000 p. 832. Parenteral iron is generally reserved for use when oral therapy is unsuccessful because the patient cannot tolerate oral iron, or does not take it reliably, or if there is continuing blood loss, or in malabsorption. Parenteral iron may also have a role in the management of chemotherapy-induced anaemia, when given with erythropoietins, in specific patient groups (see NICE guidance).

Many patients with chronic renal failure who are receiving haemodialysis (and some who are receiving peritoneal dialysis) also require iron by the intravenous route on a regular basis.

With the exception of patients with severe renal failure receiving haemodialysis, parenteral iron does not produce a faster haemoglobin response than oral iron provided that the oral iron preparation is taken reliably and is absorbed adequately. If parenteral iron is necessary, the dose should be calculated according to the patient’s body-weight and total iron deficit. Depending on the preparation used, parenteral iron is given as a total dose or in divided doses. Further treatment should be guided by monitoring haemoglobin and serum iron concentrations.

### Iron (injectable)

**Important safety information**

**MHRA/CHM ADVICE: SERIOUS HYPERSENSITIVITY REACTIONS WITH INTRAVENOUS IRON (AUGUST 2013)**

Serious hypersensitivity reactions, including life-threatening and fatal anaphylactic reactions, have been reported in patients receiving intravenous iron. These reactions can occur even when a previous administration has been tolerated (including a negative test dose). Test doses are no longer recommended and caution is needed with every dose of intravenous iron. Intravenous iron products should only be administered when appropriately trained staff and resuscitation facilities are immediately available; patients should be closely monitored for signs of hypersensitivity during and for at least 30 minutes after every administration. In the event of a hypersensitivity reaction, treatment should be stopped immediately and appropriate management initiated.

The risk of hypersensitivity is increased in patients with known allergies, immune or inflammatory conditions, or those with a history of severe asthma, eczema, or other atopic allergy; in these patients, intravenous iron should only be used if the benefits outweigh the risks. Intravenous iron should be avoided in the first trimester of pregnancy and used in the second or third trimesters only if the benefit outweighs the potential risks for both mother and fetus.

**SIDE-EFFECTS** Hypersensitivity reactions

**FURTHER INFORMATION**

**Anaphylactic reactions** Anaphylactic reactions can occur with parenteral administration of iron complexes and facilities for cardiopulmonary resuscitation must be available.

**Overdose** For details on the management of poisoning, see Iron salts, under Emergency treatment of poisoning p. 1123.

### Ferric carboxymaltose

**INDICATIONS AND DOSE**

**Iron-deficiency anaemia**

**BY SLOW INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION**

- **Adult:** Dose calculated according to body-weight and iron deficit (consult product literature)

**CAUTIONS** Allergic disorders - asthma - eczema - hypersensitivity can occur with parenteral iron and facilities for cardiopulmonary resuscitation must be available. Infection (discontinue if ongoing bacteraemia) - oral iron should not be given until 5 days after last injection

**SIDE-EFFECTS**

- **Common or very common** Dizziness - gastro-intestinal disturbances - headache - injection-site reactions - rash
- **Uncommon** Anaphylaxis - arthralgia - back pain - chest pain - fatigue - flushing - hypertension - hypotension - malaise - myalgia - paraesthesia - peripheral oedema - pruritus - pyrexia - rigors - urticaria
- **Rare** Dyspnoea

**PREGNANCY** Avoid in first trimester; crosses the placenta in animal studies. May influence skeletal development.

**HEPATIC IMPAIRMENT** Use with caution. Avoid in conditions where iron overload increases risk of impairment.
### Iron isomaltoside 1000

#### INDICATIONS AND DOSE
Iron deficiency anaemia

BY SLOW INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION

- Adult: Doses calculated according to body-weight and iron deficit (consult product literature)

#### CONTRA-INDICATIONS
Active rheumatoid arthritis - asthma - eczema - history of allergic disorders

#### CAUTIONS
Hypersensitivity can occur with parenteral iron and facilities for cardiopulmonary resuscitation must be available - infection (discontinue if ongoing bacteraemia) - oral iron should not be given until 5 days after last injection

#### SIDE-EFFECTS
- Rare Altered mental status - angioedema - arthralgia - chest pain - diarrhoea - dizziness - hypotension - loss of consciousness - malaise - myalgia - restlessness - seizures - sweating - tachycardia - tremor
- Very rare Foetal bradycardia - haemolysis - headache - hypotension - palpitation - paraesthesia - transient deafness

#### PREGNANCY
Avoid in first trimester.

#### HEPATIC IMPAIRMENT
Avoid in decompensated liver disease and hepatitis.

#### DIRECTIONS FOR ADMINISTRATION
For intravenous infusion (Cosmofer®), give intermittently in Sodium chloride 0.9% or Sodium bicarbonate 8.4%. Doses calculated according to body-weight and iron deficit (consult product literature).

#### MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

#### Solution for injection
- Cosmofer (Pharmacosmos UK Ltd)
  - Iron (as iron dextran) 50 mg per 1 ml Cosmofer 500mg/10ml solution for injection ampoules | 2 ampoule £9.70
  - Cosmofer 100mg/2ml solution for injection ampoules | 5 ampoule £38.85

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### Iron dextran

#### INDICATIONS AND DOSE
Iron-deficiency anaemia

BY DEEP INTRAMUSCULAR INJECTION

- Adult: Intramuscular injection to be administered into the gluteal muscle, doses calculated according to body-weight and iron deficit (consult product literature)

BY SLOW INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION

- Adult: Doses calculated according to body-weight and iron deficit (consult product literature)

#### CONTRA-INDICATIONS
Active rheumatoid arthritis - asthma - eczema - history of allergic disorders

#### CAUTIONS
Hypersensitivity can occur with parenteral iron and facilities for cardiopulmonary resuscitation must be available - oral iron should not be given until 5 days after last injection

#### SIDE-EFFECTS
- Rare Altered mental status - angioedema - arthralgia - chest pain - diarrhoea - dizziness - hypotension - loss of consciousness - malaise - myalgia - restlessness - seizures - sweating - tachycardia - tremor
- Very rare Foetal bradycardia - haemolysis - headache - hypotension - palpitation - paraesthesia - transient deafness

#### PREGNANCY
Avoid in first trimester.

#### HEPATIC IMPAIRMENT
Avoid in decompensated liver disease and hepatitis.

#### DIRECTIONS FOR ADMINISTRATION
For intravenous infusion (Monofer®), give intermittently in Sodium chloride 0.9%. For details consult product literature.

#### MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

#### Solution for injection
- Monofer (Vifor Pharma UK Ltd)
  - Iron (as Ferric carboxymaltose) 50 mg per 1 ml Monofer 500mg/10ml solution for injection vials | 1 vial £154.23
  - Monofer 100mg/2ml solution for injection vials | 5 vial £81.18
  - Monofer 500mg/10ml solution for injection vials | 5 vial £405.88

#### MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

#### Solution for injection
- Cosmofer (Pharmacosmos UK Ltd)
  - Iron (as iron dextran) 50 mg per 1 ml Cosmofer 500mg/10ml solution for injection ampoules | 2 ampoule £9.70
  - Cosmofer 100mg/2ml solution for injection ampoules | 5 ampoule £38.85

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### Iron sucrose

#### INDICATIONS AND DOSE
Iron-deficiency anaemia

BY SLOW INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION

- Adult: Doses calculated according to body-weight and iron deficit (consult product literature)

#### CONTRA-INDICATIONS
Anaphylaxis - asthma - eczema - history of allergic disorders

#### CAUTIONS
Hypersensitivity can occur with parenteral iron and facilities for cardiopulmonary resuscitation must be available - infection (discontinue if ongoing bacteraemia) - oral iron should not be given until 5 days after last injection

#### SIDE-EFFECTS
- Rare Altered mental status - angioedema - arthralgia - chest pain - diarrhoea - dizziness - hypotension - loss of consciousness - malaise - myalgia - restlessness - seizures - sweating - tachycardia - tremor
- Very rare Foetal bradycardia - haemolysis - headache - hypotension - palpitation - paraesthesia - transient deafness

#### PREGNANCY
Avoid in first trimester.

#### HEPATIC IMPAIRMENT
Avoid in decompensated liver disease and hepatitis.

#### DIRECTIONS FOR ADMINISTRATION
For intravenous infusion (Cosmosfer®), give intermittently in Glucose 5% or Sodium chloride 0.9%, dilute 100–200 mg in 100 mL infusion fluid; give 25mg over 15 minutes initially, then give at a rate not exceeding 6.67 mg/minute; total dose infusion diluted in 500 mL infusion fluid and given over 4–6 hours (initial dose 25 mg over 15 minutes).

#### PRESCRIBING AND DISPENSING INFORMATION
A complex of ferric hydroxide with dextran containing 5% (50 mg/mL) of iron.
Iron (oral)

- **SIDE-EFFECTS**
  - Constipation
  - Diarrhoea
  - Epigastric pain
  - Nausea
  - Vomiting

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - **Altered bowel habit** Iron preparations taken orally can be constipating and occasionally lead to faecal impaction. Oral iron, particularly modified-release preparations, can exacerbate diarrhoea in patients with inflammatory bowel disease; care is also needed in patients with intestinal strictures and diverticular disease. The relationship between dose and altered bowel habit (constipation or diarrhoea) is less clear than for nausea and epigastric pain.

- **Overdose**
  - For details on the management of poisoning, see iron salts, under Emergency treatment of poisoning p. 1123.

- **MONITORING REQUIREMENTS**
  - The haemoglobin concentration should rise by about 100–200 mg/100 mL (1–2 g/litre) per day or 2 g/100 mL (20 g/litre) over 3–4 weeks. When the haemoglobin is in the normal range, treatment should be continued for a further 3 months to replenish the iron stores. Epithelial tissue changes such as atrophic glossitis and koilonychia are usually improved, but the response is often slow.

- **INTERACTIONS**
  - Appendix 1 (iron salts).

- **PATIENT AND CARER ADVICE**
  - Although iron preparations are best absorbed on an empty stomach they can be taken after food to reduce gastro-intestinal side-effects. May discolor stools.

### Ferrous fumarate

**INDICATIONS AND DOSE**

<table>
<thead>
<tr>
<th>Iron-deficiency anaemia (prophylactic)</th>
<th>BY MOUTH</th>
<th>BY MOUTH USING TABLETS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child 12-17 years: 210 mg 2–3 times a day</td>
<td>Adult: 210 mg 2–3 times a day</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Iron-deficiency anaemia (therapeutic)</th>
<th>BY MOUTH</th>
<th>BY MOUTH USING TABLETS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child 12-17 years: 140 mg twice daily</td>
<td>Adult: 140 mg twice daily</td>
<td></td>
</tr>
</tbody>
</table>

**FERSDAY®**

<table>
<thead>
<tr>
<th>Iron-deficiency anaemia (prophylactic)</th>
<th>BY MOUTH</th>
<th>BY MOUTH USING SYRUPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult: 322 mg daily</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Iron-deficiency anaemia (therapeutic)</th>
<th>BY MOUTH</th>
<th>BY MOUTH USING SYRUPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child 12-17 years: 280 mg twice daily</td>
<td>Adult: 280 mg twice daily</td>
<td></td>
</tr>
</tbody>
</table>

**STORAGE**

- Protect from light and freezing.

**MEDICATIONS FOR CHILDREN**

- Ferrous fumarate for iron-deficiency anaemia www.medicinesforchildren.org.uk/ferrous-fumarate-for-iron-deficiency-anaemia

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Iron (as iron sucrose)**
  - 20 mg per 1 mL
  - Venofer 100mg/5mL solution for injection vials | 5 vial pack £41.52
Blood and blood-forming organs

Ferrous fumarate with folic acid

The properties listed below are those particular to the combination only. For the properties of the components please consider, ferrous fumarate p. 833, folic acid p. 836.

**INDICATIONS AND DOSE**

Iron deficiency anaemia

**BY MOUTH USING CAPSULES**

- Adult: 1 capsule daily, to be taken before food
- Adult: 1 tablet daily

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- Ferrous fumarate 28 mg per 1 ml
  
<table>
<thead>
<tr>
<th>Dosage</th>
<th>Form</th>
<th>IRONORM®</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 ml</td>
<td>Tablet</td>
<td>£3.35 DT price = £1.95</td>
</tr>
<tr>
<td>100 ml</td>
<td>Capsule</td>
<td>£5.00</td>
</tr>
<tr>
<td>1 ml</td>
<td>Oral solution</td>
<td>£1.25 DT price = £1.25</td>
</tr>
</tbody>
</table>

**Capsule**

- 100 capsule
  
<table>
<thead>
<tr>
<th>Dosage</th>
<th>Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 mg</td>
<td>Tablet</td>
</tr>
<tr>
<td>32 mg</td>
<td>Capsule</td>
</tr>
</tbody>
</table>

**Oral solution**

- Ferrous fumarate 28 mg per 1 ml
  
<table>
<thead>
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<th>Dosage</th>
<th>Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 ml</td>
<td>Oral solution</td>
</tr>
<tr>
<td>100 capsule</td>
<td>£3.73 DT price = £3.73</td>
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</table>

- Galler FA (Thornton & Ross Ltd)

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 capsule</td>
<td>£3.25 DT price = £3.25</td>
</tr>
</tbody>
</table>

**Ferrous fumarate with folic acid**

**INDICATIONS AND DOSE**

Iron deficiency anaemia (prophylactic and therapeutic)

**BY MOUTH USING TABLETS**

- Child 6–17 years: 1 capsule daily, to be taken before food
- Adult: 1 tablet daily, to be taken before food

**FEOSPAN®**

Iron deficiency anaemia (prophylactic and therapeutic)

**BY MOUTH**

- Child 12–17 years: 1 tablet daily, dose to be taken before food
- Adult: 1 tablet daily, dose to be taken before food

**INTERACTIONS**

Appendix 1 (iron salts).

**PRESCRIBING AND DISPENSING INFORMATION**

Modified-release preparations of iron are licensed for once-daily dosage, but have no therapeutic advantage and should not be used. These preparations are formulated to release iron gradually; the low incidence of side-effects may reflect the small amounts of iron available for absorption as the iron is carried past the first part of the duodenum into an area of the gut where absorption may be poor.

**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Ferrous gluconate for iron-deficiency anaemia www.medicinesforchildren.org.uk/ferrous-gluconate-for-iron-deficiency-anaemia

**NATIONAL FUNDING/ACCESS DECISIONS**

NHS restrictions Feospan® is not prescribable under the National Health Service.

**LESS SUITABLE FOR PRESCRIBING**

Feospan® and Ferrograd® are less suitable for prescribing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution
Ferrous sulfate with ascorbic acid

The properties listed below are those particular to the combination only. For the properties of the components please consider, ascorbic acid p. 884, ferrous sulfate p. 834.

INDICATIONS AND DOSE
Iron deficiency anaemia
BY MOUTH USING MODIFIED-RELEASE TABLETS
▶ Adult: 1 tablet daily, dose to be taken before food

NATIONAL FUNDING/ACCESS DECISIONS
NHS restrictions Ferrograd C® is not prescribable on the National Health Service.

LESS SUITABLE FOR PRESCRIBING Ferrograd C® is less suitable for prescribing.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Modified-release tablet
CAUTIONARY AND ADVISORY LABELS 25
▶ Ferrograd Folic (Teofarma)
Ferrograd C® is not available on prescription

Ferrograd C® modified-release tablets | 30 tablet | £2.64 DT price = £2.64

POLYSAHCHARIDE-IRON COMPLEX

Iron-deficiency anaemia (prophylactic)
BY MOUTH
▶ Child 1 month to 1 year: 1 drop (approximately 500 micrograms iron) per 450 g body-weight to be given 3 times a daily, dose to be administered from dropper bottle, prophylactic iron supplementation may be required in babies of low birth-weight who are solely breast-fed; supplementation is started 4–6 weeks after birth and continued until mixed feeding is established
▶ Child 12–17 years: 2.5 mL daily
▶ Adult: 2.5 mL daily

Iron-deficiency anaemia (therapeutic)
BY MOUTH
▶ Child 2–5 years: 2.5 mL daily
▶ Child 6–11 years: 5 mL daily
▶ Child 12–17 years: 5 mL 1–2 times a day
▶ Adult: 5 mL 1–2 times a day

Iron-deficiency anaemia (therapeutic) if required during second and third trimester of pregnancy
BY MOUTH
▶ Child 12–17 years: 5 mL once daily
▶ Adult: 5 mL once daily

INTERACTIONS → Appendix 1 (iron salts).

PATIENT AND CARER ADVICE Counselling on the use of the dropper advised.

NATIONAL FUNDING/ACCESS DECISIONS
NHS restrictions Niferex® is not available on prescription under NHS, except 30-mL paediatric dropper bottle for prophylaxis and treatment of iron deficiency in infants born prematurely; endorse prescription 'SLS'.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Oral solution
▶ Niferex® (Tillomed Laboratories Ltd)
Iron (as Polysaccharide-iron complex) 100 mg Niferex 100mg/5ml elixir (sugar-free) | 30 ml | £2.16 (sugar-free) | 240 ml | £6.06

Sodium feredate (Sodium ironedetate)

INDICATIONS AND DOSE
Iron-deficiency anaemia (therapeutic)
BY MOUTH USING ORAL SOLUTION
▶ Child 1–11 months: Up to 2.5 mL twice daily, smaller doses to be used initially
▶ Child 1–4 years: 2.5 mL 3 times a day
▶ Child 5–11 years: 5 mL 3 times a day
▶ Child 12–17 years: 5 mL 3 times a day, increased to 10 mL 3 times a day, dose to be increased gradually continued

Ferrous sulfate with folic acid

The properties listed below are those particular to the combination only. For the properties of the components please consider, folic acid p. 836.

INDICATIONS AND DOSE
Iron deficiency anaemia
BY MOUTH USING MODIFIED-RELEASE CAPSULES
▶ Adult: 1 capsule daily

BY MOUTH USING MODIFIED-RELEASE TABLETS
▶ Child 12–17 years: 1 tablet daily, to be taken before food
▶ Adult: 1 tablet daily, to be taken before food

LESS SUITABLE FOR PRESCRIBING Folic® and Ferrograd Folic® are less suitable for prescribing.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
Blood and blood-forming organs

836

1.5 Anaemias, megaloblastic

Anaemias, megaloblastic

Most megaloblastic anaemias result from a lack of either vitamin B₁₂ or folate, and it is essential to establish in every case which deficiency is present and the underlying cause. In emergencies, when delay might be dangerous, it is sometimes necessary to administer both substances after the bone marrow test while plasma assay results are awaited. Normally, however, appropriate treatment should not be instituted until the results of tests are available.

One cause of megaloblastic anaemia in the UK is pernicious anaemia in which lack of gastric intrinsic factor resulting from an autoimmune gastritis causes malabsorption of vitamin B₁₂.

Vitamin B₁₂ is also needed in the treatment of megaloblastosis caused by prolonged nitrous oxide anaesthesia, which inactivates the vitamin, and in the rare syndrome of congenital transcobalamin II deficiency.

Vitamin B₁₂ should be given prophylactically after total gastrectomy or total ileal resection or after partial gastrectomy if a vitamin B₁₂ absorption test shows vitamin B₁₂ malabsorption.

Apart from dietary deficiency, all other causes of vitamin B₁₂ deficiency are attributable to malabsorption. There is little place for the use of low-dose vitamin B₁₂ orally and none for vitamin B₁₂ intrinsic factor complexes given by mouth. Vitamin B₁₂ in larger oral doses [unlicensed] may be effective.

Hydroxocobalamin p. 837 has completely replaced cyanocobalamin p. 837 as the form of vitamin B₁₂ of choice for therapy; it is retained in the body longer than cyanocobalamin and thus for maintenance therapy can be given at intervals of up to 3 months. Treatment is generally initiated with frequent administration of intramuscular injections to replenish the depleted body stores. Thereafter, maintenance treatment, which is usually for life, can be instituted. There is no evidence that doses larger than those recommended provide any additional benefit in vitamin B₁₂ neuropathy.

Folic acid below has few indications for long-term therapy since most causes of folate deficiency are self-limiting or will yield to a short course of treatment. It should not be used in undiagnosed megaloblastic anaemia unless vitamin B₁₂ is administered concurrently otherwise neuropathy may be precipitated.

In folate-deficient megaloblastic anaemia (e.g. because of poor nutrition, pregnancy, or antiepileptic drugs), daily folic acid supplementation for 4 months brings about haematological remission and replenishes body stores.

For prophylaxis in chronic haemolytic states, malabsorption, or in renal dialysis, folic acid is given daily or sometimes weekly, depending on the diet and the rate of haemolysis.

Folic acid is also used for the prevention of methotrexate-induced side-effects in severe Crohn’s disease, rheumatic disease, and severe psoriasis.

Folic acid p. 781 is also effective in the treatment of folate deficient megaloblastic anaemia but it is generally used in association with cytotoxic drugs; it is given as calcium folinate.

There is no justification for prescribing multiple ingredient vitamin preparations containing vitamin B₁₂ or folic acid.
Anaemias, megaloblastic 837

**Prophylaxis in chronic haemolytic states**

**BY MOUTH**
- Adult: 5 mg every 1–7 days, frequency dependent on underlying disease

**Prophylaxis of folate deficiency in dialysis**

**BY MOUTH**
- Child 1–11 years: 250 micrograms/kg once daily (max. per dose 10 mg)
- Child 12–17 years: 5–10 mg once daily
- Adult: 5 mg every 1–7 days

**Haemolytic anaemia | Metabolic disorders**

**BY MOUTH**
- Child 1 month–11 years: 2.5–5 mg once daily
- Child 12–17 years: 5–10 mg once daily
- Adult 18 years: 5–10 mg once daily

**UNLICENSED USE**
- In adults Not licensed for prevention of methotrexate-induced side-effects in severe Crohn’s disease, rheumatic disease, or severe psoriasis.

**CAUTIONS** Should never be given alone for pernicious anaemia (may precipitate subacute combined degeneration of the spinal cord)

**INTERACTIONS** Appendix 1 (folicates).

**SIDE-EFFECTS**
- Rare Gastro-intestinal disturbances

**PATIENT AND CAREER ADVICE**

**EXCEPTIONS TO LEGAL CATEGORY** Can be sold to the public provided daily doses do not exceed 500 micrograms.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: modified-release tablet, capsule

**Tablet**
- **FOLIC ACID (Non-proprietary)**
  - Folic acid 400 microgram: Folic acid 400microgram tablets | 90 tablet £1.97 DT price = £2.71
  - Folic acid 5 mg: Folic acid 5mg tablets | 28 tablet £2.00 DT price = £3.09 | 100 tablet £41.75

**Oral solution**
- **FOLIC ACID (Non-proprietary)**
  - Folic acid 500 microgram per 1 ml: Folic acid 2.5mg/5ml oral solution sugar free (sugar-free) | 150 ml £3.16 DT price = £3.16
  - Brands may include Lexpec

**VITAMIN B GROUP**

**Cyanocobalamin**

**INDICATIONS AND DOSE**
- Vitamin B12 deficiency of dietary origin
  - **BY MOUTH**
    - Adult: 50–150 micrograms daily, dose to be taken between meals
  - **BY INTRAMUSCULAR INJECTION**
    - Adult: Initially 1 mg every 2–3 days for 10 doses; maintenance 1 mg every 1 month

**PRESCRIBING AND DISPENSING INFORMATION** The BP directs that when vitamin B12 injection is prescribed or demanded hydroxocobalamin injection shall be dispensed or supplied. Currently available brands of the tablet may not be suitable for vegans.

**NATIONAL FUNDING/ACCESS DECISIONS**
- NHS restrictions Cyanocobalamin liquid, Cytacon® tablets and Cyamen® injection not available on prescription under the NHS.

**LESS SUITABLE FOR PRESCRIBING** Cyanocobalamin is less suitable for prescribing.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: modified-release tablet, tablet

**Tablet**
- **CYANOCOBALAMIN (Non-proprietary)**
  - Cyanocobalamin 50 microgram: Cyanocobalamin 50microgram tablets | 50 tablet £6.24 DT price = £6.24 | 50 tablet £6.24 DT price = £6.24 | 100 tablet no price available
  - Cyanocobalamin 1 mg: Cyanocobalamin 1000microgram tablets | 28 tablet £6.24
  - Brands may include Cytacon

**Oral solution**
- **CYANOCOBALAMIN (Non-proprietary)**
  - Cyanocobalamin 7 microgram per 1 ml: Cyanocobalamin 75micrograms/5ml oral solution | 200 ml £8.75

**Solution for injection**
- **Cytamen (Focus Pharmaceuticals Ltd)**
  - Cyanocobalamin 1 mg per 1 ml: Cytamen 1000micrograms/1ml solution for injection ampoules | 5 ampoule (£5.50 DT price = £14.50

**Hydroxocobalamin**

**INDICATIONS AND DOSE**
- Prophylaxis of macrocytic anaemias associated with vitamin B12 deficiency
  - **BY INTRAMUSCULAR INJECTION**
    - Adult: 1 mg every 2–3 months
  - Pernicious anaemia and other macrocytic anaemias without neurological involvement
    - **BY INTRAMUSCULAR INJECTION**
      - Adult: Initially 1 mg 3 times a week for 2 weeks, then 1 mg every 3 months
  - Pernicious anaemia and other macrocytic anaemias with neurological involvement
    - **BY INTRAMUSCULAR INJECTION**
      - Adult: Initially 1 mg once daily on alternate days until no further improvement, then 1 mg every 2 months
  - Tobacco amblyopia
    - **BY INTRAMUSCULAR INJECTION**
      - Adult: Initially 1 mg daily for 2 weeks, then 1 mg twice weekly until no further improvement, then 1 mg every 1–3 months
  - Leber’s optic atrophy
    - **BY INTRAMUSCULAR INJECTION**
      - Adult: Initially 1 mg daily for 2 weeks, then 1 mg twice weekly until no further improvement, then 1 mg every 1–3 months

**POISONING WITH CYANIDES**
- **BY INTRAVENOUS INFUSION**
  - Child (body-weight 5 kg and above): Initially 70 mg/kg (max. per dose 5 g), to be given over 15 minutes, then 70 mg/kg (max. per dose 5 g) if required, this second dose can be given over 15 minutes–2 hours depending on severity of poisoning and patient stability
  - Adult: Initially 5 g, to be given over 15 minutes, then 5 g if required, this second dose can be given over 15 minutes–2 hours depending on severity of poisoning and patient stability

**CAUTIONS** Should not be given before diagnosis fully established
Iron overload

Iron overload can occur in aplastic and other refractory anaemias, mainly as the result of repeated blood transfusions. It is a particular problem in refractory anaemias with hyperplastic bone marrow, especially thalassaemia major, where excessive iron absorption from the gut and inappropriate iron therapy can add to the tissue siderosis.

Iron overload associated with haemochromatosis can be treated with repeated venesection. Venesection may also be used for patients who have received multiple transfusions and whose bone marrow has recovered. Where venesection is contra-indicated, the long-term administration of the iron chelating compound desferrioxamine mesilate p. 839 is useful. Desferrioxamine mesilate (up to 2 g per unit of blood) may also be given at the time of blood transfusion, provided that the desferrioxamine mesilate is not added to the blood and is not given through the same line as the blood (but the two may be given through the same cannula).

Iron excretion induced by desferrioxamine mesilate is enhanced by administration of ascorbic acid p. 884 (vitamin C) daily by mouth; it should be given separately from food since it also enhances iron absorption. Ascorbic acid should not be given to patients with cardiac dysfunction; in patients with normal cardiac function ascorbic acid should be introduced 1 month after starting desferrioxamine mesilate.

Desferrioxamine mesilate infusion can be used to treat aluminium overload in dialysis patients; theoretically 100 mg of desferrioxamine binds with 4.1 mg of aluminium.

Iron chelators

Deferasirox

Drug action
Deferasirox, is an oral iron chelator.

indications and dose
Transfusion-related chronic iron overload when desferrioxamine is contra-indicated or inadequate in children aged 2-5 years with thalassaemia major who receive frequent blood transfusions | Transfusion-related chronic iron overload when desferrioxamine is contra-indicated or inadequate in patients with thalassaemia major who receive infrequent blood transfusions (less than 7 mL/kg/month of packed red blood cells) | Transfusion-related chronic iron overload when desferrioxamine is contra-indicated or inadequate in patients with other anaemias | Treatment of chronic iron overload in patients with thalassaemia major who receive frequent blood transfusions (more than 7 mL/kg/month of packed red blood cells)

By mouth
Adult: Initially 10–30 mg/kg once daily, dose adjusted according to serum-ferritin concentration and amount of transfused blood—consult product literature; adjusted in steps of 5–10 mg/kg every 3–6 months, dose adjusted for maintenance according to serum-ferritin concentration; usual dose up to 30 mg/kg daily, increased if necessary up to 40 mg/kg daily and reduced in steps of 5–10 mg/kg, dose to be reduced once control achieved

Treatment of chronic iron overload when desferrioxamine is contra-indicated or inadequate (with non-transfusion-dependent thalassaemia syndromes)

By mouth
Adult: Initially 10 mg/kg once daily; adjusted in steps of 5–10 mg/kg every 3–6 months, dose adjusted for maintenance according to serum-ferritin concentration and liver-iron concentration (consult product literature); maximum 20 mg/kg per day

cautions
Elderly (increased risk of side-effects) | history of liver cirrhosis | not recommended in conditions which may reduce life expectancy (e.g. high-risk myelodysplastic syndromes) | platelet count less than 50 x 10^7/litre; risk of gastro-intestinal ulceration and haemorrhage | unexplained cytopenia—consider treatment interruption

interactions
Appendix 1 (deferasirox)

side-effects
Common or very common | Fatal gastro-intestinal haemorrhage | gastro-intestinal disturbances | gastro-intestinal ulceration | headache | proteinuria | pruritus | rash

uncommon | Anxiety | cholelithiasis | disturbances of hearing and vision | dizziness | fatigue | glucosuria | hepatitis | lens opacity | maculopathy | oedema | pharyngitis | pyrexia | renal tubulopathy | skin pigmentation | sleep disorder

1.6 Iron overload
Deferiprone

**Drug Action** Deferiprone, is an oral iron chelator.

**INDICATIONS AND DOSE** Treatment of iron overload in patients with thalassaemia major in whom desferrioxamine is contraindicated or is inadequate

**BY MOUTH**
- Adult: 25 mg/kg 3 times a day; maximum 100 mg/kg per day

- CONTRA-INDICATIONS History of agranulocytosis or recurrent neutropenia
- INTERACTIONS → Appendix 1 (deferriprone)
- SIDE-EFFECTS Agranulocytosis - arthropathy - blood dyscrasias - gastro-intestinal disturbances (reducing dose and increasing gradually may improve tolerance) - headache - increased appetite - neutropenia - red-brown urine discoloration - zinc deficiency
- CONCEPTION AND CONTRACEPTION Manufacturer advises avoid before intended conception - teratogenic and embryotoxic in animal studies. Contraception advised in females of child-bearing potential.
- PREGNANCY Manufacturer advises avoid during pregnancy - teratogenic and embryotoxic in animal studies.
- BREAST FEEDING Manufacturer advises avoid — no information available.
- HEPATIC IMPAIRMENT Manufacturer advises monitor liver function — interrupt treatment if persistent elevation in serum alanine aminotransferase.
- RENAL IMPAIRMENT Manufacturer advises caution — no information available.
- MONITORING REQUIREMENTS
- Monitor neutrophil count weekly and discontinue treatment if neutropenia develops.
- Monitor plasma-zinc concentration.
- PATIENT AND CARER ADVICE Blood disorders Patients or their carers should be told how to recognise signs of neutropenia and advised to seek immediate medical attention if symptoms such as fever or sore throat develop.

- MEDICATION FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension, capsule

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 14**
- Deferiprone 500 mg Ferriprox 500mg tablets | 100 tablet £75.29
- Deferiprone 1 gram Ferriprox 1000mg tablets | 50 tablet £175.25

**Oral solution**

**CAUTIONARY AND ADVISORY LABELS 14**
- Deferiprone 100 mg per 1 ml Ferriprox 100mg/ml oral solution (sugar-free) | 500 ml £70.40

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**Desferrioxamine mesilate**

*(Deferoxamine Mesilate)*

**INDICATIONS AND DOSE**

**Iron poisoning**

**BY CONTINUOUS INTRAVENOUS INFUSION**
- Adult: Initially up to 15 mg/kg/hour, dose to be reduced after 4–6 hours, in severe cases, higher doses may be given on advice from the National Poisons Information Service; maximum 80 mg/kg per day

**Aluminium overload in dialysis patients**

**BY INTRAVENOUS INFUSION**
- Adult: (consult product literature or local protocols)

**Chronic iron overload (low iron overload)**

**BY SUBCUTANEOUS INFUSION**
- Adult: The dose should reflect the degree of iron overload

**Chronic iron overload (established overload)**

**BY SUBCUTANEOUS INFUSION**
- Adult: 20–50 mg/kg daily
9

Filgrastim p. 842 is a polyethylene glycol-conjugated (‘pegylated’) derivative of filgrastim; pegylation increases the duration of filgrastim activity. Lipegfilgrastim p. 842 is a polyethylene glycol-conjugated via a glycine linker derivative of filgrastim. Granulocyte-colony stimulating factors should only be prescribed by those experienced in their use.

CHEMOKINE RECEPTOR ANTAGONISTS

Plerixafor

**INDICATIONS AND DOSE**

Mobilise haematopoietic stem cells to peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma or multiple myeloma (specialist use only)

**BY SUBCUTANEOUS INJECTION**

- Adult: 240 micrograms/kg daily usually for 2–4 days (max 7 days), to be administered 6–11 hours before initiation of apheresis, dose to be given following 4 days treatment with a granulocyte-colony stimulating factor

**SIDE-EFFECTS**

- **Common or very common** Arthralgia · dizziness · dry mouth · erythema · fatigue · gastrointestinal disturbances · headache · injection-site reactions · insomnia · musclekeletal pain · oral hypoaesthesia · sweating
- **Uncommon** Dyspnoea · hypersensitivity reactions · periorbital swelling
- **Very rare** Acute respiratory distress syndrome · diarrhoea · fever · fatigue · flushing · headache · myalgia · nausea · rash · retinopathy · visual disturbances · epistaxis · hearing loss · hypoesthesia · polyneuropathy · paraesthesia

**INTERACTIONS**

- **Drug** 
  - **Drug action**
    - Use effective contraception during treatment—teratogenic in animal studies.
    - Manufacturer advises avoid unless essential—teratogenic in animal studies.
  - **Drug interaction**
    - Muscle spasms

**CONCEPTION AND CONTRACEPTION**

Use effective contraception during treatment—teratogenic in animal studies.

**PREGNANCY**

Manufacturer advises avoid unless essential—teratogenic in animal studies.

**BREAST FEEDING**

Manufacturer advises avoid unless essential—teratogenic in animal studies.

**RENAI IMPAIRMENT**

Reduce dose to 160 micrograms/kg daily if creatinine clearance 20–50 mL/minute. No information available if creatinine clearance less than 20 mL/minute

**MONITORING REQUIREMENTS**

Monitor platelets and white blood cell count.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**

- **Desferrioxamine mesilate 500 mg** Desferrioxamine 500mg powder for solution for injection vials | 10 vial [P4T] £39.90–£50.00
- **Desferrioxamine mesilate 2 gram** Desferrioxamine 2g powder for solution for injection vials | 1 vial [P4T] £17.65–£20.00
- **Desferal (Novartis Pharmaceuticals UK Ltd)**
  - **Desferrioxamine mesilate 500 mg** Desferal 500mg powder for solution for injection vials | 10 vial [P4T] £46.63
  - **Desferrioxamine mesilate 2 gram** Desferal 2g powder for solution for injection vials | 1 vial [P4T] £18.66

**GRANULOCYTE-COLONY STIMULATING FACTORS**

**Granulocyte-colony stimulating factors**

**DRUG ACTION**

Recombinant human granulocyte-colony stimulating factor (rhG-CSF) stimulates the production of neutrophils and may reduce the duration of chemotherapy-induced neutropenia and thereby reduce the incidence of associated sepsis; there is as yet no evidence that it improves overall survival. Filgrastim (unglycosylated rhG-CSF) and lenograstim p. 842 (glycosylated rhG-CSF) have similar effects; both have been used in a variety of clinical settings, but they do not have any clear-cut routine indications. In congenital neutropenia filgrastim p. 841 usually increases the neutrophil count with an appropriate clinical response. Pegfilgrastim p. 842 is a recombinant human granulocyte-colony stimulating factor. It does not change the duration of chemotherapy-induced neutropenia but reduces the incidence of associated sepsis. Liplinepfilgrastim p. 842 is a polyethylene glycol-conjugated derivative of filgrastim; pegylation increases the duration of filgrastim. Liplinepfilgrastim p. 842 is a polyethylene glycol-conjugated via a glycine linker derivative of filgrastim. Granulocyte-colony stimulating factors should only be prescribed by those experienced in their use.
Neutrophilia and stem cell mobilisation

Filgrastim
(Recombinant human granulocyte-colony stimulating factor, G-CSF)

**INDICATIONS AND DOSE**
Reduction in duration of neutropenia and incidence of febrile neutropenia in cytotoxic chemotherapy for malignancy (except chronic myeloid leukaemia and myelodysplastic syndromes) (specialist use only)

**BY SUBCUTANEOUS INJECTION OR BY INTRAVENOUS INFUSION**
- **Adult:** 5 micrograms/kg daily until neutrophil count in normal range (up to 38 days in acute myeloid leukaemia), to be started at least 24 hours after cytotoxic chemotherapy and to be administered over 30 minutes if given by intravenous infusion.

Reduction in duration of neutropenia (and associated sequelae) in myeloblastic therapy followed by bone-marrow transplantation (specialist use only)

**BY SUBCUTANEOUS INFUSION OR BY INTRAVENOUS INFUSION**
- **Adult:** 10 micrograms/kg daily, to be started at least 24 hours following cytotoxic chemotherapy and within 24 hours of bone-marrow infusion, then adjusted according to neutrophil count—consult product literature, doses administered over 30 minutes or 24 hours via intravenous route and over 24 hours via subcutaneous route.

Mobilisation of peripheral blood progenitor cells for autologous infusion, used alone (specialist use only)

**BY SUBCUTANEOUS INFUSION OR BY SUBCUTANEOUS INJECTION**
- **Adult:** 10 micrograms/kg daily for 5–7 days, to be administered by subcutaneous infusion over 24 hours if given.

Mobilisation of peripheral blood progenitor cells for autologous infusion, used following adjunctive myelosuppressive chemotherapy—to improve yield (specialist use only)

**BY SUBCUTANEOUS INJECTION**
- **Adult:** 5 micrograms/kg daily until neutrophil count in normal range, to be started the day after completing chemotherapy, for timing of leucopheresis, consult product literature.

Mobilisation of peripheral blood progenitor cells in normal donors for allogeneic infusion (specialist use only)

**BY SUBCUTANEOUS INJECTION**
- **Adult 18–59 years:** 10 micrograms/kg daily for 4–5 days, for timing of leucopheresis, consult product literature.

Severe congenital neutropenia and history of severe or recurrent infections (distinguish carefully from other haematological disorders) (specialist use only)

**BY SUBCUTANEOUS INJECTION**
- **Adult:** Initially 12 micrograms/kg daily, adjusted according to response, can be given in single or divided doses, consult product literature and local protocol.

Severe cyclic neutropenia, or idiopathic neutropenia and history of severe or recurrent infections (distinguish carefully from other haematological disorders) (specialist use only)

**BY SUBCUTANEOUS INJECTION**
- **Adult:** Initially 1 microgram/kg daily, subsequent doses increased as necessary until neutrophil count in normal range, then adjusted to maintain neutrophil count in normal range—consult product literature; maximum 4 micrograms/kg per day.

**CONTRA-INDICATIONS**
Severe congenital neutropenia (Kostmann’s syndrome) with abnormal cytogentic.

**CAUTIONS**
Osteoporotic bone disease (monitor bone density if given for more than 6 months) - secondary acute myeloid leukaemia.

**INTERACTIONS**
Appendix 1 (filgrastim).

**SIDE-EFFECTS**
- **Common or very common**
  - Alopecia
  - Anorexia
  - Asthenia
  - Bone pain
  - Chest pain
  - Fever
  - Gastro-intestinal disturbances
  - Headache
  - Injection site reactions
  - Leucocytosis
  - Musculoskeletal pain
  - Rash
  - Thrombocytopenia
  - Acute febrile neutrophilic dermatosis
  - Cutaneous vasculitis
  - Pulmonary side effects (particularly interstitial pneumonia)

- **Rare**
  - Splenic rupture
  - Anaemia
  - Dystrophy
  - Gastro-intestinal side effects (including nausea, vomiting, abdominal pain, anorexia, dysuria, proteinuria, haematuria, decreased blood glucose, transient decrease in blood glucose, transient hypotension, urinary abnormalities)

- **Uncommon**
  - Capillary leak syndrome (including fatal cases)
  - Splenic rupture

**MONITORING REQUIREMENTS**
Regular morphological and cytogenetic bone-marrow examinations recommended in severe congenital neutropenia (possible risk of myelodysplastic syndromes or leukaemia).

**DIRECTIONS FOR ADMINISTRATION**
For intravenous infusion (Neupogen®; Nivestin®; Ratiogran®; Zarzio®) give continuously or intermittently in Glucose 5% for a filgrastim concentration of less than 1 500 000 units/mL (15 micrograms/mL) albumin solution (human albumin solution) is added to produce a final albumin concentration of 2 mg/mL: should not be diluted to a filgrastim concentration of less than 200 000 units/mL (2 micrograms/mL) and should not be diluted with sodium chloride solution.

**PRESCRIBING AND DISPENSING INFORMATION**
Products containing filgrastim are not identical and although theoretically there should be no important differences in terms of safety and efficacy, when prescribing biological products it is good practice to use the brand name.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.
Blood and nutrition

Solution for injection
- Accofil (Accord Healthcare Ltd)
  - Filgrastim 60 mega u per 1 ml: Accofil 30 million units/0.5 ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (£284.20)
  - Filgrastim 96 mega u per 1 ml: Accofil 48 million units/0.5 ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (£475.71)
- Neupogen (Amgen Ltd)
  - Filgrastim 30 mega u per 1 ml: Neupogen 30 million units/1 ml solution for injection vials | 5 vial (£263.52)
  - Neupogen Singleject (Amgen Ltd)
  - Filgrastim 60 mega u per 1 ml: Neupogen Singleject 30 million units/0.5 ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (£263.52)
  - Filgrastim 96 mega u per 1 ml: Neupogen Singleject 48 million units/0.5 ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (£420.29)
- Nivestim ( Hospira UK Ltd)
  - Filgrastim 60 mega u per 1 ml: Nivestim 30 million units/0.5 ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (£290.00 (Hospital only))
  - Nivestim 12 million units/0.2 ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (£180.00 (Hospital only))
- Filgrastim 96 mega u per 1 ml: Nivestim 48 million units/0.5 ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (£465.00 (Hospital only))
- Zarzio (Sandz Ltd)
  - Filgrastim 60 mega u per 1 ml: Zarzio 30 million units/0.5 ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (£250.75)
  - Filgrastim 96 mega u per 1 ml: Zarzio 48 million units/0.5 ml solution for injection pre-filled syringes | 5 pre-filled disposable injection (£399.50)

Lenograstim
(Recombinant human granulocyte-colony stimulating factor, rHuG-CSF)

INDICATIONS AND DOSE
Reduction in the duration of neutropenia and associated complications following bone-marrow transplantation for non-myeloid malignancy (specialist use only) / Reduction in the duration of neutropenia and associated complications following peripheral stem cells transplantation for non-myeloid malignancy (specialist use only)

BY INTRAVENOUS INFUSION OR BY SUBCUTANEOUS INJECTION
- Adult: 150 micrograms/m² daily until neutrophil count stable in acceptable range (max. 28 days), to be started the day after transplantation. Intravenous infusion to be given over 30 minutes

Reduction in the duration of neutropenia and associated complications following treatment with cytotoxic-induced neutropenia associated with a significant incidence of febrile neutropenia (specialist use only)

BY SUBCUTANEOUS INJECTION
- Adult: 150 micrograms/m² daily until neutrophil count stable in acceptable range (max. 28 days), to be started on the day after completion of chemotherapy

Mobilisation of peripheral blood progenitor cells for harvesting and subsequent infusion, used alone (specialist use only)

BY SUBCUTANEOUS INJECTION
- Adult: 10 micrograms/kg daily for 4–6 days (5–6 days in healthy donors)

Mobilisation of peripheral blood progenitor cells, used following adjunctive myelosuppressive chemotherapy (to improve yield) (specialist use only)

BY SUBCUTANEOUS INJECTION
- Adult: 150 micrograms/m² daily until neutrophil count stable in acceptable range, to be started 1–5 days after completion of chemotherapy. For timing of leucopheresis, consult product literature

SIDE-EFFECTS
- Mucositis, splenic rupture, toxic epidermal necrosis

DIRECTIONS FOR ADMINISTRATION
For intravenous infusion (Granocyte®), give intermittently in Sodium chloride 0.9%; initially reconstitute with 1 ml water for injection provided (do not shake vigorously) then dilute with up to 50 ml infusion fluid for each vial of Granocyte-13 or up to 100 ml infusion fluid for Granocyte-34; give over 30 minutes.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Powder and solvent for solution for injection
EXCipients: May contain Phenylalanine
- Granocyte (Chugai Pharma UK Ltd)
  - Lenograstim 13.4 mega u Granocyte-13 powder and solvent for solution for injection vials | 1 vial (£40.11) | 5 vial (£200.55)
  - Lenograstim 33.6 mega u Granocyte-34 powder and solvent for solution for injection vials | 1 vial (£62.54) | 5 vial (£312.69)

Lipegfilgrastim
(Glycopegylated recombinant methionyl human granulocyte-colony stimulating factor)

INDICATIONS AND DOSE
Reduction in duration of neutropenia and incidence of febrile neutropenia in cytotoxic chemotherapy for malignancy (except chronic myeloid leukaemia and myelodysplastic syndromes)

BY SUBCUTANEOUS INJECTION
- Adult (specialist use only): 5 mg, for each chemotherapy cycle, given approximately 24 hours after chemotherapy, dose expressed as filgrastim

SIDE-EFFECTS
- Myelosuppressive chemotherapy
- Hypokalaemia

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
- LongueX (Teva UK Ltd)
  - Lipegfilgrastim 10 mg per 1 ml LonqueX 6 mg/0.6 ml solution for injection pre-filled syringes | 1 pre-filled disposable injection (£652.06)

Pegfilgrastim
(Pegylated recombinant methionyl human granulocyte-colony stimulating factor)

INDICATIONS AND DOSE
Reduction in duration of neutropenia and incidence of febrile neutropenia in cytotoxic chemotherapy for malignancy (except chronic myeloid leukaemia and myelodysplastic syndromes) (specialist use only)

BY SUBCUTANEOUS INJECTION
- Adult: 6 mg for each chemotherapy cycle, to be given at least 24 hours after chemotherapy, dose expressed as filgrastim

SIDE-EFFECTS
- Acute leukaemia - myelosuppressive chemotherapy

INTERACTIONS
- Appendix 1 (pegfilgrastim).

CAUTIONS
- Acute leukaemia - myelosuppressive chemotherapy
- Rare Capillary leak syndrome (including fatal cases)
1.8 Platelet disorders, essential thrombocythaemia

**Essential thrombocythaemia**

Anagrelide below inhibits platelet formation. It is licensed for essential thrombocythaemia in patients at risk of thrombo-haemorrhagic events who have not responded adequately to other drugs or who cannot tolerate other drugs. An at risk patient is defined by one or more of the following features: over 60 years of age, or a platelet count greater than 1000 x 10^9/L or a history of thrombo-haemorrhagic events. Anagrelide should be initiated under specialist supervision.

**CYCLIC AMP PHOSPHODIESTERASE III INHIBITORS**

**Anagrelide**

**INDICATIONS AND DOSE**

Essential thrombocythaemia in patients at risk of thrombo-haemorrhagic events who have not responded adequately to other drugs or who cannot tolerate other drugs (initiated under specialist supervision)

*BY MOUTH*

- Adult: Initially 500 micrograms twice daily, dose to be adjusted at weekly intervals according to response, increased in steps of 500 micrograms daily; usual dose 1–3 mg daily in divided doses (max. per dose 2.5 mg); maximum 10 mg per day

**CAUTIONS**

Cardiovascular disease—assess cardiac function before and during treatment — concomitant use of drugs that prolong QT-interval— assess cardiac function before and regularly during treatment — risk factors for QT-interval prolongation— assess cardiac function before and regularly during treatment

**INTERACTIONS**

Appendix 1 (anagrelide).

Caution with concomitant aspirin at risk of haemorrhage.

**SIDE-EFFECTS**

- **Common or very common** Anaemia · dizziness · fatigue · fluid retention · gastro-intestinal disturbances · headache · palpititation · rash · tachycardia
- **Uncommon** Alopecia · amnesia · anorexia · arthralgias · arthralgia · back pain · blood disorders · chest pain · confusion · congestive heart failure · depression · dry mouth · dysphagia · ecchymosis · epistaxis · fever · gastro-intestinal haemorrhage · haemorrhage · hypertension · hypoaesthesia · impotence · malaise · myalgia · nervousness · oedema · pancreatitis · paraesthesia · pneumonia pleural effusion · pruritus · skin discoloration · sleep disturbances · syncope · weight changes
- **Rare** Angina · asthenia · cardiomegaly · cardiomyopathy · colitis · dry skin · dysarthria · gastritis · gingival bleeding · impaired coordination · migraine · myocardial infarction · nocturia · pericardial effusion · postural hypotension · pulmonary hypertension · pulmonary infiltrates · renal failure · somnolence · tinnitus · vasodilatation · visual disturbances

**Frequency not known** Hepatitis · interstitial lung disease · Torsade de pointes · tubulointerstitial nephritis

**CONCEPTION AND CONTRACEPTION** Effective contraception required during treatment.

**PREGNANCY** Manufacturer advises avoid (toxicity in animal studies).

**BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT** Manufacturer advises caution in mild impairment. Avoid in moderate to severe impairment.

**RENAL IMPAIRMENT** Manufacturer advises avoid if eGFR less than 50 mL/minute/1.73 m².

**MONITORING REQUIREMENTS**

- Monitor full blood count (monitor platelet count every 2 days for 1 week, then weekly until maintenance dose established).
- Monitor liver function.
- Monitor serum creatinine.
- Monitor urea.
- Monitor urea and electrolytes (including potassium, magnesium and calcium) before and during treatment.

**PATIENT AND CARER ADVICE**

Dizziness may affect performance of skilled tasks (e.g. cycling, driving).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

- Xagrid (Shire Pharmaceuticals Ltd) ▼

Anagrelide (as Anagrelide hydrochloride) 500 microgram | 100 capsule $[POM] \$404.57$

1.9 Platelet disorders, idiopathic thrombocytopenic purpura

**Idiopathic thrombocytopenic purpura**

Acute idiopathic thrombocytopenic purpura is usually self-limiting in children. In adults, idiopathic thrombocytopenic purpura can be treated with a corticosteroid, e.g. prednisolone p. 585, gradually reducing the dose over several weeks. Splenectomy is considered if a satisfactory platelet count is not achieved or if there is a relapse on reducing the dose of corticosteroid or withdrawing it.

**Immunoglobulin** preparations, are also used in idiopathic thrombocytopenic purpura or where a temporary rapid rise in platelets is needed, as in pregnancy or pre-operatively; they are also used for children often in preference to a corticosteroid. Anti-D (rh0) immunoglobulin p. 1061 is effective in raising the platelet count in about 80% of unsplenectomised rheus-positive individuals; its effects may last longer than normal immunoglobulin p. 1063 for intravenous use, but further doses are usually required.

Other therapy that has been tried in refractory idiopathic thrombocytopenic purpura includes azathioprine p. 716, cyclophosphamide p. 750, vincristine sulphate p. 773, ciclosporin p. 717, and danazol p. 636. Rituximab p. 734 may also be effective and in some cases induces prolonged remission. For patients with chronic severe...
thrombocytopenia refractory to other therapy, tranexamic acid p. 95 may be given to reduce the severity of haemorrhage.

Eltrombopag below and romiplostim p. 845 are thrombopoietin receptor agonists licensed for the treatment of chronic idiopathic thrombocytopenic purpura in splenectomised patients refractory to other treatments, such as corticosteroids or immunoglobulins, or as a second-line treatment in non-splenectomised patients when surgery is contra-indicated (see also NICE guidance).

Eltrombopag is an oral preparation and romiplostim is an injection which is made biosynthetically by recombinant DNA technology; they should both be used under the supervision of a specialist.

THROMBOPOIETIN RECEPTOR AGONISTS

Eltrombopag

INDICATIONS AND DOSE

Therapeutic indications

- Chronic idiopathic thrombocytopenic purpura in splenectomised patients refractory to other treatments (such as corticosteroids or immunoglobulins) (under expert supervision)
- Second-line treatment of chronic idiopathic thrombocytopenic purpura in non-splenectomised patients when surgery is contra-indicated (under expert supervision)

BY MOUTH

Adult: Initially 50 mg once daily, dose to be adjusted to achieve a platelet count of 50 x 10⁹/litre or more—consult product literature for dose adjustments, discontinue if inadequate response after 4 weeks treatment at maximum dose; maximum 75 mg per day

Adult (patients of East Asian origin): Initially 25 mg once daily, dose to be adjusted to achieve a platelet count of 50 x 10⁹/litre or more—consult product literature for dose adjustments, discontinue if inadequate response after 4 weeks treatment at maximum dose; maximum 75 mg per day.

Treatment of thrombocytopenia associated with chronic hepatitis C infection, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy (under expert supervision)

BY MOUTH

Adult: Initially 25 mg once daily, dose to be adjusted to achieve a platelet count sufficient to initiate antiviral therapy then a platelet count of 50–75 x 10⁹/litre during antiviral therapy—consult product literature for dose adjustments, discontinue if inadequate response after 2 weeks treatment at maximum dose; maximum 100 mg per day.

Patient and carer advice

Each dose should be taken at least 4 hours before or after any dairy products (or foods containing calcium), indigestion remedies, or medicines containing aluminium, calcium, iron, magnesium, zinc, or selenium to reduce possible interference with absorption.

Patient and carer advice

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (July 2010) that eltrombopag (Revolade) is accepted for restricted use within NHS Scotland for the treatment of both splenectomised and non-splenectomised patients with severe symptomatic immune (idiopathic) thrombocytopenic purpura or a high risk of bleeding.

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.
Romiplostim

INDICATIONS AND DOSE
Treatment of chronic idiopathic thrombocytopenic purpura in splenectomised patients refractory to other treatments (such as corticosteroids or immunoglobulins) (under expert supervision) - Second-line treatment of chronic idiopathic thrombocytopenic purpura in non-splenectomised patients when surgery is contra-indicated (under expert supervision)

BY SUBCUTANEOUS INJECTION

- Adult: Initially 1 microgram/kg once weekly, adjusted in steps of 1 microgram/kg once weekly (max. per dose 10 micrograms/kg once weekly) until a stable platelet count of 50 x 10^9/litre or more is reached, discontinue treatment if inadequate response after 4 weeks at maximum dose, consult product literature for dose adjustments

- CHILDREN AND ADULTS: Use only if essential, as manufacturers advise avoid use in children under 12 years or adolescents under 18 years

- AGED OVER 65 YEARS: Use only if essential, as manufacturers advise use only if essential

- PREGNANCY

- BRST FEEDING

- HEPATIC IMPAIRMENT

- RENAL IMPAIRMENT

- MONITORING REQUIREMENTS

- PATIENT AND CARER ADVICE

- NATIONAL FUNDING/ACCESS DECISIONS

- NICE technology appraisals (TAs)

- Scottish Medicines Consortium (SMC) Decisions

- MEDICINAL FORMS

- Powder and solvent for solution for injection

- Fluids and electrolytes

- Management of hyperkalaemia

2 Fluid and electrolyte imbalances

The electrolyte concentrations (intravenous fluid) table and the electrolyte content (gastro-intestinal secretions) table may be helpful in planning replacement electrolyte therapy; faeces, vomit, or aspiration should be saved and analysed where possible if abnormal losses are suspected.

**Oral preparations for fluid and electrolyte imbalance**

Sodium and potassium salts, may be given by mouth to prevent deficiencies or to treat established deficiencies of mild or moderate degree.

**Oral potassium**

Compensation for potassium loss is especially necessary:

- in those taking digoxin or anti-arrhythmic drugs, where potassium depletion may induce arrhythmias;
- in patients in whom secondary hyperaldosteronism occurs, e.g. renal artery stenosis, cirrhosis of the liver, the nephrotic syndrome, and severe heart failure;
- in patients with excessive losses of potassium in the faeces, e.g. chronic diarrhoea associated with intestinal malabsorption or laxative abuse.

Measures to compensate for potassium loss may also be required in the elderly since they frequently take inadequate amounts of potassium in the diet (but see warning on renal insufficiency). Measures may also be required during long-term administration of drugs known to induce potassium loss (e.g. corticosteroids). Potassium supplements are seldom required with the small doses of diuretics given to treat hypertension; potassium-sparing diuretics (rather than potassium supplements) are recommended for prevention of hypokalaemia due to diuretics such as furosemide p. 201 or the thiazides when these are given to eliminate oedema.

If potassium salts are used for the prevention of hypokalaemia, then doses of potassium chloride daily (in divided doses) by mouth are suitable in patients taking a normal diet. Smaller doses must be used if there is renal insufficiency (common in the elderly) to reduce the risk of hyperkalaemia.

Potassium salts cause nausea and vomiting and poor compliance is a major limitation to their effectiveness; when appropriate, potassium-sparing diuretics are preferable.

When there is established potassium depletion larger doses may be necessary, the quantity depending on the severity of any continuing potassium loss (monitoring of plasma-potassium concentration and specialist advice would be required). Potassium depletion is frequently associated with chloride depletion and with metabolic alkalosis, and these disorders require correction.

**Management of hyperkalaemia**

Acute severe hyperkalaemia (plasma-potassium concentration above 6.5 mmol/litre or in the presence of ECG changes) calls for urgent treatment with calcium
Blood and nutrition

Sodium bicarbonate p. 848 is given by mouth for chronic acidicotic states such as uraemic acidosis or renal tubular acidosis. The dose for correction of metabolic acidosis is not predictable and the response must be assessed. For severe metabolic acidosis, sodium bicarbonate can be given intravenously.

Sodium bicarbonate may also be used to increase the pH of the urine; it is also used in dyspepsia.

Sodium supplements may increase blood pressure or cause fluid retention and pulmonary oedema in those at risk; hypokalaemia may be exacerbated.

Where hyperchloraemic acidosis is associated with potassium deficiency, as in some renal tubular and gastrointestinal disorders it may be appropriate to give oral potassium bicarbonate, although acute or severe deficiency should be managed by intravenous therapy.

**Parenteral preparations for fluid and electrolyte imbalance**

**Electrolytes and water**

Solutions of electrolytes are given intravenously, to meet normal fluid and electrolyte requirements or to replenish substantial deficits or continuing losses, when the patient is nauseated or vomiting and is unable to take adequate amounts by mouth. When intravenous administration is not possible, fluid (as sodium chloride 0.9% p. 851 or glucose 5% p. 852) can also be given by subcutaneous infusion (hypodermoclysis).

The nature and severity of the electrolyte imbalance must be assessed from the history and clinical and biochemical investigations. Sodium, potassium, chloride, magnesium, phosphate, and water depletion can occur singly and in combination with or without disturbances of acid-base balance.

Isotonic solutions may be infused safely into a peripheral vein. Solutions more concentrated than plasma, e.g. 20% glucose p. 852, are best given through an indwelling catheter positioned in a large vein.

**Intravenous sodium**

Sodium chloride in isotonic solution provides the most important extracellular ions in near physiological concentrations and is indicated in sodium depletion, which can arise from such conditions as gastro-enteritis, diabetic ketoacidosis, ileus, and ascites. In a severe deficit of 4 to 8 litres, 2 to 3 litres of isotonic sodium chloride may be given over 2 to 3 hours; thereafter the infusion can usually be at a slower rate.

Chronic hyponatraemia arising from inappropriate secretion of antidiuretic hormone should ideally be corrected by fluid restriction. However, if sodium chloride is required for acute or chronic hyponatraemia, regardless of the cause, the deficit should be corrected slowly to avoid the risk of osmotic demyelination syndrome and the rise in plasma-sodium concentration should not exceed 10 mmol/litre in 24 hours. In severe hyponatraemia, sodium chloride 1.8% may be used cautiously.

**Compound sodium lactate** (Hartmann’s solution) can be used instead of isotonic sodium chloride solution during or after surgery, or in the initial management of the injured or wounded; it may reduce the risk of hyperchloaemic acidosis.

Glucose with sodium chloride solutions are indicated when there is combined water and sodium depletion. A 1:1 mixture of isotonic sodium chloride and 5% glucose allows some of the water (free of sodium) to enter body cells which suffer most from dehydration while the sodium salt with a volume of water determined by the normal plasma Na⁺ remains extracellular.

Combined sodium, potassium, chloride, and water depletion may occur, for example, with severe diarrhoea or persistent vomiting; replacement is carried out with sodium...
Fluid and electrolyte imbalances

Electrolyte concentrations—intravenous fluids

<table>
<thead>
<tr>
<th>Intravenous infusion</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>HCO₃⁻</th>
<th>Cl⁻</th>
<th>Ca²⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal plasma values</td>
<td>142</td>
<td>4.5</td>
<td>26</td>
<td>103</td>
<td>2.5</td>
</tr>
<tr>
<td>Sodium Chloride 0.9%</td>
<td>150</td>
<td>-</td>
<td>-</td>
<td>150</td>
<td>-</td>
</tr>
<tr>
<td>Compound Sodium Lactate (Hartmann’s)</td>
<td>131</td>
<td>5</td>
<td>29</td>
<td>111</td>
<td>2</td>
</tr>
<tr>
<td>Sodium Chloride 0.18% and Glucose 4% (Adults only)</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>Potassium Chloride 0.3% and Glucose 5%</td>
<td>-</td>
<td>40</td>
<td>-</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>Potassium Chloride 0.3% and Sodium Chloride 0.9%</td>
<td>150</td>
<td>40</td>
<td>-</td>
<td>190</td>
<td>-</td>
</tr>
</tbody>
</table>

To correct metabolic acidosis

- Sodium Bicarbonate 1.26%: 150 - 150 - - -
- Sodium Bicarbonate 8.4% for cardiac arrest: 1000 - 1000 - - -
- Sodium Lactate (m/6): 167 - 167 - - -

Electrolyte content—gastro-intestinal secretions

<table>
<thead>
<tr>
<th>Type of fluid</th>
<th>H⁺</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>HCO₃⁻</th>
<th>Cl⁻</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>40-60</td>
<td>20-80</td>
<td>5-20</td>
<td>-</td>
<td>100-150</td>
</tr>
<tr>
<td>Biliary</td>
<td>-</td>
<td>120-140</td>
<td>5-15</td>
<td>30-50</td>
<td>80-120</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>-</td>
<td>120-140</td>
<td>5-15</td>
<td>70-110</td>
<td>40-80</td>
</tr>
<tr>
<td>Small bowel</td>
<td>-</td>
<td>120-140</td>
<td>5-15</td>
<td>20-40</td>
<td>90-130</td>
</tr>
</tbody>
</table>

Bicarbonate and lactate

Sodium bicarbonate p. 848 is used to control severe metabolic acidosis (pH<7.1) particularly that caused by loss of bicarbonate (as in renal tubular acidosis or from excessive gastro-intestinal losses). Mild metabolic acidosis associated with volume depletion should first be managed by appropriate fluid replacement because acidosis usually resolves as tissue and renal perfusion are restored. In more severe metabolic acidosis or when the acidosis remains unresponsive to correction of anaemia or hypovolaemia, sodium bicarbonate (1.26%) can be infused over 3–4 hours with plasma-pH and electrolyte monitoring. In severe shock, for example in cardiac arrest, metabolic acidosis can develop without sodium or volume depletion; in these circumstances sodium bicarbonate is best given as a small volume of hypertonic solution, such as 50 mL of 8.4% solution intravenously.

Sodium lactate intravenous infusion is no longer used in metabolic acidosis because of the risk of producing lactic acidosis, particularly in seriously ill patients with poor tissue perfusion or impaired hepatic function.

For chronic acidotic states, sodium bicarbonate can be given by mouth.

Plasma and plasma substitutes

Plasma and plasma substitutes (‘colloids’) contain large molecules that do not readily leave the intravascular space where they exert osmotic pressure to maintain circulatory volume. Compared to fluids containing electrolytes such as sodium chloride p. 851 and glucose p. 852 (‘crystalloids’), a smaller volume of colloid is required to produce the same expansion of blood volume, thereby shifting salt and water from the extravascular space. If resuscitation requires a volume of fluid that exceeds the maximum dose of the colloid then crystalloids can be given; packed red cells may also be required.

Albumin solution p. 853, prepared from whole blood, contains soluble proteins and electrolytes but no clotting factors, blood group antibodies, or plasma cholinesterases; they may be given without regard to the recipient’s blood group.

Albumin is usually used after the acute phase of illness, to correct a plasma-volume deficit; hypoalbuminaemia itself is
Blood and nutrition

Concentrated albumin solution may also be used to obtain a salt and water overload than isotonic solutions. Because of interstitial fluid overload, to restore patients with an intravascular fluid deficit and oedema (e.g. in hepatic cirrhosis).

Recent evidence does not support the previous view that the use of albumin increases mortality.

Plasma substitutes

Dextran, gelatin p. 854, and the hydroxyethyl starch, tetrasacth, are macromolecular substances which are metabolised slowly. Dextran and gelatin may be used at the outset to expand and maintain blood volume in shock arising from conditions such as burns or septicaemia; they may also be used as an immediate short-term measure to treat haemorrhage until blood is available. Dextran and gelatin are rarely needed when shock is due to sodium and water depletion because, in these circumstances, the shock responds to water and electrolyte repletion.

Hydroxyethyl starches should only be used for the treatment of hypovolaemia due to acute blood loss when crystalloids alone are not sufficient; they should be used at the lowest effective dose for the first 24 hours of fluid resuscitation.

Plasma substitutes should not be used to maintain plasma volume in conditions such as burns or peritonitis where there is loss of plasma protein, water, and electrolytes over periods of several days or weeks. In these situations, plasma or plasma protein fractions containing large amounts of albumin should be given.

Large volumes of some plasma substitutes can increase the risk of bleeding through depletion of coagulation factors.

**BICARBONATE**

**Sodium bicarbonate**

**INDICATIONS AND DOSE**

Chronic acidotic states such as uraemic acidosis or renal tubular acidosis

**BY MOUTH**

- Adult: 4.8 g daily, (57 mmol each of Na⁺ and HCO₃⁻), higher doses may be required and should be adjusted according to response.

Severe metabolic acidosis

**BY SLOW INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION**

- Adult: Administer an amount appropriate to the body base deficit, to be given by slow intravenous injection of a strong solution (up to 8.4%), or by continuous intravenous infusion of a weaker solution (usually 1.26%).

Alkalisation of urine | Relief of discomfort in mild urinary-tract infections

**BY MOUTH**

- Adult: 3 g every 2 hours until urinary pH exceeds 7, to be dissolved in water.

Maintenance of alkaline urine

**BY MOUTH**

- Adult: 5–10 g daily, to be dissolved in water.

**CONTRA-INDICATIONS** Salt restricted diet

**CAUTIONS** Avoid prolonged use in urinary conditions • cardiac disease • elderly • patients on sodium-restricted diet • respiratory acidosis

**INTERACTIONS** → Appendix 1 (antacids).

**SIDE-EFFECTS**

- When used for chronic acidotic states such as uraemic acidosis or renal tubular acidosis, and for maintenance of alkaline urine fluid retention (in those at risk) • hypokalaemia may be exacerbated • increase blood pressure • pulmonary oedema (in those at risk).

- When used for alkalisation of urine, and for relief of discomfort in mild urinary-tract infections alkalaosis on prolonged use • eructation

**PREGNANCY** Use with caution in urinary conditions.

**HEPATIC IMPAIRMENT** In patients with fluid retention, avoid large amounts of sodium.

**RENAL IMPAIRMENT** Avoid (except for specialised role in some forms of renal disease).

**MONITORING REQUIREMENTS**

- With intravenous use Plasma pH and electrolytes should be monitored.

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use in adults For slow intravenous injection use a small volume of hypertonic solution (such as 50 mL of 8.4%). For continuous intravenous infusion a weaker solution of 1.26% can be infused over 3–4 hours.

- With oral use Sodium bicarbonate may affect the stability or absorption of other drugs if administered at the same time. If possible, allow 1–2 hours before administering other drugs orally.

**PRESCRIBING AND DISPENSING INFORMATION** Oral solutions of sodium bicarbonate are required occasionally; these are available from ‘special-order’ manufacturers or specialist importing companies; the strength of sodium bicarbonate should be stated on the prescription.

**PATIENT AND CARER ADVICE** Patients or carers should be given advice on the administration of sodium bicarbonate oral medicines.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, oral suspension, oral solution, powder, capsule, liquid, mouthwash

**Tablet**

- SODIUM BICARBONATE (Non-proprietary)

  Sodium bicarbonate 600 mg Sodium bicarbonate 600mg tablets

- SODIUM BICARBONATE (Non-proprietary)

  Sodium bicarbonate 500 mg Sodium bicarbonate 500mg capsules | 56 capsule | no price available DT price = £2.88 | 100 capsule | no price available

**Solution for injection**

- SODIUM BICARBONATE (Non-proprietary)

  Sodium bicarbonate 84 mg per 1 ml Sodium bicarbonate 8.4% (1mmol/ml) solution for injection 10ml ampoules | 10 ampoule | £67.01 Sodium bicarbonate 8.4% solution for injection 10ml Minijet pre-filled syringes | 11 pre-filled disposable injection | £9.71 Sodium bicarbonate 8.4% (1mmol/ml) solution for injection 250ml bottles | 10 bottle | £65.34 Sodium bicarbonate 8.4% (1mmol/ml) solution for injection 100ml bottles | 10 bottle | £62.04

**Infusion**

- SODIUM BICARBONATE (Non-proprietary)

  Sodium bicarbonate 12.6 mg per 1 ml Polyfusor BC sodium bicarbonate 1.26% infusion 500ml bottles | 1 bottle | £8.94 | 12 bottle | no price available

  Sodium bicarbonate 14 mg per 1 ml Polyfusor BD sodium bicarbonate 1.4% infusion 500ml bottles | 1 bottle | £8.94 | 12 bottle | no price available

  Sodium bicarbonate 27.4 mg per 1 ml Polyfusor V sodium bicarbonate 2.74% infusion 500ml bottles | 1 bottle | £8.94 | 12 bottle | no price available

  Sodium bicarbonate 42 mg per 1 ml Polyfusor BE sodium bicarbonate 4.2% infusion 500ml bottles | 1 bottle | £8.94 | 12 bottle | no price available
## Oral Rehydration Salts

### Disodium hydrogen citrate with glucose, potassium chloride and sodium chloride

#### Indications and Dose

**Fluid and electrolyte loss in diarrhoea**

- **By Mouth**
  - Child 1-11 months: 1–1½ times usual feed volume to be given
  - Child 11 years: 200 mL, to be given after every loose motion
  - Child 12–17 years: 200–400 mL, to be given after every loose motion, dose according to fluid loss
  - Adult: 200–400 mL, to be given after every loose motion, dose according to fluid loss

#### Directions for Administration

Reconstitute 1 sachet with 200 mL of water (freshly boiled and cooled for infants); 5 sachets reconstituted with 1 litre of water provide Na⁺ 60 mmol, K⁺ 20 mmol, Cl⁻ 60 mmol, citrate 10 mmol, and glucose 90 mmol.

#### Prescribing and Dispensing Information

Flavours of oral powder formulations may include black currant, citrus, or natural.

#### Patient and Carer Advice

- **Medicines for Children leaflet: Oral rehydration salts**
  - www.medicinesforchildren.org.uk/oral-rehydration-salts
  - After reconstitution any unused solution should be discarded no later than 1 hour after preparation unless stored in a refrigerator when it may be kept for up to 24 hours.

#### Medicinal Forms

There can be variation in the licensing of different medicines containing the same drug.

- **Powder**
  - Dioralyte® (Sanofi)
    - Disodium hydrogen citrate 530 mg, Glucose 3.56 gram,
    - Potassium chloride 300 mg, Sodium chloride 470 mg
  - Dioralyte oral powder sachets citrus | 20 sachet (£6.72)
  - Dioralyte oral powder sachets plain | 20 sachet (£6.72)
  - Dioralyte oral powder sachets blackcurrant | 20 sachet (£6.72)

### Potassium chloride with glucose, sodium bicarbonate and sodium chloride

#### Indications and Dose

**Fluid and electrolyte loss in diarrhoea**

- **By Mouth**
  - Adult: 200–400 mL, to be given after every loose motion, dose according to fluid loss

#### Directions for Administration

Reconstitute 1 sachet with 200 mL of water (freshly boiled and cooled for infants); 5 sachets when reconstituted with 1 litre of water provide Na⁺ 50 mmol, K⁺ 20 mmol, Cl⁻ 40 mmol, HCO₃⁻ 30 mmol, and glucose 111 mmol.

#### Prescribing and Dispensing Information

Flavours of oral powder formulations may include banana, orange, black current, lemon and lime, plain, or multiflavoured.

#### Patient and Carer Advice

Patients and carers should be advised how to reconstitute Electrolade® oral powder.

After reconstitution any unused solution should be discarded no later than 1 hour after preparation unless stored in a refrigerator when it may be kept for up to 24 hours.

### Potassium chloride with calcium chloride dihydrate, and sodium chloride

#### (Ringer’s solution)

The properties listed below are those particular to the combination only. For the properties of the components please consider, potassium chloride p. 863, sodium chloride p. 851.

#### Indications and Dose

**Electrolyte imbalance**

- **By Intravenous Infusion**
  - Adult: Dosed according to the deficit or daily maintenance requirements (consult product literature)

#### Prescribing and Dispensing Information

Ringer’s solution for injection provides the following ions (in mmol/ litre), Ca²⁺ 2.2, K⁺ 4, Na⁺ 147, Cl⁻ 156.

#### Medicinal Forms

There can be variation in the licensing of different medicines containing the same drug.

- **Infusion**
  - **Calcium Chloride Dihydrate with Potassium Chloride and Sodium Chloride**
    - Calcium chloride 320 microgram per 1 mL, Potassium chloride 300 microgram per 1 mL, Sodium chloride 8.6 mg per 1 mL
    - Polyfusor C ringsers infusion 500mL bottles | 1 bottle (£2.81) | 200mL bottles | 1 bottle (£6.84)
Potassium chloride with calcium chloride, sodium chloride and sodium lactate
(Sodium Lactate Intravenous Infusion, Compound; Hartmann’s Solution for Injection; Ringer-Lactate Solution for Injection)
The properties listed below are those particular to the combination only. For the properties of the components please consider, potassium chloride p. 863, sodium chloride p. 851, calcium chloride p. 857.

INDICATIONS AND DOSE
For prophylaxis, and replacement therapy, requiring the use of sodium chloride and lactate, with minimal amounts of calcium and potassium
BY INTRAVENOUS INFUSION
> Adult: (consult product literature)

PRESCRIBING AND DISPENSING INFORMATION
Compound sodium lactate intravenous infusion contains Na⁺ 131 mmol, K⁺ 5 mmol, Ca⁺⁺ 2 mmol, HCO₃⁻ (as lactate) 29 mmol, Cl⁻ 111 mmol/litre.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
Infusion
> CALCIUM CHLORIDE WITH POTASSIUM CHLORIDE AND SODIUM CHLORIDE AND SODIUM LACTATE (Non-proprietary)
Calcium chloride 270 microgram per 1 ml, Potassium chloride 400 microgram per 1 ml, Sodium chloride 6 mg per 1 ml, Sodium lactate 3.17 mg per 1 ml Sodium lactate compound infusion 1 litre | 1 bag (POM) no price available | 10 bag (POM) no price available

Potassium chloride with glucose
The properties listed below are those particular to the combination only. For the properties of the components please consider, glucose p. 852, potassium chloride p. 863.

INDICATIONS AND DOSE
Electrolyte imbalance
BY INTRAVENOUS INFUSION
> Adult: Dosed according to the deficit or daily maintenance requirements

PRESCRIBING AND DISPENSING INFORMATION
Compound potassium chloride 3 mg per 1 ml, Potassium chloride 3 mg per 1 ml, Sodium chloride 4.5 mmol/1 litre / glucose 5% infusion 500 ml bags | 1 bag (POM) £1.67

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for infusion, infusion
Infusion
> GLUCOSE WITH POTASSIUM CHLORIDE (Non-proprietary)
Glucose anhydrous 50 mg per 1 ml, Potassium chloride 3 mg per 1 ml Potassium chloride 0.3% (potassium 20mmol/500ml) / glucose 5% infusion 500ml bags | 1 bag (POM) £1.67
Potassium chloride 0.3% (potassium 40mmol/1litre) / glucose 5% infusion 1 litre bags | 1 bag (POM) £1.79
Glucose anhydrous 50 mg per 1 ml, Potassium chloride 1.5 mg per 1 ml Potassium chloride 0.15% (potassium 10mmol/500ml) / glucose 5% infusion 500ml bags | 1 bag (POM) £1.67
Potassium chloride 0.15% (potassium 20mmol/1litre) / glucose 5% infusion 1 litre bags | 1 bag (POM) £2.20
Glucose anhydrous 50 mg per 1 ml, Potassium chloride 2 mg per 1 ml Potassium chloride 0.2% (potassium 27mmol/1litre) / glucose 5% infusion 1 litre bags | 1 bag (POM) £2.20

Potassium chloride with potassium bicarbonate
The properties listed below are those particular to the combination only. For the properties of the components please consider, potassium chloride p. 863.

INDICATIONS AND DOSE
Potassium depletion
BY MOUTH
> Adult: Dosed according to the deficit or daily maintenance requirements (consult product literature)

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
Effervescent tablet
CAUTIONARY AND ADVISORY LABELS 13, 21
> Sando-K (NK Pharma Ltd) Potassium bicarbonate 400 mg, Potassium chloride 600 mg
Sando-K effervescent tablets | 100 tablet (P) £7.65 DT price + £7.65
Potassium chloride with sodium chloride

The properties listed below are those particular to the combination only. For the properties of the components please consider, potassium chloride p. 863, sodium chloride below.

INDICATIONS AND DOSE

Electrolyte imbalance

BY INTRAVENOUS INFUSION

- Adult: Depending on the deficit or the daily maintenance requirements (consult product literature)

- MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for infusion, infusion

Infusion

- POTASSIUM CHLORIDE WITH SODIUM CHLORIDE (Non-proprietary)

Potassium chloride 3 mg per 1 ml, Sodium chloride 9 mg per 1 ml Potassium chloride 0.3% (potassium 20mmol/500ml) / sodium chloride 0.9% infusion 500ml bags | 1 bag (POM) £1.42
Potassium chloride 0.3% (potassium 40mmol/litre) / Sodium chloride 0.9% infusion 1 litre bags | 1 bag (POM) £1.79
Potassium chloride 1.5 mg per 1 ml, Sodium chloride 9 mg per 1 ml Potassium chloride 0.15% (potassium 10mmol/500ml) / sodium chloride 0.9% infusion 500ml bags | 1 bag (POM) £1.67
Potassium chloride 0.15% (potassium 20mmol/litre) / sodium chloride 0.9% infusion 1 litre bags | 1 bag (POM) £2.20 | 10 bag (POM) £22.00
Potassium chloride 2 mg per 1 ml, Sodium chloride 9 mg per 1 ml Potassium chloride 0.2% (potassium 13.3mmol/500ml) / sodium chloride 0.9% infusion 500ml bags | 1 bag (POM) £1.67
Potassium chloride 0.2% (potassium 27mmol/litre) / sodium chloride 0.9% infusion 1 litre bags | 1 bag (POM) £2.20

SODIUM

Sodium chloride

INDICATIONS AND DOSE

Prophylaxis of sodium chloride deficiency

BY MOUTH USING MODIFIED-RELEASE MEDICINES

- Adult: 4–8 tablets daily, to be taken with water, up to maximum 20 tablets daily in severe depletion

Chronic renal salt wasting

BY MOUTH USING MODIFIED-RELEASE MEDICINES

- Adult: Up to 20 tablets daily, to be taken with appropriate fluid intake

Management of diabetic ketoacidosis (if systolic blood pressure is below 90 mmHg and adjusted for age, sex, and medication as appropriate)

BY INTRAVENOUS INFUSION

- Adult: 500 ml, sodium chloride 0.9% to be given over 10–15 minutes, repeat if blood pressure remains below 90 mmHg and seek senior medical advice, when blood pressure is over 90 mmHg, sodium chloride 0.9% should be given by intravenous infusion at a rate that replaces deficit and provides maintenance, management regimen also includes administration of potassium chloride, soluble insulin, long acting insulin analogues and glucose 10% solution

Diluent for instillation of drugs to the bladder

BY INTROVASCULAR INSTILLATION

- Adult: (consult product literature)

CAUTIONS

GENERAL CAUTIONS:

Dilutional hyponatraemia especially in children and the elderly

SPECIFIC CAUTIONS:

- With intravenous use avoid excessive administration - cardiac failure - hypertension - peripheral oedema - pulmonary oedema - restrict intake in impaired renal function - toxaemia of pregnancy

SIDE-EFFECTS

- With intravenous use administration of large doses may give rise to sodium accumulation - hyperchloraemic acidosis - oedema

MONITORING REQUIREMENTS

With intravenous use The jugular venous pressure should be assessed, the bases of the lungs should be examined for crepitations, and in elderly or seriously ill patients it is often helpful to monitor the right atrial (central) venous pressure.

PRESCRIBING AND DISPENSING INFORMATION

With intravenous use The term ‘normal saline’ should not be used to describe sodium chloride intravenous infusion 0.9%; the term ‘physiological saline’ is acceptable but it is preferable to give the composition (i.e. sodium chloride intravenous infusion 0.9%).

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops, solution for injection, irrigation, solution for infusion, oral solution, capsule, eye ointment, nebuliser liquid, infusion

Modified-release tablet

CAUTIONARY AND ADVISORY LABELS 25

- Slow Sodium (HK Pharma Ltd)

Sodium chloride 600 mg Slow Sodium 600mg tablets | 100 tablet (GSK) £6.05 DT price = £6.05

Solution for injection

- SODIUM CHLORIDE (Non-proprietary)

Sodium chloride 9 mg per 1 ml Sodium chloride 0.9% solution for injection 2ml ampoules | 10 ampoule (POM) £1.80–£2.57 DT price = £2.07
Sodium chloride 0.9% solution for injection 5ml ampoules | 10 ampoule (POM) £2.00–£2.12 DT price = £2.12 | 50 ampoule (POM) £10.50–£13.50
Sodium chloride 0.9% solution for injection 10ml ampoules | 10 ampoule (POM) £2.30–£2.97 DT price = £2.96 | 50 ampoule (POM) £14.75–£16.75
Sodium chloride 0.9% solution for injection 20ml ampoules | 20 ampoule (POM) £15.75–£16.75
Sodium chloride 0.9% solution for injection 50ml vials | 1 vial (POM) £3.41 | 25 vial (POM) £75.00–£85.00
Sodium chloride 300 mg per 1 ml Sodium chloride 30% solution for injection 10ml ampoules | 10 ampoule (POM) £64.25
Sodium chloride 30% solution for injection 50ml vials | 1 vial (POM) £10.67

Infusion

- SODIUM CHLORIDE (Non-proprietary)

Sodium chloride 1.8 mg per 1 ml Sodium chloride 0.18% infusion 500ml bottles | 1 bottle (POM) £3.28
Sodium chloride 4.5 mg per 1 ml Sodium chloride 0.45% infusion 500ml bottles | 1 bottle (POM) £3.28
Sodium chloride 0.45% infusion 500ml bags | 1 bag (POM) £1.38
Sodium chloride 9 mg per 1 ml Sodium chloride 0.9% infusion 500ml bags | 1 bag (POM) £1.49
Sodium chloride 0.9% infusion 100ml bags | 1 bag (POM) £1.27
Sodium chloride 0.9% infusion 250ml bags | 1 bag (POM) £1.61
Sodium chloride 0.9% infusion 500ml bags | 1 bag (POM) £1.61
Sodium chloride 0.9% infusion 1 litre bags | 1 bag (POM) no price available
Sodium chloride 0.9% infusion 2 litre bags | 1 bag (POM) £3.01
Sodium chloride 0.9% infusion 100ml polyethylene bottles | 1 bottle (POM) £0.55 | 20 bottle (POM) £11.00
Sodium chloride 18 mg per 1 ml Sodium chloride 1.8% infusion 500ml bottles | 1 bottle (POM) £3.28
Sodium chloride 27 mg per 1 ml Sodium chloride 2.7% infusion 500ml bottles | 1 bottle (POM) £3.28
Sodium chloride 50 mg per 1 ml Sodium chloride 5% infusion 500ml bottles | 1 bottle (POM) £3.28
**Blood and nutrition**

**Sodium chloride with glucose**

The properties listed below are those particular to the combination only. For the properties of the components please consider, glucose below, sodium chloride p. 851.

**INDICATIONS AND DOSE**

**Combined water and sodium depletion**

**BY INTRAVENOUS INFUSION**

- Adult: (consult product literature)

**MONITORING REQUIREMENTS**

Maintenance fluid should accurately reflect daily requirements and close monitoring is required to avoid fluid and electrolyte imbalance.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order restrictions to high dependency and intensive care units, and specialist wards, such as renal, liver, and cardiac units. Local guidelines on intravenous fluids should be consulted.

**SIDE-EFFECTS**

Glucose injections especially if hypertonic may have a low pH and may cause venous irritation and thrombophlebitis.

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use in children. Injections containing more than 10% glucose can be irritant and should be given into a central venous line; however, solutions containing up to 12.5% can be administered for a short period into a peripheral line.

**PRESCRIBING AND DISPENSING INFORMATION**

Glucose BP is the monohydrate but Glucose Intravenous Infusion BP is a sterile solution of anhydrous glucose or glucose monohydrate, potency being expressed in terms of anhydrous glucose.

**EXCEPTIONS TO LEGAL CATEGORY**

- With intravenous use. Prescription only medicine restriction does not apply to 50% solution where administration is for saving life in emergency.

**SUGARS**

**Glucose**

(Dextrose Monohydrate)

**INDICATIONS AND DOSE**

**Energy source**

- Adult: 1–3 litres daily, solution concentration of 20–50% to be administered

**Water replacement**

- Adult: The volume of glucose solution needed to replace deficits may vary (consult product literature)

**Hypoglycaemia**

- Child: 500 mg/kg, to be administered as Glucose 10% intravenous infusion into a large vein through a large-gauge needle; care is required since this concentration is irritant especially if extravasation occurs

- Adult: 10 g, to be administered as Glucose 20% intravenous infusion into a large vein through a large-gauge needle; care is required since this concentration is irritant especially if extravasation occurs

**Management of diabetic ketoacidosis**

**BY INTRAVENOUS INFUSION**

- Child: Glucose 5% or 10% should be added to replacement fluid once blood-glucose concentration falls below 14 mmol/litre

- Adult: Glucose 10% should be given once blood-glucose concentration falls below 14 mmol/litre, to be administered into a large vein through a large-gauge needle at a rate of 125 ml/hour, in addition to the sodium chloride 0.9% infusion

**Oral glucose tolerance test**

**BY MOUTH**

- Adult: Test dose 75 g, anhydrous glucose to be given to the fasting patient and blood-glucose concentrations measured at intervals, to be given with 200–300 mL fluid

**Establish presence of gestational diabetes**

**BY MOUTH**

- Adult: Test dose 75 g, anhydrous glucose to be given to the fasting patient and blood-glucose concentrations measured at intervals, to be given with 200–300 mL fluid

**Persistent cyanosis (in combination with propranolol) when blood glucose less than 3 mmol/litre (followed by morphine)**

**BY INTRAVENOUS INFUSION**

- Child: 200 mg/kg, to be administered as Glucose 10% intravenous infusion over 10 minutes

**Dose equivalence and conversion**

75 g anhydrous glucose is equivalent to Glucose BP 82.5 g.

**CAUTIONS**

Do not give alone except when there is no significant loss of electrolytes - prolonged administration of glucose solutions without electrolytes can lead to hyponatraemia and other electrolyte disturbances.

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use in children. Glucose 4% intravenous infusion fluid should not be used for fluid replacement in children aged 16 years or less because of the risk of hyponatraemia; availability of this infusion should be restricted to high dependency and intensive care units, and specialist wards, such as renal, liver, and cardiac units. Local guidelines on intravenous fluids should be consulted.

**SUGAR**

**Glucose**

(Dextrose Monohydrate)

**INDICATIONS AND DOSE**

**Energy source**

- Adult: 1–3 litres daily, solution concentration of 20–50% to be administered

**Water replacement**

- Adult: The volume of glucose solution needed to replace deficits may vary (consult product literature)

**Hypoglycaemia**

- Child: 500 mg/kg, to be administered as Glucose 10% intravenous infusion into a large vein through a large-gauge needle; care is required since this concentration is irritant especially if extravasation occurs

- Adult: 10 g, to be administered as Glucose 20% intravenous infusion into a large vein through a large-gauge needle; care is required since this concentration is irritant especially if extravasation occurs
2.1 Low blood volume

**COLLOIDS**

**Albumin solution**

*(Human albumin solution)*

### INDICATIONS AND DOSE

- Acute or sub-acute loss of plasma volume e.g. in burns, pancreatitis, trauma, and complications of surgery (with isotonic solutions)
- Plasma exchange (with isotonic solutions)
- Severe hypoalbuminaemia associated with low plasma volume and generalised oedema where salt and water restriction with plasma volume expansion are required (with concentrated solutions 20%)
- Adjunct in the treatment of hyperbilirubinaemia by exchange transfusion in the newborn (with concentrated solutions 20%)
- Paracentesis of large volume ascites associated with portal hypertension (with concentrated solutions 20%)

**BY INTRAVENOUS INFUSION**

- Adult: (consult product literature)

#### CONTRA-INDICATIONS

- Cardiac failure - severe anaemia

#### CAUTIONS

- Correct dehydration when administering concentrated solution - history of cardiac disease (administer slowly to avoid rapid rise in blood pressure and cardiac failure, and monitor cardiovascular and respiratory function) - history of circulatory disease (administer slowly to avoid rapid rise in blood pressure and cardiac failure, and monitor cardiovascular and respiratory function) - increased capillary permeability

#### SIDE-EFFECTS

- Anaphylaxis - chills - fever - hypersensitivity reactions - hypotension - increased salivation - nausea - tachycardia - vomiting

#### MONITORING REQUIREMENTS

- Plasma and plasma substitutes are often used in very ill patients whose condition is unstable. Therefore, close monitoring is required and fluid and electrolyte therapy should be adjusted according to the patient’s condition at all times.

**PRESCRIBING AND DISPENSING INFORMATION**

- A solution containing protein derived from plasma, serum, or normal placentas; at least 95% of the protein is albumin. The solution may be isotonic (containing 3.5–5% protein) or concentrated (containing 15–25% protein).

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Infusion**

- **Flexbumin** (Baxter Healthcare Ltd)
  - Albumin solution human 200 gm per 1 litre
  - 20% infusion

- **Albumin solution human 50 gm per 1 litre**
  - Human albumin Grifols 5% solution for infusion

**Solution for infusion**

- **Albumin solution human 50 gm per 1 litre**
  - Human albumin Grifols 5% solution for infusion

**Plasma and plasma substitutes**

**Dextran 70 with sodium chloride**

### INDICATIONS AND DOSE

Initial treatment of hypovolaemia with hypotension induced by traumatic injury

**BY INTRAVENOUS INFUSION**

- Adult: 250 mL, to be given over 2–5 minutes, followed immediately by administration of isotonic fluids, using RescueFlow®

#### CAUTIONS

- Cardiac disease - hypomosmolarity - severe hypoglycaemia - severe liver disease

#### SIDE-EFFECTS

- Rare: Severe anaphylactic reactions
- **FREQUENCY NOT KNOWN**
  - Hypersensitivity reactions - transient increase in bleeding time

#### PREGNANCY

- Avoid – reports of anaphylaxis in mother causing fetal anaoxia, neurological damage and death.

#### HEPATIC IMPAIRMENT

- Use with caution in severe impairment.

#### RENAL IMPAIRMENT

- Use with caution.

#### MONITORING REQUIREMENTS

- Where possible, monitor central venous pressure.
- Urine output should be monitored. Care should be taken to avoid haemocrit concentration from falling below 25–30% and the patient should be monitored for hypersensitivity reactions.

- Plasma and plasma substitutes are often used in very ill patients whose condition is unstable. Therefore, close monitoring is required and fluid and electrolyte therapy should be adjusted according to the patient’s condition at all times.
Blood and nutrition

854 Fluid and electrolyte imbalances

- **EFFECT ON LABORATORY TESTS** Can interfere with some laboratory tests—dextran may interfere with blood group cross-matching or biochemical measurements, and these should be carried out before infusion is begun.

- **PRESCRIBING AND DISPENSING INFORMATION**

  - **Medications**
    - **Plasma and plasma substitutes** are often used in very ill patients.

  - **Hepatic Impairment**
    - **Rare**
    - **Side-Effects**
      - Monitor for hypersensitivity reactions.
      - Monitor renal function.

  - **Renal Impairment**
    - Use with caution in severe impairment.

  - **Monitoring Requirements**
    - Urine output should be monitored. Care should be taken to avoid haematocrit concentration from falling below 25–30% and the patient should be monitored for hypersensitivity reactions.
    - Plasma and plasma substitutes are often used in very ill patients whose condition is unstable. Therefore, close monitoring is required and fluid and electrolyte therapy should be adjusted according to the patient’s condition at all times.

  - **Prescribing and Dispensing Information** The gelatin is partially degraded.

- **MEDICINAL FORMS**

  - **Gelatin**

    - **Indications and Dose**
      - Low blood volume in hypovolaemic shock, burns and cardiopulmonary bypass

    - **By Intravenous Infusion**
      - **Adult:** Initially 500–1000 mL, use 3.5–4% solution
        - Urine output should be monitored.
        - Care should be taken to avoid haematocrit concentration from falling below 25–30% and the patient should be monitored for hypersensitivity reactions.
        - Plasma and plasma substitutes are often used in very ill patients whose condition is unstable. Therefore, close monitoring is required and fluid and electrolyte therapy should be adjusted according to the patient’s condition at all times.

    - **Cautions** Cardiac disease • severe liver disease

    - **Side-Effects**
      - Rare: Severe anaphylactic reactions
      - Frequency not known: Hypersensitivity reactions • transient increase in bleeding time

    - **Pregnancy**
      - Manufacturer of Geloplasma® advises avoid at the end of pregnancy.

    - **Hepatic Impairment**
      - Use with caution in severe impairment.

    - **Renal Impairment**
      - Use with caution in renal impairment.

    - **Prescribing and Dispensing Information** The gelatin is partially degradable.

- **MEDICINAL FORMS**

  - **Gelatin**

    - **Indications and Dose**
      - Low blood volume in hypovolaemic shock, burns and cardiopulmonary bypass

    - **By Intravenous Infusion**
      - **Adult:** Initially 500–1000 mL, use 3.5–4% solution

    - **Cautions** Cardiac disease • severe liver disease

    - **Side-Effects**
      - Rare: Severe anaphylactic reactions
      - Frequency not known: Hypersensitivity reactions • transient increase in bleeding time

    - **Pregnancy**
      - Manufacturer of Geloplasma® advises avoid at the end of pregnancy.

    - **Hepatic Impairment**
      - Use with caution in severe impairment.

    - **Renal Impairment**
      - Use with caution in renal impairment.

    - **Prescribing and Dispensing Information**
      - The gelatin is partially degradable.

- **Tetrastarch**

  - **Indications and Dose**

    - **Voluvyn® Infusion**
      - Treatment of hypovolaemia due to acute blood loss when crystalloids alone are not sufficient
      - **By Intravenous Infusion**
        - **Adult:** Initially 10–20 mL, then increased to up to 30 mL/kg/daily for a maximum duration of treatment of 24 hours, the initial dose must be given slowly and with careful monitoring of the patient to allow any anaphylactic reaction to be detected as early as possible

    - **Voluvyn® Infusion**
      - Treatment of hypovolaemia due to acute blood loss when crystalloids alone are not sufficient
      - **By Intravenous Infusion**
        - **Adult:** Initially 10–20 mL, then increased to up to 30 mL/kg/daily for a maximum duration of treatment of 24 hours, the initial dose must be given slowly and with careful monitoring of the patient to allow any anaphylactic reaction to be detected as early as possible

  - **Contra-Indications** Burns • cerebral haemorrhage • critically ill patients • dehydration • hyperhydration • intracranial haemorrhage • pulmonary oedema • sepsis • severe coagulopathy

  - **Cautions** Cardiac disease • care should be taken to avoid haematocrit concentration from falling below 25–30% • children • renal impairment • severe liver disease • surgery • trauma

  - **Side-Effects**
    - Rare: Severe anaphylactic reactions
    - Frequency not known: Hypersensitivity reactions • pruritus • raised serum amylose • transient increase in bleeding time

  - **Hepatic Impairment**
    - Avoid in severe impairment.

  - **Renal Impairment**
    - Avoid.

  - **Monitoring Requirements**
    - Plasma and plasma substitutes are often used in very ill patients whose condition is unstable. Therefore, close monitoring is required and fluid and electrolyte therapy should be adjusted according to the patient’s condition at all times. Treatment with hydroxyethyl starches should be guided by continuous haemodynamic monitoring so that the infusion is stopped as soon as appropriate haemodynamic goals have been achieved.
    - Monitor renal function.
    - Monitor for hypersensitivity reactions.
    - Urine output should be monitored.

  - **Prescribing and Dispensing Information**
    - A starch composed of more than 90% of amylopectin that has been etherified with hydroxyethyl groups; the term tetrastarch reflects the degree of etherification. Hydroxyethyl starches should only be used for the treatment of hypovolaemia due to acute blood loss when crystalloids alone are not sufficient; they should be used at the lowest effective dose for the first 24 hours of fluid resuscitation.

- **MEDICINAL FORMS**

  - There can be variation in the licensing of different medicines containing the same drug.

  - **Infusion**
    - **Gelaspan** (B.Braun Medical Ltd)
      - Gelatin 40 mg per 1 ml
        - Gelaspan 4% infusion 500ml Ecobags | 1 bag (Freeflex) £2.78 (Hospital only) | 20 bag (Freeflex) no price available (Hospital only)
    - **Gelofusine** (B.Braun Medical Ltd)
      - Gelatin 40 mg per 1 ml
        - Gelofusine 4% infusion 1 litre Ecobags | 1 bag (Freeflex) £3.04 | 10 bag (Freeflex) no price available
        - Gelofusine 4% infusion 500ml Ecobags | 1 bag (Freeflex) £4.83 | 20 bag (Freeflex) no price available
    - **Geloplasma** (Fresenius Kabi Ltd)
      - Gelatin 30 mg per 1 ml
        - Geloplasma 3% infusion 500ml Freeflex bags | 15 no price available (Hospital only)
    - **Isoplex** (Beacon Pharmaceuticals Ltd)
      - Gelatin 40 mg per 1 ml
        - Isoplex 4% infusion 500ml bags | 10 bag (Freeflex) £7.30 (Hospital only)
    - **Voluplex** (Beacon Pharmaceuticals Ltd)
      - Gelatin 40 mg per 1 ml
        - Voluplex 4% infusion 500ml bags | 10 bag (Freeflex) £4.70 (Hospital only)
        - Voluplex 4% infusion 1 litre bags | 6 bag (Freeflex) £54.54 (Hospital only)

- **Volulyte**

  - **Volulyte** (Fresenius Kabi Ltd)
    - Magnesium chloride hexahydrate 300 mg per 1 litre, Potassium chloride 300 mg per 1 litre, Sodium acetate trihydrate 4.63 gram per 1 litre, Sodium chloride 6.02 gram per 1 litre, Tetrastarch 60 gram per 1 litre
    - Volulyte 6% infusion 500ml Freeflex bags | 15 bag (Freeflex) £229.60
2.2 Calcium imbalance

Calcium

Calcium supplement

Calcium supplements are usually only required where dietary calcium intake is deficient. This dietary requirement varies with age and is relatively greater in childhood, pregnancy, and lactation, due to an increased demand, and in old age, due to impaired absorption. In osteoporosis, a calcium intake which is double the recommended amount reduces the rate of bone loss. If the actual dietary intake is less than the recommended amount, a supplement of as much as 40 mmol is appropriate.

In severe acute hypocalcaemia or hypocalcaemic tetany, an initial slow intravenous injection of calcium gluconate 857 injection 10% should be given, with plasma-calium and ECG monitoring (risk of arrhythmias if given too rapidly), and either repeated as required or, if only temporary improvement, followed by a continuous intravenous infusion to prevent recurrence. Calcium chloride p. 857 injection is also available, but is more irritant; care should be taken to prevent extravasation. Oral supplements of calcium and vitamin D may also be required in persistent hypocalcaemia. Concurrent hypomagnesaemia should be corrected with magnesium sulfate p. 858.

See the role of calcium gluconate in temporarily reducing the toxic effects of hyperkalaemia.

Severe hypercalcaemia

Severe hypercalcaemia calls for urgent treatment before detailed investigation of the cause. Dehydration should be corrected first with intravenous infusion of sodium chloride 0.9% p. 851. Drugs (such as thiazides and vitamin D compounds) which promote hypercalcaemia, should be discontinued and dietary calcium should be restricted.

If severe hypercalcaemia persists drugs which inhibit mobilisation of calcium from the skeleton may be required. The bisphosphonates are useful and pamidronate disodium p. 623 is probably the most effective.

Corticosteroids are widely given, but may only be useful where hypercalcaemia is due to sarcoidosis or vitamin D intoxication; they often take several days to achieve the desired effect.

Calcitonin (salmon)/salcatonin p. 627 can be used for the treatment of hypercalcaemia associated with malignancy; it is rarely effective where bisphosphonates have failed to reduce serum calcium adequately.

After treatment of severe hypercalcaemia the underlying cause must be established. Further treatment is governed by the same principles as for initial therapy. Salt and water depletion and drugs promoting hypercalcaemia should be avoided; oral administration of a bisphosphonate may be useful.

Hyperparathyroidism

Paricalcitol p. 888 is licensed for the prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure. Parathyroidectomy may be indicated for hyperparathyroidism.

2.3 Hypercalcaemia and hypercalciuria

CALCIMIMETIC AGENTS

Cinacalcet

- **DRUG ACTION** Cinacalcet reduces parathyroid hormone which leads to a decrease in serum calcium concentrations.

**INDICATIONS AND DOSE**

* Secondary hyperparathyroidism in patients with end-stage renal disease on dialysis

**BY MOUTH**

- Adult: Initially 30 mg once daily, dose to be adjusted every 2–4 weeks; maximum 180 mg per day

**TREATMENT OF HYPERCALCAEMIA IN PARATHYROID CARCINOMA**

- **Primary hyperparathyroidism in patients where parathyroidectomy is inappropriate**

**BY MOUTH**

- Adult: Initially 30 mg twice daily (max. per dose 90 mg 4 times a day), dose to be adjusted every 2–4 weeks according to response

**Dose adjustments due to interactions**

Dose adjustment may be necessary if smoking started or stopped during treatment.

- **CAUTIONS** Treatment should not be initiated in patients with hypocacalcaemia

- **INTERACTIONS** → Appendix 1 (cinacalcet).

- **SIDE-EFFECTS**

  - **Common or very common** Anorexia - asthenia - dizziness - myalgia - nausea - paraesthesia - rash - reduced testosterone concentrations - vomiting

  - **Uncommon** Diarrhoea - dyspepsia - seizures

  - **Frequency not known** Allergic reactions - angioedema - heart failure - hypotension

- **PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk—no information available.

- **BREAST FEEDING** Manufacturer advises avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT** Manufacturer advises caution in moderate to severe impairment. Monitor closely in hepatic impairment especially when increasing dose.

- **MONITORING REQUIREMENTS**

  - Measure serum-calcium concentration before initiation of treatment and within 1 week after starting treatment or adjusting dose, then monthly for secondary hyperparathyroidism, and every 2–3 months for primary hyperparathyroidism and parathyroid carcinoma.

- In secondary hyperparathyroidism measure parathyroid hormone concentration 1–4 weeks after starting treatment or adjusting dose, then every 1–3 months.
2.4 Hypocalcaemia

**CALCIUM**

**Calcium salts**

- **CONTRA-INDICATIONS** Conditions associated with hypercalcaemia (e.g. some forms of malignant disease) - conditions associated with hypercalcuria (e.g. some forms of malignant disease)
- **CAUTIONS** History of nephrolithiasis - sarcoidosis
- **INTERACTIONS** → Appendix 1 (antacids, calcium salts).
- **SIDE-EFFECTS**
  - **GENERAL SIDE-EFFECTS**
    - Rare Gastro-intestinal disturbances
    - Frequency not known Hypercalcaemia
  - **SPECIFIC SIDE-EFFECTS**
    - With intravenous use arrhythmias - bradycardia - fall in blood pressure - injection-site reactions - peripheral vasodilatation - severe tissue damage with extravasation - sweating
  - **RENAI IMPAIRMENT** Use with caution.

**Calcium carbonate with calcium lactate gluconate**

The properties listed below are those particular to the combination only. For the properties of the components please consider, calcium carbonate above.

- **INDICATIONS AND DOSE**
  - Calcium deficiency
    - **BY MOUTH**
      - Adult: Dose according to requirements

- **PRESCRIBING AND DISPENSING INFORMATION** Flavours of soluble tablet formulations may include orange or fruit flavour.

**Calcium carbonate**

- **INDICATIONS AND DOSE**
  - Phosphate binding in renal failure and hyper-phosphataemia
    - **BY MOUTH**
      - Adult: (consult product literature)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, dispersible tablet, oral suspension, capsule.

- **Tablet**
  - **CAUTIONARY AND ADVISORY LABELS 25**
  - **EXCIPIENTS:** May contain Aspartame
    - **CALCIUM CARBONATE (Non-proprietary)**
      - Calcium (as Calcium carbonate) 600 mg HealthAid Strong Calcium 600mg chewable tablets | 60 tablet £3.99
      - Calcium carbonate 1.25 gram Calcium carbonate 1.25g tablets | 100 tablet no price available
      - Calcium carbonate 1.5 gram Calcium carbonate 1.5g tablets | 100 tablet no price available
  - **Chewable tablet**
    - **CAUTIONARY AND ADVISORY LABELS 24**
    - **EXCIPIENTS:** May contain Aspartame
      - **CALCIUM CARBONATE (Non-proprietary)**
        - Calcium (as Calcium carbonate) 600 mg HealthAid Strong Calcium 600mg chewable tablets | 60 tablet £3.99
      - Calcium carbonate 1.25 gram Calcium carbonate 1.25g chewable tablets sugar free (sugar-free) | 100 tablet 12.50 DT price = £9.33
      - Adcal (ProStrakan Ltd)
        - Calcium carbonate 1.5 gram Adcal 1500mg chewable tablets (sugar-free) | 100 tablet £8.70 DT price = £8.70
      - Calcichew (Forum Health Products Ltd)
        - Calcium carbonate 1.25 gram Calcichew 500mg chewable tablets (sugar-free) | 100 tablet £3.33 DT price = £9.33
      - Calcium carbonate 2.5 gram Calcichew Forte chewable tablets (sugar-free) | 60 tablet £13.16 DT price = £13.16
  - **Effervescent tablet**
    - **CAUTIONARY AND ADVISORY LABELS 13**
    - **EXCIPIENTS:** May contain Aspartame
      - Cacit (Warner Chilcott UK Ltd)
        - Calcium carbonate 1.25 gram Cacit 500mg effervescent tablets (sugar-free) | 76 tablet £11.81 DT price = £11.81

**PRESCRIBING AND DISPENSING INFORMATION** Flavours of soluble tablet formulations may include orange.
Hypomagnesaemia 857

Calcium chloride

**INDICATIONS AND DOSE**
- Severe acute hypocalcaemia or hypocalcaemic tetany
  - **BY INTRAVENOUS INJECTION**
    - Adult: Dose according to requirements
  - **MEDICINAL FORMS**
    - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for infusion
  - **DIRECTIONS FOR ADMINISTRATION**
    - Care should be taken to avoid extravasation.

**Calcium gluconate**

**INDICATIONS AND DOSE**
- Severe acute hypocalcaemia or hypocalcaemic tetany
  - **INITIALLY BY SLOW INTRAVENOUS INJECTION**
    - Adult: Initially 10–20 mL, calcium gluconate injection 10% strength (containing approximately 2.25–4.5 mmol of calcium) should be administered with plasma-calcium and ECG monitoring, and either repeated as required or, if only temporary improvement, followed by a continuous intravenous infusion to prevent recurrence; (by continuous intravenous infusion) 100 mL, adjusted according to response, dose to be diluted, calcium gluconate 10% should be administered
- Acute severe hyperkalaemia (plasma-potassium concentration above 6.5 mmol/litre or in the presence of ECG changes)
  - **BY SLOW INTRAVENOUS INJECTION**
    - Adult: 10–20 mL, calcium gluconate 10% should be administered, dose titrated and adjusted to ECG improvement
  - **Calcium deficiency / Mild asymptomatic hypocalcaemia**
    - **BY MOUTH**
      - Adult: Dose according to requirements
      - **Dose equivalence and conversion**
        - 0.11 mmol/kg is equivalent to 0.5 mL/kg of calcium gluconate 10%.

**Important safety information**
The MHRA has advised that repeated or prolonged administration of calcium gluconate injection packaged in 10 mL glass containers is contra-indicated in children under 18 years and in patients with renal impairment owing to the risk of aluminium accumulation; in these patients the use of calcium gluconate injection packaged in plastic containers is recommended.

**Monitoring requirements**
- Plasma-calcium and ECG monitoring required for administration by slow intravenous injection (risk of arrhythmias if given too rapidly).

**Directions for administration**
- For continuous intravenous infusion, dilute 100 mL of calcium gluconate 10% in 1 litre of glucose 5% or sodium chloride 0.9% and give at an initial rate of 50 mL/hour adjusted according to response. Avoid bicarbonates, phosphates, or sulfates.

**Medicinal forms**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, oral suspension, solution for infusion, oral solution, capsule

**Effervescent tablet**
- **CAUTIONARY AND ADVISORY LABELS**
  - **13 ELECTROLYTES: May contain Sodium**
  - **Calcium gluconate (Non-proprietary)**
    - Calcium gluconate 1 gram
      - Calcium gluconate 1g effervescent tablets | 28 tablet | £15.68 DT price = £15.68
  - **Solution for injection**
    - **Calcium gluconate (Non-proprietary)**
      - Calcium gluconate 100 mg per 1 mL
        - Calcium gluconate 10% solution for injection 10 mL ampoules | 10 ampoule | £74.53-£82.44

**Calcium lactate**

**INDICATIONS AND DOSE**
- Calcium deficiency
  - **BY MOUTH**
    - Adult: Dose according to requirements

**Medicinal forms**
- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **Calcium lactate (Non-proprietary)**
  - Calcium lactate 300 mg
    - Calcium lactate 300mg tablets | 84 tablet no price available DT price = £4.57 | 84 tablet | £4.57

2.5 Hypomagnesaemia

**Magnesium**

Magnesium is an essential constituent of many enzyme systems, particularly those involved in energy generation; the largest stores are in the skeleton. Magnesium salts are not well absorbed from the gastrointestinal tract, which explains the use of magnesium sulfate p. 858 as an osmotic laxative. Magnesium is excreted mainly by the kidneys and is therefore retained in renal failure, but significant hypomagnesaemia (causing muscle weakness and arrhythmias) is rare.

**Hypomagnesaemia**

Since magnesium is secreted in large amounts in the gastrointestinal fluid, excessive losses in diarrhoea, stoma or fistula are the most common causes of hypomagnesaemia; deficiency may also occur in alcoholism or as a result of treatment with certain drugs. Hypomagnesaemia often causes secondary hypocalcaemia, and also hypokalaemia and hyponatraemia.

Symptomatic hypomagnesaemia is associated with a deficit of 0.5–1 mmol/kg; up to 160 mmol Mg²⁺ over up to 5 days may be required to replace the deficit (allowing for urinary losses). Magnesium is given initially by intravenous infusion or by intramuscular injection of magnesium sulfate; the intramuscular injection is painful. Plasma magnesium concentration should be measured to determine the rate...
and duration of infusion and the dose should be reduced in renal impairment. To prevent recurrence of the deficit, magnesium may be given by mouth, but there is limited evidence of benefit; magnesium glycerophosphate below tablets and liquid [unlicensed] are available from ‘special-order’ manufacturers or specialist importing companies.

**Arrhythmias**
Magnesium sulfate injection has also been recommended for the emergency treatment of serious arrhythmias, especially in the presence of hypokalaemia (when hypomagnesaemia may also be present) and when salvos of rapid ventricular tachycardia show the characteristic twisting wave front known as *torsade de points*.

**Myocardial infarction**
Limited evidence that magnesium sulfate below prevents arrhythmias and reperfusion injury in patients with suspected myocardial infarction has not been confirmed by large studies. Routine use of magnesium sulfate for this purpose is not recommended.

**Eclampsia and pre-eclampsia**
Magnesium sulfate injection is the drug of choice for the emergency treatment of eclampsia and pre-eclampsia with developing eclampsia. The patient should be monitored carefully.

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**MAGNESIUM**

**Magnesium glycerophosphate**

<table>
<thead>
<tr>
<th>INDICATIONS AND DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevent recurrence of magnesium deficit</td>
</tr>
<tr>
<td>BY MOUTH</td>
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<tr>
<td>▶ Adult: 6 g daily in divided doses</td>
</tr>
</tbody>
</table>

**Dose equivalence and conversion**
Magnesium glycerophosphate 1 g is equivalent to Mg$^{2+}$ 4 mmol.

- **UNLICENSED USE** Not licensed.
- **INTERACTIONS** → Appendix 1 (magnesium salts, oral).
- **SIDE-EFFECTS** Arrhythmias · colic · coma · confusion · diarrhoea · drowsiness · flushing of skin · hypermagnesaemia associated side-effects · hypotension · loss of tendon reflexes · muscle weakness · nausea · respiratory depression · thirst · vomiting
- **RENAL IMPAIRMENT** Avoid or reduce dose. Increased risk of toxicity.
- **MONITORING REQUIREMENTS** Monitor blood pressure, respiratory rate, urinary output and for signs of overdosage (loss of patellar reflexes, weakness, nausea, sensation of warmth, flushing, drowsiness, double vision, and slurred speech).
- **DIRECTIONS FOR ADMINISTRATION** Tablets may be dispersed in water.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, oral suspension, oral solution, chewable tablet, powder, capsule

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**Magnesium sulfate**

<table>
<thead>
<tr>
<th>INDICATIONS AND DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe acute asthma</td>
</tr>
<tr>
<td>BY INTRAVENOUS INFUSION</td>
</tr>
<tr>
<td>▶ Child 2–17 years: 40 mg/kg (max. per dose 2 g), to be given over 20 minutes</td>
</tr>
<tr>
<td>▶ Adult: 1.2–2 g, to be given over 20 minutes</td>
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</table>

**Prevention of seizures in pre-eclampsia**
INITIALLY BY INTRAVENOUS INJECTION
▶ Adult: Initially 4 g, to be given over 5–15 minutes, followed by (by intravenous infusion) 1 gram/hour for 24 hours, if seizure occurs, additional dose of 2 g by intravenous injection to be administered

**Treatment of seizures and prevention of seizure recurrence in eclampsia**
INITIALLY BY INTRAVENOUS INJECTION
▶ Adult: Initially 4 g, to be given over 5–15 minutes, followed by (by intravenous infusion) 1 gram/hour for 24 hours after seizure or delivery (whichever is later), if seizure recurs, increase the infusion rate to 1.5–2 g/hour or give an additional dose of 2 g by intravenous injection

**Hypomagnesaemia**
BY INTRAVENOUS INFUSION OR BY INTRAMUSCULAR INJECTION
▶ Adult: Up to 40 g, dose given over up to 5 days may be required to replace the deficit (allowing for urinary losses)

**Hypomagnesaemia maintenance (e.g. in intravenous nutrition)**
BY INTRAVENOUS INFUSION OR BY INTRAMUSCULAR INJECTION
▶ Adult: 2.5–5 g daily, usual dose 3 g daily

**Emergency treatment of serious arrhythmias**
BY INTRAVENOUS INJECTION
▶ Adult: 2 g, to be given over 10–15 minutes, dose may be repeated once if necessary

**Rapid bowel evacuation (acts in 2–4 hours)**
BY MOUTH
▶ Adult: 5–10 g, dose to be mixed in a glass of water, taken preferably before breakfast

**Dose equivalence and conversion**
Magnesium sulfate heptahydrate 1 g equivalent to Mg$^{2+}$ approx. 4 mmol.
solution for infusion

- **Magnesium Sulfate (Non-proprietary)**
  - Magnesium sulfate heptahydrate 100 mg per 1 ml Magnesium sulfate 10% (magnesium 0.4 mmol/ml) solution for injection 10 ml ampoules | 10 ampoule (P97) £40.46

powder

- **Magnesium Sulfate (Non-proprietary)**
  - Magnesium sulfate dried 1 mg per 1 mg Numark Epsom Salts | 200 gram (GSS) £1.00
  - Magnesium sulfate powder | 300 gram (GSS) £1.91 | 500 gram (GSS) £3.20 DT price = £3.20 | 2000 gram (GSS) £5.60 | 5000 gram (GSS) £11.49
  - Epsom Salts | 200 gram (GSS) £0.91

2.6 Phosphate imbalance

**Phosphorus**

**Phosphate supplements**

Oral phosphate p. 861 supplements may be required in addition to vitamin D in a small minority of patients with hypophosphataemic vitamin D-resistant rickets. Phosphate infusion is occasionally needed in alcohol dependence or in phosphate deficiency arising from use of parenteral nutrition deficient in phosphate supplements; phosphate depletion also occurs in severe diabetic ketoacidosis. For phosphate requirements in total parenteral nutrition regimens, see Intravenous nutrition p. 873.

**Phosphate-binding agents**

Calcium-containing preparations are used as phosphate-binding agents in the management of hypophosphataemia complicating renal failure. Aluminium-containing preparations are rarely used as phosphate-binding agents and can cause aluminium accumulation. Sevelamer p. 861 is licensed for the treatment of hypophosphataemia in patients on haemodialysis or peritoneal dialysis. Sevelamer carbonate is also licensed for the treatment of patients with chronic kidney disease not on dialysis who have a serum-phosphate concentration of 1.78 mmol/litre or more.

Lanthanum p. 860 is licensed for the control of hypophosphataemia in patients with chronic renal failure on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD), and in patients with chronic kidney disease not on dialysis who have a serum-phosphate concentration of 1.78 mmol/litre or more that cannot be controlled by a low-phosphate diet.

2.7 Hyperphosphataemia

**Aluminium**

**Aluminium hydroxide**

**Indications and dose**

Hyperphosphataemia in renal failure

**By mouth using capsules**

- Adult: 4–20 capsules daily in divided doses, to be taken with meals

Antacid

Initial: By mouth using capsules

- Adult: 1 capsule 4 times a day and (by mouth) 1 capsule, to be taken at bedtime
CONTRA-INDICATIONS  Hypophosphataemia - infants - neonates

INTERACTIONS  Appendix 1 (antacids). Antacids should preferably not be taken at the same time as other drugs since they may impair absorption. Antacids may damage enteric coatings designed to prevent dissolution in the stomach.

SIDE-EFFECTS  Constipation - hyperaluminaemia

HEPATIC IMPAIRMENT  Avoid; can cause constipation which can precipitate coma.

RENAI IMPAIRMENT  There is a risk of accumulation and aluminium toxicity with antacids containing aluminium salts. Absorption of aluminium from aluminium salts is increased by citrates, which are contained in many effervescent preparations (such as effervescent analgesics).

PRESCRIBING AND DISPENSING INFORMATION  Alu-caps® are low in sodium.

MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: chewable tablet

Capsule
- Alu-Cap (Meda Pharmaceuticals Ltd)
- Aluminium hydroxide 475 mg Alu-Cap 475mg capsules  | 120 capsule £13.71 DT price = £13.71

Calcium acetate

The properties listed below are those particular to the drug only. For properties common to the class, see Calcium salts, p. 856.

INDICATIONS AND DOSE

PHOSEX® TABLETS

Hyphosphataemia
- Adult: Initially 1 tablet 3 times a day, to be taken with meals, dose to be adjusted according to serum-phosphate concentration, usual dose 4–6 tablets daily in divided doses, (1 or 2 tablets with each meal); maximum 12 tablets per day

RENACET® TABLETS

Hyphosphataemia
- Adult: 475–950 mg, to be taken with breakfast and with snacks, 0.95–2.85 g, to be taken with main meals and 0.95–1.9 g, to be taken with supper, dose to be adjusted according to serum-phosphate concentration; maximum 6.65 g per day

PHOSLO® CAPSULES

Hyphosphataenia
- Adult: Initially 2 capsules, to be taken with each meal, dose to be adjusted according to serum-phosphate concentration, usual dose 3–4 capsules, to be taken with each meal

DIRECTIONS FOR ADMINISTRATION

PHOSEX® TABLETS
Phose® tablets are taken with meals. Tablets can be broken to aid swallowing, but not chewed (bitter taste).

RENACET® TABLETS
Manufacturer advises that other drugs should be taken 1 to 2 hours before or after Renacet® to reduce the possible interference with absorption of other drugs. Renacet® tablets are taken with meals.

PATIENT AND CARER ADVICE

Patients or carers should be given advice on how to administer Phose®, Renacet® tablets, and PhosLo® tablets.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet

Tablet
CAUTIONARY AND ADVISORY LABELS 25
- Phose (Pharmacosmos UK Ltd)
- Calcium acetate 1 gram Phosex 1g tablets  | 180 tablet £19.79
- Renacet (Stanningley Pharma Ltd)
- Calcium acetate 475 mg Renacet 475mg tablets  | 100 tablet £5.38
- Calcium acetate 950 mg Renacet 950mg tablets  | 100 tablet £10.25

Capsule
EXCIPIENTS: May contain Propylene glycol
- PhosLo (Stanningley Pharma Ltd)
- Calcium acetate 667 mg PhosLo 667mg capsules  | 200 capsule £14.40 DT price = £14.40

PHOSPHATE BINDERS

Lanthanum

INDICATIONS AND DOSE

Hyperphosphataemia in patients with chronic renal failure on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD) | Hyperphosphataemia in patients with chronic kidney disease not on dialysis who have a serum-phosphate concentration of 1.78 mmol/litre or more who cannot be controlled by a low-phosphate diet

BY MOUTH
- Adult: 1.5–3 g daily in divided doses, dose to be adjusted according to serum-phosphate concentration every 2–3 weeks, to be taken with or immediately after meals

CAUTIONS  Acute peptic ulcer· bowel obstruction · Crohn’s disease – ulcerative colitis

INTERACTIONS  Appendix 1 (lanthanum).

SIDE-EFFECTS
- Common or very common  Gastro-intestinal disturbances · headache · hypocalcaemia
- Uncommon  Alopecia · anorexia · arthralgia · asthenia · chest pain · dizziness · dry mouth · eosinophilia · hypercalcaemia · hyperglycaemia · hyperparathyroidism · hypophosphataemia · increased appetite · malaise · myalgia · osteoporosis · peripheral oedema · stomatitis · sweating · taste disturbances · thirst · vertigo
- Frequency not known  Accumulation of lanthanum in bone · transient changes in QT interval

PREGNANCY  Manufacturer advises avoid—toxicity in animal studies.

BREAST FEEDING  Manufacturer advises caution—no information available.

HEPATIC IMPAIRMENT  Lanthanum excreted in bile—possible accumulation in obstructive jaundice.

DIRECTIONS FOR ADMINISTRATION  Tablets are to be chewed. Each sachet of powder to be mixed with soft food and consumed within 15 minutes.

PATIENT AND CARER ADVICE  Patient and carers should be given advice on how to administer lanthanum tablets and powder.

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (March 2007) that lanthanum (Fosrenol®) is accepted for restricted use within NHS Scotland for the control of...
hyperphosphataemia in patients with chronic renal failure on haemodialysis or continuous ambulatory peritoneal dialysis, as a second-line agent, where a non-aluminium, non-calcium phosphate binder is required.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  **Chewable tablet**
  **CAUTIONARY AND ADVISORY LABELS 21**
  - Sevelamer (as Lanthanum carbonate) 500 mg: Fosrenol 500mg chewable tablets (sugar-free) | 90 tablet | £124.06 DT price = £124.06
  - Lanthanum (as Lanthanum carbonate) 750 mg: Fosrenol 750mg chewable tablets (sugar-free) | 90 tablet | £182.60 DT price = £182.60
  - Lanthanum (as Lanthanum carbonate) 1 gram: Fosrenol 1000mg chewable tablets (sugar-free) | 90 tablet | £193.59 DT price = £193.59

  **Powder**
  **CAUTIONARY AND ADVISORY LABELS 21**
  - Sevelamer (as Lanthanum carbonate) 750 mg: Fosrenol 750mg oral powder sachets | 90 sachet | £182.60 DT price = £182.60
  - Lanthanum (as Lanthanum carbonate) 1 gram: Fosrenol 1000mg oral powder sachets | 90 sachet | £193.59 DT price = £193.59

**Sevelamer**

**INDICATIONS AND DOSE**

**RENVELA®**
Hyperphosphataemia in patients on haemodialysis or peritoneal dialysis | Hyperphosphataemia in patients with chronic kidney disease not on dialysis who have a serum-phosphate concentration of 1.78 mmol/litre or more

**BY MOUTH**
- Adult: Initially 2.4–4.8 g daily in 3 divided doses, dose to be taken with meals and adjusted according to serum-phosphate concentration every 2–4 weeks; usual dose 6 g daily in 3 divided doses

**RENAVEL®**
Hyperphosphataemia in patients on haemodialysis or peritoneal dialysis

**BY MOUTH**
- Adult: Initially 2.4–4.8 g daily in 3 divided doses, dose to be given with meals and adjusted according to serum-phosphate concentration; usual dose 2.4–12 g daily in 3 divided doses

**CONTRA-INDICATIONS** Bowel obstruction

**CAUTIONS** Gastro-intestinal disorders

**INTERACTIONS** Appendix 1 (sevelamer).

**SIDE-EFFECTS**

**GENERAL SIDE-EFFECTS**
- Common or very common Abdominal pain · constipation · diarrhea · dyspepsia · flatulence · nausea · vomiting
- Frequency not known Ileus · intestinal obstruction (higher incidence with sevelamer hydrochloride salt) · intestinal perforation · pruritus · rash

**RENAVEL®**
- Frequency not known Diverticulitis

**PREGNANCY** Manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING**

**RENVELA®**
Unlikely to be present in milk (however, manufacturer advises avoid).

**RENAVEL®** Manufacturer advises use only if potential benefit outweighs risk.

**DIRECTIONS FOR ADMINISTRATION**

**RENVELA®**
For powder for oral suspension, each sachet to be dispersed in 60 mL water.

**PATIENT AND CARER ADVICE**

**RENVELA®**
Patients and carers should be advised on how to administer Renvela powder for oral suspension.

**MEDICINAL FORMS**

There can be variation in the licensing of the different medicines containing the same drug.

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 25**

| EXCIPIENTS: May contain Propylene glycol |
| SEVELAMER (Non-proprietary) |
| Sevelamer 800 mg: Sevelamer 800mg tablets | 180 tablet | £134.48-£167.04 DT price = £167.04 |
| Renvela (Sanofi) |
| Sevelamer 800 mg: Renagel 800mg tablets | 180 tablet | £167.04 DT price = £167.04 |
| Renvela (Sanofi) |
| Sevelamer 800 mg: Renvela 800mg tablets | 180 tablet | £167.04 DT price = £167.04 |

**Powder**

**CAUTIONARY AND ADVISORY LABELS 13**

| Renvela (Sanofi) |
| Sevelamer carbonate 2.4 gram: Renvela 2.4g oral powder sachets (sugar-free) | 60 sachet | £167.04 |

**2.8 Hypophosphataemia**

**Phosphate**

**INDICATIONS AND DOSE**

Treatment of moderate to severe hypophosphataemia

**BY INTRAVENOUS INFUSION**
- Adult: (consult product literature)

For established hypophosphataemia (with monobasic potassium phosphate)

**BY INTRAVENOUS INFUSION**
- Adult: 9 mmol every 12 hours, increased if necessary up to 0.5 mmol/kg (max. per dose 50 mmol), dose only increased in critically ill patients; dose is approximately equivalent to 30 mmol in adults, dose to be infused over 6–12 hours, according to severity in the following situations

- Vitamin D-resistant hypophosphataemic osteomalacia

**BY MOUTH USING EFFERVESCENT TABLETS**
- Adult: 4–6 tablets daily

**SIDE-EFFECTS**

- Common or very common Diarrhoea
- Frequency not known Acute renal failure · hypocalcaemia · hypotension · metastatic calcification · nausea · oedema · phlebitis · tissue necrosis on extravasation

**SIDE-EFFECTS, FURTHER INFORMATION**

Diarrhoea is a common side-effect and should prompt a reduction in dosage.

**RENAL IMPAIRMENT** Reduce dose. Monitor closely in renal impairment.

**MONITORING REQUIREMENTS** It is essential to monitor closely plasma concentrations of calcium, phosphate, potassium, and other electrolytes—excessive doses of phosphates may cause hypocalcaemia and metastatic calcification.
Blood and nutrition

2.9 Hyperkalaemia

Drugs used for Hyperkalaemia not listed below; Calcium gluconate, p. 857 · Insulin, p. 603

CATION-EXCHANGE RESINS

Calcium polystyrene sulfonate

INDICATIONS AND DOSE

CALCIUM RESONIUM®

Hyperkalaemia associated with anuria or severe oliguria, and in dialysis patients
BY MOUTH
→ Adult: 15 g 3–4 times a day
BY RECTUM
→ Adult: 30 g, retained for 9 hours followed by irrigation to remove resin from colon

SORBISTERIT® POWDER

Hyperkalaemia associated with anuria or severe oliguria, and in dialysis patients
BY MOUTH
→ Adult: 20 g 1–3 times a day
BY RECTUM
→ Adult: 40 g 1–3 times a day, retained for 6 hours followed by irrigation to remove resin from colon

CONTRA-INDICATIONS

Hyperparathyroidism · metastatic carcinoma · multiple myeloma · obstructive bowel disease · sarcoidosis

INTERACTIONS → Appendix 1 (polystyrene sulfonate resins).

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

Anorexia · constipation (discontinue treatment—avoid magnesium-containing laxatives) · diarrhoea · gastric irritation · gastro-intestinal obstruction · hypercalcaemia (including in dialysed patients and occasionally in those with renal impairment) · hypomagnesaemia · intestinal necrosis (reported with concomitant use of sorbitol) · ischaemic colitis · nausea · necrosis · ulceration · vomiting

SPECIFIC SIDE-EFFECTS

→ With oral use · gastro-intestinal concretions
→ With rectal use · faecal impaction

PREGNANCY

Manufacturers advise use only if potential benefit outweighs risk—no information available.

Sodium polystyrene sulfonate

INDICATIONS AND DOSE

Hyperkalaemia associated with anuria or severe oliguria, and in dialysis patients
BY MOUTH
→ Adult: 15 g 3–4 times a day
BY RECTUM
→ Adult: 30 g, retain for 9 hours followed by irrigation to remove resin from colon

CONTRA-INDICATIONS

Obstructive bowel disease

CAUTIONS

Congestive heart failure · hypertension · oedema

INTERACTIONS → Appendix 1 (polystyrene sulfonate resins).

SIDE-EFFECTS

GENERAL SIDE-EFFECTS

Anorexia · constipation (discontinue treatment—avoid magnesium-containing laxatives) · diarrhoea · gastric irritation · gastro-intestinal obstruction · hypercalcaemia · hypomagnesaemia · intestinal necrosis (reported with concomitant use of sorbitol) · ischaemic colitis · nausea · necrosis · sodium retention · ulceration · vomiting

SPECIFIC SIDE-EFFECTS

→ With oral use · gastro-intestinal concretions
→ With rectal use · faecal impaction

PREGNANCY

Manufacturers advise use only if potential benefit outweighs risk—no information available.

BREAST FEEDING

Manufacturers advise use only if potential benefit outweighs risk—no information available.

MONITORING REQUIREMENTS

Monitor for electrolyte disturbances (stop if plasma-potassium concentration below 5 mmol/litre).
Hypokalaemia

Potassium bicarbonate with potassium acid tartrate

**INDICATIONS AND DOSE**
Hyperchloraemic acidosis associated with potassium deficiency (as in some renal tubular and gastro-intestinal disorders)

**BY MOUTH**
- Adult: (consult product literature)

**CONTRA-INDICATIONS**
- Hypochloraemia

**CAUTIONS**
- Cardiac disease
- Elderly

**INTERACTIONS**
- Appendix 1 (potassium salts).

**SIDE-EFFECTS**
- Abdominal pain
- Diarrhoea
- Flatulence
- Nausea
- Vomiting

**RE/LN IMPAIRMENT**
- Avoid in severe impairment. Close monitoring required in renal impairment—high risk of hyperkalaemia.

**DIRECTIONS FOR ADMINISTRATION**
- To be dissolved in water before administration.

**PRESCRIBING AND DISPENSING INFORMATION**
- Tablets do not contain chloride.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Potassium chloride**

**INDICATIONS AND DOSE**
Prevention of hypokalaemia (patients with normal diet)

**BY MOUTH**
- Adult: 2–4 g daily in divided doses
Medicinal forms

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for infusion, oral solution, infusion.

Oral solution

CAUTIONARY AND ADVISORY LABELS 21

- Kay-Cee-L (Geistlich Sons Ltd)
  Potassium chloride 75 mg per 1 ml Kay-Cee-L syrup (sugar-free) 500 ml (£1.29)

Solution for infusion

- POTASSIUM CHLORIDE (Non-proprietary)
  Potassium chloride 75 mg per 1 ml (potassium chloride 15%) solution for infusion 10 ml ampoules 10 ampoule (PZN) £1.85  20 ampoule (PZN) £4.50
  Potassium chloride 200 mg per 1 ml (potassium chloride 20%) solution for infusion 5 ml ampoules 10 ampoule (PZN) £3.84-£4.00
  Potassium chloride 20% (potassium 27 mmol/10 ml) solution for infusion 10 ml ampoules 10 ampoule (PZN) £10.98

3 Metabolic disorders

3.1 Acute porphyrias

Acute porphyrias

The acute porphyrias (acute intermittent porphyria, variegate porphyria, hereditary coproporphyria, and 5-aminolaevulinic acid dehydratase deficiency porphyria) are hereditary disorders of haem biosynthesis; they have a prevalence of about 1 in 10 000 of the population.

Great care must be taken when prescribing for patients with acute porphyria, since certain drugs can induce acute porphyric crises. Since acute porphyrias are hereditary, relatives of affected individuals should be screened and advised about the potential danger of certain drugs.

Treatment of serious or life-threatening conditions should not be withheld from patients with acute porphyria. When there is no safe alternative, treatment should be started and urinary porphobilinogen excretion should be measured regularly; if it increases or symptoms occur, the drug can be withdrawn and the acute attack treated. If an acute attack of porphyria occurs during pregnancy, contact an expert porphyria service for further advice.

Haem arginate p. 865 is administered by short intravenous infusion as haem replacement in moderate, severe, or unremitting acute porphyria crises. In the United Kingdom the National Acute Porphyria Service (NAPS) provides clinical support and treatment with haem arginate from three centres (University Hospital of Wales, Addenbrooke’s Hospital, and King’s College Hospital). To access the service telephone (029) 2074 7747 and ask for the Acute Porphyria Service.

Drugs unsafe for use in acute porphyrias

The following list contains drugs on the UK market that have been classified as ‘unsafe’ in porphyria because they have been shown to be porphyrinogenic in animals or in vitro, or have been associated with acute attacks in patients. Absence of a drug from the following lists does not necessarily imply that the drug is safe. For many drugs no information about porphyria is available.

An up-to-date list of drugs considered safe in acute porphyrias is available at www.wmic.wales.nhs.uk/porphyria_info.php.

Further information may be obtained from: www.porphyria-europe.org and also from:

Welsh Medicines Information Centre

- Welsh Medicines Information Centre

- University Hospital of Wales
- Cardiff
- (029) 2074 2979/3877

Quite modest changes in chemical structure can lead to changes in porphyrinogenicity but where possible general statements have been made about groups of drugs; these should be checked first.

Unsafe Drug Groups (check first)

- Alkylation drugs (contact Welsh Medicines Information Centre for further advice)
- Anabolic steroids
- Antidepressants (includes tricyclic (and related) antidepressants and MAOIs; fluoxetine, duloxetine, venlafaxine, and trazodone thought to be safe)
- Antihistamines (alimemazine, chlorphenamine, desloratadine, fexofenadine, ketotifen, loratadine, and promethazine thought to be safe)
- Barbiturates (includes primidone and thiopental)
- Calcium channel blockers (amlodipine, felodipine, and nifedipine thought to be safe)
- Contraceptives, hormonal (progestogens are more porphyrinogenic than oestrogens; oestrogens may be safe at least in replacement doses. Progestogens should be avoided whenever possible by all women susceptible to acute porphyria; however, when non-hormonal contraception is inappropriate, progestogens may be used with extreme caution if the potential benefit outweighs risk. The risk of an acute attack is greatest in women who have had a previous attack or are aged under 30 years. Long-acting progestogen preparations should never be used in those at risk of acute porphyria.)
- Ergot derivatives (includes ergometrine (oxytocin probably safe) and pergolide)
- Hormone replacement therapy (progestogens are more porphyrinogenic than oestrogens; oestrogens may be safe at least in replacement doses. Progestogens should be avoided whenever possible by all women susceptible to acute porphyria; however, when non-hormonal contraception is inappropriate, progestogens may be used with extreme caution if the potential benefit outweighs risk. The risk of an acute attack is greatest in women who have had a previous attack or are aged under 30 years. Long-acting progestogen preparations should never be used in those at risk of acute porphyria.)
- Imidazole antifungals (applies to oral and intravenous use; topical antifungals are thought to be safe due to low systemic exposure)
- Non-nucleoside reverse transcriptase inhibitors (contact Welsh Medicines Information Centre for further advice)
- Progestogens (progestogens are more porphyrinogenic than oestrogens; oestrogens may be safe at least in replacement doses. Progestogens should be avoided whenever possible by all women susceptible to acute porphyria; however, when non-hormonal contraception is inappropriate, progestogens may be used with extreme caution if the potential benefit outweighs risk. The risk of an acute attack is greatest in women who have had a previous attack or are aged under 30 years. Long-acting progestogen preparations should never be used in those at risk of acute porphyria.)
- Sulphonamides (includes co-trimoxazole and sulfasalazine)
- Sulfonylureas (glipizide and glimepiride are thought to be safe)
- Taxanes (contact Welsh Medicines Information Centre for further advice)
Thiazolidinediones (contact Welsh Medicines Information Centre for further advice)
Triazole antifungals (applies to oral and intravenous use; topical antifungals are thought to be safe due to low systemic exposure)

Unsafe Drugs (check groups above first)
- Aceclofenac
- Alcohol
- Amiodarone
- Aprepitant (contact Welsh Medicines Information Centre for further advice)
- Artemether with lumefantrine
- Bexarotene
- Bosantan
- Bromocriptine
- Buspirone
- Cabergoline
- Carbamazepine
- Chloral hydrate (although evidence of hazard is uncertain, manufacturer advises avoid)
- Chloramphenicol
- Chloroform (small amounts in medicines probably safe)
- Clindamycin
- Cocaine
- Colistimethate sodium
- Danazol
- Dapsone
- Disopyramide
- Disulfiram
- Erythromycin
- Ethosuximide
- Etamsylate
- Ethosuximide
- Etomidate
- Fenfluramine
- Flupentixol
- Flutamide
- Fosaprepitant (contact Welsh Medicines Information Centre for further advice)
- Fosphenytoin
- Griseofulvin
- Hydralazine
- Indapamide
- Isometheptene mucate
- Isoniazid (safety uncertain, contact Welsh Medicines Information Centre for further advice)
- Ketamine
- Mefenamic acid (may be used with caution if safer alternative not available)
- Meprobamate
- Methyldopa
- Metolazone
- Metoprolol
- Mifepristone
- Minoxidil (may be used with caution if safer alternative not available)
- Mitotane
- Nalidixic acid
- Nitrazepam
- Nitrofurantoin
- Orphenadrine
- Oxcarbazepine
- Oxycodone
- Pentazocine (buprenorphine, codeine, diacorphine, dihydrocodeine, fentanyl, methadone, morphine, oxycodone, pethidine, and tramadol are thought to be safe)
- Pentoxifylline
- Phenoxybenzamine
- Phenyltoin
- Pivmecillinam
- Porfimer
- Raloxifene
- Rifabutin (safety uncertain, contact Welsh Medicines Information Centre for further advice)
- Rifampicin
- Rizulore
- Risperidone
- Selegiline
- Spirolactone
- Sulfinpyrazole
- Tamoxifen
- Teliromycin
- Temoparin
- Tiagabine
- Tizolone
- Tindizole
- Topiramate
- Toremifene
- Trimethoprim
- Valproate
- Xipamide
- Zidovudine (contact Welsh Medicines Information Centre for further advice)
- Zuclopenthixol

HAEM DERIVATIVES

Haem arginate
(Human hemin)

INDICATIONS AND DOSE

Acute porphyrias | Acute intermittent porphyria | Porphryia variegata | Hereditary coproporphyria

BY INTRAVENOUS INFUSION
- Adult: Initially 3 mg/kg once daily for 4 days, if response inadequate, repeat 4-day course with close biochemical monitoring; maximum 250 mg per day

SIDE-EFFECTS
- Common or very common pain at injection site - thrombophlebitis at injection site
- Rare Fever - hypersensitivity reactions
- Frequency not known Headache

PREGNANCY
Manufacturer advises avoid unless essential.

BREAST FEEDING
Manufacturer advises avoid unless essential—no information available.

DIRECTIONS FOR ADMINISTRATION For intravenous infusion (Normosang®), give intermittently in Sodium chloride 0.9%; dilute requisite dose in 100 mL infusion fluid in glass bottle and give over at least 30 minutes through a filter via large antebrachial or central vein; administer within 1 hour after dilution.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Solution for infusion
- Normosang (Orphan Europe (UK) Ltd)
Haem arginate 25 mg per 1 ml Normosang 250mg/10ml solution for infusion ampoules | 4 ampoule £1,737.00
3.2 Carnitine deficiency

CARNITINE DERIVATIVES
Levocarnitine
(Carnitine)

INDICATIONS AND DOSE
Primary carnitine deficiency due to inborn errors of metabolism
BY MOUTH
- Adult: Up to 200 mg/kg daily in 2–4 divided doses; maximum 3 g per day
BY SLOW INTRAVENOUS INJECTION
- Adult: Up to 100 mg/kg daily in 2–4 divided doses, to be administered over 2–3 minutes
Secondary carnitine deficiency in haemodialysis patients
INITIALLY BY SLOW INTRAVENOUS INJECTION
- Adult: 20 mg/kg, to be administered over 2–3 minutes, after each dialysis session, dosage adjusted according to plasma-carnitine concentration, then (by mouth) maintenance 1 g daily, administered if benefit is gained from first intravenous course

- CAUTIONS
  - Diabetes mellitus

- SIDE-EFFECTS
  - Abdominal pain • body odour • diarrhoea • nausea • vomiting

SIDE-EFFECTS, FURTHER INFORMATION
Side-effects may be dose-related during first week and after any dose increase.

- PREGNANCY
  - Appropriate to use; no evidence of teratogenicity in animal studies.

- RENAL IMPAIRMENT
  - Accumulation of metabolites may occur with chronic oral administration in severe impairment.

- MONITORING REQUIREMENTS
  - Monitoring of free and acyl carnitine in blood and urine recommended.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: capsule
    - Carnitor (Sigma-Tau Pharma Ltd)
      - L-Carnitine 330 mg • Carnitor 330mg tablets | 90 tablet £103.95
    - Chewable tablet
      - Carnitor (Sigma-Tau Pharma Ltd)
      - L-Carnitine 1 gram • Carnitor 1g chewable tablets | 10 tablet £35.00
    - Capsule
      - LEVOCARNITINE (Non-proprietary)
        - L-Carnitine 250 mg • Carnitine 250mg capsules | 125 capsule £11.96
        - L-Carnitine 500 mg • Carnitine 500mg capsules | 60 capsule £11.67
    - Oral solution
      - LEVOCARNITINE (Non-proprietary)
        - L-Carnitine 300 mg per 1 ml • Levocarnitine 1.5g/5ml (30%) oral solution paediatric | 20 ml £5.55
      - Carnitor (Sigma-Tau Pharma Ltd)
        - L-Carnitine 100 mg per 1 ml • Carnitor oral single dose 1g solution (sugar-free) | 10 unit dose £35.00
    - Solution for injection
      - Carnitor (Sigma-Tau Pharma Ltd)
      - L-Carnitine 200 mg per 1 ml • Carnitor 1g/5ml solution for injection ampoules | 5 ampoule £59.50

3.3 Fabry’s disease

ENZYMES
Agalsidase alfa

- DRUG ACTION
  - Agalsidase alfa, an enzyme produced by recombinant DNA technology are licensed for long-term enzyme replacement therapy in Fabry’s disease (a lysosomal storage disorder caused by deficiency of alpha-galactosidase A).

INDICATIONS AND DOSE
Fabry’s disease (specialist use only)
BY INTRAVENOUS INFUSION
- Adult: 200 micrograms/kg every 2 weeks

- INTERACTIONS
  - Appendix 1 (agalsidase alfa and beta).

- SIDE-EFFECTS
  - Common or very common Acne • angioedema • arthralgia • asthenia • bradycardia • chest pain • cough • dizziness •
    - Hypersensitivity reactions • hypertension • hypotension • influenza-like symptoms • muscle spasms • myalgia • nasopharyngitis • neutropenic pain • oedema • palpitation • paraesthesia • pruritus • rash • rhinorrhea • sleep disturbances • syncope • tachycardia • taste disturbances • tinnitus • tremor • urticaria

- Uncommon
  - Cold extremities • ear pain • ear swelling • injection-site reactions • parosmia • skin discoloration

SIDE-EFFECTS, FURTHER INFORMATION
Infusion-related reactions
Infusion-related reactions very common; manage by slowing the infusion rate or interrupting the infusion, or minimise by pre-treatment with an antihistamine, antipyretic, or corticosteroid—consult product literature.

- PREGNANCY
  - Use with caution.

- BREAST FEEDING
  - Use with caution—no information available.

- DIRECTIONS FOR ADMINISTRATION
  - Administration for intravenous infusion, give intermittently in sodium chloride 0.9%; dilute requisite dose with 100 mL infusion fluid and give over 40 minutes using an in-line filter; use within 3 hours of dilution.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.

Solution for infusion
- Replagal (Shire Pharmaceuticals Ltd)
  - Agalsidase alfa 1 mg per 1 ml • Replagal 3.5mg/3.5ml solution for infusion vials | 1 vial £1.068 & 64

Agalsidase beta

- DRUG ACTION
  - Agalsidase beta, an enzyme produced by recombinant DNA technology are licensed for long-term enzyme replacement therapy in Fabry’s disease (a lysosomal storage disorder caused by deficiency of alpha-galactosidase A).

INDICATIONS AND DOSE
Fabry’s disease (specialist use only)
BY INTRAVENOUS INFUSION
- Adult: 1 mg/kg every 2 weeks

- INTERACTIONS
  - Appendix 1 (agalsidase alfa and beta).

- SIDE-EFFECTS
  - Common or very common Acne • angioedema • arthralgia • asthenia • bradycardia • chest pain • cough • dizziness •

- Chest pain • cough • dizziness •

- Eye irritation • fatigue • flushing • gastrointestinal disturbances • headache • hypersensitivity reactions • hypertension • hypotension • influenza-like symptoms • muscle spasms • myalgia • nasopharyngitis • neutropenic pain • oedema • palpitation • paraesthesia • pruritus • rash • rhinorrhea • sleep disturbances • syncope • tachycardia • taste disturbances • tinnitus • tremor • urticaria

- **Uncommon** Cold extremities - ear pain - ear swelling - injection-site reactions - parosmia - skin discoloration

### SIDE-EFFECTS, FURTHER INFORMATION

#### Infusion-related reactions

Infusion-related reactions very common; manage by slowing the infusion rate or interrupting the infusion, or minimise by pre-treatment with an antihistamine, antipyretic, or corticosteroid—consult product literature.

- **PREGNANCY** Use with caution.
- **BREAST FEEDING** Use with caution—no information available.

#### DIRECTIONS FOR ADMINISTRATION

For *intravenous infusion*, reconstitute initially with Water for Injections (5 mg in 1.1 mL, 35 mg in 7.2 mL) to produce a solution containing 5 mg/mL. Dilute with Sodium Chloride 0.9% (for doses less than 35 mg dilute with at least 50 mL; doses 35–70 mg dilute with at least 100 mL; doses 70–100 mg dilute with at least 250 mL; doses greater than 100 mg dilute with 500 mL) and give through an in-line low protein-binding 0.2 micron filter at an initial rate of no more than 15 mg/hour; for subsequent infusions infusion rate may be increased gradually once tolerance has been established.

- **MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

#### Powder for solution for infusion

- **Fabrazyme (Genzyme Therapeutics Ltd)**
  - Agalsidase beta 5 mg Fabrazyme 5mg powder for solution for infusion vials | 1 vial (£315.08)
- **Agalsidase beta 35 mg** Fabrazyme 35mg powder for solution for infusion vials | 1 vial (£2,196.59)

### 3.4 Gaucher’s disease

**Drugs used for Gaucher’s disease not listed below; Miglustat, p. 870**

#### ENZYMES

**Imiglucerase**

- **DRUG ACTION** Imiglucerase is an enzyme produced by recombinant DNA technology that is administered as enzyme replacement therapy for the treatment of type I Gaucher’s disease.

#### INDICATIONS AND DOSE

**Non-neurological manifestations of type I Gaucher’s disease (specialist use only)**

**By intravenous infusion**

- Adult: Initially 60 units/kg every 2 weeks; maintenance, adjusted according to response, doses as low as 15 units/kg once every 2 weeks may improve haematological parameters and organomegaly

- **SIDE-EFFECTS**
  - **Common or very common** Angioedema - backache - cyanosis - flushing - hypersensitivity reactions - hypotension - paraesthesia - tachycardia - urticaria
  - **Uncommon** Abdominal cramps - arthralgia - diarrhoea - dizziness - fatigue - fever - headache - injection-site reactions - nausea - vomiting

- **PREGNANCY** Manufacturer advises use with caution—limited information available.

- **BREAST FEEDING** No information available.

- **MONITORING REQUIREMENTS**
  - Monitor for immunoglobulin G (IgG) antibodies to imiglucerase.
  - When stabilised, monitor all parameters and response to treatment at intervals of 6–12 months.

- **DIRECTIONS FOR ADMINISTRATION** For *intravenous infusion* (Cerezyme®), give intermittently in Sodium chloride 0.9%; initially reconstitute with water for injections (200 units in 5.1 mL, 400 units in 10.2 mL) to give 40 units/mL solution; dilute requisite dose with infusion fluid to a final volume of 100–200 mL and give initial dose at a rate not exceeding 0.5 units/kg/minute, subsequent doses to be given at a rate not exceeding 1 unit/kg/minute; administer within 3 hours after reconstitution.

- **MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**

**ELECTROLYTES:** May contain Sodium

- **Cerezyme (Genzyme Therapeutics Ltd)**
  - Imiglucerase 400 unit Cerezyme 400unit powder for solution for infusion vials | 1 vial (£1,071.29)

**Velaglucerase alfa**

- **DRUG ACTION** Velaglucerase alfa is an enzyme produced by recombinant DNA technology that is administered as enzyme replacement therapy for the treatment of type I Gaucher’s disease.

#### INDICATIONS AND DOSE

**Type I Gaucher’s disease (specialist use only)**

**By intravenous infusion**

- Adult: Initially 60 units/kg every 2 weeks; adjusted according to response to 15–60 units/kg every 2 weeks

- **SIDE-EFFECTS** Abdominal pain - arthralgia - back pain - bone pain - dizziness - flushing - headache - hypersensitivity reactions - hypotension - hypertension - malaise - nausea - pyrexia - rash - tachycardia - urticaria

- **SIDE-EFFECTS, FURTHER INFORMATION**

  **Infusion-related reactions** Infusion-related reactions very common; manage by slowing the infusion rate, or interrupting the infusion, or minimise by pre-treatment with an antihistamine, antipyretic, or corticosteroid—consult product literature.

- **PREGNANCY** Manufacturer advises use with caution—limited information available.

- **BREAST FEEDING** Manufacturer advises use with caution—no information available.

- **MONITORING REQUIREMENTS** Monitor immunoglobulin G (IgG) antibody concentration in severe infusion-related reactions.

- **DIRECTIONS FOR ADMINISTRATION** For *intravenous infusion* (VPRIV®), give intermittently in Sodium chloride 0.9%; reconstitute each 400-unit vial with 4.3 mL water for injections to produce a 100 units/mL solution; dilute requisite dose in 100 mL infusion fluid; give over 60
minutes through a 0.22 micron filter; start infusion within 24 hours of reconstitution.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**
ELECTROLYTES: May contain Sodium
- VPRIV (Shire Human Genetic Therapies UK Ltd)
  - Velaglucerase alfa 400 unit VPRIV 400 units powder for solution for infusion vials | 1 vial no price available

### 3.5 Homocystinuria

#### Methyl Donors

**Betaine**

**INDICATIONS AND DOSE**
Adjunctive treatment of homocystinuria involving deficiencies or defects in cystathionine beta-synthase, 5,10-methylene-tetrahydrofolate reductase, or cobalamin cofactor metabolism (specialist use only)

**BY MOUTH**
- Adult: 3 g twice daily (max. per dose 10 g), adjusted according to response; maximum 20 g per day

**SIDE-EFFECTS**
- Uncommon: Agitation, alopecia, anorexia, depression; gastro-intestinal disorders; personality disorder; reversible cerebral oedema; sleep disturbances; urinary incontinence; urticaria
- PREGNANCY: Manufacturer advises avoid unless essential—limited information available.
- BREAST FEEDING: Manufacturer advises caution—no information available.
- MONITORING REQUIREMENTS: Monitor plasma-methionine concentration before and during treatment—interrupt treatment if symptoms of cerebral oedema occur.
- DIRECTIONS FOR ADMINISTRATION: Powder should be mixed with water, juice, milk, formula, or food until completely dissolved and taken immediately; measuring spoons are provided to measure 1 g, 150 mg, and 100 mg of Cystadane® powder.
- PRESCRIBING AND DISPENSING INFORMATION: Betaine should be used in conjunction with dietary restrictions and may be given with supplements of Vitamin B₁₂, pyridoxine, and folate under specialist advice.
- NATIONAL FUNDING/ACCESS DECISIONS
  - Scottish Medicines Consortium (SMC) Decisions
  - The Scottish Medicines Consortium has advised (July 2010) that betaine anhydrous (Cystadane®) is accepted for restricted use within NHS Scotland for the adjunctive treatment of homocystinuria involving deficiencies or defects in cystathionine beta-synthase, 5,10-methylene-tetrahydrofolate reductase, or cobalamin cofactor metabolism in patients who are not responsive to pyridoxine treatment.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, tablet

- **Powder**
  - Cystadane (Orphan Europe (UK) Ltd)
  - Betaine 1 gram per 1 gram Cystadane oral powder | 180 gram no price available

### 3.6 Mucopolysaccharidosis

#### Enzymes

**Galsulfase**

**DRUG ACTION**
Galsulfase is a recombinant form of human N-acetylgalactosamine-4-sulfatase.

**INDICATIONS AND DOSE**
Mucopolysaccharidosis VI (specialist use only)
- **BY INTRAVENOUS INFUSION**
  - Adult: 1 mg/kg once weekly

**CAUTIONS**
- Acute febrile illness (consider delaying treatment) - acute respiratory illness (consider delaying treatment) - infusion-related reactions can occur - respiratory disease

**SIDE-EFFECTS**

**SIDE-EFFECTS, FURTHER INFORMATION**
Infusion-related reactions
Infusion-related reactions often occur, they can be managed by slowing the infusion rate or interrupting the infusion, and can be minimised by pre-treatment with an antihistamine and an antipyretic. Recurrent infusion-related reactions may require pre-treatment with a corticosteroid—consult product literature for details.

**PREGNANCY**
- Manufacturer advises avoid unless essential.

**BREAST FEEDING**
- Manufacturer advises avoid—no information available.

**DIRECTIONS FOR ADMINISTRATION**
For intravenous infusion (Naglaze®), give intermittently in Sodium chloride 0.9%; dilute requisite dose with infusion fluid to final volume of 250 mL and mix gently; infuse through a 0.2 micron in-line filter; give approx. 2.5% of the total volume over 1 hour, then infuse remaining volume over next 3 hours; if body-weight under 20 kg and at risk of fluid overload, dilute requisite dose in 100 mL infusion fluid and give over at least 4 hours.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**
- Naglaze® (BioMarin Europe Ltd)
  - Galsulfase 1 mg per 1 ml Naglaze 5mg/5ml solution for infusion vials | 1 vial no price available

**Idursulfase**

**DRUG ACTION**
Idursulfase is an enzyme produced by recombinant DNA technology licensed for long-term replacement therapy in mucopolysaccharidosis II (Hunter syndrome), a lysosomal storage disorder caused by deficiency of iduronate-2-sulfatase.

**INDICATIONS AND DOSE**
Mucopolysaccharidosis II (specialist use only)
- **BY INTRAVENOUS INFUSION**
  - Adult: 500 micrograms/kg once weekly

**CAUTIONS**
- Acute febrile respiratory illness (consider delaying treatment) - infusion-related reactions can occur - severe respiratory disease
Laronidase

**INDICATIONS AND DOSE**

**Non-neurological manifestations of mucopolysaccharidosis I (specialist use only)**

**BY INTRAVENOUS INFUSION**

- Adult: 100 units/kg once weekly

**SIDE-EFFECTS, FURTHER INFORMATION**

Infusion-related reactions often occur, they can be managed by slowing the infusion rate or interrupting the infusion, and can be minimised by pre-treatment with an antihistamine and an antipyrretic. Recurrent infusion-related reactions may require pre-treatment with a corticosteroid—consult product literature for details.

**PREGNANCY**

Manufacturer advises avoid unless essential—no information available.

**BREAST FEEDING**

Manufacturer advises avoid—no information available.

**MONITORING REQUIREMENTS**

Monitor immunoglobulin G (IgG) antibody concentration.

**DIRECTIONS FOR ADMINISTRATION**

For intravenous infusion (Aldurazyme®) give intermittently in Sodium chloride 0.9%; body-weight over 20 kg use 100 mL infusion fluid; body-weight over 20 kg use 250 mL infusion fluid; withdraw volume of infusion fluid equivalent to volume of laronidase concentrate being added; give through in-line filter (0.22 micron) initially at a rate of 2 units/kg/hour then increase gradually every 15 minutes to max. 45 units/kg/hour.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

- Elaprase (Shire Pharmaceuticals Ltd)
  - Idursulfase 2 mg per 1 ml Elaprase 6mg/3ml concentrate for solution for infusion vials | 1 vial (£25) £1065.00

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**

ELECTROLYTES: May contain Sodium

- Aldurazyme (Genzyme Therapeutics Ltd)
  - Laronidase 100 unit per 1 ml Aldurazyme 500units/5ml solution for infusion vials | 1 vial (£34) £444.70

3.7 Nephropathic cystinosis

**AMINO ACIDS AND DERIVATIVES**

**Mercaptamine**

(Cysteamine)

**INDICATIONS AND DOSE**

Nephropathic cystinosis (specialist use only)

**BY MOUTH**

- Adult (body-weight 50 kg and above): Initially one-sixth to one-quarter of the expected maintenance dose, increased gradually over 4–6 weeks to avoid intolerance, maintenance 2 g daily in 4 divided doses

**Important safety information**

**SAFE PRACTICE**

Mercaptamine has been confused with mercaptopurine; care must be taken to ensure the correct drug is prescribed and dispensed.

**CAUTIONS**

Dose of phosphate supplement may need to be adjusted if transferring from phosphocysteamine to mercaptamine.

**SIDE-EFFECTS**

- Common or very common Abdominal pain · alopecia · anaphylaxis · angioedema · blood pressure changes · cold extremities · cough · diarrhoea · dizziness · dysphonia · fatigue · flushing · headache · influenza-like symptoms · infusion-site reactions · musculoskeletal pain · nausea · pain in extremities · pailor · paraesthesia · pruritus · rash · restlessness · tachycardia · urticaria · vomiting

**FREQUENCY NOT KNOWN**

- Bronchospasm · infusion-related reactions · respiratory arrest

**SIDE-EFFECTS, FURTHER INFORMATION**

Infusion-related reactions Infusion-related reactions often occur, they can be managed by slowing the infusion rate or interrupting the infusion, and can be minimised by pre-treatment with an antihistamine and an antipyrretic. Recurrent infusion-related reactions may require pre-treatment with a corticosteroid—consult product literature.

**ALLERGY AND CROSS-SENSITIVITY**

Contraindicated if history of hypersensitivity to penicillamine.

**PREGNANCY**

Avoid—teratogenic and toxic in animal studies.

**BREAST FEEDING**

Avoid.

**MONITORING REQUIREMENTS**

Leucocyte-cystine concentration and haematological monitoring required—consult product literature.
3.8 Niemann-Pick type C disease

GLUCOSYLCERAMIDE SYNTHASE INHIBITORS

Miglustat

**DRUG ACTION** Miglustat is an inhibitor of glucosylceramide synthase.

**INDICATIONS AND DOSE**

Mild to moderate type I Gaucher’s disease for whom enzyme replacement therapy is unsuitable (under expert supervision)

**BY MOUTH**

- Adult: 100 mg 3 times a day, reduced if not tolerated to 100 mg 1–2 times a day

Treatment of progressive neurological manifestations of Niemann-Pick type C disease (under expert supervision)

**BY MOUTH**

- Adult: 200 mg 3 times a day

**SIDE-EFFECTS** Abdominal pain · anamnesis · anorexia · ataxia · chills · constipation · decreased libido · depression · diarrhoea · dizziness · dyspepsia · flatulence · headache · hypoaesthesia · insomnia · malaise · muscle spasm · muscle weakness · nausea · paraesthesia · peripheral neuropathy · thrombocytopenia · tremor · vomiting · weight changes

**CONCEPTION AND CONTRACEPTION** Effective contraception must be used during treatment. Men should avoid fathering a child during and for 3 months after treatment.

**PREGNANCY** Manufacturer advises avoid—toxicity in animal studies.

**BREAST FEEDING** Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT** No information available—manufacturer advises caution.

**RENAL IMPAIRMENT** For Gaucher’s disease initially 100 mg twice daily if eGFR 50–70 mL/minute/1.73 m². Initially 100 mg once daily if eGFR 30–50 mL/minute/1.73 m². For Niemann-Pick type C disease, initially 200 mg twice daily if eGFR 50–70 mL/minute/1.73 m². Initially 100 mg twice daily if eGFR 30–50 mL/minute/1.73 m². Avoid if eGFR less than 30 mL/minute/1.73 m².

**MONITORING REQUIREMENTS**

- Monitor cognitive and neurological function.
- Monitor growth and platelet count in Niemann-Pick type C disease.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

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### 3.9 Pompe disease

**ENZYMES**

**Alglucosidase alfa**

**DRUG ACTION** Alglucosidase alfa is an enzyme produced by recombinant DNA technology licensed for long-term replacement therapy in Pompe disease, a lysosomal storage disorder caused by deficiency of acid alpha-glucosidase.

**INDICATIONS AND DOSE**

**Pompe disease (specialist use only)**

- **BY INTRAVENOUS INFUSION**
  - **Adult:** 20 mg/kg every 2 weeks

**CAUTIONS**

- Cardiac dysfunction · infusion-related reactions—consult product literature · respiratory dysfunction

**SIDE-EFFECTS**

- Common or very common Agitation · anaphylaxis · antibody formation · blood pressure changes · bronchospasm · chest discomfort · cold extremities · cough · cyanosis · diarrhoea · dizziness · facial oedema · fatigue · flushing · headache · hypersensitivity reactions · injection-site reactions · irritability · muscle spasm · myalgia · nausea · paraesthesia · pruritus · pyrexia · rash · restlessness · sweating · tachycardia · tachypnoea · tremor · urticaria · vomiting

**Frequency not known** Infusion-related reactions · necrotising skin lesions · severe skin reactions · ulcerative skin lesions

**SIDE-EFFECTS, FURTHER INFORMATION**

**Infusion-related reactions** Infusion-related reactions very common, calling for use of antihistamine, antipyretic, or corticosteroid; consult product literature for details.

**PREGNANCY** Toxicity in animal studies, but treatment should not be withheld.

**BREAST FEEDING** Manufacturer advises avoid—no information available.

**MONITORING REQUIREMENTS**

- Monitor closely if cardiac dysfunction.
- Monitor closely if respiratory dysfunction.
- Monitor immunoglobulin G (IgG) antibody concentration.

**DIRECTIONS FOR ADMINISTRATION** For intravenous infusion (Myozyme®), give intermittently in Sodium chloride 0.9%; reconstitute 50 mg with 10.3 mL water for injections to produce 5 mg/mL solution; gently rotate vial without shaking; dilute requisite dose with infusion fluid to give a final concentration of 0.5–4 mg/mL; give through a low protein-binding in-line filter (0.2 micron) at an initial rate of 1 mg/kg/hour increased by 2 mg/kg/hour every 30 minutes to max. 7 mg/kg/hour.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for infusion**

- **Myozyme (Genzyme Therapeutics Ltd)**
  - Alglucosidase alfa 50 mg Myozyme 50 mg powder for concentrate solution for infusion vials | 1 vial (BH) £356.06 (Hospital only)

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3.10 Tyrosinaemia type I

4-HYDROXYPHENYLPYRUVATE DIOXYGENASE INHIBITORS

Nitisinone (NTBC)

INDICATIONS AND DOSE

Hereditary tyrosinaemia type I (in combination with dietary restriction of tyrosine and phenylalanine) (specialist use only)

BY MOUTH

Adult: Initially 500 micrograms/kg twice daily, adjusted according to response; maximum 2 mg/kg per day

SIDE-EFFECTS

- Common or very common Conjunctivitis · corneal opacity · eye pain · granulocytopenia · keratitis · leucopenia · photophobia · thrombocytopenia
- Uncommon Blepharitis · erythematous rash · exfoliative dermatitis · leucocytosis · pruritus
- PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risks—toxicity in animal studies.
- BREAST FEEDING Manufacturer advises avoid—adverse effects in animal studies.
- PRE-TREATMENT SCREENING Slit-lamp examination of eyes recommended before treatment.
- MONITORING REQUIREMENTS
  - Monitor liver function regularly.
  - Monitor platelet and white blood cell count every 6 months.
- DIRECTIONS FOR ADMINISTRATION Capsules can be opened and the contents suspended in a small amount of water or formula diet and taken immediately.
- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.

Capsule

- Orfadin (Swedish Orphan Biavitrum Ltd)
  - Nitisinone 2 mg Orfadin 2mg capsules | 60 capsule £564.00
  - Nitisinone 5 mg Orfadin 5mg capsules | 60 capsule £1,127.00
  - Nitisinone 10 mg Orfadin 10mg capsules | 60 capsule £2,062.00

3.11 Urea cycle disorders

AMINO ACIDS AND DERIVATIVES

Carglumic acid

INDICATIONS AND DOSE

Hyperammonaemia due to N-acetylglutamate synthase deficiency (under expert supervision)

BY MOUTH

Adult: Initially 50–125 mg/kg twice daily, to be taken immediately before food, dose adjusted according to plasma-ammonia concentration; maintenance 5–50 mg/kg twice daily, the total daily dose may alternatively be given in 3–4 divided doses

Hyperammonaemia due to organic acidaemia (under expert supervision)

BY MOUTH

Adult: Initially 50–125 mg/kg twice daily, to be taken immediately before food, dose adjusted according to plasma-ammonia concentration, the total daily dose may alternatively be given in 3–4 divided doses

Important safety information

EMERGENCY MANAGEMENT OF UREA CYCLE DISORDERS

For further information on the emergency management of urea cycle disorders consult the British Inherited Metabolic Disease Group (BIMDG) website at www.bimdg.org.uk.

SIDE-EFFECTS

- Common or very common Sweating
- Uncommon Bradycardia · diarrhea · pyrexia · vomiting
- PREGNANCY Manufacturer advises avoid unless essential—no information available.
- BREAST FEEDING Manufacturer advises avoid—present in milk in animal studies.
- DIRECTIONS FOR ADMINISTRATION Dispersible tablets must be dispersed in at least 5–10 mL of water and taken orally immediately, or administered via a nasogastric tube.
- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.

Dispersible tablet

CAUTIONARY AND ADVISORY LABELS 13

- Carbaglu (Orphan Europe (UK) Ltd)
  - Carglumic acid 200 mg Carbaglu 200mg dispersible tablets (sugar-free) | 5 tablet £299.00 (sugar-free) | 60 tablet £3,499.00

AMMONIA LOWERING DRUGS

Sodium phenylbutyrate

INDICATIONS AND DOSE

Long-term treatment of urea cycle disorders (as adjunctive therapy in all patients with neonatal-onset disease and in those with late-onset disease who have a history of hyperammonaemic encephalopathy) (under expert supervision)

BY MOUTH

- Adult: 9.9–13 g/m² daily in divided doses, with meals; maximum 20 g per day

Important safety information

EMERGENCY MANAGEMENT OF UREA CYCLE DISORDERS

For further information on the emergency management of urea cycle disorders consult the British Inherited Metabolic Disease Group (BIMDG) website at www.bimdg.org.uk.

CAUTIONS

- Congestive heart failure (preparations contain significant amounts of sodium)
- INTERACTIONS → Appendix 1 (sodium phenylbutyrate).
- SIDE-EFFECTS
  - Common or very common Alkalosis · blood disorders · body odour · decreased appetite · depression · gastro-intestinal disturbances · headache · irritability · menstrual disorders · metabolic acidosis · oedema · rash · renal tubular acidosis · syncope · taste disturbance · weight gain
  - Uncommon Arrhythmias · pancreatitis · peptic ulcer · rectal bleeding
- SIDE-EFFECTS, FURTHER INFORMATION
  - Gastro-intestinal side-effects may be reduced by giving smaller doses more frequently.
- CONCEPTION AND CONTRACEPTION
  - Manufacturer advises adequate contraception during administration in women of child-bearing potential.
- PREGNANCY
  - Avoid—toxicity in animal studies.
9

872 Trace element deficiencies

**Zinc acetate**

- **DRUG ACTION** Zinc prevents the absorption of copper in Wilson’s disease.

**INDICATIONS AND DOSE**

Wilson’s disease (initiated under specialist supervision)

**BY MOUTH**

- Adult: 50 mg 3 times a day (max. per dose 50 mg 5 times a day), adjusted according to response

**Dose equivalence and conversion**

Doses expressed as elemental zinc.

**PHARMACOKINETICS**

Symptomatic Wilson’s disease patients should be treated initially with a chelating agent because zinc has a slow onset of action. When transferring from chelating treatment to zinc maintenance therapy, chelating treatment should be co-administered for 2–3 weeks until zinc produces its maximal effect.

- **CAUTIONS** Portal hypertension (risk of hepatic decompensation when switching from chelating agent)

- **INTERACTIONS** → Appendix 1 (zinc).

- **SIDE-EFFECTS**
  - Common or very common Gastric irritation (usually transient)
  - Uncommon Leucopenia - sideroblastic anaemia

**SIDE-EFFECTS, FURTHER INFORMATION**

Transient gastric irritation may be reduced if first dose is taken mid-morning or with a little protein.

- **PREGNANCY** Reduce dose to 25 mg 3 times daily adjusted according to plasma-copper concentration and urinary copper excretion.

- **BREAST FEEDING** Manufacturer advises avoid; present in milk—may cause zinc-induced copper deficiency in infant.

**MONITORING REQUIREMENTS** Monitor full blood count and serum cholesterol.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **CAPSULE**
  - **CAUTIONARY AND ADVISORY LABELS** 6, 22
  - **TRIENTINE DIHYDROCHLORIDE (Non-proprietary)**
    - Trientine dihydrochloride 300 mg Trientine dihydrochloride 300mg capsules | 100 capsule (BNF) no price available

3.12 Wilson’s disease

Drugs used for Wilson’s disease not listed below; Penicillamine, p. 896

**COPPER ABSORPTION INHIBITORS**

**Zinc acetate**

- **DRUG ACTION** Zinc prevents the absorption of copper in Wilson’s disease.

**INDICATIONS AND DOSE**

Wilson’s disease (initiated under specialist supervision)

**BY MOUTH**

- Adult: 1.2–2.4 g daily in 2–4 divided doses, adjusted according to response, to be taken before food

- **INTERACTIONS** → Appendix 1 (trientine).

- **SIDE-EFFECTS**
  - Common or very common Nausea - rash
  - Very rare Anaemia
  - Frequency not known Colitis - duodenitis

- **PREGNANCY** Teratogenic in animal studies—use only if benefit outweighs risk. Monitor maternal and neonatal serum-copper concentrations.

- **PRESCRIBING AND DISPENSING INFORMATION** Trientine is not an alternative to penicillamine for rheumatoid arthritis or cystinuria. Penicillamine-induced systemic lupus erythematosus may not resolve on transfer to trientine.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **CAPSULE**
  - **CAUTIONARY AND ADVISORY LABELS** 6, 22
  - **TRIENTINE DIHYDROCHLORIDE (Non-proprietary)**
    - Trientine dihydrochloride 300 mg Trientine dihydrochloride 300mg capsules | 100 capsule (BNF) no price available

4 Trace element deficiencies

**Trace elements**

**Selenium**

Selenium deficiency can occur as a result of inadequate diet or prolonged parenteral nutrition. A selenium supplement should not be given unless there is good evidence of deficiency.

**Zinc**

Zinc supplements should not be given unless there is good evidence of deficiency (hypoproteinaemia spuriously lowers plasma-zinc concentration) or in zinc-losing conditions. Zinc deficiency can occur as a result of inadequate diet or malabsorption; excessive loss of zinc can occur in trauma, burns, and protein-losing conditions. A zinc supplement is given until clinical improvement occurs, but it may need to be continued in severe malabsorption, metabolic disorders p. 864, or in zinc-losing states.
Zinc is used in the treatment of Wilson’s disease and acrodermatitis enteropathica, a rare inherited abnormality of zinc absorption.

Parenteral nutrition regimens usually include trace amounts of zinc. If necessary, further zinc can be added to intravenous feeding regimens.

## 4.1 Selenium deficiency

### SELENIUM

#### Indications and dose

**Selenium deficiency**

BY MOUTH OR BY INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INJECTION

- Adult: 100–500 micrograms daily

- **Interactions** Appendix 1 (selenium).

- **Medicinal forms**

  There can be variation in the licensing of different medicines containing the same drug.

  **Tablet**

  - SELENIUM (Non-proprietary)
  
  Selenium (as L-Selenomethionine) 100 microgram Solgar Selenium 100microgram tablets | 100 tablet no price available
  L-Selenomethionine 200 microgram EN-Selenium 200microgram tablets | 30 tablet £8.60
  Solgar Selenium 200microgram tablets | 50 tablet no price available 250 tablet no price available
  HealthAid Selenium 200microgram tablets | 60 tablet £3.90
  Lamberts Selenium 200microgram tablets | 60 tablet £4.08
  SelenoPrecise (Pharma Nord (UK) Ltd)
  
  Selenium (as L-Selenomethionine) 100 microgram SelenoPrecise 100microgram tablets | 60 tablet £6.75
  L-Selenomethionine 200 microgram SelenoPrecise 200microgram tablets | 60 tablet £4.02

  **Capsule**

  - SELENIUM (Non-proprietary)
  
  L-Selenomethionine 200 microgram Selenium 200microgram capsules | 30 capsule £2.98 | 60 capsule £5.39

  **Oral solution**

  - Solenase (Baxter Healthcare Ltd)
  
  Selenium (as Sodium selenite) 50 microgram per 1 ml Solenase 100micrograms/2ml oral solution 2ml unit dose ampoules | 20 unit dose | no price available
  Selenium 500micrograms/10ml oral solution unit dose vials | 10 unit dose | no price available

  **Solution for injection**

  - Solenase (Baxter Healthcare Ltd)
  
  Selenium (as Sodium selenite) 50 microgram per 1 ml Solenase 100micrograms/2ml solution for injection ampoules | 10 ampoule (POT) no price available
  Selenium 500micrograms/10ml solution for injection vials | 10 vial (POT) no price available

  **Solution for infusion**

  - SELENIUM (Non-proprietary)
  
  Selenium (as Sodium selenite) 10 microgram per 1 ml Selenium 100micrograms/10ml solution for infusion vials | 10 vial no price available

## 4.2 Zinc deficiency

### Zinc

#### Zinc sulfate

**Indications and dose**

**Zinc deficiency or supplementation in zinc-losing conditions**

BY MOUTH USING EFFERVESCENT TABLETS

- Child (body-weight up to 10 kg): 22.5 mg daily, dose to be adjusted as necessary, to be dissolved in water and taken after food, dose expressed as elemental zinc
  
  - Child (body-weight 10–30 kg): 22.5 mg 1–3 times a day, dose to be adjusted as necessary, to be dissolved in water and taken after food, dose expressed as elemental zinc
  
  - Child (body-weight 30 kg and above): 45 mg 1–3 times a day, dose to be adjusted as necessary, to be dissolved in water and taken after food, dose expressed as elemental zinc
  
  - Adult (body-weight 30 kg and above): 45 mg 1–3 times a day, dose to be adjusted as necessary, to be dissolved in water and taken after food, dose expressed as elemental zinc

**Additional elemental zinc for intravenous nutrition**

BY INTRAVENOUS INJECTION

- Adult: 6.5 mg daily (Zn$^{2+}$ 100 micromol)

**Unlicensed use** Solvazine$^{	ext{®}}$ is not licensed for use in acrodermatitis enteropathica.

**Interactions** → Appendix 1 (zinc).

**Side-effects** Abdominal pain · diarrhoea · dyspepsia · gastric irritation · gastritis · headache · irritability · lethargy · nausea · vomiting

**Pregnancy** Crosses placenta; risk theoretically minimal, but no information available.

**Breast-feeding** Present in milk; risk theoretically minimal, but no information available.

**Renal impairment** Accumulation may occur in acute renal failure.

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, oral solution, capsule, liquid

**Effervescent tablet**

CAUTIONARY AND ADVISORY LABELS 13, 21

- Solvazine (Galen Ltd)
  
  Zinc sulfate monohydrate 125 mg Solvazinc 125mg effervescent tablets (sugar-free) | 90 tablet (POT) £14.95 OT price = £14.95

## 5 Nutrition

### Intravenous nutrition

When adequate feeding through the alimentary tract is not possible, nutrients may be given by intravenous infusion. This may be in addition to ordinary oral or tube feeding—supplemental parenteral nutrition, or may be the sole source of nutrition—total parenteral nutrition (TPN). Indications for this method include preparation of undernourished patients for surgery, chemotherapy, or radiation therapy; severe or prolonged disorders of the gastro-intestinal tract; major surgery, trauma, or burns;
### Proprietary Infusion Fluids for Parenteral Feeding

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Nitrogen g/litre</th>
<th>1kJ Energy kJ/litre</th>
<th>Electrolytes mmol/litre</th>
<th>Other components/litre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoven 25 (Fresenius Kabi) Net price 500 ml = £19.72</td>
<td>25.7</td>
<td>-</td>
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<tr>
<td>Clinimix N9G20E (Baxter) Net price (dual compartment bag of amino acids with electrolytes 1000 mL and glucose 20% with calcium 1000 mL) 2 litre: no price available</td>
<td>4.6 1680</td>
<td>30.0 2.5 35.0 50.0 40.0</td>
<td>Ca++ 2.3 mmol, phosphate 15 mmol, anhydrous glucose 100 g</td>
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<tr>
<td>Clinimix N14G30E (Baxter) Net price (dual compartment bag of amino acids with electrolytes 1000 mL and glucose 30% with calcium 1000 mL) 2 litre: no price available</td>
<td>7.0 2520</td>
<td>30.0 2.5 35.0 70.0 40.0</td>
<td>Ca++ 2.3 mmol, phosphate 15 mmol, anhydrous glucose 150 g</td>
<td></td>
</tr>
<tr>
<td>ClinOleic 20% (Baxter) Net price 100 ml: no price available; Net price 250 ml: no price available; Net price 500 ml: no price available</td>
<td>- 8360</td>
<td>- - - -</td>
<td>purified olive and soya oil 200 g, glycerol 22.5 g, egg phosphatides 12 g</td>
<td></td>
</tr>
<tr>
<td>Hyperamine 30 (B.Braun) Net price 500 ml: no price available</td>
<td>30.0</td>
<td>- - - 5.0 -</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intralipid 10% (Fresenius Kabi) Net price 100 ml = £4.12; Net price 500 ml = £9.01</td>
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<td>soya oil 100 g, glycerol 22 g, purified egg phospholipids 12 g, phosphate 15 mmol</td>
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<tr>
<td>Intralipid 20% (Fresenius Kabi) Net price 100 ml = £6.21; Net price 250 ml = £10.16; Net price 500 ml = £13.52</td>
<td>- 8400</td>
<td>- - - -</td>
<td>soya oil 200 g, glycerol 22 g, purified egg phospholipids 12 g, phosphate 15 mmol</td>
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<td>Intralipid 30% (Fresenius Kabi) Net price 333 ml = £17.80</td>
<td>- 12600</td>
<td>- - - -</td>
<td>soya oil 300 g, glycerol 16.7 g, purified egg phospholipids 12 g, phosphate 15 mmol</td>
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<tr>
<td>Kabiven (Fresenius Kabi) Net price (triple compartment bag of amino acids and electrolytes 300 mL, 450 mL, 600 mL, or 750 mL; glucose 526 mL, 790 mL, 1053 mL; or 1316 mL; lipid emulsion 200 mL, 300 mL, 400 mL, or 500 mL) 1.026 litre: no price available; Net price 1.54 litre = £44.09; Net price 2.053 litre = £57.42; Net price 2.566 litre = £59.92</td>
<td>5.3 3275</td>
<td>23.0 4.0 31.0 38.0 45.0</td>
<td>Ca++ 2 mmol, phosphate 7.5 mmol, anhydrous glucose 67.5 g, soya oil 35.4 g</td>
<td></td>
</tr>
<tr>
<td>Kabiven peripheral (Fresenius Kabi) Net price (triple compartment bag of amino acids and electrolytes 300 mL, 400 mL, or 500 mL; glucose 885 mL, 1180 mL, or 1475 mL; lipid emulsion 255 mL, 340 mL, or 425 mL) 1.44 litre = £30.77; Net price 1.92 litre = £44.09; Net price 2.4 litre = £55.72</td>
<td>3.75 2625</td>
<td>17.0 2.8 22.0 27.0 33.0</td>
<td>Ca++ 1.4 mmol, phosphate 7.5 mmol, anhydrous glucose 67.5 g, soya oil 35.4 g</td>
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<tr>
<td>Lipidem (B.Braun) Net price 100 ml = £19.11; Net price 250 ml = £31.85; Net price 500 ml = £40.34</td>
<td>- 7900</td>
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<td>omega-3-acid triglycerides 20 g, soya oil 80 g, medium chain triglycerides 100 g</td>
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<tr>
<td>Lipofundin MCT/LCT 10% (B.Braun) Net price 100 ml: no price available; Net price 500 ml = £13.70</td>
<td>- 4430</td>
<td>- - - -</td>
<td>soya oil 50 g, medium-chain triglycerides 50 g</td>
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</tr>
<tr>
<td>Lipofundin MCT/LCT 20% (B.Braun) Net price 100 ml = £13.28; Net price 250 ml: no price available; Net price 500 ml = £20.36</td>
<td>- 8000</td>
<td>- - - -</td>
<td>soya oil 100 g, medium-chain triglycerides 100 g</td>
<td></td>
</tr>
</tbody>
</table>

1. 1000 kcal = 4200kJ; 1000 kJ = 238.8 kcal. All entries are Prescription-only medicines.
2. Excludes protein- or amino acid-derived energy.
### Nutrition (intravenous) 875

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Nitrogen g/litre</th>
<th>1 kcal/litre K+</th>
<th>1 kcal/litre Mg²⁺</th>
<th>1 kcal/litre Na⁺</th>
<th>1 kcal/litre Acet</th>
<th>1 kcal/litre Cl⁻</th>
<th>Other components/litre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutriflex basal (B.Braun)</td>
<td>4.6</td>
<td>2095</td>
<td>30.0</td>
<td>5.7</td>
<td>49.9</td>
<td>35.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Nutriflex peri (B.Braun)</td>
<td>5.7</td>
<td>1340</td>
<td>15.0</td>
<td>4.0</td>
<td>27.0</td>
<td>19.5</td>
<td>31.6</td>
</tr>
<tr>
<td>Nutriflex plus (B.Braun)</td>
<td>6.8</td>
<td>2510</td>
<td>25.0</td>
<td>5.7</td>
<td>37.2</td>
<td>22.9</td>
<td>35.5</td>
</tr>
<tr>
<td>Nutriflex special (B.Braun)</td>
<td>10.0</td>
<td>4020</td>
<td>25.7</td>
<td>5.0</td>
<td>40.5</td>
<td>22.0</td>
<td>49.5</td>
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<tr>
<td>Nutriflex Lipid peri (B.Braun)</td>
<td>4.56</td>
<td>2664</td>
<td>24.0</td>
<td>2.4</td>
<td>40.0</td>
<td>32.0</td>
<td>38.4</td>
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<tr>
<td>Nutriflex Lipid plus (B.Braun)</td>
<td>5.44</td>
<td>3600</td>
<td>28.0</td>
<td>3.2</td>
<td>40.0</td>
<td>36.0</td>
<td>36.0</td>
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<tr>
<td>Nutriflex Lipid plus without Electrolytes (B.Braun)</td>
<td>5.44</td>
<td>3600</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nutriflex Lipid special (B.Braun)</td>
<td>8.0</td>
<td>4004</td>
<td>37.6</td>
<td>4.24</td>
<td>53.6</td>
<td>48.0</td>
<td>48.0</td>
</tr>
<tr>
<td>Nutriflex Lipid special without Electrolytes (B.Braun)</td>
<td>8.0</td>
<td>4004</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

1 1000 kcal = 4200kJ; 1000 kJ = 238.8 kcal. All entries are Prescription-only medicines.
2 Excludes protein- or amino acid-derived energy.
### Preparation | Nitrogen g/litre | 1-2 Energy kJ/litre | Electrolytes mmol/litre | Other components/litre
--- | --- | --- | --- | ---
**NutriFlex Omega plus (B.Braun)**
Net price (triple compartment bag of amino acids 500 mL, 750 mL or 1000 mL; glucose 500 mL, 750 mL or 1000 mL; lipid emulsion 250 mL, 375 mL or 500 mL) 1.25 litre = £47.43; Net price 1.875 litre = £60.57; Net price 2.5 litre = £69.66 5.4 | 3600 | 28.0 | 3.2 | 40.0 | 36.0 | 36.0 | Ca²⁺ 3.2 mmol, Zn²⁺ 24 micromol, phosphate 12 mmol, anhydrous glucose 120 g, refined soya oil 16 g, medium-chain triglycerides 20 g, omega-3-acid triglycerides 4 g

**NutriFlex Omega special (B.Braun)**
Net price (triple compartment bag of amino acids 250 mL, 500 mL, 750 mL or 1000 mL; glucose 250 mL, 500 mL, 750 mL or 1000 mL; lipid emulsion 125 mL, 250 mL, 375 mL or 500 mL) 525 mL = £43.62; Net price 1.25 litre = £58.01; Net price 1.875 litre = £76.01; Net price 2.5 litre = £89.71 8.0 | 4004 | 37.6 | 4.24 | 53.6 | 48.0 | 48.0 | Ca²⁺ 4.24 mmol, Zn²⁺ 30 micromol, phosphate 16 mmol, anhydrous glucose 144 g, refined soya oil 16 g, medium-chain triglycerides 20 g, omega-3-acid triglycerides 4 g

**OliClinomel N4-550E (Baxter)**
Net price (triple compartment bag of amino acids with electrolytes 1000 mL; glucose 20% 1000 mL; lipid emulsion 10% 500 mL) 2.5 litre: no price available 3.6 | 2184 | 16.0 | 2.2 | 21.0 | 30.0 | 33.0 | Ca²⁺ 2 mmol, phosphate 8.5 mmol, refined olive and soya oil 20 g, anhydrous glucose 80 g

**OliClinomel N4-720E (Baxter)**
Net price (triple compartment bag of amino acids with electrolytes 1000 mL; glucose 20% 1000 mL; lipid emulsion 20% 500 mL) 2.5 litre: no price available 3.64 | 3024 | 24.0 | 2.0 | 28.0 | 40.0 | 40.0 | Ca²⁺ 1.8 mmol, phosphate 8 mmol, refined olive and soya oil 40 g, anhydrous glucose 80 g

**OliClinomel N5-800E (Baxter)**
Net price (triple compartment bag of amino acids with electrolytes 800 mL or 1000 mL; glucose 25% 800 mL or 1000 mL; lipid emulsion 20% 400 mL or 500 mL) 2 litre: no price available; Net price 2.5 litre: no price available 4.6 | 3360 | 24.0 | 2.2 | 32.0 | 49.0 | 44.0 | Ca²⁺ 2 mmol, phosphate 10 mmol, refined olive and soya oil 40 g, anhydrous glucose 100 g

**OliClinomel N6-900E (Baxter)**
Net price (triple compartment bag of amino acids with electrolytes 800 mL or 1000 mL; glucose 30% 800 mL or 1000 mL; lipid emulsion 20% 400 mL or 500 mL) 2 litre: no price available; Net price 2.5 litre: no price available 5.6 | 3696 | 24.0 | 2.2 | 32.0 | 53.0 | 46.0 | Ca²⁺ 2 mmol, phosphate 10 mmol, refined olive and soya oil 40 g, anhydrous glucose 120 g

**OliClinomel N7-1000 (Baxter)**
Net price (triple compartment bag of amino acids 600 mL; glucose 40% 600 mL; lipid emulsion 20% 300 mL) 1.5 litre: no price available 6.6 | 4368 | - | - | - | 37.0 | 16.0 | phosphate 3 mmol, refined olive and soya oil 40 g, anhydrous glucose 160 g

**OliClinomel N7-1000E (Baxter)**
Net price (triple compartment bag of amino acids with electrolytes 800 mL; glucose 40% 800 mL; lipid emulsion 20% 400 mL) 2 litre: no price available 6.6 | 4368 | 24.0 | 2.2 | 32.0 | 57.0 | 48.0 | Ca²⁺ 2 mmol, phosphate 10 mmol, refined olive and soya oil 40 g, anhydrous glucose 160 g

**OliClinomel N8-800 (Baxter)**
Net price (triple compartment bag of amino acids 800 mL; glucose 31.25% 800 mL; lipid emulsion 15% 400 mL) 2 litre: no price available 8.25 | 3360 | - | - | - | 42.5 | 20.0 | phosphate 2.25 mmol, refined olive and soya oil 30 g, anhydrous glucose 125 g

**Omegaven (Fresenius Kabi)**
Net price 100 ml: no price available - | 4700 | - | - | - | - | highly refined fish oil 100 g, glycerol 25 g, egg phosphatide 12 g

**Plasma-Lyte 148 (water) (Baxter)**
Net price 1 litre: no price available - | - | 5.0 | 1.5 | 140.0 | 27.0 | 98.0 | gluconate 23 mmol

---

1. 1000 kcal = 4200kJ; 1000 kJ = 238.8 kcal. All entries are Prescription-only medicines.
2. Excludes protein- or amino acid-derived energy.
The nutrition solution is infused through a central venous catheter inserted under full surgical precautions. Alternatively, infusion through a peripheral vein may be used for supplementary as well as total parenteral nutrition for periods of up to a month, depending on the availability of peripheral veins; factors prolonging cannula life and preventing thrombophlebitis include the use of soft polyurethane paediatric cannulas and use of feeds of low osmolality and neutral pH. Only nutritional fluids should be given by the dedicated intravenous line.

Before starting, the patient should be well oxygenated and peritoneal dialysis is contraindicated. Parenteral nutrition requires the use of a solution containing amino acids, glucose, fat, electrolytes, trace elements, and vitamins. This is now commonly provided by the pharmacy in the form of a 3-litre bag. A single dose of vitamin B₁₂, as hydroxocobalamin p. 837, is given by intramuscular injection; regular vitamin B₉ injections are not usually required unless total parenteral nutrition continues for many months. Folic acid p. 836 is given in a dose of 15 mg once or twice each week, usually in the nutrition solution. Other vitamins are usually given daily; they are generally introduced in the parenteral nutrition solution. Alternatively, if the patient is able to take small amounts by mouth, vitamins may be given orally.

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Nitrogen g/litre</th>
<th>1 kcal energy kJ/litre</th>
<th>Electrolytes mmol/litre</th>
<th>Other components/litre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma-Lyte 148 (dextrose 5%) (Baxter)</td>
<td>-</td>
<td>840</td>
<td>K⁺ 5.0, Mg²⁺ 1.5, Na⁺ 140.0, Cl⁻ 27.0, Ca²⁺ 98.0</td>
<td>Glucose 22 mmol, anhydrous glucose 50 g</td>
</tr>
<tr>
<td>Plasma-Lyte M (dextrose 5%) (Baxter)</td>
<td>-</td>
<td>840</td>
<td>K⁺ 16.0, Mg²⁺ 1.5, Na⁺ 40.0, Cl⁻ 12.0, Ca²⁺ 40.0</td>
<td>Ca²⁺ 2.5 mmol, lactate 12 mmol, anhydrous glucose 50 g</td>
</tr>
<tr>
<td>SMOFlipid (Fresenius Kabi)</td>
<td>-</td>
<td>840</td>
<td>-</td>
<td>Fish oil 30 g, olive oil 50 g, soya oil 60 g, medium-chain triglycerides 60 g</td>
</tr>
<tr>
<td>Synthamin 9 (Baxter)</td>
<td>9.1</td>
<td>60.0</td>
<td>K⁺ 5.0, Mg²⁺ 1.5, Na⁺ 70.0, Cl⁻ 100.0, Ca²⁺ 70.0</td>
<td>Acid phosphate 30 mmol</td>
</tr>
<tr>
<td>Synthamin 9 EF electrolyte-free (Baxter)</td>
<td>9.1</td>
<td>-</td>
<td>-</td>
<td>44.0, 22.0</td>
</tr>
<tr>
<td>Synthamin 14 (Baxter)</td>
<td>14.0</td>
<td>60.0</td>
<td>K⁺ 5.0, Mg²⁺ 1.5, Na⁺ 70.0, Cl⁻ 140.0, Ca²⁺ 70.0</td>
<td>Acid phosphate 30 mmol</td>
</tr>
<tr>
<td>Synthamin 14 EF electrolyte-free (Baxter)</td>
<td>14.0</td>
<td>-</td>
<td>-</td>
<td>68.0, 34.0</td>
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<tr>
<td>Synthamin 17 (Baxter)</td>
<td>16.5</td>
<td>60.0</td>
<td>K⁺ 5.0, Mg²⁺ 1.5, Na⁺ 70.0, Cl⁻ 150.0, Ca²⁺ 70.0</td>
<td>Acid phosphate 30 mmol</td>
</tr>
<tr>
<td>Synthamin 17 EF electrolyte-free (Baxter)</td>
<td>16.5</td>
<td>-</td>
<td>-</td>
<td>82.0, 40.0</td>
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<td>Vamin 9 Glucose (Fresenius Kabi)</td>
<td>9.4</td>
<td>1700</td>
<td>20.0, 1.5, 50.0, -</td>
<td>Ca²⁺ 2.5 mmol, anhydrous glucose 100 g</td>
</tr>
<tr>
<td>Vamin 14 (Fresenius Kabi)</td>
<td>13.5</td>
<td>50.0</td>
<td>8.0, 100.0, 135.0, 100.0</td>
<td>Ca²⁺ 5 mmol, SO₄²⁻ 8 mmol</td>
</tr>
<tr>
<td>Vamin 14 electrolyte-free (Fresenius Kabi)</td>
<td>13.5</td>
<td>-</td>
<td>-</td>
<td>90.0</td>
</tr>
<tr>
<td>Vamin 18 electrolyte-free (Fresenius Kabi)</td>
<td>18.0</td>
<td>-</td>
<td>-</td>
<td>110.0</td>
</tr>
</tbody>
</table>

1 1000 kcal = 4200kJ; 1000 kJ = 238.8 kcal. All entries are Prescription-only medicines.
2 Excludes protein- or amino acid-derived energy
Blood and nutrition utilisation of amino acids than glucose alone. Glucose p.

amino acids; they often contain an energy source (usually with electrolytes. Solutions vary in their composition of

Energy is provided in a ratio of 0.6 to 1.1 megajoules (150–250 kcal) per gram of protein nitrogen. Energy requirements must be met if amino acids are to be utilised for tissue maintenance. A mixture of carbohydrate and fat energy sources (usually 30–50% as fat) gives better utilisation of amino acids than glucose alone.

Glucose p. 852 is the preferred source of carbohydrate, but if more than 180 g is given per day frequent monitoring of blood glucose is required, and insulin may be necessary. Glucose p. 852 in various strengths from 10 to 50% must be infused through a central venous catheter to avoid thrombosis.

In parenteral nutrition regimens, it is necessary to provide adequate phosphate in order to allow phosphorylation of glucose and to prevent hypophosphataemia; between 20 and 30 mmol of phosphate is required daily.

Fructose and sorbitol have been used in an attempt to avoid the problem of hyperosmolar hyperglycaemic non-ketotic acidosis but other metabolic problems may occur, as with xylitol and ethanol which are now rarely used.

Fat emulsions have the advantages of a high energy to fluid volume ratio, neutral pH, and iso-osmolarity with plasma, and provide essential fatty acids. Several days of adaptation may be required to attain maximal utilisation. Reactions include occasional febrile episodes (usually only with 20% emulsions) and rare anaphylactic responses. Interference with biochemical measurements such as those for blood gases and calcium may occur if samples are taken before fat has been cleared. Daily checks are necessary to ensure complete clearance from the plasma in conditions where fat metabolism may be disturbed. Additives should not be mixed with fat emulsions unless compatibility is known.

Administration
Because of the complex requirements relating to parenteral nutrition full details relating to administration have been omitted. In all cases product literature and other specialist literature should be consulted.

PARENTERAL NUTRITION

Parenteral nutrition supplements

**INDICATIONS AND DOSE**

**Dipeptiven 20G/100mL Concentrate for Solution for Infusion Bottles**

Amino acid supplement for hypercatabolic or hypermetabolic states

**By Intravenous Infusion**

- Adult: 300–400 mg/kg daily, dose not to exceed 20% of total amino acid intake

### CAUTIONS

**Peditrace®**

Reduced biliary excretion, reduced biliary excretion in cholestatic liver disease, reduced biliary excretion in markedly reduced urinary excretion (careful biochemical monitoring required), total parenteral nutrition exceeding one month.

CAUTIONS, FURTHER INFORMATION

Total parental nutrition exceeding one month

Measure serum manganese concentration and check liver function before commencing treatment and regularly during treatment—discontinue if manganese concentration raised or if cholestasis develops.

**DIRECTIONS FOR ADMINISTRATION**

Because of the complex requirements relating to parenteral nutrition, full details relating to administration have been omitted. In all cases specialist pharmacy advice, product literature, and other specialist literature should be consulted.

Compatibility with the infusion solution must be ascertained before adding supplementary preparations. Additives should not be mixed with fat emulsions unless compatibility is known.

**Dipeptiven 20G/100mL Concentrate for Solution for Infusion Bottles**

For addition to infusion solutions containing amino acids.

**Peditrace®**

For addition to Vaminolact®, Vamin® 14 Electrolyte-Free solutions, and glucose intravenous infusions.

**Decan®**

For addition to infusion solutions.

**Additrace®**

For addition to Vamin® solutions and glucose intravenous infusions.

**Tracutril®**

For addition to infusion solutions.

**Glycophos®**

For addition to Vamin® and Vaminolact® solutions, and glucose intravenous infusions.

**Addiphos®**

For addition to Vamin® solutions and glucose intravenous infusions.

**Cernivet®**

Dissolve in 5mL water for injection.

**Vitlipid N Infant**

For addition to Intralipid®.

**Vitlipid®**

For addition to Intralipid®.

**Solvitio®**

Dissolve in water for injections or glucose intravenous infusion for adding to glucose intravenous infusion or Intralipid®; dissolve in Vitlipid N® or Intralipid® for adding to Intralipid® only.

**PRESCRIBING AND DISPENSING INFORMATION**

**Dipeptiven®**

Dipeptiven® solution contains N(2)-L-alanyl-glutamine 200mg/mL (providing L-alanine 82 mg, L-glutamine 134.6mg)

**Peditrace®**

For use in neonates (when kidney function established, usually second day of life), infants, and children.

**Decan®**

For patients over 40kg.

**Additrace®**

For patients over 40kg.

**Tracutril®**

For adults.

**Glycophos®**

Glycophos® Sterile Concentration solution contains phosphate 20mmol, Na+ 40mmol/20mL

**Addiphos®**

Addiphos sterile solution contains phosphate 40mmol, K+ 30mmol, Na+ 30 mmol/20mL

**Vitlipid N Adult®**

For adults and children over 11 years.
## 5.2 Nutrition (oral)

### Enteral nutrition

The body’s reserves of protein rapidly become exhausted in severely ill patients, especially during chronic illness or in those with severe burns, extensive trauma, pancreatitis, or intestinal fistula. Much can be achieved by frequent meals and by persuading the patient to take supplementary snacks of ordinary food between the meals.

However, extra calories, proteins, other nutrients, and vitamins are often best given by supplementing ordinary meals with enteral sip or tube feeds.

When patients cannot feed normally, for example, patients with severe facial injury, oesophageal obstruction, or coma, a nutritionally complete diet of enteral feeds must be given. The advice of a dietitian should be sought to determine the protein and total energy requirement of the patient and the form and relative contribution of carbohydrate and fat to the energy requirements.

Most enteral feeds contain protein derived from cows’ milk or soya. Elemental feeds containing protein hydrolysates or free amino acids can be used for patients who have diminished ability to break down protein, for example in inflammatory bowel disease or pancreatic insufficiency.

Even when nutritionally complete feeds are given, water and electrolyte balance should be monitored. Haematological and biochemical parameters should also be monitored, particularly in clinically unstable patients. Extra minerals (e.g. magnesium and zinc) may be needed in patients where gastro-intestinal secretions are being lost. Additional vitamins may also be needed.

### Enteral nutrition in children

Children have special requirements and in most situations liquid feeds prepared for adults are totally unsuitable—the advice of a paediatric dietitian should be sought.

## 5.3 Phenyketonuria

**Phenyketonuria**

**Phenyketonuria** (hyperphenylalaninaemia, PKU), which results from the inability to metabolise phenylalanine, is managed by restricting dietary intake of **phenylalanine** to a small amount sufficient for tissue building and repair. Sapropterin dihydrochloride p. 880, a synthetic form of tetrahydrobiopterin, is licensed as an adjunct to dietary restriction of **phenylalanine** in the management of patients with **phenylketonuria** and **tetrahydrobiopterin deficiency**.
Blood and nutrition

5.4 Special diets

Nutrition in special diets

These are preparations that have been modified to eliminate a particular constituent from a food or that are nutrient mixtures formulated as food substitutes for patients who either cannot tolerate or cannot metabolise certain common constituents of food. In certain clinical conditions, some food preparations are regarded as drugs and can be prescribed within the NHS if they have been approved by the Advisory Committee on Borderline Substances (ACBS).

Aspartame (used as a sweetener in some foods and medicines) contributes to the phenylalanine intake and may affect control of phenylketonuria. Where the presence of aspartame is specified in the product literature this is indicated in the BNF against the preparation; the patient should be informed of this.

Coeliac disease
Intolerance to gluten in coeliac disease is managed by completely eliminating gluten from the diet. A range of gluten-free products is available for prescription.

6 Vitamin deficiencies

Vitamins

Vitamins are used for the prevention and treatment of specific deficiency states or where the diet is known to be inadequate; they may be prescribed in the NHS to prevent or treat deficiency but not as dietary supplements. Their use as general ‘pick-me-ups’ is of unproven value and, in the case of preparations containing vitamin A or D, may actually be harmful if patients take more than the prescribed dose. The ‘fad’ for mega-vitamin therapy with water-soluble vitamins, such as ascorbic acid p. 884 and pyridoxine hydrochloride p. 882, is unscientific and can be harmful.

Dietary reference values for vitamins are available in the Department of Health publication:


Dental patients

It is unjustifiable to treat stomatitis or glossitis with mixtures of vitamin preparations; this delays diagnosis and correct treatment.

Most patients who develop a nutritional deficiency despite an adequate intake of vitamins have malabsorption and if this is suspected the patient should be referred to a medical practitioner.

Vitamin A

Deficiency of vitamin A (retinol) is associated with ocular defects (particularly xerophthalmia) and an increased susceptibility to infections, but deficiency is rare in the UK (even in disorders of fat absorption).

Vitamin B group

Deficiency of the B vitamins, other than vitamin B₁₂, is rare in the UK and is usually treated by preparations containing thiamine p. 882 (B₁), riboflavin (B₂), and nicotinamide, which is used in preference to nicotinic acid, as it does not cause vasodilatation. Other members (or substances traditionally classified as members) of the vitamin B complex such as aminobenzoic acid, biotin, choline, inositol nicotinate p. 206, and pantothenic acid or panthenol may be included in vitamin B preparations but there is no evidence of their value.

The severe deficiency states Wernicke’s encephalopathy and Korsakoff’s psychosis, especially as seen in chronic alcoholism, are best treated initially by the parenteral administration of B vitamins (Pabrinex®), followed by oral...
administration of thiamine p. 882 in the longer term. Anaphylaxis has been reported with parenteral B vitamins. As with other vitamins of the B group, pyridoxine hydrochloride p. 882 (B6) deficiency is rare, but it may occur during isoniazid therapy or penicillamine treatment in Wilson’s disease and is characterised by peripheral neuritis. High doses of pyridoxine hydrochloride p. 882 are given in some metabolic disorders, such as hyperoxaluria, and it is also used in sideroblastic anaemia. There is evidence to suggest that pyridoxine hydrochloride may provide some benefit in premenstrual syndrome. It has been tried for a wide variety of other disorders, but there is little sound evidence to support the claims of efficacy.

Nicotinic acid p. 177 inhibits the synthesis of cholesterol and triglyceride. Folic acid p. 836 and vitamin B12 are used in the treatment of megaloblastic anaemia. Folic acid p. 781 (available as calcium folinate) is used in association with cytotoxic therapy.

**Vitamin C**

Vitamin C (ascorbic acid p. 884) therapy is essential in scurvy, but less florid manifestations of vitamin C deficiency are commonly found, especially in the elderly. Severe scurvy causes gingival swelling and bleeding margins as well as petechiae on the skin. This is, however, exceedingly rare and a patient with these signs is more likely to have leukaemia. Investigation should not be delayed by a trial period of vitamin treatment. Claims that vitamin C ameliorates colds or promotes wound healing have not been proven.

**Vitamin D**

The term Vitamin D is used for a range of compounds which possess the property of preventing or curing rickets. They include ergocalciferol p. 887 (calciferol, vitamin D2), colecalciferol (vitamin D3) p. 886, dihydrotrachysterol p. 887, alfacalcidol (1α-hydroxycholecalciferol) p. 885, and calcitriol (1,25-dihydroxycholecalciferol) p. 885. Simple vitamin D deficiency can be prevented by taking an oral supplement of ergocalciferol (calciferol, vitamin D2) or colecalciferol (vitamin D3) daily. Vitamin D deficiency can occur in people whose exposure to sunlight is limited and in those whose diet is deficient in vitamin D. In these individuals, ergocalciferol or colecalciferol daily by mouth may be given to treat vitamin D deficiency; higher doses may be necessary for severe deficiency. Patients who do not respond should be referred to a specialist.

Preparations containing calcium carbonate with colecalciferol p. 886 are available for the management of combined calcium and vitamin D deficiency, or for those at high risk of deficiency.

Vitamin D deficiency caused by intestinal malabsorption or chronic liver disease usually requires vitamin D in pharmacological doses.

Vitamin D requires hydroxylation by the kidney to its active form, therefore the hydroxylated derivatives alfacalcidol p. 885 or calcitriol p. 885 should be prescribed if patients with severe renal impairment require vitamin D therapy. Calcitriol is also licensed for the management of postmenopausal osteoporosis. Paricalcitol p. 888, a synthetic vitamin D analogue, is licensed for the prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure.

**Vitamin E**

The daily requirement of vitamin E (tocopherol) has not been well defined but is probably 3 to 15 mg daily. There is little evidence that oral supplements of vitamin E are essential in adults, even where there is fat malabsorption secondary to cholestatics. In young children with congenital cholestatics, abnormally low vitamin E concentrations may be found in association with neuromuscular abnormalities, which usually respond only to the parenteral administration of vitamin E. Vitamin E has been tried for various other conditions but there is little scientific evidence of its value.

**Vitamin K**

Vitamin K is necessary for the production of blood clotting factors and proteins necessary for the normal calcification of bone.

Because vitamin K is fat soluble, patients with fat malabsorption, especially in biliary obstruction or hepatic disease, may become deficient. Menadion sodium phosphate p. 889 is a water-soluble synthetic vitamin K derivative that can be given orally to prevent vitamin K deficiency in malabsorption syndromes.

Oral coumarin anticoagulants act by interfering with vitamin K metabolism in the hepatic cells and their effects can be antagonised by giving vitamin K.

**Other compounds**

Potassium aminobenzoate p. 882 has been used in the treatment of various disorders associated with excessive fibrosis such as scleroderma and Peyronie’s disease. In Peyronie’s disease there is some evidence to support efficacy in reducing progression when given early in the disease; however, there is no evidence for reversal of the condition. The therapeutic value of potassium aminobenzoate in scleroderma is doubtful.

**MULTIVITAMINS**

**Vitamins A and D**

**INDICATIONS AND DOSE**

Prevention of vitamin A and D deficiency

**BY MOUTH**

- Child: 1 capsule daily, 1 capsule contains 4000 units vitamin A and 400 units (10 micrograms) vitamin D
- Adult: (consult product literature)

**UNLICENSED USE** Not licensed in children under 6 months of age.

**INTERACTIONS** → Appendix 1 (vitamins).

**SIDE-EFFECTS**

**Overdose** Prolonged excessive ingestion of vitamins A and D can lead to hypervitaminosis.

**PRESCRIBING AND DISPENSING INFORMATION** This drug contains vitamin D; consult individual vitamin D monographs.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Capsule**

**VITAMINS A AND D (Non-proprietary)**

Vitamin A 4000 unit, Vitamin D 400 unit


**Vitamins A, C and D**

The properties listed below are those particular to the combination only. For the properties of the components please consider, ascorbic acid p. 884, vitamin D p. 884.
Vitamin B6

Pyridoxine hydrochloride

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Oral drops**
- **VITAMINS A, C AND D (Non-proprietary)**
  - Ascorbic acid 150 mg per 1 ml, Sodium ascorbate 18.58 mg per 1 ml, Vitamin A 5000 iu per 1 ml, Vitamin A and D3 concentrate 0.55 mg per 1 ml, Vitamin D 2000 iu per 1 ml
  - Healthy Start Children’s Vitamin drops | 10 ml no price available

**INTERACTIONS** → Appendix 1 (vitamins).

**SIDE-EFFECTS** Sensory neuropathy (with high doses when given for extended periods)

**Overdose**
Overdosage induces toxic effects.

**INDICATIONS AND DOSE**

**Deficiency states**
- Adult: 20–50 mg 1–3 times a day
- Isoniazid-induced neuropathy (prophylaxis)
  - Adult: 10–20 mg daily
- Isoniazid-induced neuropathy (treatment)
  - Adult: 50 mg 3 times a day

**UNLICENSED USE**

**PRESCRIBING AND DISPENSING INFORMATION**
This drug contains vitamin D; consult individual vitamin D monographs.

Available free of charge to children under 4 years in families on the Healthy Start Scheme, or alternatively may be available direct to the public—further information for healthcare professionals can be accessed at www.healthystart.nhs.uk. Beneficiaries can contact their midwife or health visitor for further information on where to obtain supplies. Healthy Start Vitamins for women (containing ascorbic acid, vitamin D, and folic acid) are also available free of charge to women on the Healthy Start Scheme during pregnancy and until their baby is one year old, or alternatively may be available direct to the public—further information for healthcare professionals can be accessed at www.healthystart.nhs.uk. Beneficiaries can contact their midwife or health visitor for further information on where to obtain supplies.

**VITAMIN B GROUP**

Potassium aminobenzoate

**INDICATIONS AND DOSE**

Peyronie’s disease | Scleroderma

**BY MOUTH**
- Adult: 12 g daily in divided doses, to be taken after food

**INTERACTIONS** → Appendix 1 (potassium aminobenzoate).

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**INTERACTIONS** → Appendix 1 (potassium aminobenzoate).

Thiamine

(Vitamin B1)

**INDICATIONS AND DOSE**

**Mild deficiency**
- Adult: 25–100 mg daily

**Severe deficiency**
- Adult: 200–300 mg daily in divided doses

**Important safety information**
MHRA/CHM ADVICE (SEPTEMBER 2007)
Although potentially serious allergic adverse reactions may rarely occur during, or shortly after, parenteral administration, the CHM has recommended that:
- This should not preclude the use of parenteral thiamine in patients where this route of administration is required, particularly in patients at risk of Wernicke-Korsakoff syndrome where treatment with thiamine is essential;
Vitamin B substances with ascorbic acid

The properties listed below are those particular to the combination only. For the properties of the components please consider ascorbic acid p. 884, thiamine p. 882.

**INDICATIONS AND DOSE**

Parenteral vitamins B and C for rapid correction of severe depletion or malabsorption (e.g. in alcoholism, after acute infections, postoperatively, or in psychiatric states) | Maintenance of vitamins B and C in chronic intermittent haemodialysis

**BY INTRAVENOUS INFUSION**

- Adult: See MHRA/CHM advice in Thiamine monograph (consult product literature).

**Treatment of Wernicke’s encephalopathy**

- Adult: 2–3 pairs 3 times a day for 2 days, discontinue if no response, continue treatment if symptoms respond after 2 days; (by intravenous infusion or by deep intramuscular injection) 1 pair once daily for 5 days or for as long as improvement continues, give deep intramuscular injection into the gluteal muscle

**Prophylaxis of Wernicke’s encephalopathy in alcohol dependence**

**BY INTRAVENOUS INFUSION OR BY DEEP INTRAMUSCULAR INJECTION**

- Adult: 1 pair once daily for at least 3–5 days, give deep intramuscular injection into the gluteal muscle

**Caution**

Anaphylaxis may occasionally follow injection.

**Breast Feeding**

Severely thiamine-deficient mothers should avoid breast-feeding as toxic methylglyoxal present in milk.

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Tablet**

- Thiamine (Non-proprietary) Thiamine hydrochloride 50 mg Thiamine 50mg tablets | 100 tablet [p] no price available DT price = £7.13 | 100 tablet £7.13 DT price = £7.13
- Thiamine hydrochloride 100 mg Thiamine 100mg tablets | 100 tablet [p] no price available DT price = £11.55 | 100 tablet £11.55 DT price = £11.55
- Benerva (Bayer Pic) Thiamine hydrochloride 50 mg Benerva 50mg tablets | 100 tablet [p] £3.98 DT price = £7.13
- Thiamine hydrochloride 100 mg Benerva 100mg tablets | 100 tablet [p] £6.16 DT price = £11.55
- Tyvera (Teva UK Ltd, Almus Pharmaceuticals Ltd) Thiamine hydrochloride 50 mg Tyvera 50mg tablets | 100 tablet [p] £5.46–6.72 DT price = £7.13
- Thiamine hydrochloride 100 mg Tyvera 100mg tablets | 100 tablet [p] £8.46–9.18 DT price = £11.55

**Modified-release tablet**

- Thiamine (Non-proprietary) Thiamine hydrochloride 100 mg HealthAid Vitamin B1 100mg modified-release tablets | 90 tablet £4.18

**Unlicensed use**

Pabrinex® doses in BNF may differ from those in product literature.

**Directions for administration**

Give (Pabrinex® I/V High Potency) intermittently or via drip tubing in Glucose 5% or Sodium chloride 0.9%. Ampoules contents should be mixed, diluted, and administered without delay; give over 30 minutes.

**Prescribing and dispensing information**

Some formulations of Pabrinex® may contain benzyl alcohol (avoid in neonates). Pabrinex® I/M High Potency injection is for intramuscular use only. Pabrinex® I/V High Potency injection is for intravenous use only.

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug.

**Not applicable**

**Excipients:** May contain benzyl alcohol

- Pabrinex Intramuscular High Potency (Archimedes Pharma UK Ltd) Pabrinex Intramuscular High Potency solution for injection 5ml and 2ml ampoules | 20 ampoule | £22.53 DT price = £22.53
- Pabrinex Intravenous High Potency (Archimedes Pharma UK Ltd) Pabrinex Intravenous High Potency solution for injection 5ml and 5ml ampoules | 20 ampoule | £22.53 DT price = £22.53

**Vitamin B complex**

**Indications and dose**

Prophylaxis of deficiency

**By mouth using tablets**

- Adult: 1–2 tablets daily, this dose is for vitamin B compound tablets

**Treatment of deficiency**

**By mouth using tablets**

- Adult: 1–2 tablets 3 times daily as a single dose, this dose is for vitamin B compound strong tablets

**Less suitable for prescribing**

Vitamin B compound tablets are less suitable for prescribing. Vitamin B compound strong tablets are less suitable for prescribing.

**Medicinal forms**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- VITAMIN B COMPLEX (Non-proprietary) Nicotinamide 15 mg, Riboflavin 1 mg, Thiamine hydrochloride 1 mg Vitamin B compound tablets | 28 tablet | no price available DT price = £26.62 | 1000 tablet £10.50 Nicotinamide 20 mg, Pyridoxine hydrochloride 2 mg, Riboflavin 2 mg, Thiamine hydrochloride 5 mg Vitamin B compound strong tablets | 28 tablet | no price available DT price = £1.95 | 1000 tablet no price available | 1000 tablet [p] no price available

**Psychosis following narciss or electroconvulsive therapy**

Toxicity from acute infections

**By intravenous infusion or by deep intramuscular injection**

- Adult: 1 pair twice daily for up to 7 days, give deep intramuscular injection into the gluteal muscle

**Haemodialysis**

**By intravenous infusion**

- Adult: 1 pair every 2 weeks
Blood and nutrition

Vitamins with minerals and trace elements

**INDICATIONS AND DOSE**

**KETOVITE® TABLETS**

Prevention of vitamin deficiency in disorders of carbohydrate or amino-acid metabolism / Adjunct in restricted, specialised, or synthetic diets

**BY MOUTH**

▶ Adult: 1 tablet 3 times a day, use with Ketonal® Liquid for complete vitamin supplementation.

**FORCEVAL® CAPSULES**

Vitamin and mineral deficiency and as adjunct in synthetic diets

**BY MOUTH**

▶ Adult: 1 capsule daily, one hour after a meal

**CAUTIONS, FURTHER INFORMATION**

Iron overload: Ascorbic acid should not be given to patients with cardiac dysfunction.

In patients with normal cardiac function ascorbic acid should be introduced 1 month after starting desferrioxamine.

**INTERACTIONS** → Appendix 1 (vitamins).

**PRESCRIBING AND DISPENSING INFORMATION**

To avoid potential toxicity, the content of all vitamin preparations, particularly vitamin A, should be considered when used together with other supplements.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

▶ VITAMINS WITH MINERALS AND TRACE ELEMENTS (Non-proprietary)

<table>
<thead>
<tr>
<th>Vitamin and mineral combination</th>
<th>Manufacturers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascorbic acid 50 mg, Biotin 100 microgram, Calcium pantothenate 1.16 mg, Folic acid 250 microgram, Inositol 50 mg, Nicotinamide 3.3 mg, Pyridoxine hydrochloride 330 microgram, Riboflavin 1 mg, Thiamine hydrochloride 1 mg</td>
<td>Forceval (Alliance Pharmaceuticals Ltd)</td>
</tr>
</tbody>
</table>

**Capsule**

▶ Forceval (Alliance Pharmaceuticals Ltd)

Ascorbic acid 60 mg, Biotin 100 microgram, Calcium 100 mg, Chromium 200 microgram, Copper 2 mg, Cyanocobalamin 3 microgram, Ergocalciferol 400 unit, Folic acid 400 microgram, Iodine 140 microgram, Iron 12 mg, Magnesium 30 mg, Manganese 3 mg, Molybdenum 250 microgram, Nicotinamide 18 mg, Panthenolic acid 4 mg, Phosphorus 77 mg, Potassium 4 mg, Pyridoxine 2 mg, Riboflavin 1.6 mg, Selenium 50 microgram, Thiamine 1.2 mg, Tocopherol acetate 10 mg, Vitamin A 2500 unit, Zinc 15 mg | Forceval capsules | 15 capsule £3.40 | 30 capsule £5.93 | 90 capsule £14.32

**VITAMIN D AND ANALOGUES**

Vitamin D and analogues (systemic)

**CONTRA-INDICATIONS**

Hypercalcaemia - metastatic calcification

**INTERACTIONS** → Appendix 1 (vitamins).

**SIDE-EFFECTS**

Overdose: Symptoms of overdosage include anorexia, lassitude, nausea and vomiting, diarrhoea, constipation, weight loss, polyuria, sweating, headache, thirst, vertigo, and raised concentrations of calcium and phosphate in plasma and urine.

**PREGNANCY**

High doses teratogenic in animals but therapeutic doses unlikely to be harmful.

**BRACE FEEDING**

Caution with high doses; may cause hypercalcaemia in infant—monitor serum-calcium concentration.

**MONITORING REQUIREMENTS**

Important: All patients receiving pharmacological doses of vitamin D should have their plasma–calcium concentration checked at intervals (initially once or twice weekly) and whenever nausea or vomiting occur.
Vitamin deficiencies 885

Alfacalcidol (1α-Hydroxycholecalciferol)

**INDICATIONS AND DOSE**

Patients with severe renal impairment requiring vitamin D therapy

**BY MOUTH OR BY INTRAVENOUS INJECTION**

- Adult: Initially 1 microgram daily, dose to be adjusted to avoid hypercalcemia; maintenance 0.25–1 microgram daily
- Elderly: Initially 500 nanograms daily, dose adjusted to avoid hypercalcemia; maintenance 0.25–1 microgram daily

**Hypophosphataemic rickets** | **Persistent hypocalcaemia due to hypoparathyroidism or pseudohypoparathyroidism**

**BY MOUTH OR BY INTRAVENOUS INJECTION**

- Child 1 month–11 years: 25–50 nanograms/kg once daily, dose to be adjusted as necessary; maximum 1 microgram per day
- Child 12–17 years: 1 microgram once daily, dose to be adjusted as necessary

**Prevention of vitamin D deficiency in renal or cholestatic liver disease**

**BY MOUTH OR BY INTRAVENOUS INJECTION**

- Child 1 month–11 years (body-weight up to 20 kg): 15–30 nanograms/kg once daily (max. per dose 500 nanograms)
- Child 1 month–11 years (body-weight 20 kg and above): 250–500 nanograms once daily, dose to be adjusted as necessary
- Child 12–17 years: 250–500 nanograms once daily, dose to be adjusted as necessary

**Dose equivalence and conversion**

One drop of alfacalcidol 2 microgram/mL oral drops contains approximately 100 nanograms alfacalcidol.

- **CAUTIONS** Nephrolithiasis · take care to ensure correct dose in infants
- **SIDE-EFFECTS**
  - Rare Nephrocalcinosis · pruritus · rash · urticaria
- **RENAL IMPAIRMENT** Monitor plasma-calcium concentration in renal impairment.
- **MONITORING REQUIREMENTS** Monitor plasma-calcium concentration in patients receiving high doses.
- **DIRECTIONS FOR ADMINISTRATION**
  - With intravenous use: For injection, shake ampoule for at least 5 seconds before use, and give over 30 seconds.
- **PRESCRIBING AND DISPENSING INFORMATION**
  - The concentration of alfacalcidol in One-Alpha® drops is 10 times greater than that of the former preparation One-Alpha® solution.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

**Capsule**

- **EXCIPIENTS**: May contain Sesame oil
- **ALFACALCIDOL (Non-proprietary)**
  - Alfacalcidol 250 nanogram Alfacalcidol 250nanogram capsules | 30 capsule (PO) £6.33 DT price + £2.51
  - Alfacalcidol 500 nanogram Alfacalcidol 500nanogram capsules | 30 capsule (PO) £11.25 DT price + £5.18
  - Alfacalcidol 1 microgram Alfacalcidol 1microgram capsules | 30 capsule no price available DT price + £5.74 | 30 capsule (PO) £15.25 DT price + £5.74
  - One-Alpha (LEO Pharma)
    - Alfacalcidol 250 nanogram One-Alpha 250nanogram capsules | 30 capsule (PO) £3.37 DT price + £2.51
    - Alfacalcidol 500 nanogram One-Alpha 0.5microgram capsules | 30 capsule (PO) £6.27 DT price + £5.18

- **Solution for injection**

- **EXCIPIENTS**: May contain Alcohol, propylene glycol
- **One-Alpha (LEO Pharma)**
  - Alfacalcidol 2 microgram per 1 ml One-Alpha 2micrograms/ml oral drops (sugar-free) | 10 ml (PO) £21.30 DT price + £21.30

Calcitriol (1,25-Dihydroxycholecalciferol)

**INDICATIONS AND DOSE**

**Renal osteodystrophy**

**BY MOUTH**

- Adult: Initially 250 nanograms daily, adjusted in steps of 250 nanograms every 2–4 weeks if required; usual dose 0.5–1 microgram daily

**Renal osteodystrophy (in patients with normal or only slightly reduced plasma-calcium concentration)**

**BY MOUTH**

- Adult: Initially 250 nanograms once daily on alternate days, adjusted in steps of 250 nanograms every 2–4 weeks if required; usual dose 0.5–1 microgram daily

**Established postmenopausal osteoporosis**

**BY MOUTH**

- Adult: 250 nanograms twice daily, plasma-calcium concentration and creatinine to be monitored (consult product literature)

- **HEPATIC IMPAIRMENT** Manufacturer advises avoid—no information available.
- **RENA L IMPAIRMENT** Manufacturer advises avoid—no information available. Monitor plasma-calcium concentration in renal impairment.
- **MONITORING REQUIREMENTS** Monitor plasma calcium, phosphate, and creatinine during dosage titration. Monitor plasma-calcium concentration in patients receiving high doses.
- **DIRECTIONS FOR ADMINISTRATION** Contents of capsule may be administered by oral syringe.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension
Colecalciferol
(Cholecalciferol; Vitamin D₃)

**INDICATIONS AND DOSE**

**Prevention of vitamin D deficiency**

- **BY MOUTH**
  - Adult: 400 units daily

**Treatment of vitamin D deficiency**

- **BY MOUTH**
  - Adult: 800 units daily, higher doses may be necessary for severe deficiency

**RENAL IMPAIRMENT**

Monitor plasma-calcium concentration in renal impairment.

**MONITORING REQUIREMENTS**

Monitor plasma-calcium concentration in patients receiving high doses.

**DIRECTIONS FOR ADMINISTRATION**

**INVITA D3**

- May be mixed with a small amount of cold or lukewarm food immediately before administration.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, oral suspension, oral drops, oral solution, capsule

**Tablet**

- **COLECALCIFEROL (Non-proprietary)**
  - Colecalciferol 400 unit | Colecalciferol 400 unit tablets | 120 tablet | £3.21
  - Colecalciferol 1000 unit | Colecalciferol 1,000 unit tablets | 28 tablet | £20.95 | 90 tablet | £34.50 | 180 tablet | no price available
  - Colecalciferol 5000 unit | Colecalciferol 5,000 unit tablets | 60 tablet | £5.00 | 100 tablet | £9.99 | 200 tablet | £18.66
  - Colecalciferol 20000 unit | Colecalciferol 20,000 unit tablets | 30 tablet | no price available
  - Brands may include Aciferol D, Cubico D3, Desunin, D-3, Iso D3, Sterexol-D3, and SunVit D3

**Chewable tablet**

- **COLECALCIFEROL (Non-proprietary)**
  - Colecalciferol 280 unit | Colecalciferol 280 unit chewable tablets | 180 tablet | £5.00

**Oral dispersible tablet**

- **COLECALCIFEROL (Non-proprietary)**
  - Colecalciferol 2000 unit | Colecalciferol 2,000 unit tablets (sugar-free) | 120 tablet | £4.88

**Capsule**

**CAUTIONARY AND ADVISORY LABELS 25**

- **COLECALCIFEROL (Non-proprietary)**
  - Colecalciferol 400 unit | Colecalciferol 400 unit capsules | 30 capsule | no price available | 60 capsule | no price available | 100 capsule | no price available
  - Colecalciferol 500 unit | Colecalciferol 500 unit capsules | 90 capsule | no price available
  - Colecalciferol 600 unit | Colecalciferol 600 unit capsules | 60 capsule | no price available | 120 capsule | no price available
  - Colecalciferol 800 unit | Colecalciferol 800 unit capsules | 30 capsule | £3.60 | 60 capsule | £3.60
  - Colecalciferol 1000 unit | Colecalciferol 1,000 unit capsules | 28 capsule | £36.50 | 30 capsule | £29.50
  - Colecalciferol 2000 unit | Colecalciferol 2,000 unit capsules | 50 capsule | no price available | 100 capsule | no price available
  - Colecalciferol 5000 unit | Colecalciferol 5,000 unit capsules | 40 capsule | no price available
  - Colecalciferol 20000 unit | Colecalciferol 20,000 unit capsules | 20 capsule | £37.59 | 30 capsule | £35.99 | 60 capsule | £59.00

**Oral solution**

**CAUTIONARY AND ADVISORY LABELS 21**

- **COLECALCIFEROL (Non-proprietary)**
  - Colecalciferol 3000 unit per 1 ml | Colecalciferol 3,000 units/ml oral solution | 100 ml | £119.70 | 200 ml | £218.90
  - Brands may include Aciferol D3, E-D3, and Pro D3

**INDICATIONS AND DOSE**

- **Aciferol D3 (Discrepant Medical Equipment Ltd)**
  - Colecalciferol 2000 unit per 1 ml | Colecalciferol 2,000 units/ml liquid | 100 ml | £18.00

- **Baby D** (Kofa Healthcare)
  - Colecalciferol 1000 unit per 1 ml | Baby D 1,000 units/ml oral solution | 30 ml | £4.50

- **E-D3** (Enogen Healthcare Ltd)
  - Colecalciferol 1000 unit per 1 ml E-D3 1,000 units/ml oral solution | 15 ml | no price available
  - Colecalciferol 10000 unit per 1 ml E-D3 10,000 units/ml oral solution | 10 ml | no price available

- **Invita D3** (Consilient Health Ltd)
  - Colecalciferol 25000 IU per 1 ml | Invita D3 25,000 units/ml oral solution (sugar-free)| 3 ampoule ( DT price ) £4.45 | DT price | £4.45

- **Pro D3** (Synergy Biologics Ltd)
  - Colecalciferol 2000 unit per 1 ml | Pro D3 2,000 units/ml liquid | 50 ml | £16.00 | 100 ml | £22.50

- **Thorens** (Galen Ltd)
  - Colecalciferol 10000 unit per 1 ml | Thorens 25,000 units/ml oral solution (sugar-free) | 2.5 ml | DT price £1.55 (sugar-free) | 10 ml | DT price £5.85

**Oral drops**

- **COLECALCIFEROL (Non-proprietary)**
  - Colecalciferol 200 unit per 1 drop | Colecalciferol 200 units/drop oral drops (sugar-free) | 15 ml | £4.46 | 50 ml | £3.86
  - Colecalciferol 2400 unit per 1 ml | Colecalciferol 2,400 units/ml oral drops (sugar-free) | 10 ml | DT price £3.60
  - Colecalciferol 2740 unit per 1 ml | Colecalciferol 2,740 units/ml oral drops (sugar-free) | 25 ml | DT price £13.70
  - Brands may include E-D3, Invita D3, Pro D3, Thorens

**Colecalciferol with calcium carbonate**

The properties listed below are those particular to the combination only. For the properties of the components please consider, colecalficiferol above, calcium carbonate p. 856.

**INDICATIONS AND DOSE**

- Prevention and treatment of vitamin D and calcium deficiency
  - **BY MOUTH**
    - Adult: Dosed according to the deficit or daily maintenance requirements (consult product literature)

**PRESCRIBING AND DISPENSING INFORMATION**

- Flavours of chewable and soluble forms may include orange, lemon, aniseed, peppermint, molasses, or tutti-frutti.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **EXCIPIENTS**: May contain Propylene glycol

- **CALCIUM CARBONATE WITH COLECALCIFEROL (Non-proprietary)**
  - Calcium carbonate 400 mg, Colecalciferol 100 unit | Calcium & Vitamin D tablets | 30 tablet | £0.59

- **Accrete D3** (Internis Pharmaceuticals Ltd)
  - Calcium carbonate 1.5 gram, Colecalciferol 400 unit | Accrete D3 tablets | 60 tablet | £2.95 DT price | £2.95

- **Adcal-D3** (Prostrakan Ltd)
  - Calcium carbonate 750 mg, Colecalciferol 200 unit | Adcal-D3 750mg/200unit caplets | 112 tablet | £3.65 DT price | £3.65

- **Calcichew D3** (Forum Health Products Ltd)
  - Calcium carbonate 1.25 gram, Colecalciferol 400 unit | Calcichew D3 500mg/400unit caplets | 100 tablet | £7.43 DT price | £7.43

- **Kalcips-D** (Meda Pharmaceuticals Ltd)
  - Calcium carbonate 1.25 gram, Colecalciferol 800 unit | Kalcips-D 500mg/800unit tablets | 30 tablet | DT price £4.21 | DT price | £4.21

**Chewable tablet**

**CAUTIONARY AND ADVISORY LABELS 24**

- **EXCIPIENTS**: May contain Aspartame

- **CALCIUM CARBONATE WITH COLECALCIFEROL (Non-proprietary)**
  - Calcium carbonate 400 mg, Colecalciferol 100 unit | Seven Seas Calcium and Vitamin D chewable tablets | 30 tablet | £1.76
  - Calcium carbonate 1.25 gram, Colecalciferol 400 unit | Colecalciferol 400 unit | Calcium carbonate 1.25g chewable tablets | 100 tablet | £14.75-£15.69
Colecalciferol with calcium phosphate

The properties listed below are those particular to the combination only. For the properties of the components please consider, colecaciferol p. 886, calcium p. 856.

**INDICATIONS AND DOSE**

Calcium and vitamin D deficiency

**BY MOUTH**

- Adult: (consult product literature)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder**

- CAUTIONARY AND ADVISORY LABELS 13, 21
- Calfivit D3 (A. Menarini Farmaceutica Internazionale SRL)
- Cacit D3 (A. Menarini Farmaceutica Internazionale SRL)
- Cacit D3 Forte (A. Menarini Farmaceutica Internazionale SRL)
- Natecal

Dihydrotachysterol

**INDICATIONS AND DOSE**

Acute, chronic, and latent forms of hypocalcaemic tetany due to hypoparathyroidism

**BY MOUTH**

- Adult: (consult product literature)

**RENAI IMPAIRMENT** Monitor plasma-calcium concentration in renal impairment.

**MONITORING REQUIREMENTS** Monitor plasma-calcium concentration in patients receiving high doses.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

### Ergocalciferol

(Calciferol; Vitamin D<sub>2</sub>)

#### INDICATIONS AND DOSE

Vitamin D deficiency caused by intestinal malabsorption or chronic liver disease

**BY MOUTH**

- Adult: Up to 40 000 units daily
- Hypocalcaemia of hypoparathyroidism to achieve normocalcaemia

**BY MOUTH**

- Adult: Up to 100 000 units daily
- Prevention of vitamin D deficiency

**BY MOUTH**

- Adult: 400 units daily
- Treatment of vitamin D deficiency

**BY MOUTH**

- Adult: 800 units daily, higher doses may be necessary for severe deficiency

**CAUTIONS** Take care to ensure correct dose in infants

**RENAI IMPAIRMENT** Monitor plasma-calcium concentration in hepatic impairment.

**MONITORING REQUIREMENTS** Monitor plasma-calcium concentration in patients receiving high doses.

**PRESCRIBING AND DISPENSING INFORMATION** The BP directs that when calciferol is prescribed or demanded, colecaciferol or ergocalciferol should be dispensed or supplied. When the strength of the medicines ordered or prescribed is not clear, the intention of the prescriber with respect to the strength (expressed in micrograms or milligrams per tablet) should be ascertained.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, solution for injection, oral suspension, oral solution, capsule

**Tablet**

- ERGOCALCIFEROL (Non-proprietary)
  - Ergocalciferol 12.5 microgram (Dispersible Medical Equipment Ltd)
  - Ergocalciferol 125 microgram (Stirling Anglian Pharmaceuticals Ltd)

**Capsule**

- ERGOCALCIFEROL (Non-proprietary)
  - Ergocalciferol 1.25 mg (Warner Chilcott UK Ltd)

**Oral solution**

- Eciferol (Disposable Medical Equipment Ltd)

Ergocalciferol with calcium lactate and calcium phosphate

The properties listed below are those particular to the combination only. For the properties of the components please consider, ergocalciferol above, calcium lactate p. 857.
**VITAMIN E**

**Alpha tocopherol**
(Tocopherol)

**INDICATIONS AND DOSE**
Vitamin E deficiency because of malabsorption in congenital or hereditary chronic cholestasis

**BY MOUTH USING ORAL SOLUTION**
- Child: 17 micrograms/kg daily, dose to be adjusted as necessary

- **CONTRA-INDICATIONS**
  - Preterm neonates

- **CAUTIONS**
  - Predisposition to thrombosis

- **INTERACTIONS**
  - Appendix 1 (Vitamin E)

- **SIDE-EFFECTS**
  - Common or very common: Diarrhoea
  - Uncommon: Alopecia, asthenia, disturbances in serum-potassium concentration, disturbances in serum-sodium concentration, headache, pruritus, rash

- **PREGNANCY**
  - Manufacturer advises caution, no evidence of harm in animal studies.

- **BREAST FEEDING**
  - Manufacturer advises use only if potential benefit outweighs risk—no information available.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises caution—no information available. Manufacturer advises monitor closely in hepatic impairment.

- **RENAL IMPAIRMENT**
  - Manufacturer advises caution. Risk of renal toxicity due to polyethylene glycol content. Manufacturer advises monitor closely in renal impairment.

- **PRESCRIBING AND DISPENSING INFORMATION**
  - Tocofersolan is a water-soluble form of D-alpha tocopherol.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

- **Oral solution**
  - Vedrop (Orphan Europe (UK) Ltd)
  - D-alpha tocopherol (as Tocofersolan) 50 micrograms/1 ml Vedrop 50mg/ml oral solution (sugar-free) 20 ml £5.45 (sugar-free) 60 ml £16.65

**Alpha tocopheryl acetate**
(Tocopherol)

**INDICATIONS AND DOSE**
Vitamin E deficiency

**BY MOUTH**
- Child: 2–10 micrograms/kg daily, increased if necessary up to 20 micrograms/kg daily

**Malabsorption in cystic fibrosis**

**BY MOUTH**
- Child 1–11 months: 50 micrograms once daily, dose to be adjusted as necessary, to be taken with food and pancreatic enzymes
- Child 1–11 years: 100 micrograms once daily, dose to be adjusted as necessary, to be taken with food and pancreatic enzymes
- Child 12–17 years: 200–200 micrograms once daily, dose to be adjusted as necessary, to be taken with food and pancreatic enzymes
- Adult: 100–200 micrograms once daily, dose to be adjusted as necessary, to be taken with food and pancreatic enzymes
Phytomenadione
(Vitamin K<sub>1</sub>)

**INDICATIONS AND DOSE**

Major bleeding in patients on warfarin (in combination with dried prothrombin complex or fresh frozen plasma)

**BY SLOW INTRAVENOUS INJECTION**
- Adult: 5 mg for 1 dose, stop warfarin treatment
- INR &gt; 8.0 with minor bleeding in patients on warfarin

**BY SLOW INTRAVENOUS INJECTION**
- Adult: 1–3 mg, stop warfarin treatment, dose may be repeated if INR still too high after 24 hours, restart warfarin treatment when INR &lt;5
- INR &gt; 8.0 with no bleeding in patients on warfarin

**BY MOUTH**
- Adult: 1–5 mg, intravenous preparation to be used orally, stop warfarin treatment, repeat dose if INR still too high after 24 hours, restart warfarin treatment when INR &lt;5

**5.0–8.0 with minor bleeding in patients on warfarin**

**BY SLOW INTRAVENOUS INJECTION**
- Adult: 1–3 mg, stop warfarin treatment, restart warfarin treatment when INR &lt;5

**Peri-operative antiocoagulation (after warfarin stopped)**

**BY MOUTH**
- Adult: 1–5 mg, intravenous preparation to be used orally, dose to be given the day before surgery if INR &gt;1.5

**CAUTIONS**
- Intravenous injections should be given very slowly—risk of vascular collapse
- KONAKION<sup>®</sup> MM
  - Reduce dose in elderly.
- **INTERACTIONS** ▶ Appendix 1 (vitamins).
- **SIDE-EFFECTS**
  - KONAKION<sup>®</sup> MM
  - Anaphylactoid reactions.
- **PREGNANCY** Use if potential benefit outweighs risk.
- **BREAST FEEDING** Present in milk.
- **HEPATIC IMPAIRMENT**
  - KONAKION<sup>®</sup> MM
  - Caution—glycocholic acid may displace bilirubin.
- **DIRECTIONS FOR ADMINISTRATION**
  - KONAKION<sup>®</sup> MM
  - May be administered by slow intravenous injection or by intravenous infusion in glucose 5%: not for intramuscular injection. For *intravenous infusion*, give intermittently in glucose 5%; dilute with 55ml; may be injected into lower part of infusion apparatus.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: tablet, oral suspension, drops, oral solution

**Capsule**
- PHOTOMENADIONE (Non-proprietary)
  - Phytomenadione 10 mg
  - Phytomenadione 10 mg capsules | 50 capsule £29.00

**Drops**
- Neokay (Neoceuticals Ltd)
  - Phytomenadione 1 mg
  - NeoKay 1mg capsules | 12 capsule £3.95 DF price + £3.95 | 100 capsule £24.00

**Menadiol sodium phosphate**

**MEDICATIONS**
- Prevention of Vitamin K deficiency in malabsorption syndromes
- **BY MOUTH**
  - Adult: 10–40 mg daily, dose to be adjusted as necessary

**CONTRA-INDICATIONS**
- Infants · neonates
- **CAUTIONS**
  - G6PD deficiency (risk of haemolysis) · vitamin E deficiency (risk of haemolysis)
  - **INTERACTIONS** ▶ Appendix 1 (vitamins).
  - **PREGNANCY** Avoid in late pregnancy and labour unless benefit outweighs risk of neonatal haemolytic anaemia, hyperbilirubinaemia, and kernicterus in neonate.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

**Tablet**
- MENADIOL SODIUM PHOSPHATE (Non-proprietary)
  - Menadiol phosphate (as Menadiol sodium phosphate)
  - 10 mg
  - Menadiol 10 mg tablets | 100 tablet £128.60 DF price + £128.60
Solution for injection
EXCIPIENTS: May contain Glycocholic acid, lecithin
▶ Konakion MM (Roche Products Ltd)
Phytomenadione 10 mg per 1 ml Konakion MM Paediatric
2mg/0.2ml solution for injection ampoules | 5 ampoule (PO) £4.71
Konakion MM 10mg/1ml solution for injection ampoules |
10 ampoule (PO) £3.78 DT price = £3.78

6.1 Neural tube defects
(prevention in pregnancy)

Neural tube defects (prevention in pregnancy)
Folic acid p. 836 supplements taken before and during pregnancy can reduce the occurrence of neural tube defects. The risk of a neural tube defect occurring in a child should be assessed and folic acid given as follows:

- Women at a low risk of conceiving a child with a neural tube defect should be advised to take folic acid as a medicinal or food supplement daily (at low-risk group dose) before conception and until week 12 of pregnancy. Women who have not been taking folic acid and who suspect they are pregnant should start at once and continue until week 12 of pregnancy.
- Couples are at a high risk of conceiving a child with a neural tube defect if either partner has a neural tube defect (or either partner has a family history of neural tube defects), if they have had a previous pregnancy affected by a neural tube defect, or if the woman has coeliac disease (or other malabsorption state), diabetes mellitus, sickle-cell anaemia, or is taking antiepileptic medicines.
- Women in the high-risk group who wish to become pregnant (or who are at risk of becoming pregnant) should be advised to take folic acid daily (at high-risk group dose) and continue until week 12 of pregnancy (women with Sickle-cell disease p. 820 should continue taking their normal dose of folic acid (or to increase the dose to high-risk group daily dose) and continue this throughout pregnancy).

There is no justification for prescribing multiple-ingredient vitamin preparations containing vitamin B₁₂ or folic acid.
Chapter 10
Musculoskeletal system

CONTENTS
1 Arthritis
2 Hyperuricaemia and gout
3 Neuromuscular disorders
3.1 Myasthenia gravis and Lambert-Eaton myasthenic syndrome
3.2 Nocturnal leg cramps
4 Pain and inflammation in musculoskeletal disorders
5 Soft tissue and joint disorders
3.3 Spasticity

1 Arthritis

Arthritis

Rheumatoid arthritis and other inflammatory disorders
A non-steroidal anti-inflammatory drug (NSAID) is indicated for pain and stiffness resulting from inflammatory rheumatic disease; analgesics such as paracetamol p. 354 or codeine phosphate p. 360 can also be used.

Drugs are also used to influence the rheumatic disease process itself. For rheumatoid arthritis these disease-modifying antirheumatic drugs (DMARDs) include methotrexate p. 762, cyclosporin p. 717, cyclophosphamide p. 750, leflunomide p. 895, penicillamine p. 896, gold, antimalarials (chloroquine p. 536 and hydroxychloroquine sulfate p. 894), and sulfasalazine p. 37. Corticosteroids also have a significant role in the management of rheumatoid arthritis.

Drugs which may affect the disease process in psoriatic arthritis include sulfasalazine, gold, azathioprine, methotrexate, leflunomide, and cytokine modulators.

Osteoarthritis and soft-tissue disorders
For pain relief in osteoarthritis and soft-tissue disorders, paracetamol p. 354 should be used first and may need to be taken regularly. A topical NSAID or topical capsaicin p. 354 may provide temporary benefit in osteoarthritis, especially if associated with soft-tissue inflammation. Non-drug measures, such as weight reduction and exercise, should also be encouraged.

Glucosamine p. 693 and rubefacients are not recommended for the treatment of osteoarthritis.

Hyaluronic acid and its derivatives are available for osteoarthritis of the knee, but are not recommended. Sodium hyaluronate (Suplasyrn®, Synovis®, Hylan G-F 20, Synvisc®) is injected intra-articularly to supplement natural hyaluronic acid in the synovial fluid. These injections may reduce pain over 1–6 months, but are associated with a short-term increase in knee inflammation. Sodium hyaluronate (SportVis®) is also licensed for the relief of pain and optimisation of recovery following ankle sprain, and for the relief of chronic pain and disability associated with tennis elbow.

Rheumatic disease, suppressing drugs
Certain drugs such as those affecting the immune response can suppress the disease process in rheumatoid arthritis and psoriatic arthritis; gold, penicillamine p. 896, hydroxychloroquine sulfate p. 894, chloroquine p. 536, and sulfasalazine p. 37 can also suppress the disease process in rheumatoid arthritis while sulfasalazine p. 37 and possibly gold can suppress the disease process in psoriatic arthritis. Unlike NSAIDs, which are used only for symptom control, disease-modifying anti-rheumatic drugs (DMARDs) can affect the progression of disease but may require 2–6 months of treatment for a full therapeutic response. Response to DMARDs may allow the NSAID dose to be reduced or withdrawn. All patients with suspected inflammatory joint disease should be referred to a specialist as soon as possible to confirm diagnosis and evaluate disease activity; early initiation of DMARDs is recommended to control the signs and symptoms, and to limit joint damage.

Choice
The choice of a disease-modifying antirheumatic drug should take into account co-morbidity and patient preference. Methotrexate p. 762, sulfasalazine p. 37, intramuscular gold, and penicillamine p. 896 are similar in efficacy. However, methotrexate or sulfasalazine may be better tolerated.

A combination of DMARDs (including methotrexate and at least one other DMARD) and a short-term corticosteroid, should be given to patients with newly diagnosed active rheumatoid arthritis, ideally within 3 months of the onset of persistent symptoms. If the use of particular DMARDs is contra-indicated and combination therapy is not possible, monotherapy with a suitable DMARD should be given and the dose rapidly increased until clinically effective. In patients with established and stable rheumatoid arthritis, cautiously reduce drug doses to the lowest that are clinically effective. Response to drug treatment often produces a reduction in requirements of both corticosteroids and other drugs.

Gold and penicillamine p. 896 are effective in palindromic rheumatism. Systemic and discoid lupus erythematosus are
Musculoskeletal system

sometimes treated with chloroquine p. 536 or hydroxychloroquine sulfate p. 894. If a disease-modifying anti-rheumatic drug does not lead to an objective benefit within 6 months, it should be replaced by a different one.

Gold

Gold can be given as sodium aurothiomalate p. 897 for active progressive rheumatoid arthritis; it must be given by deep intramuscular injection and the area gently massaged. A test dose must be given followed by doses at weekly intervals until there is definite evidence of remission. In patients who do respond, the interval between injections is then gradually increased to 4 weeks and treatment is continued for up to 5 years after complete remission. If relapse occurs the dosage frequency may be immediately increased and only once control has been obtained again should the dosage frequency be decreased; if no response is seen within 2 months, alternative treatment should be sought. It is important to avoid complete relapse since second courses of gold are not usually effective.

Penicillamine

Penicillamine p. 896 has a similar action to gold. More patients are able to continue treatment than with gold but side-effects are common. Patients should be warned not to expect improvement for at least 6 to 12 weeks after treatment is initiated. Penicillamine should be discontinued if there is no improvement within 1 year.

Sulfasalazine

Sulfasalazine p. 37 has a beneficial effect in suppressing the inflammatory activity of rheumatoid arthritis. Sulfasalazine may also be used by specialists, in the management of psoriatic arthritis affecting peripheral joints [unlicensed indication]. Haematological abnormalities occur usually in the first 3 to 6 months of treatment and are reversible on cessation of treatment.

Antimalarials

The antimalarial hydroxychloroquine sulfate p. 894 is used to treat rheumatoid arthritis of moderate inflammatory activity; chloroquine p. 536 is also licensed for treating inflammatory disorders but is used much less frequently and is generally reserved for use if other drugs have failed. Chloroquine and hydroxychloroquine sulfate are effective for mild systemic lupus erythematosus, particularly involving the skin and joints. These drugs should not be used for psoriatic arthritis. Chloroquine and hydroxychloroquine sulfate are better tolerated than gold or penicillamine. Retinopathy rarely occurs provided that the recommended doses are not exceeded; in the elderly it is difficult to distinguish drug-induced retinopathy from changes of ageing.

Mepacrine hydrochloride p. 438 is sometimes used in discoid lupus erythematosus [unlicensed].

Drugs affecting the immune response

Methotrexate p. 762 is a disease-modifying anti-rheumatic drug suitable for moderate to severe rheumatoid arthritis. Azathioprine p. 716, ciclosporin p. 717, cyclophosphamide p. 750, leflunomide p. 895, and the cytokine modulators are considered more toxic and are used in cases that have not responded to other disease-modifying drugs.

Methotrexate is usually given by mouth once a week, adjusted according to response. In patients who experience mucosal or gastro-intestinal side-effects with methotrexate, folic acid p. 836 given every week [unlicensed indication], on a different day from the methotrexate, may help to reduce the frequency of such side-effects.

Leflunomide acts on the immune system as a disease-modifying anti-rheumatic drug. Its therapeutic effect starts after 4–6 weeks and improvement may continue for a further 4–6 months. Leflunomide, which is similar in efficacy to sulfasalazine p. 37 and methotrexate p. 762, may be chosen when these drugs cannot be used.

Ciclosporin p. 717 is licensed for severe active rheumatoid arthritis when conventional second-line therapy is inappropriate or ineffective. There is some evidence that ciclosporin may retard the rate of erosive progression and improve symptom control in those who respond only partially to methotrexate.

Cyclophosphamide p. 750 may be used for rheumatoid arthritis with severe systemic manifestations [unlicensed indication]; it is toxic and regular blood counts (including platelet counts) should be carried out. Cyclophosphamide can also be given for severe systemic rheumatoid arthritis and for other connective tissue diseases (especially with active visceralitis).

Drugs that affect the immune response are also used in the management of severe cases of systemic lupus erythematosus and other connective tissue disorders. They are often given in conjunction with corticosteroids for patients with severe or progressive renal disease. They may be used in cases of polymyositis that are resistant to corticosteroids. They are used for their corticosteroid-sparing effect in patients whose corticosteroid requirements are excessive. Azathioprine p. 716 is usually used.

In the specialist management of psoriatic arthritis affecting peripheral joints, leflunomide p. 895, methotrexate p. 762, or azathioprine p. 716 [unlicensed indication] may be used.

Juvenile idiopathic arthritis

Many children with juvenile idiopathic arthritis (juvenile chronic arthritis) do not require disease-modifying anti-rheumatic drugs. Methotrexate p. 762 is effective; sulfasalazine p. 37 is an alternative [unlicensed indication] but it should be avoided in systemic-onset juvenile idiopathic arthritis. Gold and penicillamine p. 896 are no longer used.

Cytokine modulators have a role in juvenile idiopathic arthritis.

Cytokine modulators

Cytokine modulators should be used under specialist supervision.

Adalimumab p. 901, certolizumab pegol p. 902, etanercept p. 903, golimumab p. 904, and infliximab p. 906 inhibit the activity of tumour necrosis factor alpha (TNF-α).

Adalimumab is licensed for moderate to severe active rheumatoid arthritis when response to other disease-modifying anti-rheumatic drugs (including methotrexate p. 762) has been inadequate; it is also licensed for severe, active, and progressive disease in adults not previously treated with methotrexate. In the treatment of rheumatoid arthritis, adalimumab should be used in combination with methotrexate, but it can be given alone if methotrexate is inappropriate. Adalimumab is also licensed for the treatment of active and progressive psoriatic arthritis and severe active ankylosing spondylitis that have not responded adequately to other disease-modifying anti-rheumatic drugs. It is also licensed for the treatment of severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation, in patients who have had an inadequate response to, or are intolerant of NSAIDs. Adalimumab also has a role in inflammatory bowel disease and plaque psoriasis.

Certolizumab pegol is licensed for use in patients with moderate to severe active rheumatoid arthritis when response to disease-modifying anti-rheumatic drugs (including methotrexate p. 762) has been inadequate. Certolizumab pegol can be used in combination with
methotrexate, or as a monotherapy if methotrexate is not tolerated or is contra-indicated. Certolizumab pegol is also licensed for the treatment of severe active *ankylosing spondylitis* in patients who have had an inadequate response to, or are intolerant of NSAIDs. It is also licensed for the treatment of severe active *axial spondylarthropathy*, without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation, in patients who have had an inadequate response to, or are intolerant of NSAIDs.

Etanercept p. 903 is licensed for the treatment of moderate to severe active *rheumatoid arthritis* either alone or in combination with methotrexate p. 762 when the response to other disease-modifying antirheumatic drugs is inadequate and in severe, active and progressive *rheumatoid arthritis* in patients not previously treated with methotrexate. It is also licensed for the treatment of active and progressive *psoriatic arthritis* inadequately responsive to other disease-modifying antirheumatic drugs, and for severe *ankylosing spondylitis* inadequately responsive to conventional therapy. Etanercept also has a role in plaque psoriasis.

Golimumab p. 904 is licensed in combination with methotrexate for the treatment of moderate to severe active *rheumatoid arthritis* when response to disease-modifying antirheumatic drug (DMARD) therapy (including methotrexate) has been inadequate; it is also licensed in combination with methotrexate for patients with severe, active, and progressive rheumatoid arthritis not previously treated with methotrexate. Golimumab is also licensed for the treatment of active and progressive *psoriatic arthritis*, as monotherapy or in combination with methotrexate, when response to DMARD therapy has been inadequate; it is also licensed for the treatment of severe active *ankylosing spondylitis* when there is an inadequate response to conventional treatment.

Infliximab p. 906 is licensed for the treatment of active *rheumatoid arthritis* in combination with methotrexate when the response to other disease-modifying antirheumatic drugs, including methotrexate, is inadequate; it is also licensed in combination with methotrexate for patients not previously treated with methotrexate or other DMARDs who have severe, active, and progressive rheumatoid arthritis. Infliximab is also licensed for the treatment of *ankylosing spondylitis*, in patients with severe axial symptoms who have not responded adequately to conventional therapy, and in combination with methotrexate (or alone if methotrexate is not tolerated or is contra-indicated) for the treatment of active and progressive *psoriatic arthritis* which has not responded adequately to disease-modifying antirheumatic drugs.

Rituximab p. 734 is licensed in combination with methotrexate for the treatment of severe active *rheumatoid arthritis* in patients whose condition has not responded adequately to other disease-modifying antirheumatic drugs (including one or more tumour necrosis factor inhibitors) or who are intolerant of them. Rituximab has a role in malignant disease.

Abatacept p. 900 prevents the full activation of T-lymphocytes. It is licensed for moderate to severe active *rheumatoid arthritis* in combination with methotrexate, in patients unresponsive to other disease-modifying antirheumatic drugs (including methotrexate or a tumour necrosis factor (TNF) inhibitor). Abatacept is not recommended for use in combination with TNF inhibitors.

Anakinra p. 897 inhibits the activity of interleukin-1. Anakinra (in combination with methotrexate) is licensed for the treatment of *rheumatoid arthritis* which has not responded to methotrexate alone. Anakinra is not recommended for the treatment of rheumatoid arthritis except when used in a controlled long-term clinical study. Patients who are already receiving anakinra for rheumatoid arthritis should continue treatment until they and their specialist consider it appropriate to stop.

Belimumab p. 725 inhibits the activity of B-lymphocyte stimulator. Belimumab is licensed as adjunctive therapy in patients with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity despite standard therapy.

Tocilizumab p. 898 antagonises the actions of interleukin-6. Tocilizumab is licensed for use in patients with moderate to severe active *rheumatoid arthritis* when response to at least one disease-modifying antirheumatic drug or tumour necrosis factor inhibitor has been inadequate, or in those who are intolerant of these drugs. Tocilizumab can be used in combination with methotrexate, or as monotherapy if methotrexate is not tolerated or is contra-indicated.

Ustekinumab p. 899 inhibits the activity of interleukins 12 and 23. It is licensed for the treatment of active *psoriatic arthritis* (in combination with methotrexate or alone) in patients who have had an inadequate response to one or more disease-modifying antirheumatic drugs.

### CHONDROPROTECTIVE DRUGS

#### Glucosamine

- **DRUG ACTION** Glucosamine is a natural substance found in mucopolysaccharides, mucoproteins, and chitin.

#### INDICATIONS AND DOSE

**ALATERIS®**

- Symptomatic relief of mild to moderate osteoarthritis of the knee
  - **BY MOUTH**
  - ▶ Adult: 2 tablets once daily, review treatment if no benefit after 2–3 months

**DOLENIO®**

- Symptomatic relief of mild to moderate osteoarthritis of the knee
  - **BY MOUTH**
  - ▶ Adult: 1 tablet once daily, review treatment if no benefit after 2–3 months

**GLUSARTEL®**

- Symptomatic relief of mild to moderate osteoarthritis of the knee
  - **BY MOUTH**
  - ▶ Adult: 1 sachet once daily, dose to be dissolved in at least 250 mL of water, review treatment if no benefit after 2–3 months

#### CAUTIONS

- Asthma · impaired glucose tolerance · predisposition to cardiovascular disease

#### INTERACTIONS

- Appendix 1 (glucosamine).

#### SIDE-EFFECTS

- Common or very common: Abdominal pain · constipation · diarrhoea · drowsiness · dyspepsia · fatigue · flatulence · headache · nausea
- Uncommon: Flushing · pruritus · rash
- Frequency not known: Hair loss · visual disturbances

#### ALLERGY AND CROSS-SENSITIVITY

- Contraindicated if patient has a shellfish allergy.

#### PREGNANCY

- Manufacturers advise avoid—no information available.

#### BREAST FEEDING

- Manufacturers advise avoid—no information available.

#### MONITORING REQUIREMENTS

- Monitor blood-glucose concentration before treatment and periodically thereafter in patients with impaired glucose tolerance.
- Monitor cholesterol in patients with predisposition to cardiovascular disease.
**NATIONAL FUNDING/ACCESS DECISIONS**

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (May 2008) that glucosamine (Alateris®) and (July 2011) glucosamine (Glusartel®) are not recommended for use within NHS Scotland for the symptomatic relief of mild to moderate osteoarthritis of the knee.

**LESS SUITABLE FOR PRESCRIBING** Less suitable for prescribing—the mechanism of action is not understood and there is limited evidence to show it is effective.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**
- **ELECTROLYTES:** May contain Sodium
- **GLUCOSAMINE (Non-proprietary)**
  - Glucosamine hydrochloride 1.5g tablets | 30 tablet £4.69
  - Glucosamine hydrochloride 750mg tablets | 60 tablet £6.64
  - Glucosamine sulfate 750mg tablets | 30 tablet £9.00 | 90 tablet £22.00
  - 100 tablet no price available Glucosamine sulfate 500mg tablets | 30 tablet £5.50 | 90 tablet £27.49 | 100 tablet £22.50
  - Glucosamine sulfate 1000mg tablets | 180 tablet £5.79 | 360 tablet £10.75
  - Glucosamine sulfate 1.5g tablets | 30 tablet £6.20 DT price = £18.20 | 90 tablet £6.35
- **Alateris (MWK Healthcare Ltd)**
  - Glucosamine (as Glucosamine hydrochloride) 625 mg Alateris 625mg tablets | 60 tablet £18.40 DT price = £18.40
- **Dolenio (Alissa Healthcare Research Ltd)**
  - Dolenio 1500mg tablets | 30 tablet £9.20 DT price = £18.20

**Chewable tablet**
- **Gosachew (Glucosamine hydrochloride)** (Enmogen Healthcare Ltd)
  - Gosachew 1500mg chewable tablets | 30 tablet £93.50
- **GLUCOSAMINE (Non-proprietary)**
  - Glucosamine hydrochloride 750mg capsules | 60 capsule £8.51
  - Glucosamine sulfate 500mg capsules | 30 capsule £5.20 | 30 capsule £15.55 | 90 capsule £7.23
  - 100 capsule £22.50 | 180 capsule £13.01
  - Glucosamine sulfate 1g capsules | 90 capsule £6.00

**Oral solution**
- **GLUCOSAMINE (Non-proprietary)**
  - Glucosamine 5mg/ml liquid (sugar-free) | 500 ml £7.08 (sugar-free) | 1000 ml £12.50

**Powder**

**CAUTIONARY AND ADVISORY LABELS 13**

**EXCIPIENTS:** May contain Aspartame

**ELECTROLYTES:** May contain Sodium

- **Glusartel (HFA Healthcare Ltd)**
  - Glusartel 1500mg oral powder sachets (sugar-free) | 30 sachet £18.40

**DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS**

**Hydroxychloroquine sulfate**

**INDICATIONS AND DOSE**

Active rheumatoid arthritis (including juvenile idiopathic arthritis) (administered on expert advice) | Systemic and discoid lupus erythematosus (administered on expert advice) | Dermatological conditions caused or aggravated by sunlight (administered on expert advice) **BY MOUTH**

- **Adult:** 200–400 mg daily, daily maximum dose to be based on ideal body-weight; maximum 6.5 mg/kg per day

**CAUTIONS**

- Acute porphyrias p. 864 | elderly | G6PD deficiency | may aggravate myasthenia gravis | may exacerbate psoriasis | neurological disorders (especially in those with a history of epilepsy) | severe gastro-intestinal disorders

**CAUTIONS, FURTHER INFORMATION**

**Screening for ocular toxicity** A review group convened by the Royal College of Ophthalmologists has updated guidelines for screening to prevent ocular toxicity on long-term treatment with chloroquine and hydroxychloroquine (Hydroxychloroquine and Ocular Toxicity: Recommendations on Screening 2009). The following recommendations relate to hydroxychloroquine, which is only rarely associated with toxicity.

**Before treatment:**
- Assess renal and liver function (adjust dose if impaired)
- Ask patient about visual impairment (not corrected by glasses). If impairment or eye disease present, assessment by an optometrist is advised and any abnormality should be referred to an ophthalmologist
- Record near visual acuity of each eye (with glasses where appropriate) using a standard reading chart
- Initiate hydroxychloroquine treatment if no abnormality detected (at a dose not exceeding hydroxychloroquine sulfate 6.5 mg/kg daily)

**During treatment:**
- Ask patient about visual symptoms and monitor visual acuity annually using the standard reading chart
- Refer to ophthalmologist if visual acuity changes or if vision blurred and warn patient to seek prescribing doctor’s advice about stopping treatment
- If long-term treatment is required (more than 5 years), individual arrangement should be agreed with the local ophthalmologist

**INTERACTIONS** Appendix 1 (chloroquine and hydroxychloroquine). Concurrent use of hepatotoxic drugs should be avoided.

**SIDE-EFFECTS**

- **Common or very common** Gastro-intestinal disturbances - headache - pruritus - rashes - skin reactions
- **Uncommon** Convulsions - discoloration of skin, nails, and mucous membranes - ECG changes - hair depigmentation - hair loss - keratopathy - ototoxicity - retinal damage - visual changes
- **Rare** Acute generalised exanthematous pustulosis - agranulocytosis - angioedema - aplastic anaemia - blood disorders - cardiomyopathy - emotional disturbances - exfoliative dermatitis - hepatic damage - mental changes - myopathy - neuromyopathy - photosensitivity - psychosis - Stevens-Johnson syndrome - thrombocytopenia

**Frequency not known** Bronchospasm - diffuse parenchymal lung disease - drug rash with eosinophilia and systemic symptoms

**Overdose** Hydroxychloroquine is very toxic in overdose; overdose is extremely hazardous and difficult to treat. Urgent advice from the National Poisons Information Service is essential. Life-threatening features include arrhythmias (which can have a very rapid onset) and convulsions (which can be intractable).

**PREGNANCY** It is not necessary to withdraw an antimarial drug during pregnancy if the rheumatic disease is well controlled; however, the manufacturer of hydroxychloroquine advises avoiding use.

**BREAST FEEDING** Avoid—risk of toxicity in infant.

**HEPATIC IMPAIRMENT** Caution in moderate to severe hepatic impairment.

**RENAL IMPAIRMENT** Manufacturer advises caution. Monitor plasma-hydroxychloroquine concentration in severe renal impairment.

**MONITORING REQUIREMENTS** Manufacturers recommend regular ophthalmological examination but the evidence of practical value is unsatisfactory (see advice of the Royal College of Ophthalmologists, above).

**PRESCRIBING AND DISPENSING INFORMATION** To avoid excessive dosage in obese patients, the dose of hydroxychloroquine should be calculated on the basis of ideal body-weight.

**PATIENT AND CARER ADVICE** Do not take antacids for at least 4 hours before or after hydroxychloroquine to reduce
possible interference with hydroxychloroquine absorption.

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

Tablet

Table CAUTIONARY AND ADVISORY LABELS 21

Hepatic failure 
Stevens-Johnson syndrome
Eosinophilia
Tendon rupture
Hypokalaemia
Anaemia
Tenosynovitis
Oral mucosal disorders
Headache
Anorexia
Diarrhoea
Vomiting
Nausea
Pruritus
Rash
Tenosynovitis
Vomiting
Anemia
Tenosynovitis
Oral mucosal disorders
Headache
Anorexia
Diarrhoea
Vomiting
Nausea
Pruritus
Rash
Tenosynovitis
Vomiting

● INDICATIONS AND DOSE

Moderate to severe active rheumatoid arthritis (specialist use only)

BY MOUTH
Adult: Initially 100 mg once daily for 3 days, then reduced to 10–20 mg once daily

Active psoriatic arthritis

BY MOUTH
Adult: Initially 100 mg once daily for 3 days, then reduced to 20 mg once daily

● CONTRA-INDICATIONS
Serious infection - severe hypoproteinaemia - severe immunodeficiency

● CAUTIONS
Anaemia (avoid if significant and due to causes other than rheumatoid arthritis) - history of tuberculosis - impaired bone-marrow function (avoid if significant and due to causes other than rheumatoid arthritis) - leucopenia (avoid if significant and due to causes other than rheumatoid arthritis) - thrombocytopenia (avoid if significant and due to causes other than rheumatoid arthritis)

● INTERACTIONS
Increased risk of toxicity with other haematotoxic and hepatotoxic drugs. Caution if recent treatment with other myelotoxic disease-modifying anti-rheumatic drugs. Caution - washout procedures recommended before switching to other disease-modifying antirheumatic drugs (consult product literature).

● SIDE-EFFECTS

Common or very common Abdominal pain - alopecia - anorexia - arthralgia - arthralgia - dizziness - dry skin - headache - increased blood pressure - leucopenia - nausea - oral mucosal disorders - paraesthesia - pruritus - rash - tenosynovitis - vomiting

Uncommon Anaemia - anxiety - hyperlipidaemia - hypokalaemia - hypophosphataemia - taste disturbance - tendon rupture - thrombocytopenia

Rare Eosinophilia - hepatitis - interstitial lung disease - jaundice - pancytopenia - severe infection

Very rare Hepatic failure - pancreatitis - peripheral neuropathy - progressive multifocal leucoencephalopathy - Stevens-Johnson syndrome - toxic epidermal necrolysis - vasculitis

Frequency not known Bone-marrow toxicity - hypouricaemia - malignancy - reduced sperm count - renal failure

SIDE-EFFECTS, FURTHER INFORMATION
Discontinue treatment and institute washout procedure in case of serious side-effect (consult product literature).

Hepatotoxicity Potentially life-threatening hepatotoxicity reported usually in the first 6 months. Discontinue treatment (and institute washout procedure - consult product literature) or reduce dose according to liver-function abnormality; if liver-function abnormality persists after dose reduction, discontinue treatment and institute washout procedure.

● CONCEPTION AND CONTRACEPTION
Effective contraception essential during treatment and for at least 2 years after treatment in women and at least 3 months after treatment in men (plasma concentration monitoring required; waiting time before conception may be reduced with washout procedure). The concentration of the active metabolite after washout should be less than 20 micrograms/litre (measured on 2 occasions 14 days apart) in men or women before conception - consult product literature.

● PREGNANCY
Avoid - active metabolite teratogenic in animal studies.

● BREAST FEEDING
Present in milk in animal studies - manufacturer advises avoid.

● HEPATIC IMPAIRMENT
Avoid - active metabolite may accumulate.

● RENAL IMPAIRMENT
Manufacturer advises avoid in moderate or severe impairment - no information available.

● PRE-TREATMENT SCREENING
Exclude pregnancy before treatment.

● MONITORING REQUIREMENTS
Monitor full blood count (including differential white cell count and platelet count) before treatment and every 2 weeks for 6 months then every 8 weeks.

● TREATMENT CESSATION
Washout Procedure The active metabolite persists for a long period; to aid drug elimination in case of serious adverse effect, or before starting another disease-modifying antirheumatic drug, or before conception, stop treatment and give either colysetamine p. 173 or charcoal, activated p. 1130. Procedure may be repeated as necessary.

● MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Tablet

Table CAUTIONARY AND ADVISORY LABELS 4

Leflunomide (Non-proprietary)

Leflunomide 10 mg Leflunomide 10 mg tablets | 30 tablet £15.13 DT price = £11.28
Leflunomide 15 mg Leflunomide 15 mg tablets | 30 tablet £15.13 DT price = £11.28
Leflunomide 20 mg Leflunomide 20 mg tablets | 30 tablet £15.13 DT price = £11.28
Leflunomide 100 mg Arava 100 mg tablets | 3 tablet £30.67
Penicillamine

**DRUG ACTION** Penicillamine aids the elimination of copper ions in Wilson’s disease (hepatolenticular degeneration).

**INDICATIONS AND DOSE**

**Severe active rheumatoid arthritis (administered on expert advice)**

**BY MOUTH**
- Adult: Initially 125–250 mg daily for 1 month, then increased in steps of 125–250 mg at intervals of not less than 4 weeks; maintenance 500–750 mg daily in divided doses, then reduced in steps of 125–250 mg every 12 weeks, dose reduction attempted only if remission sustained for 6 months; maximum 1.5 g per day
- Elderly: Initially up to 125 mg daily for 1 month, then increased in steps of up to 125 mg at intervals of at least 4 weeks; maximum 1 g per day

**Wilson’s disease**

**BY MOUTH**
- Adult: 1.5–2 g daily in divided doses, to be taken before food; maintenance 0.75–1 g daily for 1 year; maximum 2 g per day
- Elderly: 20 mg/kg daily in divided doses, adjusted according to response; maximum 2 g per day

**Autoimmune hepatitis (used rarely; after disease controlled with corticosteroids)**

**BY MOUTH**
- Adult: Initially 500 mg daily in divided doses, to be increased slowly over 3 months; maintenance 1.25 g daily

**Cystinuria, therapeutic**

**BY MOUTH**
- Adult: 1–3 g daily in divided doses, to be adjusted to maintain urinary cystine below 200 mg/litre, to be taken before food

**Cystinuria, prophylactic**

**BY MOUTH**
- Adult: 0.5–1 g daily, maintain urinary cystine below 300 mg/litre and adequate fluid intake (at least 3 litres daily), to be taken at bedtime
- Elderly: Minimum dose to maintain urinary cystine below 200 mg/litre is recommended

**CONTRA-INDICATIONS** Lupus erythematosus

**CAUTIONS** Neurological involvement in Wilson’s disease

**INTERACTIONS** → Appendix 1 (penicillamine).

Caution with gold treatment (avoid concomitant use if possible).

**SIDE-EFFECTS**
- Common or very common Anorexia · fever · nausea · proteinuria · rash · thrombocytopenia
- Rare Alopecia · breast enlargement (male and female) · elastosis perforans · haematuria (withdraw immediately if cause unknown) · mouth ulceration · pseudoxanthoma elasticum · skin laxity · stomatitis
- Frequency not known Agranulocytosis · aplastic anaemia · blood disorders · bronchiolitis · cholestatic jaundice · dermatomyositis · glomerulonephritis · Goodpasture’s syndrome · haemolytic anaemia · haemolytic leucopenia · late rashes (consider dose reduction) · lupus erythematosus · myasthenia gravis · nephrotic syndrome · neuropsychiatric complications (especially if neurological involvement in Wilson’s disease—prophylactic pyridoxine recommended) · neuropathy · pancreatitis · polymyositis · pneumonitis · pulmonary haemorrhage · rheumatoid arthritis · septic arthritis (in patients with rheumatoid arthritis) · Stevens-Johnson syndrome · taste loss (mineral supplements not recommended) · urticaria · vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

**Proteinuria** Proteinuria, associated with immune complex nephritis, occurs in up to 30% of patients, but may resolve despite continuation of treatment; treatment may be continued provided that renal function tests remain normal, oedema is absent, and the 24-hour urinary excretion of protein does not exceed 2 g.

**Rash** Rashes are a common side-effect. Those that occur in the first few months of treatment disappear when the drug is stopped and treatment may then be re-introduced at a lower dose level and gradually increased.

**Taste loss** Loss of taste can occur about 6 weeks after treatment is started but usually returns 6 weeks later irrespective of whether treatment is discontinued.

**Nausea** Nausea may occur but is not usually a problem provided that penicillamine is taken before food or on retting and that low initial doses are used and only gradually increased.

**ALLERGY AND CROSS-SENSITIVITY** Patients who are hypersensitive to penicillin may react rarely to penicillamine.

**PREGNANCY** Fetal abnormalities reported rarely; avoid if possible.

**BRONCOPLASTIC SIMULATIONS** Manufacturer advises avoid unless potential benefit outweighs risk—no information available.

**RENAI IMPAIRMENT** Reduce dose and monitor renal function or avoid (consult product literature).

**MONITORING REQUIREMENTS**

- Blood counts, including platelets, and urine examinations should be carried out before starting treatment and then every 1 or 2 weeks for the first 2 months then every 4 weeks to detect blood disorders and proteinuria (they should also be carried out in the week after any dose increase).
- A reduction in platelet count calls for discontinuation with subsequent re-introduction at a lower dosage and then, if possible, gradual increase.
- Longer intervals may be adequate in cystinuria and Wilson’s disease.
- Consider withdrawal if platelet count falls below 120 000/mm³ or white blood cells below 3 × 10⁹/litre or if 3 successive falls within reference range (can restart at reduced dose when counts return to within reference range but permanent withdrawal necessary if recurrence of leucopenia or thrombocytopenia).

**PATIENT AND CARER ADVICE** Counselling on the symptoms of blood disorders is advised. Warn patient and carers to tell doctor immediately if sore throat, fever, infection, non-specific illness, unexplained bleeding and bruising, purpura, mouth ulcers, or rashes develop.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

**Tablet**

CAUTIONARY AND ADVISORY LABELS 5, 22

- **PENICILLAMINE (Non-proprietary)**
  - Penicillamine 125 mg Penicillamine 125mg tablets 56 tablet [PTE] £25.80 DT price = £11.20
  - Penicillamine 250 mg Penicillamine 250mg tablets 56 tablet [PTE] £52.45 DT price = £21.46
  - Distamine (Alliance Pharmaceuticals Ltd)
  - Penicillamine 125 mg Distamine 125mg tablets 100 tablet [PTE] £10.34
  - Penicillamine 250 mg Distamine 250mg tablets 100 tablet [PTE] £17.78
Sodium aurothiomalate

**INDICATIONS AND DOSE**

Active progressive rheumatoid arthritis (administered on expert advice)

**BY DEEP INTRAMUSCULAR INJECTION**

- Adult: Test dose 10 mg, followed by 50 mg once weekly until there is definite evidence of remission, then gradually reduced to 50 mg every 4 weeks for up to 5 years after complete remission, benefit is not expected until 300–500 mg has been given; it should be discontinued if there is no remission after 1 g has been given

Relapse in patients who have previously received sodium aurothiomalate therapy for active progressive rheumatoid arthritis (administered on expert advice)

**BY DEEP INTRAMUSCULAR INJECTION**

- Adult: 50 mg once weekly until control has been obtained again, then reduced to 50 mg every 4 weeks continued for up to 5 years after complete remission, if no response is seen within 2 months, alternative treatment should be sought

- **CONTRA-INDICATIONS** Exfoliative dermatitis - history of blood disorders - history of bone marrow aplasia - necrotising enterocolitis - pulmonary fibrosis - systemic lupus erythematosus

- **CAUTIONS** Colitis - eczema - elderly - history of urticaria

**CAUTIONS, FURTHER INFORMATION**

Sodium aurothiomalate should be discontinued in the presence of blood disorders, gastro-intestinal bleeding (associated with ulcerative enterocolitis), or unexplained proteinuria (associated with immune complex nephritis) which is repeatedly above 300 mg/litre.

- **INTERACTIONS** → Appendix 1 (sodium aurothiomalate).

- **SIDE-EFFECTS** Alopecia - blood disorders (sometimes sudden and fatal) - colitis - gold deposits in eye - heparotoxicity with cholestatic jaundice - irreversible pigmentation in sun-exposed areas (on prolonged parenteral treatment) - mouth ulcers - nephrotic syndrome - peripheral neuropathy - proteinuria - pulmonary fibrosis - severe anaphylactic reactions - skin reactions - stomatitis - taste disturbances

**SIDE-EFFECTS, FURTHER INFORMATION**

Rashes with pruritus often occur after 2 to 6 months of treatment and may necessitate discontinuation.

- **PREGNANCY** Consider reducing dose and frequency. Manufacturer advises avoid but limited data suggests usually not necessary to withdraw if condition well controlled.

- **BREAST FEEDING** Manufacturer advises avoid—present in milk; theoretical possibility of rashes and idiiosyncratic reactions.

- **HEPATIC IMPAIRMENT** Caution in mild to moderate impairment. Avoid in severe impairment.

- **RENAL IMPAIRMENT** Caution in mild to moderate impairment. Avoid in severe impairment.

- **MONITORING REQUIREMENTS**

  - Urine tests and full blood counts (including total and differential white cell and platelet counts) must be performed before starting treatment and before each intramuscular injection.
  - Monitor for pulmonary fibrosis with annual chest X-ray.

- **PATIENT AND CARER ADVICE** Patients should be advised to seek prompt medical attention if diarrhoea, sore throat, fever, infection, non-specific illness, unexplained bleeding and bruising, purpura, mouth ulcers, metallic taste, rash, breathlessness, or cough develop.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  **Solution for injection**

  **CAUTIONARY AND ADVISORY LABELS 11**

  - **Myocrisin** (Sanofi)
    - Sodium aurothiomalate 20 mg per 1 ml
    - Sodium aurothiomalate 100 mg per 1 ml
  - **Kineret** (Swedish Orphan Biovitrum Ltd)
    - Anakinra 150 mg per 1 ml

**INTERLEUKIN INHIBITORS**

Anakinra

**INDICATIONS AND DOSE**

Treatment of rheumatoid arthritis (in combination with methotrexate) which has not responded to methotrexate alone

**BY SUBCUTANEOUS INJECTION**

- Adult: 100 mg once daily

- **CONTRA-INDICATIONS** Neutropenia

- **CAUTIONS** History of asthma (risk of serious infection) - predisposition to infection

- **INTERACTIONS** → Appendix 1 (anakinra).

- **SIDE-EFFECTS**

  - Common or very common Neutropenia
  - Frequency not known Antibody formation - headache - infections - injection-site reactions - malignancy

**SIDE-EFFECTS, FURTHER INFORMATION**

Blood disorders Neutropenia reported commonly—discontinue if neutropenia develops.

- **CONCEPTION AND CONTRACEPTION** Effective contraception must be used during treatment.

- **PREGNANCY** Manufacturer advises avoid.

- **BREAST FEEDING** Manufacturer advises avoid—no information available.

- **RENAL IMPAIRMENT** Caution if eGFR 30–50 mL/minute/1.73 m². Avoid if eGFR less than 30 mL/minute/1.73 m².

- **MONITORING REQUIREMENTS** Monitor neutrophil count before treatment, then every month for 6 months, then every 3 months.

- **PATIENT AND CARER ADVICE** Blood disorders Patients should be instructed to seek medical advice if symptoms suggestive of neutropenia (such as fever, sore throat, bruising or, bleeding) develop.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  **Scottish Medicines Consortium (SMC) Decisions**

  The Scottish Medicines Consortium has advised (July 2002) that anakinra is not recommended for the treatment of rheumatoid arthritis within NHS Scotland.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  **Solution for injection**

  - **Kineret** (Swedish Orphan Biovitrum Ltd)
    - Anakinra 150 mg per 1 ml
      - Kineret 100mg/0.67ml solution for injection pre-filled syringes | 28 pre-filled disposable injection \( \text{POD} \) £734.44
Tocilizumab

INDICATIONS AND DOSE
Moderate to severe active rheumatoid arthritis (in combination with methotrexate or alone if methotrexate inappropriate) when response to at least one disease-modifying antirheumatic drug or tumour necrosis factor inhibitor has been inadequate, or in those who are intolerant of these drugs

BY INTRAVENOUS INFUSION
- Adult: 8 mg/kg every 4 weeks (max. per dose 800 mg); for dose adjustment in patients with liver enzyme abnormalities, or low absolute neutrophil or platelet count, consult product literature

CONTRA-INDICATIONS
Do not initiate if absolute neutrophil count less than 2 x 10^9/litre - severe active infection

CAUTIONS
History of diverticulitis - history of intestinal ulceration - history of recurrent or chronic infection - pre-existing severe active infection

CAUTIONS, FURTHER INFORMATION
Tuberculosis Patients with latent tuberculosis should be treated with standard therapy before starting tocilizumab.

INTERACTIONS
Appendix 1 (tocilizumab).

SIDE-EFFECTS
- Common or very common Abdominal pain - antibody formation - dizziness - gastritis - headache - hypercholesterolaemia - hypersensitivity - hypertension - injection - leukopenia - mouth ulceration - neutropenia - peripheral oedema - pruritus - raised hepatic transaminases - rash - upper respiratory-tract infection
- Uncommon Anaphylaxis - gastric ulcer - gastro-intestinal perforation - hypertriglyceridaemia - hypothyroidism - infusion related reactions - nephrolithiasis
- Frequency not known Thrombocytopenia

SIDE-EFFECTS, FURTHER INFORMATION
Neutrophil and platelet counts Discontinue if absolute neutrophil count less than 0.5 x 10^9/litre or platelet count less than 50 x 10^9/microlitre.

CONCEPTION AND CONTRACEPTION
Effective contraception required during and for 3 months after treatment.

PREGNANCY
Manufacturer advises avoid unless essential - toxicity in animal studies.

BREAST FEEDING
Manufacturer advises use only if potential benefit outweighs risk - no information available.

HEPATIC IMPAIRMENT
Manufacturer advises caution - consult product literature.

RENAL IMPAIRMENT
Manufacturer advises monitor renal function closely in moderate or severe impairment.

PRE-TREATMENT SCREENING
Tuberculosis Patients should be evaluated for tuberculosis before treatment.

MONITORING REQUIREMENTS
- Monitor hepatic transaminases every 4–8 weeks for first 6 months, then every 12 weeks.
- Monitor neutrophil and platelet counts 4–8 weeks after starting treatment and then as indicated.
- Monitor lipid profile 4–8 weeks after starting treatment and then as indicated.
- Monitor for demyelinating disorders.

DIRECTIONS FOR ADMINISTRATION
For intravenous infusion (RoActemra®), give intermittently in Sodium chloride

0.9%; dilute requisite dose to a volume of 100 mL with infusion fluid and give over 1 hour.

PATIENT AND CARER ADVICE
An alert card should be provided. Patients and their carers should be advised to seek immediate medical attention if symptoms of infection occur, or if symptoms of diverticular perforation such as abdominal pain, haemorrhage, or fever accompanying change in bowel habits occur.

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)
- Tocilizumab for the treatment of rheumatoid arthritis (February 2012) NICE TA247
Tocilizumab, in combination with methotrexate, is recommended as an option for the treatment of rheumatoid arthritis in adults if:
- the disease has responded inadequately to disease-modifying anti-rheumatic drugs (DMARDs) and is used as described for tumour necrosis factor (TNF) inhibitor treatments (specifically the recommendations on disease activity and treatment) in the NICE guidance (October 2007) Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis, or
- the disease has responded inadequately to DMARDs and a TNF inhibitor and the patient cannot receive rituximab because of contra-indications or intolerance, and tocilizumab is used as described for TNF inhibitor treatments (specifically the recommendations on disease activity) in the NICE guidance (August 2010) Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor, or
- the disease has responded inadequately to one or more TNF inhibitor treatments and to rituximab
- and the manufacturer provides tocilizumab with the discount agreed as part of the patient access scheme.

Patients currently receiving tocilizumab for the treatment of rheumatoid arthritis who do not meet these criteria should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

Scottish Medicines Consortium (SMC) Decisions
The Scottish Medicines Consortium has advised (August 2012) that tocilizumab (RoActemra®) is accepted for restricted use within NHS Scotland as monotherapy in patients who are intolerant to methotrexate or where continued treatment with methotrexate is inappropriate, for the treatment of moderate to severe active rheumatoid arthritis in adults who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying antirheumatic drugs or tumour necrosis factor inhibitors, in accordance with the British Society for Rheumatology guidance on prescribing TNF-α blockers in adults with rheumatoid arthritis (2005).

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
- RoActemra (Roche Products Ltd)
  Tocilizumab 180 mg per 1 ml RoActemra 162mg/0.9ml solution for injection pre-filled syringes | 4 pre-filled disposable injection £913.12 (Hospital only)

Solution for infusion
- RoActemra (Roche Products Ltd)
  Tocilizumab 20 mg per 1 ml RoActemra 400mg/20ml concentrate for solution for infusion vials | 1 vial £512.00 (Hospital only)
  RoActemra 200mg/10ml concentrate for solution for infusion vials | 1 vial £256.00 (Hospital only)
  RoActemra 80mg/4ml concentrate for solution for infusion vials | 1 vial £102.40 (Hospital only)
### Ustekinumab

#### INDICATIONS AND DOSE

Severe plaque psoriasis that has not responded to at least 2 standard systemic treatments and phototherapy, or when these treatments cannot be used because of intolerance or contra-indications

**BY SUBCUTANEOUS INJECTION**
- Adult (body-weight up to 100 kg): Initially 45 mg, then 45 mg every 4 weeks, review treatment if no response within 28 weeks
- Adult (body-weight 100 kg and above): Initially 80 mg, then 80 mg every 4 weeks, review treatment if no response within 28 weeks

#### CONTRA-INDICATIONS
- Active psoriatic arthritis (in combination with methotrexate or alone) in patients who have had an inadequate response to one or more disease-modifying antirheumatic drugs

**BY SUBCUTANEOUS INJECTION**
- Adult (body-weight up to 100 kg): Initially 45 mg, then 45 mg every 4 weeks, review treatment if no response within 28 weeks
- Adult (body-weight 100 kg and above): Initially 80 mg, then 80 mg every 4 weeks, review treatment if no response within 28 weeks

Active psoriatic arthritis (in combination with methotrexate or alone) in patients who have had an inadequate response to one or more disease-modifying antirheumatic drugs

#### INTERACTIONS
- **Appendix 1 (ustekinumab).**
- **SIDE-EFFECTS**
  - **Common or very common**
    - Arthralgia, diarrhoea, dizziness, headache, infections (sometimes severe), injection-site reactions, malaise, myalgia, nausea, ophthalmic pain, pruritus
  - **Uncommon**
    - Depression, facial palsy, hypersensitivity reactions (possibly delayed onset), nasal congestion, pustular psoriasis
  - **Rare**
    - Exfoliative dermatitis

#### CONCEPTION AND CONTRACEPTION
- Manufacturer advises effective contraception during treatment and for 3 months after stopping treatment.

#### PREGNANCY
- Avoid.

#### BREAST FEEDING
- Manufacturer advises avoid—present in milk in animal studies.

#### PRE-TREATMENT SCREENING
- Tuberculosis Patients should be evaluated for tuberculosis before treatment.

#### MONITORING REQUIREMENTS
- Monitor for non-melanoma skin cancer, especially in patients with a history of PUVA treatment or prolonged immunosuppressant therapy, or those over 60 years of age.

- Monitor for signs and symptoms of exfoliative dermatitis or erythrodermic psoriasis.

#### PATIENT AND CARER ADVICE
- Exfoliative dermatitis Patients should be advised to seek prompt medical attention if symptoms suggestive of exfoliative dermatitis or erythrodermic psoriasis (such as increased redness and shedding of skin over a larger area of the body) develop.

- Tuberculosis Patients should be advised to seek medical attention if symptoms suggestive of tuberculosis (e.g. persistent cough, weight loss, and fever) develop.

#### NATIONAL FUNDING/ACCESS DECISIONS

- **NICE technology appraisals (TAs)**
  - **Ustekinumab for plaque psoriasis in adults (September 2009)**
    - NICE TA180
    - Ustekinumab is recommended for the treatment of severe plaque psoriasis which has failed to respond to standard systemic treatments (including ciclosporin and methotrexate) and to phototherapy, or when standard treatments cannot be used because of intolerance or contra-indications. Ustekinumab should be withheld if the response is not adequate after 16 weeks.
    - For patients weighing over 100 kg, the manufacturer should provide the 90-mg dose of ustekinumab at the same price as the 45-mg dose. [www.nice.org.uk/TA180](http://www.nice.org.uk/TA180)
  - **Ustekinumab for treating active psoriatic arthritis (June 2015)**
    - NICE TA340
    - Ustekinumab is an option, alone or in combination with methotrexate, for the treatment of active psoriatic arthritis in adults only when:
      - treatment with tumour necrosis factor (TNF) alpha inhibitors is contraindicated but would otherwise be considered (as described in the NICE guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (April 2011) or goltimubumab for the treatment of psoriatic arthritis (August 2010)) and
      - the patient has had treatment with 1 or more TNF-alpha inhibitors.
    - Ustekinumab is recommended only if the manufacturer provides the 90 mg dose of ustekinumab for patients who weigh more than 100 kg at the same cost as the 45 mg dose, as agreed in the patient access scheme.

#### MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS</th>
<th>10</th>
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</thead>
<tbody>
<tr>
<td>Stelara (Janssen-Cilag Ltd)</td>
<td>5mg</td>
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<tr>
<td>Ustekinumab 90 mg per 1 ml</td>
<td>0.1 ml solution for injection pre-filled syringes</td>
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</table>
T-CELL ACTIVATION INHIBITORS

Abatacept

**INDICATIONS AND DOSE**
Moderate to severe active rheumatoid arthritis (in combination with methotrexate) in patients unresponsive to other disease-modifying antirheumatic drugs (including methotrexate or a tumour necrosis factor (TNF) inhibitor) initially by intravenous infusion

- Adult (body-weight up to 60 kg): 500 mg every 2 weeks for 3 doses (loading dose), then (by intravenous infusion) 500 mg every 4 weeks, alternatively (by subcutaneous injection) 125 mg once weekly, first subcutaneous dose to be given within 1 day of the intravenous loading dose; patients who are unable to receive an infusion may initiate subcutaneous abatacept without receiving an intravenous loading dose
- Adult (body-weight 60-100 kg): 750 mg every 2 weeks for 3 doses (loading dose), then (by intravenous infusion) 750 mg every 4 weeks, alternatively (by subcutaneous injection) 125 mg once weekly, first subcutaneous dose to be given within 1 day of the intravenous loading dose; patients who are unable to receive an infusion may initiate subcutaneous abatacept without receiving an intravenous loading dose
- Adult (body-weight 101 kg and above): 1 g every 2 weeks for 3 doses (loading dose), then (by intravenous infusion) 1 g every 4 weeks, alternatively (by subcutaneous injection) 125 mg once weekly, first subcutaneous dose to be given within 1 day of the intravenous loading dose; patients who are unable to receive an infusion may initiate subcutaneous abatacept without receiving an intravenous loading dose

**SIDE-EFFECTS**
- Common or very common Abdominal pain - conjunctivitis - cough - diarrhoea - dizziness - dyspepsia - fatigue - flushing - headache - hypertension - infection - leucopenia - nausea - pain in extremities - paraesthesia - stomatitis - vomiting
- Frequency not known Lung cancer - lymphoma
- **CONTRA-INDICATIONS** Severe infection
- **CAUTIONS** Do not initiate until active infections are controlled - elderly (increased risk of side-effects) - predisposition to infection (screen for latent tuberculosis and viral hepatitis) - progressive multifocal leucoencephalopathy (discontinue treatment if neurological symptoms present)
- **INTERACTIONS** → Appendix 1 (abatacept).

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **ABATACEPT (Non-proprietary)**
  - Abatacept 125 mg per 1 ml Orencia ClickJet 125mg/1ml solution for injection pre-filled pen | 4 pre-filled disposable injection £1.60
  - Orencia (Bristol-Myers Squibb Pharmaceuticals Ltd)
  - Abatacept 125 mg per 1 ml Orencia 125mg/1ml solution for injection pre-filled syringes | 4 pre-filled disposable injection £1.60

- **Powder for solution for infusion**
  - **ELECTROLYTES:** May contain Sodium
  - Orencia (Bristol-Myers Squibb Pharmaceuticals Ltd)
  - Abatacept 250 mg Orencia 250mg powder for concentrate for solution for infusion vials | 1 vial £3.02

**NATIONAL FUNDING/ACCESS DECISIONS**

- **NICE technology appraisals (TAs)**
  - Adalimumab, etanercept, infliximab, rituximab, and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (August 2010) NICE TA195
  - Rituximab, in combination with methotrexate, is an option for the treatment of severe active rheumatoid arthritis in adults who have had an inadequate response to, or are intolerant of, other disease-modifying antirheumatic drugs (DMARDs), including at least 1 tumour necrosis factor (TNF) inhibitor. Repeat courses of rituximab should be given no more frequently than every 6 months, and should only be continued if an adequate response is achieved and maintained.
  - Adalimumab, etanercept, infliximab, or abatacept, in combination with methotrexate, are options for the treatment of severe active rheumatoid arthritis in adults who have had an inadequate response to, or have an intolerance of, other DMARDs including at least 1 TNF inhibitor, and who cannot use rituximab because of contra-indications or intolerance. In patients who cannot use methotrexate because of intolerance or contra-indications, adalimumab or etanercept can be given as monotherapy. Treatment should be continued only if there is adequate response. Patients should be monitored at least every 6 months. www.nice.org.uk/TA195
  - Abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying antirheumatic drugs (April 2013) NICE TA280

- **Scottish Medicines Consortium (SMC) Decisions**
  - The Scottish Medicines Consortium has advised (July 2013) that abatacept (Orencia®) is accepted for restricted use within NHS Scotland for adults with severe active rheumatoid arthritis, confirmed on at least two occasions, one month apart. This advice is contingent upon the patient access scheme.

**CONCEPTION AND CONTRACEPTION**
Effective contraception required during treatment and for 14 weeks after last dose.

**PREGNANCY**
Manufacturer advises avoid unless essential.

**BREAST FEEDING**
Present in milk in animal studies—manufacturer advises avoid breast-feeding during treatment and for 14 weeks after last dose.

**DIRECTIONS FOR ADMINISTRATION**
For intravenous infusion, reconstitute each vial with 10 mL water for injections using the silicone-free syringe provided; dilute requisite dose in Sodium Chloride 0.9% to 100 mL (using the same silicone-free syringe); give over 30 minutes through a low protein-binding filter (pore size 0.2–1.2 micron).
TUMOR NECROSIS FACTOR ALPHA (TNF-α) INHIBITORS

Adalimumab

INDICATIONS AND DOSE
Severe plaque psoriasis either refractory to at least 2 standard systemic treatments or phototherapy, or when standard treatments cannot be used because of intolerance or contra-indications.

BY SUBCUTANEOUS INJECTION
- Adult: Initially 80 mg, then 40 mg every 2 weeks, to be started 1 week after initial dose, discontinue treatment if no response within 16 weeks.

Moderate to severe active rheumatoid arthritis (in combination with methotrexate or alone if methotrexate inappropriate) when response to other disease-modifying drugs (including methotrexate) has been inadequate.

Severe, active, and progressive rheumatoid arthritis (in combination with methotrexate or alone if methotrexate inappropriate) not previously treated with methotrexate.

BY SUBCUTANEOUS INJECTION
- Adult: 40 mg every 2 weeks, then increased if necessary to 40 mg once weekly, dose to be increased only in patients receiving adalimumab alone, review treatment if no response within 12 weeks.

Active and progressive psoriatic arthritis that has not responded adequately to other disease-modifying antirheumatic drugs. Severe active ankylosing spondylitis that has not responded adequately to other disease-modifying antirheumatic drugs. Severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation, in patients who have had an inadequate response to, or are intolerant of, NSAIDs.

BY SUBCUTANEOUS INJECTION
- Adult: 40 mg every 2 weeks, discontinue treatment if no response within 12 weeks.

Severe active Crohn’s disease.

BY SUBCUTANEOUS INJECTION
- Adult: Initially 80 mg, then 40 mg after 2 weeks; maintenance 40 mg every 2 weeks, increased if necessary to 40 mg once weekly, maximum 40 mg administered at a single site, review treatment if no response within 12 weeks of initial dose.

Severe active Crohn’s disease (accelerated regimen).

BY SUBCUTANEOUS INJECTION
- Adult: Initially 160 mg, dose can alternatively be given as divided injections over 2 days, then 80 mg after 2 weeks; maintenance 40 mg every 2 weeks, increased if necessary to 40 mg once weekly, maximum 40 mg administered at a single site, review treatment if no response within 12 weeks of initial dose.

Severe active ulcerative colitis.

BY SUBCUTANEOUS INJECTION
- Adult: Initially 160 mg, dose can alternatively be given as divided injections over 2 days, then 80 mg after 2 weeks; maintenance 40 mg every 2 weeks, increased if necessary to 40 mg once weekly, maximum 40 mg administered at a single site, review treatment if no response within 8 weeks of initial dose.

CONTRA-INDICATIONS Moderate or severe heart failure - severe infection.

CAUTIONS Children should be brought up to date with current immunisation schedule before initiating therapy - demyelinating disorders (risk of exacerbation) - development of malignancy - do not initiate until active infections are controlled (discontinue if new serious infection develops) - hepatitis B virus—monitor for active infection - history of malignancy - mild heart failure (discontinue if symptoms develop or worsen) - predisposition to infection.

CAUTIONS, FURTHER INFORMATION

Tuberculosis Active tuberculosis should be treated with standard treatment for at least 2 months before starting adalimumab. Patients who have previously received adequate treatment for tuberculosis can start adalimumab but should be monitored every 3 months for possible recurrence. In patients without active tuberculosis but who were previously not treated adequately, chemoprophylaxis should ideally be completed before starting adalimumab. In patients at high risk of tuberculosis who cannot be assessed by tuberculin skin test, chemoprophylaxis can be given concurrently with adalimumab.

INTERACTIONS Appendix 1 (adalimumab).

SIDE-EFFECTS

Common or very common Anxiety· benign tumours· chest pain· cough· dehydration· dermatitis· dizziness· dyspepsia· dyspnoea· electrolyte disturbances· eye disorders· flushing· gastrointestinal haemorrhage· haematuria· hyperlipidaemia· hypertension· hyperuricaemia· impaired healing· mood changes· musculoskeletal pain· oedema· onycholysis· paraesthesia· rash· renal impairment· skin cancer· sleep disturbances· tachycardia· vomiting

Uncommon Aortic aneurysm· arthrythmias· cholecytis· cholelithiasis· dysphagia· erectile dysfunction· hearing loss· hepatic steatosis· intestinal lung disease· leukaemia· lymphoma· malignancy· neuropathy· nocturia· pancreatitis· pneumonitis· rhadomolysis· solid tumours· tinnitus· tremor· vascular occlusion

Rare Autoimmune hepatitis· demyelinating disorders· myocardial infarction

Frequency not known Abdominal pain· anaemia· antibody formation· aplastic anaemia· blood disorders· cutaneous vasculitis· depression· fever· headache· hypersensitivity reactions· injection-site reactions· leucopenia· lupus erythematosus-like syndrome· nausea· new onset psoriasis· pancytopenia· pleural effusion· pruritus· pulmonary embolism· sarcoidosis· Stevens-Johnson syndrome· thrombocytopenia· worsening heart failure· worsening psoriasis

SIDE-EFFECTS, FURTHER INFORMATION

Associated with infections, sometimes severe, including tuberculosis, sepsicaemia, and hepatitis B reactivation.

CONCEPTION AND CONTRACEPTION Manufacturer advises effective contraception required during treatment and for at least 5 months after last dose.

PREGNANCY Avoid.

BREAST FEEDING Avoid; manufacturer advises avoid for at least 5 months after last dose.

PRE-TREATMENT SCREENING
Tuberculosis Patients should be evaluated for tuberculosis before treatment.

MONITORING REQUIREMENTS
Monitor for infection before, during, and for 4 months after treatment.

Monitor for non-melanoma skin cancer before and during treatment, especially in patients with a history of PUVA treatment for psoriasis or extensive immunosuppressant therapy.

PATIENT AND CARER ADVICE An alert card should be provided.

Tuberculosis Patients and their carers should be advised to seek medical attention if symptoms suggestive of tuberculosis (e.g. persistent cough, weight loss, and fever) develop.
Blood disorders Patients and their carers should be advised to seek medical attention if symptoms suggestive of blood disorders (such as fever, sore throat, bruising, or bleeding) develop.

● NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

△ Adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis (October 2007) [NICE TA130]

The tumour necrosis factor alpha (TNF-α) inhibitors adalimumab, etanercept, and infliximab are options for the treatment of adults with active rheumatoid arthritis who have failed to respond to at least 2 disease-modifying antirheumatic drugs (DMARDs), including methotrexate (unless contra-indicated). TNF-α inhibitors should be given in combination with methotrexate; however, when methotrexate cannot be used because of intolerance or contraindications, adalimumab or etanercept can be given as monotherapy. Adalimumab, etanercept, and infliximab should be withdrawn if response is not adequate within 6 months. Response to treatment should be monitored at least every 6 months in patients who respond initially; treatment should be withdrawn if response is not maintained. An alternative TNF-α inhibitor may be considered for patients in whom treatment is withdrawn because of intolerance before the initial 6-month assessment of efficacy. Use of TNF-α inhibitors for the treatment of severe, active, and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs is not recommended. www.nice.org.uk/TA130

△ Adalimumab, etanercept, and infliximab for the treatment of ankylosing spondylitis (May 2008) [NICE TA143]

Adalimumab or etanercept are treatment options for adults with severe active ankylosing spondylitis whose disease satisfies specific criteria for diagnosis where there is confirmation of sustained active spinal disease, and where treatment with two or more NSAIDs taken sequentially at maximum tolerated or recommended doses for 4 weeks has failed to control symptoms. Response to adalimumab or etanercept treatment should be assessed at 12-week intervals and continued only if response is adequate. If response to treatment is not maintained, a repeat assessment should be made after a further 6 weeks and treatment discontinued if there is an inadequate response. Patients who are intolerant of adalimumab or etanercept during the initial 12 weeks may receive the alternative TNF-α inhibitor (adalimumab or etanercept). However an alternative TNF-α inhibitor is not recommended in patients who fail to respond initially or fail to maintain an adequate response. Infliximab is not recommended for the treatment of ankylosing spondylitis. Patients who are already receiving infliximab for the treatment of ankylosing spondylitis can continue treatment until they and their specialist consider it appropriate to stop. See full NICE guidance for specific criteria to diagnose severe active ankylosing spondylitis, confirm sustained active spinal disease, and assess response to treatment. www.nice.org.uk/TA143

△ Adalimumab for plaque psoriasis in adults (June 2008) [NICE TA146]

Adalimumab is recommended for the treatment of severe plaque psoriasis which has failed to respond to standard systemic treatments (including ciclosporin and methotrexate) and phototherapy, or when standard treatments cannot be used because of intolerance or contra-indications. Adalimumab should be withdrawn if the response is not adequate after 16 weeks. www.nice.org.uk/TA146

△ Infliximab and adalimumab for Crohn’s disease (May 2010) [NICE TA187]


△ Adalimumab, etanercept, infliximab, rituximab, and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (August 2010) [NICE TA195]


△ Etanercept, infliximab, and adalimumab for the treatment of psoriatic arthritis (August 2010) [NICE TA199]


△ Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (February 2015) [NICE TA239]

NICE recommended. See Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (February 2015) TA239 www.nice.org.uk/TA239 p. 907

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium issued similar advice for plaque psoriasis to NICE TA146 in May 2008.

● MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

CAUTIONARY AND ADVISORY LABELS 1D

- Humira (AbbVie Ltd)

Adalimumab 50 mg per 1 ml Humira 40mg/0.8ml solution for injection pre-filled syringes | 2 pre-filled disposable injection [Post] £704.28
Humira 40mg/0.8ml solution for injection vials | 2 vial [Post] £704.28
Humira 40mg/0.8ml solution for injection pre-filled disposable devices | 2 pre-filled disposable injection [Post] £704.28

Certolizumab pegol

INDICATIONS AND DOSE

Moderate to severe active rheumatoid arthritis when response to disease-modifying antirheumatic drugs (including methotrexate) has been inadequate (as monotherapy or in combination with methotrexate)

BY SUBCUTANEOUS INJECTION

- Adult: 400 mg every 2 weeks for 3 doses, then 200 mg every 2 weeks, review treatment if no response within 12 weeks

Treatment of severe active ankylosing spondylitis in patients who have had an inadequate response to, or are intolerant of NSAIDs | Treatment of severe active axial spondyloarthritis, without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation, in patients who have had an inadequate response to, or are intolerant of NSAIDs

BY SUBCUTANEOUS INJECTION

- Adult: 400 mg every 2 weeks for 3 doses, then 200 mg every 2 weeks, alternatively 400 mg every 4 weeks, review treatment if no response within 12 weeks

● CONTRA-INDICATIONS

Moderate to severe heart failure - severe active infection

● CAUTIONS

Demyelinating CNS disorders (risk of exacerbation) - do not initiate until active infections are controlled (discontinue if new serious infection develops and until infection controlled) - hepatitis B virus (monitor for active infection) - history or development of
malignancy • mild heart failure (discontinue if symptoms develop or worsen) • predisposition to infection

**CAUTIONS, FURTHER INFORMATION**

**Tuberculosis** Active tuberculosis should be treated with standard treatment for at least 2 months before starting certolizumab pegol. Patients who have previously received adequate treatment for tuberculosis can start certolizumab pegol but should be monitored every 3 months for possible recurrence. In patients without active tuberculosis but who were previously not treated adequately, chemoprophylaxis should ideally be completed before starting certolizumab pegol. Patients at high risk of tuberculosis who cannot be assessed by tuberculin skin test, chemoprophylaxis is given concurrently with certolizumab pegol.

**INTERACTIONS** → Appendix 1 (certolizumab pegol).

**SIDE-EFFECTS**

- **Common or very common** Hypertension • rash • sensory abnormalities
- **Uncommon** Acne • alopecia • anxiety • appetite disorders • arrhythmias • ascites • asthma • benign tumours • cardiomyopathies • cholestasis • cough • dermatitis • dizziness • dyslipidaemia • ecchymosis • electrolyte disorders • gastro-intestinal disorders • gastro-intestinal perforation • gastro-intestinal ulcer • haematuria • haemorrhage • heart failure • hepatic disorders • impaired healing • influenza-like illness • ischaemic coronary artery disorders • leukaemia • lymphoma • malignancy • menstrual disorders • mood disorders • muscle disorders • nail disorders • new onset or worsening psoriasis • ocular inflammation • oedema • peripheral neuropathy • photosensitivity • pleural effusion • renal impairment • skin cancer • skin discoloration • solid tumours • syncope • tinnitus • tremor • visual disturbance
- **Rare** Atiroyentricular block • cerebrovascular accident • cholelithiasis • impaired coordination • interstitial lung disease • nephropathy • Raynaud’s phenomenon • seizures • sexual dysfunction • splenomegaly • thyroid disorders • trigeminal neuralgia
- **Frequency not known** Abdominal pain • anaemia • antibody formation • aplastic anaemia • blood disorders • depression • fever • headache • hypersensitivity reactions • infections • injection-site reactions • leucopenia • lupus erythematosus-like syndrome • multiple sclerosis • nausea • pancytopenia • pruritus • thrombocytopenia • worsening heart failure

**SIDE-EFFECTS, FURTHER INFORMATION**

**Infection** Associated with infections, sometimes severe, including tuberculosis, septicemia, and hepatitis B reactivation.

**CONCEPTION AND CONTRACEPTION** Manufacturer advises adequate contraception during treatment and for at least 5 months after last dose.

**PREGNANCY** Avoid.

**BREAST FEEDING** Manufacturer advises use only if potential benefit outweighs risk—no information available.

**PRE-TREATMENT SCREENING**

**Tuberculosis** Patients should be evaluated for tuberculosis before treatment.

**MONITORING REQUIREMENTS** Monitor for infection before, during, and for 5 months after treatment.

**PATIENT AND CARER ADVICE** An alert card should be provided.

Blood disorders Patients should be advised to seek medical attention if symptoms suggestive of blood disorders (such as fever, sore throat, bruising, or bleeding) develop.

Tuberculosis Patients should be advised to seek medical attention if symptoms suggestive of tuberculosis (e.g. persistent cough, weight loss and fever) develop.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- **Certolizumab pegol for the treatment of rheumatoid arthritis** (February 2010) NICE TA186

Certolizumab pegol is an option for the treatment of patients with rheumatoid arthritis only if:

- certolizumab pegol is used as described in the NICE guidance (October 2007) for other tumour necrosis factor (TNF) inhibitors (see Adalimumab, Etanercept and Infliximab for the treatment of Rheumatoid Arthritis), and
- the manufacturer provides the first 12 weeks of certolizumab pegol (10 prefilled 200-mg syringes) free of charge to all patients starting treatment. [www.nice.org.uk/TA186](http://www.nice.org.uk/TA186)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

**CAUTIONARY AND ADVISORY LABELS** 10

- **Certolizumab pegol 200 mg per 1 ml** Cimzia 200mg/1ml solution for injection pre-filled syringes | 2 syringe [£715.00](http://www.nice.org.uk/TA186)

**Etanercept**

**INDICATIONS AND DOSE**

Moderate to severe active rheumatoid arthritis (alone or in combination with methotrexate) when the response to other disease-modifying antirheumatic drugs is inadequate | Severe, active, and progressive rheumatoid arthritis not previously treated with methotrexate | Active and progressive psoriatic arthritis inadequately responsive to other disease-modifying antirheumatic drugs | Severe ankylosing spondylitis inadequately responsive to conventional therapy

**BY SUBCUTANEOUS INJECTION**

- Adult: 25 mg twice weekly, alternatively 50 mg once weekly
- Severe plaque psoriasis either refractory to at least 2 standard systemic treatments and photochemotherapy, or when standard treatments cannot be used because of intolerance or contra-indications

**BY SUBCUTANEOUS INJECTION**

- Adult: 25 mg twice weekly for up to 24 weeks, alternatively 50 mg once weekly for up to 24 weeks, discontinue if no response after 12 weeks

**CONTRA-INDICATIONS** Active infection

**CAUTIONS** Children should be brought up to date with current immunisation schedule before initiating therapy • development of malignancy • diabetes mellitus • heart failure (risk of exacerbation) • hepatitis B virus—monitor for active infection • hepatitis C infection (monitor for worsening infection) • history of blood disorders • history of malignancy • history or increased risk of demyelinating disorders • predisposition to infection (avoid if predisposition to septicemia) • significant exposure to herpes zoster virus—interrupt treatment and consider varicella–zoster immunoglobulin

**CAUTIONS, FURTHER INFORMATION**

**Tuberculosis** Active tuberculosis should be treated with standard treatment for at least 2 months before starting etanercept. Patients who have previously received adequate treatment for tuberculosis can start etanercept but should be monitored every 3 months for possible recurrence. In patients without active tuberculosis but who were previously not treated adequately, chemoprophylaxis should ideally be completed before starting etanercept. In patients at high risk of tuberculosis...
who cannot be assessed by tuberculin skin test, chemoprophylaxis can be given concurrently with etanercept.

- **INTERACTIONS** → Appendix 1 (etanercept).

- **SIDE-EFFECTS**
  - **Uncommon** Interstitial lung disease - new onset or worsening psoriasis - rash - skin cancer - uveitis
  - **Rare** Demyelinating disorders - lymphoma - seizures - Stevens-Johnson syndrome - vasculitis
  - **Very rare** Toxic epidermal necrolysis

- **SIDE-EFFECTS, FURTHER INFORMATION**
  - Associated with infections, sometimes severe, including tuberculosis, sepsis, and hepatitis B reactivation.

- **CONCEPTION AND CONTRACEPTION**
  - Manufacturer advises effective contraception required during treatment and for 3 weeks after last dose.

- **PREGNANCY**
  - Avoid—limited information available.

- **BREAST FEEDING**
  - Manufacturer advises avoid—present in milk in animal studies.

- **HEPATIC IMPAIRMENT**
  - Use with caution in moderate to severe alcoholic hepatitis.

- **PRE-TREATMENT SCREENING**
  - Tuberculosis
  - Patients should be evaluated for tuberculosis before treatment.

- **MONITORING REQUIREMENTS**
  - Monitor for skin cancer before and during treatment, particularly in those at risk (including patients with psoriasis or a history of PUVA treatment).

- **PATIENT AND CARER ADVICE**
  - An alert card should be provided.
  - Blood disorders
  - Patients and their carers should be advised to seek medical attention if symptoms suggestive of blood disorders (such as fever, sore throat, bruising, or bleeding) develop.
  - Tuberculosis
  - Patients and their carers should be advised to seek medical attention if symptoms suggestive of tuberculosis (e.g. persistent cough, weight loss, and fever) develop.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  - **NICE technology appraisals (TAs)**
    - Etanercept and efalizumab for plaque psoriasis in adults (July 2006) NICE TA103
    - Etanercept is recommended for severe plaque psoriasis which has failed to respond to standard systemic treatments (including ciclosporin and methotrexate) and to phototherapy, or when standard treatments cannot be used because of intolerance or contraindications. Etanercept should be withdrawn if the response is not adequate after 12 weeks. www.nice.org.uk/TA103
    - Adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis (October 2007) NICE TA130
    - NICE recommended. See Adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis (October 2007) TA130 www.nice.org.uk/TA130 p. 902
    - Adalimumab, etanercept, and infliximab for the treatment of ankylosing spondylitis (May 2008) NICE TA141

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Solution for injection**
    - CAUTIONARY AND ADVISORY LABELS 10
    - **Brand Name**
      - **Etanercept** (Pfizer Ltd)
      - **Enbrel** (Pfizer Ltd)
    - **NICE TA195**
      - Eta nercept 50 mg per 1 ml Enbrel 50mg/1ml solution for injection pre-filled disposable injection [p.o.]: £115.00
      - Eta nercept 25mg/0.5ml solution for injection pre-filled syringes: £357.50
    - **Brands may include Enbrel MyClic.
      - Powder and solvent for solution for injection**
    - **NICE TA195**
      - Eta nercept 10 mg Enbrel Paediatric 10mg powder and solvent for solution for injection vials: £357.50
      - Eta nercept 25 mg Enbrel Paediatric 25mg powder and solvent for solution for injection vials: £357.50

**Golimumab**

**INDICATIONS AND DOSE**

Treatment of severe ulcerative colitis in patients whose condition has not responded adequately to conventional therapy, or who are intolerant of it

- **By subcutaneous injection**
  - **Adult (body-weight up to 80 kg):** Initially 200 mg, then 100 mg after 2 weeks; maintenance 50 mg every 4 weeks, review treatment if no response after 4 doses
  - **Adult (body-weight 80 kg and above):** Initially 200 mg, then 100 mg after 2 weeks; maintenance 100 mg every 4 weeks, review treatment if no response after 4 doses
Treatment of moderate to severe active rheumatoid arthritis (in combination with methotrexate) when response to disease-modifying antirheumatic drug (DMARD) therapy (including methotrexate) has been inadequate. Treatment of severe, active, and progressive rheumatoid arthritis (in combination with methotrexate) in patients not previously treated with methotrexate. Treatment of active and progressive psoriatic arthritis as monotherapy or in combination with methotrexate when response to DMARD therapy has been inadequate. Treatment of severe active ankylosing spondylitis when there is inadequate response to conventional treatment.

**CONTRA-INDICATIONS** Moderate or severe heart failure - severe active infection

**CAUTIONS** Active infection (do not initiate until active infections are controlled; discontinue if new serious infection develops until infection controlled) - demyelinating disorders (risk of exacerbation) - hepatitis B virus - monitor for active infection - history or development of malignancy - mild heart failure (discontinue if symptoms develop or worsen) - predisposition to infection - risk factors for dysplasia or carcinoma of the colon - screen for dysplasia regularly

**Tuberculosis** Active tuberculosis should be treated with standard treatment for at least 2 months before starting golimumab. Patients who have previously received adequate treatment for tuberculosis can start golimumab but should be monitored every 2 months for possible recurrence. In patients without active tuberculosis but who were previously not treated adequately, chemoprophylaxis should ideally be completed before starting golimumab. In patients at high risk of tuberculosis who cannot be assessed by tuberculin skin test, chemoprophylaxis can be given concurrently with golimumab. Patients who have tested negative for latent tuberculosis, and those who are receiving or who have completed treatment for latent tuberculosis, should be monitored closely for symptoms of active infection.

**INTERACTIONS** → Appendix 1 (golimumab).

**SIDE-EFFECTS**

- **Common or very common** Asthenia - dizziness - dyspepsia - hypertension
- **Rare** Impaired wound healing

**SIDE-EFFECTS, FURTHER INFORMATION**

Associated with infections, sometimes severe, including tuberculosis, septicaemia, and hepatitis B reactivation.

**CONCEPTION AND CONTRACEPTION** Manufacturer advises adequate contraception during treatment and for at least 6 months after last dose.

**PREGNANCY** Use only if essential.

**BREAST FEEDING** Manufacturer advises avoid during and for at least 6 months after treatment – present in milk in animal studies.

**HEPATIC IMPAIRMENT** Manufacturer advises caution – no information available.

**PRE-TREATMENT SCREENING**

Tuberculosis Patients should be evaluated for tuberculosis before treatment.

**MONITORING REQUIREMENTS** Monitor for infection before, during, and for 5 months after treatment.

**DIRECTIONS FOR ADMINISTRATION** For doses requiring multiple injections, each injection should be administered at a different site.

Missed dose: if dose administered more than 2 weeks late, subsequent doses should be administered on the new monthly due date.

**PATIENT AND CARER ADVICE** An alert card should be provided.

Tuberculosis All patients and their carers should be advised to seek medical attention if symptoms suggestive of tuberculosis (e.g. persistent cough, weight loss, and fever) develop.

Blood disorders Patients and their carers should be advised to seek medical attention if symptoms suggestive of blood disorders (such as fever, sore throat, bruising, or bleeding) develop.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- **Golimumab for the treatment of psoriatic arthritis** (April 2011) NICE TA220

Golimumab is an option for the treatment of active and progressive psoriatic arthritis in adults only if:

- golimumab is used as described in the NICE guidance (August 2010) for other tumour necrosis factor (TNF) inhibitors, and
- the manufacturer provides the 100-mg dose of golimumab at the same price as the 50-mg dose.

www.nice.org.uk/TA220

- **Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying antirheumatic drugs** (June 2011) NICE TA225

Golimumab, in combination with methotrexate, is an option for the treatment of rheumatoid arthritis in adults who have had an inadequate response to conventional disease-modifying antirheumatic drugs (DMARDs) only, including methotrexate, if:

- golimumab is used as described in the NICE guidance (October 2007) for other tumour necrosis factor (TNF) inhibitors, and
- the manufacturer provides the 100-mg dose of golimumab at the same price as the 50-mg dose.

Alternatively, golimumab, in combination with methotrexate, is an option for the treatment of rheumatoid arthritis in adults who have had an inadequate response to DMARDs including a TNF inhibitor, if:

- golimumab is used as described in the NICE guidance (August 2010) for other TNF inhibitors, and
- the manufacturer provides the 100-mg dose of golimumab at the same price as the 50-mg dose.

www.nice.org.uk/TA225
Golimumab for the treatment of ankylosing spondylitis (August 2011) NICE TA233

Golimumab is an option for the treatment of severe, active ankylosing spondylitis in adults only if:

- Golimumab is used as described in the NICE guidance (May 2008) for adalimumab and etanercept, and
- the manufacturer provides the 100-mg dose of golimumab at the same price as the 50-mg dose.

Patients who are already receiving golimumab for the treatment of severe, active ankylosing spondylitis who do not fulfill the criteria for treatment with adalimumab and etanercept, described in the NICE guidance (May 2008), can continue treatment until they and their specialist consider it appropriate to stop. www.nice.org.uk/TA233

Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (February 2015) NICE TA329

NICE recommended. See Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (February 2015) TA329 www.nice.org.uk/TA329 p. 907

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (June 2012) that golimumab (Simponi®) is accepted for restricted use within NHS Scotland at a dose of 50 mg, alone or in combination with methotrexate, for the treatment of active and progressive psoriatic arthritis in adults whose disease has not responded to adequate trials of at least two standard DMARDs, administered either individually or in combination.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

CAUTIONARY AND ADVISORY LABELS 10

- Simponi (Merck Sharp & Dohme Ltd)
  - Golimumab 100 mg per 1 ml Simponi 50mg/0.5ml solution for injection pre-filled disposable devices | 1 pre-filled disposable injection [PFS] £762.97 Simponi 100mg/1ml solution for injection pre-filled pen | 1 pre-filled disposable injection [PFS] £1,525.94
  - Simponi 50mg/0.5ml solution for injection pre-filled syringes | 1 pre-filled disposable injection [PFS] £627.97

Infliximab

INDICATIONS AND DOSE

Severe active Crohn’s disease

BY INTRavenous INFUSION

Adult: Initially 5 mg/kg, then 5 mg/kg after 2 weeks, then 5 mg/kg after 4 weeks, if condition has responded, then maintenance 5 mg/kg every 8 weeks

Fistulating Crohn’s disease

BY INTRavenous INFUSION

Adult: Initially 5 mg/kg, then 5 mg/kg after 2 weeks, followed by 5 mg/kg after 4 weeks, if condition has responded consult product literature for guidance on further doses

Severe active ulcerative colitis

BY INTRavenous INFUSION

Adult: Initially 5 mg/kg, then 5 mg/kg after 2 weeks, followed by 5 mg/kg after 4 weeks, then 5 mg/kg every 8 weeks, discontinue if no response 14 weeks after initial dose

Rheumatoid arthritis (in combination with methotrexate)

BY INTRavenous INFUSION

Adult: Initially 3 mg/kg, then 3 mg/kg after 2 weeks, followed by 3 mg/kg after 4 weeks, then 3 mg/kg every 8 weeks, dose to be increased only if response is inadequate after 12 weeks of initial treatment; increased in steps of 1.5 mg/kg every 8 weeks,

increased if necessary up to 7.5 mg/kg every 8 weeks, alternatively increased if necessary to 3 mg/kg every 4 weeks, discontinue if no response by 12 weeks of initial infusion or after dose adjustment

Ankylosing spondylitis

BY INTRavenous INFUSION

Adult: 5 mg/kg, then 5 mg/kg after 2 weeks, followed by 5 mg/kg after 4 weeks, then 5 mg/kg every 6–8 weeks, discontinue if no response by 6 weeks of initial infusion

Psoriatic arthritis (in combination with methotrexate)

BY INTRavenous INFUSION

Adult: 5 mg/kg, then 5 mg/kg after 2 weeks, followed by 5 mg/kg after 4 weeks, followed by 5 mg/kg every 8 weeks

Plaque psoriasis

BY INTRavenous INFUSION

Adult: 5 mg/kg, then 5 mg/kg after 2 weeks, followed by 5 mg/kg after 4 weeks, then 5 mg/kg every 8 weeks, discontinue if no response within 14 weeks of initial infusion

Important safety information

Adequate resuscitation facilities must be available when infliximab is used.

CONTRA-INDICATIONS

Moderate or severe heart failure - severe infections

CAUTIONS

Demyelinating disorders (risk of exacerbation) - development of malignancy - hepatitis B virus—monitor for active infection - history of colon carcinoma (in inflammatory bowel disease) - history of dysplasia (in inflammatory bowel disease) - history of malignancy - history of prolonged immunosuppressant or PUVA treatment in patients with psoriasis - mild heart failure (discontinue if symptoms develop or worsen) - predisposition to infection (discontinue if new serious infection develops) - risk of delayed hypersensitivity reactions if drug-free interval exceeds 16 weeks

CAUTIONS, FURTHER INFORMATION

Tuberculosis

Active tuberculosis should be treated with standard treatment for at least 2 months before starting infliximab. Patients who have previously received adequate treatment for tuberculosis can start infliximab but should be monitored every 3 months for possible recurrence. In patients without active tuberculosis but who were previously not treated adequately, chemoprophylaxis should ideally be completed before starting infliximab. In patients at high risk of tuberculosis who cannot be assessed by tuberculin skin test, chemoprophylaxis can be given concurrently with infliximab.

Hypersensitivity reactions

Hypersensitivity reactions (including fever, chest pain, hypotension, hypertension, dyspnoea, transient visual loss, pruritus, urticaria, serum sickness-like reactions, angioedema, anaphylaxis) reported during or within 1–2 hours after infusion (risk greatest during first or second infusion or in patients who discontinue other immunosuppressants). Prophylactic antipyretics, antihistamines, or hydrocortisone may be administered.

INTERACTIONS

Appendix 1 (infliximab).

SIDE-EFFECTS

Common or very common - Alopecia - arthralgia - constipation - diarrhoea - dizziness - dry skin - dyspepsia - ecchymosis - epistaxis - flushing - gastro-intestinal haemorrhage - gastro-oesophageal reflux - hyperhydrosis - hypertension - hypoaesthesia - hypotension - myalgia - new onset or worsening psoriasis - palpititation - paraesthesia - rash - sleep disturbances - tachycardia
PATIENT AND CARER ADVICE

DIRECTIONS FOR ADMINISTRATION

When used for plaque psoriasis, monitor for non-

Monitor for symptoms of delayed hypersensitivity if

Monitor for infection before, during, and for

PRE-TREATMENT SCREENING

Tuberculosis Patients should be evaluated for tuberculosis before treatment.

MONITORING REQUIREMENTS

Monitor for infection before, during, and for

All patients should be observed carefully for 1–2 hours

Monitor for symptoms of delayed hypersensitivity if

DIRECTIONS FOR ADMINISTRATION

For intravenous infusion (Remicade®), give intermittently in Sodium chloride 0.9%; reconstitute each 100-mg vial with 10 mL water for injections using a 21-gauge or smaller needle; gently swirl vial without shaking to dissolve; allow to stand for 5 minutes; dilute requisite dose with infusion fluid to a final volume of 250 mL and give through a low protein-binding filter (1.2 micron or less) over at least 2 hours (adults over 18 years who have tolerated 3 initial 2-hour infusions may be given subsequent infusions of up to 6 mg/kg over at least 1 hour); start infusion within 3 hours of reconstitution.

PATIENT AND CARER ADVICE

An alert card should be provided.

Tuberculosis Patients and carers should be advised to seek medical attention if symptoms suggestive of tuberculosis (e.g. persistent cough, weight loss, and fever) develop.

Blood disorders Patients and carers should be advised to seek medical attention if symptoms suggestive of blood disorders (such as fever, sore throat, bruising, or bleeding) develop.

Hypersensitivity reactions Patients and carers should be advised to keep Alert card with them at all times and seek medical advice if symptoms of delayed hypersensitivity develop.

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

Adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis (October 2007) NICE TAI30

NICE recommended. See Adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis (October 2007) TAI30 www.nice.org.uk/TAI30 p. 902

Infliximab for plaque psoriasis in adults (January 2008) NICE TAI34

Infliximab is recommended for the treatment of very severe plaque psoriasis which has failed to respond to standard systemic treatments (including ciclosporin and methotrexate) or to photochemotherapy, or when standard treatments cannot be used because of intolerance or contra-indications. Infliximab should be withdrawn if the response is not adequate after 10 weeks.

Adalimumab, etanercept, and infliximab for the treatment of ankylosing spondylitis (May 2008) NICE TAI43

NICE recommended. See Adalimumab, etanercept, and infliximab for the treatment of ankylosing spondylitis (May 2008)TAI43 www.nice.org.uk/TAI43 p. 902

Infliximab for acute exacerbations of ulcerative colitis (December 2008) NICE TAI63

Infliximab is recommended as an option for the treatment of acute exacerbations of severe ulcerative colitis when treatment with ciclosporin is contra-indicated or inappropriate. www.nice.org.uk/TAI63

Infliximab and adalimumab for Crohn’s disease (May 2010) NICE TAI87

Infliximab or adalimumab is recommended for the treatment of severe active Crohn’s disease that has not responded to conventional therapy (including corticosteroids and other drugs affecting the immune response) or when conventional therapy cannot be used because of intolerance or contra-indications; infliximab can also be used in a similar way in children over 6 years of age. In adults over 18 years of age, infliximab is recommended for the treatment of fistulating Crohn’s disease that has not responded to conventional therapy (including antibacterials, drainage, and other drugs affecting the immune response) or when conventional therapy cannot be used because of intolerance or contra-indications.

Infliximab or adalimumab should be given as a planned course of treatment for 12 months or until treatment failure, whichever is shorter. Treatment should be continued beyond 12 months only if there is evidence of active disease—in these cases the need for treatment should be reviewed at least annually. If the disease relapses after stopping treatment, adalimumab or infliximab can be restarted [but see Hypersensitivity Reactions under Infliximab]. www.nice.org.uk/TAI87

Adalimumab, etanercept, infliximab, rituximab, and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (August 2010) NICE TAI95

NICE recommended. See Adalimumab, etanercept, infliximab, rituximab, and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (August 2010) TAI95 www.nice.org.uk/TAI95 p. 900

Etanercept, infliximab, and adalimumab for the treatment of psoriatic arthritis (August 2010) NICE TAI99


Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (February 2015) NICE TA329

Infliximab, adalimumab and golimumab are options for treating moderately to severely active ulcerative colitis in adults whose disease has responded inadequately to conventional therapy including corticosteroids and
mercaptopurine or azathioprine, or in adults who are intolerant to or have contra-indications for conventional therapies. Gollimubam is recommended only if the manufacturer provides the 100 mg dose of gollimubam at the same cost as the 50 mg dose, as agreed in the patient access scheme. The choice of treatment should be made on an individual basis and if more than one treatment is suitable, the least expensive should be chosen. Infliximab, adalimumab or gollimubam should be given as a planned course of treatment until treatment fails (including the need for surgery) or until 12 months after starting treatment, whichever is shorter. Treatment should be continued only if there is clear evidence of a response. Patients who continue treatment should be reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate.

Hyperuricaemia and gout

Gout

It is important to distinguish drugs used for the treatment of acute attacks of gout from those used in the long-term control of the disease. The latter exacerbate and prolong the acute manifestations if started during an attack. The management of gout in adolescents requires specialist supervision.

Acute attacks of gout

Acute attacks of gout are usually treated with high doses of NSAIDs such as diclofenac sodium p. 921, diclofenac potassium p. 920, etoricoxib p. 925, indometacin p. 929, ketoprofen p. 930, naproxen p. 934 or sulindac p. 937. Colchicine below is an alternative in patients with renal impairment or urate stones when uricosuric drugs cannot be used; it is not indicated for the treatment of asymptomatic hyperuricaemia. It can cause rashes. Sulfinpyrazone p. 909 can be used instead of allopurinol or in conjunction with it in cases that are resistant to treatment.

Allopurinol is widely used and is especially useful in patients with renal impairment or urate stones when uricosuric drugs cannot be used; it is not indicated for the treatment of asymptomatic hyperuricaemia. It can cause rashes. Aspirin and other salicylates antagonise the uricosuric drugs; they do not antagonise allopurinol but are nevertheless not indicated in gout.

Colchicine

INDICATIONS AND DOSE

Acute gout

BY MOUTH

- Adult: 500 micrograms 2–4 times a day until symptoms relieved, maximum 6 mg per course, do not repeat course within 3 days

Short-term prophylaxis during initial therapy with allopurinol and uricosuric drugs

BY MOUTH

- Adult: 500 micrograms twice daily

Prophylaxis of familial Mediterranean fever (recurrent polyserositis)

BY MOUTH

- Adult: 0.5–2 mg once daily

- UNLICENSED USE: BNF doses may differ from those in the product literature. Use of colchicine for prophylaxis of familial Mediterranean fever (recurrent polyserositis) is an unlicensed indication.

- CONTRA-INDICATIONS: Blood disorders

Long-term control of gout

Frequent recurrence of acute attacks of gout, the presence of tophi, or signs of chronic gouty arthritis may call for the initiation of long-term (‘interval’) treatment. For long-term control of gout the formation of uric acid from purines may be reduced with the xanthine-oxidase inhibitors allopurinol p. 909 or febuxostat p. 910 alternatively the uricosuric drug sulfinpyrazone p. 909 may be used to increase the excretion of uric acid in the urine. Treatment should be continued indefinitely to prevent further attacks of gout by correcting the hyperuricaemia. These drugs should never be started during an acute attack; they are usually started 1–2 weeks after the attack has settled. The initiation of treatment may precipitate an acute attack, and therefore an anti-inflammatory analgesic or colchicine below should be used as a prophylactic and continued for at least one month after the hyperuricaemia has been corrected. However, if an acute attack develops during treatment, then the treatment should continue at the same dosage and the acute attack treated in its own right.

Febuxostat is licensed for the treatment of chronic hyperuricaemia where urate deposition has already occurred; it is not indicated for patients in whom the rate of urate formation is greatly increased, such as in malignant disease or in Lesch-Nyhan syndrome.

Sulfinpyrazone p. 909 can be used instead of allopurinol or in conjunction with it in cases that are resistant to treatment.

Benzbromarone (available from ’special-order’ manufacturers or specialist importing companies) is a uricosuric drug that can be used in patients with mild renal impairment.

Crystallisation of urate in the urine can occur with the uricosuric drugs and it is important to ensure an adequate urine output especially in the first few weeks of treatment. As an additional precaution the urine may be rendered alkaline.

Aspirin and other salicylates antagonise the uricosuric drugs; they do not antagonise allopurinol but are nevertheless not indicated in gout.

ALKALOIDS

Colchicine

- MEDICINAL FORMS

| Powder for solution for infusion |
| Header  | Cautionary and Advisory Labels 10 |
| Remicade (Merck Sharp & Dohme Ltd) |
| Infliximab 100 mg Remicade 100mg powder for concentrate for solution for infusion (1 vial (500) 141962 (Hospital only)) |
| Brands may include Inflectra; Remsima |

- Hyperuricaemia and gout

- Acute gout

- INFLIXIMAB

- INFliximab 100 mg Remicade 100mg powder for concentrate for solution for infusion (1 vial (500) 141962 (Hospital only))

- Brands may include Inflectra; Remsima
Hyperuricaemia and gout 909

XANTHINE OXIDASE INHIBITORS

Allopurinol

INDICATIONS AND DOSE
Prophylaxis of gout of and uric acid and calcium oxalate renal stones | Prophylaxis of hyperuricaemia associated with cancer chemotherapy

BY MOUTH
- Adult: Initially 100 mg daily, adjust dose according to plasma or urinary uric acid concentration, dose to be taken preferably after food
- Adult: 100–200 mg daily, dose to be taken preferably after food
- Adult: 300–600 mg daily in divided doses (max. per dose 300 mg), dose to be taken preferably after food

CONTRA-INDICATIONS
Not a treatment for acute gout but continue if attack develops when already receiving allopurinol, and treat attack separately

CAUTIONS
Ensure adequate fluid intake (2–3 litres/day) for hyperuricaemia associated with cancer therapy, allopurinol treatment should be started before cancer therapy

CAUTIONS, FURTHER INFORMATION
Administer prophylactic NSAID (not aspirin or salicylates) or colchicine until at least 1 month after hyperuricaemia corrected (usually for first 3 months) to avoid precipitating an acute attack.

INTERACTIONS
Appendix 1 (allopurinol).

SIDE-EFFECTS
- Common or very common Gastro-intestinal disorders - rashes (withdraw therapy); if rash mild re-introduce cautiously but discontinue promptly if recurrence
- Very rare Seizures

Tablet
CAUTIONARY AND ADVISORY LABELS 12, 21
- SULFINPYRAZONE (Non-proprietary)
  - Sulfinpyrazone 100 mg Sulfinpyrazone 100mg tablets | 84 tablet [P] £9.40 DT price + £41.25
  - Sulfinpyrazone 200 mg Sulfinpyrazone 200mg tablets | 84 tablet [P] £113.76 DT price + £79.00

Sulfinpyrazone

(Sulphinpyrazone)

INDICATIONS AND DOSE
- Gout prophylaxis | Hyperuricaemia

BY MOUTH
- Adult: Initially 60–80 mg daily, dose to be increased to 800 mg daily after several weeks; dose to be taken preferably after food
- Adult: 100–300 mg daily, dose to be increased to 800 mg daily over 3–6 weeks; dose to be taken preferably after food
- Adult: 800 mg daily, dose to be increased to 800 mg daily over 3–6 weeks; dose to be taken preferably after food

CONTRA-INDICATIONS
Acute porphyrias p. 864 - acute gout attack - history of blood disorders - peptic ulceration

CAUTIONS
Cardiac disease (may cause salt and water retention) - ensure adequate fluid intake (2–3 litres daily) and render urine alkaline during initial treatment

INTERACTIONS
Appendix 1 (sulfinpyrazone).

SIDE-EFFECTS
- Rare Acute renal failure - blood disorders - gastrointestinal bleeding - gastrointestinal ulceration - hepatitis - jaundice - raised liver enzymes
- Frequency not known Allergic skin reactions - gastrointestinal disturbances - salt retention - water retention

ALLERGY AND CROSS-SENSITIVITY Avoid in hypersensitivity to aspirin, salicylates, NSAIDs.

PREGNANCY
Manufacturer advises caution—no information available.

BREAST FEEDING
No information available.

HEPATIC IMPAIRMENT
Avoid in severe impairment.

RENAL IMPAIRMENT
Reduce dose. Avoid in severe impairment.

MONITORING REQUIREMENTS
Regular blood counts before treatment and at regular intervals during treatment.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

URICOSURICS

Sulfinpyrazone

(Sulphinpyrazone)

INDICATIONS AND DOSE
- Gout prophylaxis | Hyperuricaemia

BY MOUTH
- Adult: 300–800 mg daily in divided doses (max. per dose 300 mg), dose to be increased to 800 mg daily over 2–3 weeks; dose to be taken preferably after food
- Adult: 800 mg daily, dose to be increased to 800 mg daily over 2–3 weeks; dose to be taken preferably after food
- Adult: 800 mg daily, dose to be increased to 800 mg daily over 2–3 weeks; dose to be taken preferably after food

CONTRA-INDICATIONS
Acute gout attacks - gastrointestinal bleeding - gastrointestinal ulceration - hepatitis - jaundice - raised liver enzymes

CAUTIONS
Cardiac disease (may cause salt and water retention) - ensure adequate fluid intake (2–3 litres daily) and render urine alkaline during initial treatment

INTERACTIONS
Appendix 1 (sulfinpyrazone).

SIDE-EFFECTS
- Common or very common Gastro-intestinal disorders - rashes (withdraw therapy); if rash mild re-introduce cautiously but discontinue promptly if recurrence
- Very rare Seizures
Febuxostat

**INDICATIONS AND DOSE**

Treatment of chronic hyperuricaemia in gout

**BY MOUTH**

- **Adult:** Initially 80 mg once daily, if after 2–4 weeks of initial dose, serum uric acid greater than 6 mg/100 mL then increase dose; increased if necessary to 120 mg daily

**Important safety information**

**MHRA/CHM ADVICE: SERIOUS HYPERSENSITIVITY REACTIONS (JUNE 2012)**

There have been rare but serious reports of hypersensitivity reactions, including Stevens-Johnson syndrome and acute anaphylactic shock with febuxostat. Patients should be advised of the signs and symptoms of severe hypersensitivity; febuxostat must be stopped immediately if these occur (early withdrawal is associated with a better prognosis), and must not be restarted in patients who have ever developed a hypersensitivity reaction to febuxostat. Most cases occur during the first month of treatment; a prior history of hypersensitivity to allopurinol and/or renal disease may indicate potential hypersensitivity to febuxostat.

**CONTRA-INDICATIONS**

- Not a treatment for acute gout but continue if attack develops when already receiving febuxostat, and treat attack separately

**CAUTIONS**

- Congestive heart failure - ischaemic heart disease - thyroid disorders - transplant recipients

**CAUTIONS. FURTHER INFORMATION**

Administer prophylactic NSAID (not aspirin or salicylates) or colchicine for at least 6 months after starting febuxostat to avoid precipitating an acute attack.

**INTERACTIONS**

- Appendix 1 (febuxostat).

**SIDE-EFFECTS**

- Common or very common: Abnormal liver function tests - gastro-intestinal disturbances - headache - oedema - rash
- Uncommon: Appetite change - arthralgia - arthritis - atrial fibrillation - bronchitis - bursitis - chest pain - cholelithiasis

**PREGNANCY**

Manufacturer advises avoid—limited information available.

**BREAST FEEDING**

Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT**

Max. 80 mg daily in mild impairment. No dose information available in moderate or severe impairment.

**RENAL IMPAIRMENT**

- Use with caution if eGFR less than 30 mL/minute/1.73 m²—no information available.
- **PRE-TREATMENT SCREENING**
  - Monitor liver function tests before treatment as indicated.
  - **MONITORING REQUIREMENTS**
  - Monitor liver function tests periodically during treatment as indicated.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Febuxostat for the management of hyperuricaemia in patients with gout (December 2008) NICE TA164
  - Febuxostat is recommended as an option for the management of chronic hyperuricaemia in gout only for patients who are intolerant of allopurinol or for whom allopurinol is contra-indicated.
  - For the purposes of this guidance, intolerance of allopurinol is defined as adverse effects that are sufficiently severe to warrant discontinuation, or to prevent full dose escalation for optimal effectiveness.
  - [www.nice.org.uk/TA164](http://www.nice.org.uk/TA164)

- Scottish Medicines Consortium (SMC) Decisions
  - The Scottish Medicines Consortium issued similar advice to NICE guidance: Febuxostat for the management of hyperuricaemia in patients with gout (December 2008), in August 2010.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **FEBUXOSTAT (Non-proprietary)**
  - **Febuxostat 80 mg**
    - **Febuxostat 120 mg**
  - Brands may include Uriceto, Zyloric
  - [Price information available.](http://www.nice.org.uk/TA164)

**3 Neuromuscular disorders**

**Neuromuscular disorders**

**Drugs that enhance neuromuscular transmission**

Anticholinesterases are used as first-line treatment in *ocular myasthenia gravis* and as an adjunct to immunosuppressant therapy for *generalised myasthenia gravis*.

Corticosteroids are used when anticholinesterases do not control symptoms completely. A second line
Myasthenia gravis and Lambert-Eaton myasthenic syndrome


immunosuppressant such as azathioprine p. 716 is frequently used to reduce the dose of corticosteroid. Plasmapheresis or infusion of intravenous immunoglobulin [unlicensed indication] may induce temporary remission in severe relapses, particularly where bulbar or respiratory function is compromised or before thymectomy.

Anticholinesterases
Anticholinesterase drugs enhance neuromuscular transmission in voluntary and involuntary muscle in myasthenia gravis. Excessive dosage of these drugs can impair neuromuscular transmission and precipitate cholinergic crises by causing a depolarising block. This may be difficult to distinguish from a worsening myasthenic state.

Muscarinic side-effects of anticholinesterases include increased sweating, increased salivary and gastric secretions, increased gastro-intestinal and uterine motility, and bradycardia. These parasympathomimetic effects are antagonised by atropine sulfate p. 1099.

Neostigmine p. 912 produces a therapeutic effect for up to 4 hours. Its pronounced muscarinic action is a disadvantage, and simultaneous administration of an antimuscarinic drug such as atropine sulfate or propantheline bromide p. 74 may be required to prevent colic, excessive salivation, or diarrhoea. In severe disease neostigmine can be given every 2 hours. The maximum that most patients can tolerate is 180 mg daily.

Pyridostigmine bromide p. 912 is less powerful and slower in action than neostigmine but it has a longer duration of action. It is preferable to neostigmine because of its smoother action and the need for less frequent dosage. It is particularly preferred in patients whose muscles are weak on waking. It has a comparatively mild gastrointestinal effect but an antimuscarinic drug may still be required.

Neostigmine is also used to reverse the actions of the non-depolarising neuromuscular blocking drugs.

Immunosuppressant therapy
Corticosteroids are established as treatment for myasthenia gravis; although they are commonly given on alternate days there is little evidence of benefit over daily administration. Corticosteroid treatment is usually initiated under in-patient supervision and all patients should receive osteoporosis prophylaxis.

In generalised myasthenia gravis prednisolone p. 585 is given. About 10% of patients experience a transient but very serious worsening of symptoms in the first 2–3 weeks, especially if the corticosteroid is started at a high dose. Smaller doses of corticosteroid are usually required in ocular myasthenia. Once clinical remission has occurred (usually after 2–6 months), the dose of prednisolone should be reduced slowly to the minimum effective dose.

In generalised myasthenia gravis azathioprine p. 716 is usually started at the same time as the corticosteroid and it allows a lower maintenance dose of the corticosteroid to be used. Ciclosporin p. 717, methotrexate p. 762, or mycophenolate mofetil p. 725 can be used in patients unresponsive or intolerant to other treatments [unlicensed indications].

Acetylcholine-release enhancers
Amifampridine below is licensed for the symptomatic treatment of Lambert-Eaton myasthenic syndrome (LEMS), a rare disorder of neuromuscular transmission.

Fampridine p. 726 is licensed for the improvement of walking in patients with multiple sclerosis who have a walking disability.

Skeletal muscle relaxants
The drugs described are used for the relief of chronic muscle spasm or spasticity associated with multiple sclerosis or other neurological damage; they are not indicated for spasm associated with minor injuries. Baclofen, diazepam, and tizanidine act principally on the central nervous system. Dantrolene has a peripheral site of action; cannabis extract has both a central and a peripheral action. Skeletal muscle relaxants differ in action from the muscle relaxants used in anaesthesia, which block transmission at the neuromuscular junction.

The underlying cause of spasticity should be treated and any aggravating factors (e.g. pressure sores, infection) remedied. Skeletal muscle relaxants are effective in most forms of spasticity except the rare alpha variety. The major disadvantage of treatment with these drugs is that reduction in muscle tone can cause a loss of splinting action of the spastic leg and trunk muscles and sometimes lead to an increase in disability.

Baclofen p. 914 inhibits transmission at spinal level and also depresses the central nervous system. The dose should be increased slowly to avoid the major side-effects of sedation and muscular hypotonia (other adverse events are uncommon).

A cannabis extract p. 913 containing dronabinol (delta-9-tetrahydrocannabinol) and cannabidiol is licensed as an adjunct treatment for moderate to severe spasticity associated with multiple sclerosis in patients who have not responded adequately to other skeletal muscle relaxants. The dose should be titrated over 2 weeks; response to treatment should be reviewed after 4 weeks and treatment stopped if an adequate response is not achieved.

Dantrolene sodium p. 1101 acts directly on skeletal muscle and produces fewer central adverse effects making it a drug of choice. The dose should be increased slowly. Diazepam p. 267 can also be used. Sedation and occasionally extensor hypotonus are disadvantages. Other benzodiazepines also have muscle-relaxant properties. Muscle-relaxant doses of benzodiazepines are similar to anticonvulsants.

Tizanidine p. 913 is an alpha-2-adrenoceptor agonist indicated for spasticity associated with multiple sclerosis or spinal cord injury.

Other muscle relaxants
The clinical efficacy of methocarbamol p. 915 and meprobamate p. 265 as muscle relaxants is not well established, although they have been included in compound analgesic preparations.

3.1 Myasthenia gravis and Lambert-Eaton myasthenic syndrome

ACETYLCHOLINE-RELEASE ENHANCERS

Amifampridine

INDICATIONS AND DOSE
Symptomatic treatment of Lambert-Eaton myasthenic syndrome (specialist use only)

BY MOUTH
• Adult: Initially 15 mg daily in 3 divided doses, then increased in steps of 5 mg every 4–5 days, increased to up to 60 mg daily in 3–4 divided doses (max. per dose 20 mg); maximum 60 mg per day

● CONTRA-INDICATIONS Congenital QT syndromes • epilepsy • uncontrolled asthma

● CAUTIONS Non-paraneoplastic form of Lambert-Eaton myasthenic syndrome
Neostigmine methysulfate

**INDICATIONS AND DOSE**

**Treatment of myasthenia gravis**

**BY MOUTH**

- **Adult:** Initially 15–30 mg, dose repeated at suitable intervals throughout the day, total daily dose 75–300 mg, the maximum that most patients can tolerate is 180 mg daily

**BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION**

- **Adult:** 1–2.5 mg, dose repeated at suitable intervals throughout the day (usual total daily dose 5–20 mg)

**Reversal of non-depolarising (competitive) neuromuscular blockade**

**BY INTRAVENOUS INJECTION**

- **Adult:** 2.5 mg (max. per dose 5 mg), repeated if necessary after or with glycopyrrolate or atropine, to be given over 1 minute

**UNLICENSED USE**

Dose for treatment of myasthenia gravis by subcutaneous or intramuscular injection in neonate is unlicensed.

**CAUTIONS**

- With intravenous use glycopyrrolate or atropine should also be given when reversing neuromuscular blockade

**INTERACTIONS → Appendix 1 (parasympathomimetics).**

**RENAI IMPAIRMENT**

May need dose reduction.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution

**Tablet**

| Neostigmine bromide 15 mg | Neostigmine 15mg tablets |
| Neostigmine bromide 15 mg | Neostigmine 15mg tablets |
| 140 tablet | £93.60 |

**Solution for injection**

- **NEOSTIGMINE (Non-proprietary)**
  - Neostigmine methylsulfate 2.5 mg per 1 ml | Neostigmine 2.5mg/1ml solution for injection ampoules | 10 ampoule | £4.95-5.06

Pyridostigmine bromide

**DRUG ACTION**

Pyridostigmine bromide has weaker muscarinic action than neostigmine.

**INDICATIONS AND DOSE**

**Myasthenia gravis**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

- **Adult:** 30–120 mg, dose to be given at suitable intervals throughout the day; usual dose 0.3–1.2 g daily in divided doses, it is advisable to exceed a total daily dose of 450 mg in order to avoid acetylcholine receptor downregulation; patients requiring doses exceeding 450 mg daily will usually require input from a specialist neuromuscular service. Immunosuppressant therapy is usually considered if the dose of pyridostigmine exceeds 360 mg daily
3.2 Nocturnal leg cramps

Nocturnal leg cramps
Quinine salts, such as quinine sulfate are effective in reducing the frequency of nocturnal leg cramps by about 25% in ambulatory patients; however, because of potential toxicity, quinine is not recommended for routine treatment and should not be used unless cramps cause regular disruption to sleep. Quinine p. 540 should only be considered when cramps are very painful or frequent; when other treatable causes of cramp have been excluded; and when non-pharmacological treatments have not worked (e.g. passive stretching exercises). It may take up to 4 weeks for improvement to become apparent; if there is benefit, quinine treatment can be continued. Treatment should be interrupted at intervals of approximately 3 months to assess the need for further quinine treatment. In patients taking quinine long term, a trial discontinuation may be considered. Quinine is toxic in overdose and accidental fatalities have occurred.

3.3 Spasticity

Drugs used for Spasticity not listed below; Dantrolene sodium, p. 1101 - Diazepam, p. 267

ALPHA₂-ADRENOCEPTOR AGONISTS

Tizanidine

INDICATIONS AND DOSE
Spasticity associated with multiple sclerosis or spinal cord injury or disease

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES

Adult: Initially 2 mg for 1 dose, then increased in steps of 2 mg/24 hours every 3–4 days in divided doses, adjusted according to response; usual dose up to 24 mg daily in 3–4 divided doses; maximum 36 mg per day

● CAUTIONS Elderly
● INTERACTIONS Appendix 1 (muscle relaxants). Caution with concomitant administration of drugs that prolong QT interval.

● SIDE-EFFECTS
  ● Common or very common Altered liver enzymes (discontinue if persistently raised—consult product literature) - dizziness - drowsiness - dry mouth - fatigue - gastro-intestinal disturbance - hypotension - nausea
  ● Uncommon Bradycardia
  ● Frequency not known Asthenia - blurred vision - confusion - convulsions - hallucinations - hepatitis - insomnia - liver failure - syncope

● PRENANCY Avoid (toxicity in animal studies).
● BREAST FEEDING Avoid (present in milk in animal studies).
● HEPATIC IMPAIRMENT Avoid in severe impairment; use in moderate impairment only if potential benefit outweighs risk.
● RENAL IMPAIRMENT Manufacturer advises caution.
● MONITORING REQUIREMENTS Monitor liver function monthly for first 4 months and in those who develop unexplained nausea, anorexia or fatigue.
● TREATMENT CESSATION Avoid abrupt withdrawal (risk of rebound hypertension and tachycardia); to minimise risk, discontinue gradually and monitor blood pressure.
● PATIENT AND CARER ADVICE Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

● MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

Tablet
PYRIDOSTIGMINE BROMIDE (Non-proprietary) Pyridostigmine bromide 60 mg tablets | 200 tablet | £45.58 DT price = £45.58
Mestinon (Meda Pharmaceuticals Ltd) Pyridostigmine bromide 60 mg Mestinon 60mg tablets | 200 tablet | £45.57 DT price = £45.58

CANNABINODS

Cannabis extract

INDICATIONS AND DOSE
Adjunct in moderate to severe spasticity in multiple sclerosis (specialist use only)

BY BUCCAL ADMINISTRATION

Adult: (consult product literature)

● CONTRA-INDICATIONS Family history of psychosis - history of other severe psychiatric disorder - personal history of psychosis
● CAUTIONS History of epilepsy - significant cardiovascular disease
● INTERACTIONS Appendix 1 (cannabis extract).
● SIDE-EFFECTS
  ● Common or very common Amnesia - blurred vision - constipation - depression - diarrhoea - disorientation - dissociation - dizziness - drowsiness - dry mouth - dystarhria - impaired attention - increased or decreased appetite - malaise - mood disturbance - mouth ulcer - nausea - oral pain - taste disturbance - vertigo - vomiting
  ● Uncommon Abdominal pain - delusions - hallucinations - hypertension - oomucosal discoloration - palpititation - paranoia - pharyngitis - stomatitis - suicidal thoughts - syncope - tachycardia - tooth discoloration
  ● Frequency not known Anxiety - seizures
● CONCEPTION AND CONTRACEPTION Manufacturer recommends effective contraception during and for 3 months after treatment in men and women.
● PREGNANCY Manufacturer advises use only if potential benefit outweighs risks.
● BREAST FEEDING Avoid—present in milk.
● HEPATIC IMPAIRMENT Manufacturer advises more frequent monitoring in significant hepatic impairment—possible risk of prolonged or enhanced effect.
RENAL IMPAIRMENT  Manufacturer advises more frequent monitoring in significant renal impairment—possible risk of prolonged or enhanced effect.

MONITORING REQUIREMENTS  Monitor oral mucosa—interrupt treatment if lesions or persistent soreness.

PATIENT AND CARER ADVICE  For information on 2015 legislation regarding driving whilst taking certain controlled drugs, including cannabis, see Drugs and Driving under Guidance on prescribing, p. 1

MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug.

Spray  EXCIPIENTS: May contain Propylene glycol
- Sativex (Bayer Plc)  Cannabinoids 2.5 mg per 1 dose, Dronabinol 2.7 mg per 1 dose  Sativex oromucosal spray | 270 dose (BNF) £375.00 (CPD-1)

gamma-AMINOBUTYRIC ACID ANALOGUES AND DERIVATIVES

Baclofen

INDICATIONS AND DOSE  Pain of muscle spasm in palliative care

BY MOUTH  
- Adult: 5–10 mg 3 times a day  
- Adult: 5 mg twice daily  

Chronic severe spasticity resulting from disorders such as multiple sclerosis or traumatic partial section of spinal cord

BY MOUTH  
- Adult: Initially 5 mg 3 times a day, gradually increased; maintenance up to 60 mg daily in divided doses, review treatment if no benefit within 6 weeks of achieving maximum dose; maximum 100 mg per day

Severe chronic spasticity unresponsive to oral antispastic drugs (or where side-effects of oral therapy unacceptable) or as alternative to ablative neurosurgical procedures (specialist use only)

BY INTRATECAL INJECTION  
- Adult: Test dose 25–50 micrograms, to be given over at least 1 minute via catheter or lumbar puncture, then increased in steps of 25 micrograms (max. per dose 100 micrograms), not given more often than every 24 hours to determine appropriate dose, then dose-titration phase, most often using infusion pump (implanted into chest wall or abdominal wall tissues) to establish maintenance dose (ranging from 12 micrograms to 2 mg daily for spasticity of spinal origin or 22 micrograms to 1.4 mg daily for spasticity of cerebral origin) retaining some spasticity to avoid sensation of paralysis

CONTRA-INDICATIONS  
- With intrathecal use Local infection - systemic infection
- With oral use Avoid oral route in active peptic ulceration

CAUTIONS  GENERAL CAUTIONS  Cerebrovascular disease - diabetes - elderly - epilepsy - history of peptic ulcer - hypertonic bladder - sphincter - Parkinson’s disease - psychiatric illness - respiratory impairment

SPECIFIC CAUTIONS  
- With intrathecal use Coagulation disorders - malnutrition (increased risk of post-surgical complications) - previous spinal fusion procedure

INTERACTIONS  → Appendix 1 (muscle relaxants).

SIDE-EFFECTS  

- Rare  Abdominal pain - changes in hepatic function - dysarthria - erectile dysfunction - paraesthesia - taste disturbances

- Very rare  Hypothermia

PREGNANCY  Manufacturer advises use only if potential benefit outweighs risk (toxicity in animal studies).

BREAST FEEDING  Present in milk—amount probably too small to be harmful.

HEPATIC IMPAIRMENT  With oral use Manufacturer advises use with caution.

RENAL IMPAIRMENT  With oral use Risk of toxicity—use smaller doses (e.g. 5 mg daily by mouth) and if necessary increase dosage interval; if eGFR less than 15 mL/minute/1.73 m² manufacturer advises use by mouth only if potential benefit outweighs risk. Excreted by kidney.

TREATMENT CESSATION  Avoid abrupt withdrawal (risk of hyperactive state, may exacerbate spasticity, and precipitate autonomic dysfunction including hyperthermia, psychiatric reactions and convulsions; to minimise risk, discontinue by gradual dose reduction over at least 1–2 weeks (longer if symptoms occur)).

PRESCRIBING AND DISPENSING INFORMATION  Flavours of oral liquid formulations may include raspberry.

PATIENT AND CARER ADVICE  Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

MEDICINAL FORMS  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, oral suspension, oral solution

Tablet  
EXCIPIENTS: May contain Gluten
- BACLOFEN (Non-proprietary)  Baclofen 10 mg  Baclofen 10mg tablets | 84 tablet (BNF) £9.99 DT price = £1.85
- Lioresal (Novartis Pharmaceuticals UK Ltd)  Baclofen 10 mg  Lioresal 10mg tablets | 100 tablet (BNF) £12.38

Oral solution  
EXCIPIENTS: May contain Gluten
- BACLOFEN (Non-proprietary)  Baclofen 1 mg per 1 ml  Baclofen 5mg/5ml oral solution sugar free (sugar-free) | 300 ml (BNF) £22.45 DT price = £4.59
- Lioresal (Novartis Pharmaceuticals UK Ltd)  Baclofen 1 mg per 1 ml  Lioresal 5mg/5ml liquid (sugar-free) | 300 ml (BNF) £8.59 DT price = £4.59

Brands may include Lyflex

Important safety information  Consult product literature for details on test dose and titration—important to monitor patients closely in appropriately equipped and staffed environment during screening and immediately after pump implantation. Resuscitation equipment must be available for immediate use. Treatment with continuous pump-administered intrathecal baclofen should be initiated within 3 months of a satisfactory response to intrathecal baclofen testing.
Solution for injection
▶ BACLOFEN (Non-proprietary)
Baclofen 50 microgram per 1 ml Baclofen 50micrograms/1ml solution for injection ampoules | 1 ampoule (£9.10) 10 ampoule (£77.60)
▶ Lioresal (Novartis Pharmaceuticals UK Ltd)
Baclofen 50 microgram per 1 ml Lioresal Intrathecal 50micrograms/1ml solution for injection ampoules | 1 ampoule (£2.63)

Solution for infusion
▶ BACLOFEN (Non-proprietary)
Baclofen 500 microgram per 1 ml Baclofen 10mg/20ml solution for infusion ampoules | 1 ampoule (£5.70)
Baclofen 2 mg per 1 ml Baclofen 10mg/5ml solution for infusion ampoules | 5 ampoule (£243.10) 10 ampoule (£570.00)
▶ Lioresal (Novartis Pharmaceuticals UK Ltd)
Baclofen 500 microgram per 1 ml Lioresal Intrathecal 10mg/20ml solution for infusion ampoules | 1 ampoule (£58.34)
Baclofen 2 mg per 1 ml Lioresal Intrathecal 10mg/5ml solution for infusion ampoules | 1 ampoule (£68.34)

MUSCLE RELAXANTS

Methocarbamol

INDICATIONS AND DOSE
Short-term symptomatic relief of muscle spasm
BY MOUTH
▶ Adults: 1.5 g 4 times a day; reduced to 750 mg 3 times a day if required
▶ Elderly: Up to 750 mg 4 times a day, may be sufficient

CONTRA-INDICATIONS
Brain damage - coma - epilepsy - myasthenia gravis - precoma

INTERACTIONS → Appendix 1 (muscle relaxants).

SIDE-EFFECTS

PREGNANCY
Manufacturer advises avoid unless potential benefit outweighs risk.

BREAST FEEDING
Present in milk in animal studies—manufacturer advises caution.

HEPATIC IMPAIRMENT
Manufacturer advises caution; half-life may be prolonged.

RENAL IMPAIRMENT
Manufacturer advises caution.

PATIENT AND CARER ADVICE
Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

LESS SUITABLE FOR PRESCRIBING
Less suitable for prescribing.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

Tablet
CAUTIONARY AND ADVISORY LABELS 2
▶ METHOCARBAMOL (Non-proprietary)
Methocarbamol 750 mg Methocarbamol 750mg tablets | 100 tablet (£12.65) DT price = £12.65
Roibaxin (Almirall Ltd)
Methocarbamol 750 mg Methocarbamol 750 tablets | 100 tablet (£12.65) DT price = £12.65

4 Pain and inflammation in musculoskeletal disorders

Non-steroidal anti-inflammatory drugs

In single doses non-steroidal anti-inflammatory drugs (NSAIDs) have analgesic activity comparable to that of paracetamol p. 354, but paracetamol is preferred, particularly in the elderly.

In regular full dosage NSAIDs have both a lasting analgesic and an anti-inflammatory effect which makes them particularly useful for the treatment of continuous or regular pain associated with inflammation. Therefore, although paracetamol often gives adequate pain control in osteoarthritis, NSAIDs are more appropriate than paracetamol or the opioid analgesics in the inflammatory arthritides (e.g. rheumatoid arthritis) and in some cases of advanced osteoarthritis. NSAIDs can also be of benefit in the less well defined conditions of back pain and soft-tissue disorders.

Choice
Differences in anti-inflammatory activity between NSAIDs are small, but there is considerable variation in individual response and tolerance to these drugs. About 60% of patients will respond to any NSAID; of the others, those who do not respond to one may well respond to another. Pain relief starts soon after taking the first dose and a full analgesic effect should normally be obtained within a week, whereas an anti-inflammatory effect may not be achieved (or may not be clinically assessable) for up to 3 weeks. If appropriate responses are not obtained within these times, another NSAID should be tried.

NSAIDs reduce the production of prostaglandins by inhibiting the enzyme cyclo-oxygenase. They vary in their selectivity for inhibiting different types of cyclo-oxygenase; selective inhibition of cyclo-oxygenase-2 is associated with less gastro-intestinal intolerance. Several other factors also influence susceptibility to gastrointestinal effects, and a NSAID should be chosen on the basis of the incidence of gastro-intestinal and other side-effects.

Ibuprofen p. 927 is a propionic acid derivative with anti-inflammatory, analgesic, and antipyretic properties. It has fewer side-effects than other non-selective NSAIDs but its anti-inflammatory properties are weaker. It is unsuitable for conditions where inflammation is prominent, such as acute gout. Dextibuprofen p. 919 is the active enantiomer of ibuprofen. It has similar properties to ibuprofen and is licensed for the relief of mild to moderate pain and inflammation.

Other propionic acid derivatives:
Naproxen p. 934 is one of the first choices because it combines good efficacy with a low incidence of side-effects (but more than ibuprofen).
Fenoprofen p. 926 is as effective as naproxen, and flurbiprofen may be slightly more effective. Both are associated with slightly more gastro-intestinal side-effects than ibuprofen.
Ketoprofen p. 930 has anti-inflammatory properties similar to ibuprofen and has more side-effects. Dextketoifen p. 919, an isomer of ketoprofen, has been introduced for the short-term relief of mild to moderate pain.
Tiaprofenic acid p. 938 is as effective as naproxen; it has more side-effects than ibuprofen.
Drugs with properties similar to those of propionic acid derivatives:
Diclofenac sodium p. 921 and aceclofenac below are similar in efficacy to naproxen.
Etodolac p. 924 is comparable in efficacy to naproxen p. 934; it is licensed for symptomatic relief of osteoarthritis and rheumatoid arthritis.
Indomethacin p. 929 has an action equal to or superior to that of naproxen, but with a high incidence of side-effects including headache, dizziness, and gastro-intestinal disturbances.
Mefenamic acid p. 932 has minor anti-inflammatory properties. It has occasionally been associated with diarrohoea and haemolytic anaemia which require discontinuation of treatment.
Meloxicam p. 933 is licensed for the short-term relief of pain in osteoarthritis and for long-term treatment of rheumatoid arthritis and ankylosing spondylitis.
Nabumetone p. 934 is comparable in effect to naproxen p. 934.
Phenytoin is licensed for ankylosing spondylitis, but is not recommended because it is associated with serious side-effects, in particular haematological reactions; it should be used only by a specialist in severe cases where other treatments have been found unsuitable.
Piroxicam p. 936 is as effective as naproxen and has a long duration of action which permits once-daily administration. However, it has more gastro-intestinal side-effects than most other NSAIDs, and is associated with more frequent serious skin reactions.
Sulindac p. 937 is similar in tolerance to naproxen. Tenoxicam p. 937 is similar in activity and tolerance to naproxen. Its long duration of action allows once-daily administration.
Tolfenamic acid p. 381 is licensed for the treatment of migraine.
The selective inhibitors of cyclo-oxygenase-2, etoricoxib p. 925 and celecoxib p. 918, are as effective as non-selective NSAIDs such as diclofenac sodium and naproxen. Although selective inhibitors can cause serious gastro-intestinal events, available evidence appears to indicate that the risk of serious upper gastro-intestinal events is lower with selective inhibitors compared to non-selective NSAIDs; this advantage may be lost in patients who require concomitant low-dose aspirin.
Celecoxib and etoricoxib are licensed for the relief of pain in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis; etoricoxib is also licensed for the relief of pain from acute gout.
Aspirin p. 104 has been used in high doses to treat rheumatoid arthritis, but other NSAIDs are now preferred.

**Dental and orofacial pain**
Most mild to moderate dental pain and inflammation is effectively relieved by NSAIDs. Those used for dental pain include ibuprofen p. 927, diclofenac sodium p. 921, and diclofenac potassium p. 920.

**Asthma**
Any degree of worsening of asthma may be related to the ingestion of NSAIDs, either prescribed or (in the case of ibuprofen and others) purchased over the counter.

**NSAIDs and cardiovascular events**
All NSAID use (including cyclo-oxygenase-2 selective inhibitors) can, to varying degrees, be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of baseline cardiovascular risk factors or duration of NSAID use; however, the greatest risk may be in those receiving high doses long term.

Cyclo-oxygenase-2 selective inhibitors, diclofenac (150 mg daily) and ibuprofen (2.4 g daily) are associated with an increased risk of thrombotic events. Although there are limited data regarding the thrombotic effects of celecoxib, treatment advice has been updated in line with diclofenac, based on celecoxib’s structural similarity to diclofenac and its metabolism to diclofenac. The increased risk for diclofenac is similar to that of licensed doses of etoricoxib. Naproxen (1 g daily) is associated with a lower thrombotic risk, and low doses of ibuprofen (1.2 g daily or less) have not been associated with an increased risk of myocardial infarction.

The lowest effective dose of NSAID should be prescribed for the shortest period of time to control symptoms and the need for long-term treatment should be reviewed periodically.

**NSAIDs and gastro-intestinal events**
All NSAIDs are associated with serious gastro-intestinal toxicity; the risk is higher in the elderly. Evidence on the relative safety of non-selective NSAIDs indicates differences in the risks of serious upper gastro-intestinal side-effects—piroxicam, ketorolac, and ketoprofen are associated with the highest risk; indomethacin, diclofenac, and naproxen are associated with intermediate risk, and ibuprofen with the lowest risk (although high doses of ibuprofen have been associated with intermediate risk). Selective inhibitors of cyclo-oxygenase-2 are associated with a lower risk of serious upper gastro-intestinal side-effects than non-selective NSAIDs.

Recommendations are that NSAIDs associated with a low risk e.g. ibuprofen are generally preferred, to start at the lowest recommended dose and not to use more than one oral NSAID at a time.

The combination of a NSAID and low-dose aspirin can increase the risk of gastro-intestinal side-effects; this combination should be used only if absolutely necessary and the patient should be monitored closely.

While it is preferable to avoid NSAIDs in patients with previous NSAID therapy, those with active or previous gastro-intestinal ulceration or bleeding, and to withdraw them if gastro-intestinal lesions develop, nevertheless patients with serious rheumatoid diseases (e.g. rheumatoid arthritis) are usually dependent on NSAIDs for effective relief of pain and stiffness.

Patients at risk of gastro-intestinal ulceration (including the elderly), who need NSAID treatment should receive gastroprotective treatment.

Systemic as well as local effects of NSAIDs contribute to gastro-intestinal damage; taking oral formulations with milk or food, or using enteric-coated formulations, or changing the route of administration may only partially reduce symptoms such as dyspepsia.

**NON-STEROIDAL ANTI-INFLAMMATORY DRUGS**

**Aceclofenac**

**INDICATIONS AND DOSE**

Pain and inflammation in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis

**BY MOUTH**

> **Adult:** 100 mg twice daily

- **CONTRA-INDICATIONS** Active gastro-intestinal bleeding · active gastro-intestinal ulceration · cerebrovascular disease · history of gastro-intestinal bleeding related to previous NSAID therapy · history of gastro-intestinal perforation related to previous NSAID therapy · history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) · history of recurrent gastro-intestinal
ulceration (two or more distinct episodes) • ischaemic heart disease • mild heart failure • peripheral arterial disease • severe heart failure

- **CAUTIONS** Allergic disorders • avoid in Acute porphyrias p. 864 • cardiac impairment (NSAIDs may impair renal function) • coagulation defects • connective-tissue disorders • Crohn’s disease (may be exacerbated) • elderly (risk of serious side-effects and fatalities) • history of cardiac failure • hypertension • left ventricular dysfunction • oedema • risk factors for cardiovascular events • ulcerative colitis (may be exacerbated)

- **INTERACTIONS** → Appendix 1 (NSAIDs).

- **SIDE-EFFECTS**
  - **Rare** Alveolitis • asceptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) • hepatic damage • interstitial fibrosis associated with NSAIDs can lead to renal failure • pancreatitis • papillary necrosis associated with NSAIDs can lead to renal failure • pulmonary eosinophilia • Stevens-Johnson syndrome • toxic epidermal necrolysis • visual disturbances
  - **Frequency not known** Angioedema • blood disorders • bronchospasm • colitis (induction of or exacerbation of) • Crohn’s disease (induction of or exacerbation of) • depression • diarrhoea • dizziness • drowsiness • fluid retention (rarely precipitating congestive heart failure) • gastro-intestinal bleeding • gastro-intestinal discomfort • gastro-intestinal disturbances • gastro-intestinal ulceration • haematuria • headache • hearing disturbances • hypersensitivity reactions • insomnia • nausea • nervousness • photosensitivity • raised blood pressure • rashes • renal failure (especially in patients with pre-existing renal impairment) • tinnitus • vertigo

- **SIDE-EFFECTS, FURTHER INFORMATION**

- **Serious side-effects** For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 915.

- **ALLERGY AND CROSS-SENSITIVITY** Contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

- **CONCEPTION AND CONTRACEPTION** Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

- **PREGNANCY** Most manufacturers advise avoiding the use of NSAIDs during pregnancy or avoiding them unless the potential benefit outweighs the risk. NSAIDs should be avoided during the third trimester because use is associated with a risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn. In addition, the onset of labour may be delayed and its duration may be increased.

- **BREAST FEEDING** Use with caution during breast-feeding. Manufacturer advises avoid.

- **HEPATIC IMPAIRMENT** Initially 100 mg daily.
  
  Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

- **RENAL IMPAIRMENT** Avoid if possible or use with caution; avoid in moderate to severe impairment. The lowest effective dose should be used for the shortest possible duration. In renal impairment, monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

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**Tablet**

**CAUTIONARY AND ADVISORY LABELS 21**

- **ACECOLFENAC (Non-proprietary)**
  - Accefenac 100 mg Accefenac 100mg tablets | 60 tablet POM £10.78 DT price + £3.63
  - Accefenac 200 mg Accefenac 200mg tablets | 60 tablet POM £21.98 DT price + £3.63

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**Acemetacin**

- **DRUG ACTION** Glycolic acid ester of indometacin.

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**INDICATIONS AND DOSE**

- **Pain and inflammation in rheumatic disease** | **Pain and inflammation in other musculoskeletal disorders** | **Postoperative analgesia**
  
  **BY MOUTH**
  
  - *Adult:* 120 mg daily in divided doses, then increased if necessary to 180 mg daily in divided doses, dose to be taken with food

- **CONTRA-INDICATIONS** Active gastro-intestinal bleeding • active gastro-intestinal ulceration • history of gastro-intestinal bleeding related to previous NSAID therapy • history of gastro-intestinal perforation related to previous NSAID therapy • history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) • history of recurrent gastro-intestinal ulceration (two or more distinct episodes) • severe heart failure

- **CAUTIONS** Allergic disorders • cardiac impairment (NSAIDs may impair renal function) • cerebrovascular disease • coagulation defects • connective-tissue disorders • Crohn’s disease (may be exacerbated) • elderly (risk of serious side-effects and fatalities) • epilepsy • heart failure • ischaemic heart disease • parkinsonism • peripheral arterial disease • psychiatric disturbances • risk factors for cardiovascular events • ulcerative colitis (may be exacerbated) • uncontrolled hypertension

- **INTERACTIONS** → Appendix 1 (NSAIDs).

- **SIDE-EFFECTS**
  - **Rare** Alveolitis • asceptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) • blood disorders • bronchospasm • colitis (induction of or exacerbation of) • Crohn’s disease (induction of or exacerbation of) • depression • diarrhoea • dizziness • drowsiness • fluid retention (rarely precipitating congestive heart failure) • gastro-intestinal bleeding • gastro-intestinal discomfort • gastro-intestinal disturbances • gastro-intestinal ulceration • haematuria • headache • hearing disturbances • hypersensitivity reactions • insomnia • nausea • nervousness • photosensitivity • raised blood pressure • rashes • renal failure (especially in patients with pre-existing renal impairment) • tinnitus • vertigo

- **Frequency not known** Angioedema • blood disorders • bronchospasm • colitis (induction of or exacerbation of) • Crohn’s disease (induction of or exacerbation of) • depression • diarrhoea • dizziness • drowsiness • fluid retention (rarely precipitating congestive heart failure) • gastro-intestinal bleeding • gastro-intestinal discomfort • gastro-intestinal disturbances • gastro-intestinal ulceration • haematuria • headache • hearing disturbances • hypersensitivity reactions • insomnia • nausea • nervousness • photosensitivity • raised blood pressure • rashes • renal failure (especially in patients with pre-existing renal impairment) • tinnitus • vertigo

**SIDE-EFFECTS, FURTHER INFORMATION**

- **Serious side-effects** For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 915.

- **ALLERGY AND CROSS-SENSITIVITY** Contraindicated in patients with a history of hypersensitivity to aspirin or
any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

- **CONCEPTION AND CONTRACEPTION** Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

- **PREGNANCY** Most manufacturers advise avoiding the use of NSAIDs during pregnancy or avoiding them unless the potential benefit outweighs the risk. NSAIDs should be avoided during the third trimester because use is associated with a risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn. In addition, the onset of labour may be delayed and its duration may be increased.

- **BREAST FEEDING** Use with caution during breast-feeding. Manufacturer advises avoid.

- **HEPATIC IMPAIRMENT** Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

- **RENAL IMPAIRMENT** Avoid if possible or use with caution. The lowest effective dose should be used for the shortest possible duration. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

- **MONITORING REQUIREMENTS** During prolonged therapy ophthalmic and blood examinations particularly advisable.

- **PATIENT AND CARER ADVICE** Dizziness may affect performance of skilled tasks (e.g. driving).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Capsule**

  **CAUTIONARY AND ADVISORY LABELS**
  
  ▶ **Emflex** (Merck Serono Ltd)
  
  Acemetacin 60 mg Emflex 60mg capsules £28.20

**Pain and inflammation in musculoskeletal disorders**

918 Pain and inflammation in musculoskeletal disorders

**Celecoxib**

**INDICATIONS AND DOSE**

**Pain and inflammation in osteoarthritis**

- **BY MOUTH**
  
  ▶ Adult: 200 mg daily in 1–2 divided doses, then increased if necessary up to 200 mg twice daily, discontinue if no improvement after 2 weeks on maximum dose

**Pain and inflammation in rheumatoid arthritis**

- **BY MOUTH**
  
  ▶ Adult: 100 mg twice daily, then increased if necessary to 200 mg twice daily, discontinue if no improvement after 2 weeks on maximum dose

**Ankylosing spondylitis**

- **BY MOUTH**
  
  ▶ Adult: 200 mg daily in 1–2 divided doses, then increased if necessary up to 400 mg daily in 1–2 divided doses, discontinue if no improvement after 2 weeks on maximum dose

**CONTRA-INDICATIONS** Active gastro-intestinal bleeding - active gastro-intestinal ulceration - cerebrovascular disease - inflammatory bowel disease - ischaemic heart disease - mild to severe heart failure - peripheral arterial disease

**CAUTIONS** Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - elderly (risk of serious side-effects and fatalities) - history of cardiac failure - hypertension - left ventricular dysfunction - oedema - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated)

**INTERACTIONS** Appendix 1 (NSAIDs).

**SIDE-EFFECTS**

- **Common or very common** Dyspnoea - influenza-like symptoms

- **Uncommon** Cerebral infarction - fatigue - muscle cramps - palpitation - pain - paraesthesia - stomatitis

- **Rare** Alopecia - alveolitis - aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) - hepatic damage - interstitial fibrosis associated with NSAIDs can lead to renal failure - pancreatitis - papillary necrosis associated with NSAIDs can lead to renal failure - pulmonary eosinophilia - Stevens-Johnson syndrome - taste disturbance - toxic epidermal necrolysis - visual disturbances

- **Very rare** Seizures

- **Frequency not known** Angioedema - blood disorders - bronchospasm - chest pain - colitis (induction of or exacerbation of) - Crohn’s disease (induction of or exacerbation of) - depression - diarrhoea - dizziness - drowsiness - fluid retention (rarely precipitating congestive heart failure) - gastro-intestinal bleeding - gastro-intestinal discomfort - gastro-intestinal disturbances - gastro-intestinal ulceration - haematuria - headache - hearing disturbances - hypersensitivity reactions - insomnia - nausea - nervousness - photosensitivity - raised blood pressure - rashes - renal failure (especially in patients with pre-existing renal impairment) - tinnitus - vertigo

**SIDE-EFFECTS, FURTHER INFORMATION**

Serious side-effects For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 915.

**ALLERGY AND CROSS-SENSITIVITY** Contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID. Contraindicated in patients with sulphonamide sensitivity.

**CONCEPTION AND CONTRACEPTION** Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

**PREGNANCY** Avoid (teratogenic in animal studies).

**BREAST FEEDING** Avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT** Halve initial dose in moderate impairment. Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

**RENAL IMPAIRMENT** Avoid if possible or use with caution. The lowest effective dose should be used for the shortest possible duration. Avoid if eGFR less than 30 mL/minute/1.73 m². In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

**MONITORING REQUIREMENTS** Monitor blood pressure before and during treatment.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Capsule**

  ▶ **CELECOXIB** (Non-proprietary)
  
  Celecoxib 100 mg Celecoxib 100mg capsules £21.55 DT price £4.20
Dexibuprofen

**INDICATIONS AND DOSE**

<table>
<thead>
<tr>
<th>Pain and inflammation associated with osteoarthritis and other musculoskeletal disorders</th>
<th>Mild to moderate pain and inflammation including dental pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BY MOUTH</strong></td>
<td></td>
</tr>
<tr>
<td>Adult: 600–900 mg daily in up to 3 divided doses; increased if necessary up to 1.2 g daily (max. per dose 400 mg)</td>
<td>Mild to moderate pain and inflammation in dysmenorrhoea</td>
</tr>
<tr>
<td><strong>CONTRA-INDICATIONS</strong></td>
<td>Active gastro-intestinal bleeding</td>
</tr>
<tr>
<td><strong>CAUTIONS</strong></td>
<td>Allergic disorders</td>
</tr>
<tr>
<td><strong>INTERACTIONS</strong></td>
<td>Appendix 1 (NSAIDs).</td>
</tr>
<tr>
<td><strong>SIDE-EFFECTS</strong></td>
<td>Rare</td>
</tr>
<tr>
<td><strong>SIDE-EFFECTS, FURTHER INFORMATION</strong></td>
<td>Serious Side-effects</td>
</tr>
<tr>
<td><strong>ALLERGY AND CROSS-SENSITIVITY</strong></td>
<td>Contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks</td>
</tr>
</tbody>
</table>

Dexketoprofen

**INDICATIONS AND DOSE**

<table>
<thead>
<tr>
<th>Short-term treatment of mild to moderate pain including dysmenorrhoea</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BY MOUTH</strong></td>
</tr>
<tr>
<td>Adult: 12.5 mg every 4–6 hours, alternatively 25 mg every 8 hours, initial maximum daily dose of 50 mg to be given in elderly; maximum 75 mg per day</td>
</tr>
<tr>
<td><strong>CONTRA-INDICATIONS</strong></td>
</tr>
<tr>
<td><strong>CAUTIONS</strong></td>
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<tr>
<td><strong>INTERACTIONS</strong></td>
</tr>
<tr>
<td><strong>SIDE-EFFECTS</strong></td>
</tr>
</tbody>
</table>

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**Conception and Contraception**

Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

**Pregnancy**

Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

**Breastfeeding**

Use with caution during breast-feeding. Present in milk—but risk to infant minimal.

**Hepatic Impairment**

Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

**Renal Impairment**

Avoid if possible or use with caution. Reduce initial dose. The lowest effective dose should be used for the shortest possible duration. Avoid if eGFR less than 30 mL/minute/1.73 m². In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

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**Medicinal Forms**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

CAUTIONARY AND ADVISORY LABELS 21

- **Seracit** (Thornton & Ross Ltd) 
  - **Dexibuprofen 300 mg** Seracit 300mg tablets | 60 tablet | £3.47 DT price | £3.47  
  - **Dexibuprofen 400 mg** Seracit 400mg tablets | 60 tablet | £3.97 DT price | £3.97  

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**Florfenicol**

**INDICATIONS AND DOSE**

- CAUTIONARY AND ADVISORY LABELS 21

**SIDE-EFFECTS**

- Rare | Alveolitis | Aseptic meningitis | Patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible | Hepatic damage | Interstitial fibrosis associated with NSAIDs can lead to renal failure | Pancreatitis | Papillary necrosis |
associated with NSAIDs can lead to renal failure • pulmonary eosinophilia • Stevens-Johnson syndrome • toxic epidermal necrolysis • visual disturbances

- **Frequency not known** Angioedema • blood disorders • bronchospasm • colitis (induction of or exacerbation of) • Crohn’s disease (induction of or exacerbation of) • depression • diarrhoea • dizziness • drowsiness • fluid retention (rarely precipitating congestive heart failure) • gastro-intestinal bleeding • gastro-intestinal discomfort • gastro-intestinal disturbances • gastro-intestinal ulceration • haematuria • headache • hearing disturbances • hypersensitivity reactions • insomnia • nausea • nervousness • photosensitivity • raised blood pressure • rashes • renal failure (especially in patients with pre-existing renal impairment) • tinnitus • vertigo

**SIDE-EFFECTS, FURTHER INFORMATION**

**Serious side-effects** For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 915.

- **ALLERGY AND CROSS-SENSITIVITY** Contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

- **CONCEPTION AND CONCEPTION** Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

- **PREGNANCY** Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

- **BREAST FEEDING** Use with caution during breast-feeding. Manufacturer advises avoid—no information available.

- **HEPATIC IMPAIRMENT** Reduce initial dose to max. 50 mg daily in mild to moderate impairment. Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

- **RENAL IMPAIRMENT** Avoid if possible or use with caution. Avoid in moderate to severe impairment. Reduce initial dose to 50 mg daily. The lowest effective dose should be used for the shortest possible duration. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **CAUTIONARY AND ADVISORY LABELS** 22
- **Keral (A Menarini Farmaceutica Internazionale SRL)**
  - Diclofenac (as Diclofenac trometamol) 25 mg Keral
  - 25mg tablets | 20 tablet (PDP) £3.67 | 50 tablet (PDP) £9.18 DT price = £9.18

**Diclofenac potassium**

**INDICATIONS AND DOSE**

**Pain and inflammation in rheumatic disease and other musculoskeletal disorders**

- **BY MOUTH**
  - Child 14-17 years: 75–100 mg daily in 2–3 divided doses
  - Adult: 75–150 mg daily in 2–3 divided doses

**Acute gout**

- **BY MOUTH**
  - Adult: 75–150 mg daily in 2–3 divided doses

**Postoperative pain**

- **BY MOUTH**
  - Child 9-13 years (body-weight 35 kg and above): Up to 2 mg/kg daily in 3 divided doses; maximum 100 mg per day
  - Child 14-17 years: 75–100 mg daily in 2–3 divided doses
  - Adult: 75–150 mg daily in 2–3 divided doses

**Migraine**

- **BY MOUTH**
  - Adult: 50 mg, to be given at onset of migraine, then 50 mg after 2 hours if required, then 50 mg after 4–6 hours; maximum 200 mg per day

**Fever in ear, nose, or throat infection**

- **BY MOUTH**
  - Child 9-17 years (body-weight 35 kg and above): Up to 2 mg/kg daily in 3 divided doses; maximum 100 mg per day

**UNLICENSED USE** Voltarol® Rapid not licensed for use in children under 14 years or in fever.

**CONTRA-INDICATIONS** Active gastro-intestinal bleeding • active gastro-intestinal ulceration • cerebrovascular disease • history of gastro-intestinal bleeding related to previous NSAID therapy • history of gastro-intestinal perforation related to previous NSAID therapy • history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) • history of recurrent gastro-intestinal ulceration (two or more distinct episodes) • ischaemic heart disease • mild to severe heart failure • peripheral arterial disease

**CAUTIONS**

**GENERAL CAUTIONS** Allergic disorders • cardiac impairment (NSAIDs may impair renal function) • coagulation defects • connective-tissue disorders • Crohn’s disease (may be exacerbated) • history of cardiac failure • hypertension • left ventricular dysfunction • oedema • risk factors for cardiovascular events • ulcerative colitis (may be exacerbated)

**SPECIFIC CAUTIONS** Elderly (risk of serious side-effects and fatalities) (in adults)

**INTERACTIONS** → Appendix 1 (NSAIDs).

**SIDE-EFFECTS**

- **Rare** Alveolitis • aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) • hepatic damage • interstitial fibrosis associated with NSAIDs can lead to renal failure • pancreatitis • papillary necrosis associated with NSAIDs can lead to renal failure • pulmonary eosinophilia • Stevens-Johnson syndrome • toxic epidermal necrolysis • visual disturbances

**Frequency not known** Angioedema • blood disorders • bronchospasm • colitis (induction of or exacerbation of) • Crohn’s disease (induction of or exacerbation of) • depression • diarrhoea • dizziness • drowsiness • fluid retention (rarely precipitating congestive heart failure) • gastro-intestinal bleeding • gastro-intestinal discomfort • gastro-intestinal disturbances • gastro-intestinal ulceration • haematuria • headache • hearing disturbances • hypersensitivity reactions • insomnia • nausea • nervousness • photosensitivity • raised blood pressure • rashes • renal failure (especially in patients with pre-existing renal impairment) • tinnitus • vertigo

**ALLERGY AND CROSS-SENSITIVITY** Contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.
CONCEPTION AND CONTRACEPTION Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

PREGNANCY Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

BREAST FEEDING Use with caution during breast-feeding. Amount in milk too small to be harmful.

HEPATIC IMPAIRMENT Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

RENAI IMPAIRMENT Avoid if possible or use with caution. Avoid in severe impairment. The lowest effective dose should be used for the shortest possible duration. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

PATIENT AND CARER ADVICE Medicines for Children leaflet: Diclofenac for pain and inflammation www.medicinesforchildren.org.uk/diclofenac-for-pain-and-inflammation

MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

CAUTIONARY AND ADVISORY LABELS 21

DICLOFENAC POTASSIUM (Non-proprietary)

Diclofenac potassium 25 mg Diclofenac potassium 25mg tablets | 28 tablet | £3.23

Diclofenac potassium 50 mg Diclofenac potassium 50mg tablets | 28 tablet | £6.18

Voltarol Rapid (Novartis Pharmaceuticals UK Ltd)

Diclofenac potassium 25 mg Voltarol Rapid 25mg tablets | 30 tablet | £3.46 DT price = £3.46

Diclofenac potassium 50 mg Voltarol Rapid 50mg tablets | 30 tablet | £6.62 DT price = £6.62

Diclofenac sodium

INDICATIONS AND DOSE

Pain and inflammation in musculoskeletal disorders | Acute gout

BY MOUTH

Adult: 75–150 mg daily in 2–3 divided doses

BY RECTUM

Adult: 75–150 mg daily in divided doses

Pain and inflammation in rheumatic disease including juvenile idiopathic arthritis

BY MOUTH

Adult: 75–150 mg daily in 2–3 divided doses

BY RECTUM

Adult: 75–150 mg daily in divided doses

Postoperative pain

BY MOUTH

Adult: 75–150 mg daily in 2–3 divided doses

BY RECTUM

Adult: 75–150 mg daily in divided doses

VOLTAROL® RETARD

Pain and inflammation in rheumatic disease (including juvenile idiopathic arthritis) and other musculoskeletal disorders | Acute gout | Postoperative pain

BY MOUTH

Adult: 1 tablet once daily

VOLTAROL® 75MG SR TABLETS

Pain and inflammation in rheumatic disease (including juvenile idiopathic arthritis) and other musculoskeletal disorders | Acute gout | Postoperative pain

BY MOUTH

Adult: 1 tablet 1–2 times a day

DICLOMAX SR®

Pain and inflammation in rheumatic disease (including juvenile idiopathic arthritis) and other musculoskeletal disorders | Acute gout | Postoperative pain

BY MOUTH

Adult: 1 capsule 1–2 times a day, alternatively 2 capsules once daily

MOTIFENE®

Pain and inflammation in rheumatic disease (including juvenile idiopathic arthritis) and other musculoskeletal disorders | Acute gout | Postoperative pain

BY MOUTH

Adult: 1 capsule once daily

DYLOJECT®

Acute exacerbations of pain and postoperative pain

BY DEEP INTRAMUSCULAR INJECTION

Adult: 75 mg once daily for maximum 2 days, to be administered into the gluteal muscle

Acute exacerbations of pain and postoperative pain (severe cases)

BY DEEP INTRAMUSCULAR INJECTION

Adult: 75 mg twice daily for maximum 2 days, to be administered into the gluteal muscle

Ureteric colic

BY DEEP INTRAMUSCULAR INJECTION

Adult: 75 mg, then 75 mg after 30 minutes if required

Acute postoperative pain (in supervised settings)

BY INTRAVENOUS INJECTION

Adult: 75 mg every 4–6 hours if required for maximum 2 days; maximum 150 mg per day

Prevention of postoperative pain

BY INTRAVENOUS INJECTION

Adult: 25–50 mg, to be given after surgery; further doses given after 4–6 hours if necessary; maximum 150 mg in 24 hours for 2 days

VOLTAROL® SOLUTION FOR INJECTION

Postoperative pain

BY DEEP INTRAMUSCULAR INJECTION

Adult: 75 mg 1–2 times a day for maximum 2 days, twice daily administration in severe cases, to be injected into the gluteal muscle

Acute exacerbations of pain

BY DEEP INTRAMUSCULAR INJECTION

Adult: 75 mg 1–2 times a day for maximum 2 days, twice daily administration in severe cases, to be injected into the gluteal muscle

Ureteric colic

BY DEEP INTRAMUSCULAR INJECTION

Adult: 75 mg, then 75 mg after 30 minutes if required

Acute postoperative pain (in hospital setting)

BY INTRAVENOUS INFUSION

Adult: 75 mg, then 75 mg after 4–6 hours if required for maximum 2 days; maximum 150 mg per day.

continued
Prevention of postoperative pain (in hospital setting)

**BY INTRAVENOUS INFUSION**

- **Adult:** Initially 25–50 mg, to be given after surgery over 15–60 minutes, then 5 mg/hour for maximum 2 days; maximum 150 mg per day

**VOLTAROL® EMULGEL**

Relief of pain in musculoskeletal conditions | Adjunctive treatment in knee or hand osteoarthritis

**TO THE SKIN**

- **Adult:** Apply 3–4 times a day, therapy should be reviewed after 14 days (or after 28 days for osteoarthritis)

**SOLARAZE®**

Actinic keratosis

**TO THE SKIN**

- **Adult:** Apply twice daily for 60–90 days, to be applied thinly; maximum 8 g per day

**VOLTAROL® GEL PATCH**

Ankle sprain

**TO THE SKIN**

- **Adult:** Apply 1 patch daily for up to 3 days

Epicondylitis

**TO THE SKIN**

- **Adult:** Apply 1 patch twice daily for up to 14 days

**CONTRA-INDICATIONS**

- **With systemic use** Active gastro-intestinal bleeding, active gastro-intestinal ulceration, avoid suppositories in proctitis, cerebrovascular disease, history of gastro-intestinal bleeding related to previous NSAID therapy, history of gastro-intestinal perforation related to previous NSAID therapy, history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes), history of recurrent gastro-intestinal ulceration (two or more distinct episodes), ischaemic heart disease, mild to severe heart failure, peripheral arterial disease

- **With intravenous use** Dehydration, history of asthma, history of confirmed or suspected cerebrovascular bleeding, history of haemorrhagic diathesis, hypovolaemia, operations with high risk of haemorrhage

**CAUTIONS**

- **With systemic use** Allergic disorders, cardiac impairment (NSAIDs may impair renal function), coagulation defects, connective-tissue disorders, Crohn’s disease (may be exacerbated), elderly (risk of serious side-effects and fatalities), history of cardiac failure, hypertension, left ventricular dysfunction, oedema, risk factors for cardiovascular events, ulcerative colitis (may be exacerbated)

- **With topical use** Avoid contact with eyes, avoid contact with inflamed or broken skin, avoid contact with mucous membranes, not for use with occlusive dressings, topical application of large amounts can result in systemic effects, including hypersensitivity and asthma (renal disease has also been reported)

**INTERACTIONS**

- **With intravenous use** Contra-indicated in concomitant NSAID use. Contra-indicated in concomitant anticoagulant use (including low-dose heparins).

**SIDE-EFFECTS**

- **Rare**

  - **With systemic use** Alveolitis, aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible), hepatic damage, interstitial fibrosis associated with NSAIDs can lead to renal failure, pancreatitis, papillary necrosis associated with NSAIDs can lead to renal failure, pulmonary eosinophilia, Stevens-Johnson syndrome, toxic epidermal necrolysis, visual disturbances

  - **Frequency not known**

    - With systemic use Angioedema, blood disorders, bronchospasm, colitis (induction of or exacerbation of), Crohn’s disease (induction of or exacerbation of), depression, diarrhoea, dizziness, drowsiness, fluid retention (rarely precipitating congestive heart failure), gastro-intestinal bleeding, gastro-intestinal discomfort, gastro-intestinal disturbances, gastro-intestinal ulceration, haematuria, headache, hearing disturbances, hypersensitivity reactions, insomnia, nervousness, photosensitivity, raised blood pressure, rashes, renal failure (especially in patients with pre-existing renal impairment), tinnitus, vertigo

    - With parenteral use Injection site reactions

    - With rectal use Suppositories may cause rectal irritation

    - With topical use Paraesthesia, photosensitivity, rash (discontinue use if develops)

**SIDE-EFFECTS, FURTHER INFORMATION**

- Serious side-effects For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 915.

- With topical use Topical application of large amounts can result in systemic effects, including hypersensitivity and asthma (renal disease has also been reported)

**ALLERGY AND CROSS-SENSITIVITY**

- Contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

**CONCEPTION AND CONTRACEPTION**

- With systemic use Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

**PREGNANCY**

- With systemic use Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in uterus and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

- With topical use Patient packs for topical preparations carry a warning to avoid during pregnancy

**BREAST FEEDING**

- With systemic use Use with caution during breast-feeding. Amount in milk too small to be harmful.

**HEPATIC IMPAIRMENT**

- With systemic use Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

**RENAL IMPAIRMENT**

- With systemic use Avoid if possible or use with caution. Avoid in severe impairment. The lowest effective dose should be used for the shortest possible duration. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

- With intravenous use Avoid intravenous use if serum creatinine greater than 160 micromol/litre. Contra-indicated in moderate or severe renal impairment.

**DIRECTIONS FOR ADMINISTRATION**

- For **intravenous infusion** (Voltarol®), give continuously or intermittently in Glucose 5% or Sodium chloride 0.9%. Dilute 75 mg with 100–500 mL infusion fluid (previously buffered with 0.5 mL sodium bicarbonate 8.4% solution or with 1 mL sodium bicarbonate 4.2% solution). For intermittent infusion give 25–50 mg over 15–60 minutes or 75 mg over 30–120 minutes. For continuous infusion give at a rate of
5 mg/hour. For topical preparations, apply with a gentle massage only.

- **PRESCRIBING AND DISPENSING INFORMATION** Voltarol® dispensible tablets are more suitable for short-term use in acute conditions for which treatment required for no more than 3 months (no information on use beyond 3 months). Caution—topical preparations not generally suitable for children.

- **PATIENT AND CARER ADVICE** For topical preparations, patients and their carers should be advised to wash hands immediately after use. Photosensitivity: Patients should be advised against excessive exposure to sunlight of area treated in order to avoid possibility of photosensitivity.

- **PROFESSION SPECIFIC INFORMATION**
  - Dental practitioners’ formulary: Diclofenac Sodium Tablets may be prescribed.
  - **NATIONAL FUNDING/ACCESS DECISIONS**
  - **Scottish Medicines Consortium (SMC) Decisions** The Scottish Medicines Consortium has advised (February 2008) that Dylloject® is accepted for restricted use within NHS Scotland for the treatment or prevention of postoperative pain by intravenous injection in supervised healthcare settings.

- **EXCEPTIONS TO LEGAL CATEGORY** Various pack sizes of gel preparations may be available on sale to the public.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: dispensible tablet, oral suspension, oral solution.

- **Dispersible tablet** CAUTIONARY AND ADVISORY LABELS 13, 21
  - Voltarol® (Novartis Pharmaceuticals UK Ltd)
  - Diclofenac sodium 50 mg: Voltarol® 50mg dispensible tablets (sugar-free) | 21 tablet | P 6.19 DT price = £6.19
  - **Modified-release tablet** CAUTIONARY AND ADVISORY LABELS 21, 25
  - **Diclofenac Sodium (Non-proprietary)**
    - Diclofenac sodium 75 mg: Diclofenac sodium 75mg modified-release tablets | 28 tablet | P 6.46 | 56 tablet | P 9.97 no price available DT price = £12.92
    - Diclofenac sodium 100 mg: Diclofenac sodium 100mg modified-release tablets | 28 tablet | P 9.47 DT price = £9.47
    - Voltarol® (Novartis Pharmaceuticals UK Ltd)
    - Diclofenac sodium 100 mg: Voltarol® Retard 100mg tablets | 28 tablet | P 9.47 DT price = £9.47
    - Voltarol® SR (Novartis Pharmaceuticals UK Ltd)
    - Diclofenac sodium 75 mg: Voltarol® 75mg SR tablets | 28 tablet | P 6.46 | 56 tablet | P 9.97 no price available DT price = £12.92
    - Brands may include Dicloflex; Dicloflex SR; Econac SR; Econac XL; Enstar XL; Fenactol Retard; Fenactol SR; Flamrase SR; Volsaid Retard

- **Gastro-resistant tablet** CAUTIONARY AND ADVISORY LABELS 5, 25
  - **Diclofenac Sodium (Non-proprietary)**
    - Diclofenac sodium 25 mg: Diclofenac sodium 25mg gastro-resistant tablets | 28 tablet | P 1.78 DT price = £1.93 | 84 tablet | P 5.89 DT price = £6.93
    - Diclofenac sodium 50 mg: Diclofenac sodium 50mg gastro-resistant tablets | 28 tablet | P 1.52 DT price = £1.63 | 84 tablet | P 5.31 DT price = £6.32
    - Brands may include Dicloflex; Dicloflex SR; Dicloflex; Dicloflex SR; Econac SR; Econac XL; Enstar XL; Fenactol Retard; Fenactol SR; Flamrase SR; Volsaid Retard

- **Modified-release capsule** CAUTIONARY AND ADVISORY LABELS 21, 25
  - **EXCIPIENTS:** May contain Propylene glycol
    - Diclofenac sodium 50 mg; Diclofenac sodium 75mg modified-release capsules | 56 capsule | P 6.09 DT price = £6.69
    - Diclofenac sodium 100 mg: Diclofenac sodium 100mg modified-release capsules | 28 capsule | P 8.09 no price available DT price = £9.97
    - Brands may include Dicloxom Retard; Dicloxom SR; Motifene; Rhumalgin XL

- **Solution for injection** EXCIPIENTS: May contain Benzyl alcohol, propylene glycol
  - **Diclofenac sodium 37.5 mg per 1 ml** Diclofenac sodium 75mg/ml solution for injection vials | 10 vial | P 0.60 no price available
  - **Voltarol®** (Novartis Pharmaceuticals UK Ltd)
  - Diclofenac sodium 25 mg per 1 ml: Voltarol® 75mg/ml solution for injection ampoules | 10 ampoule | P 8.26 DT price = £8.26

- **Suppository**
  - **Diclofenac sodium 100 mg (Non-proprietary)**
    - Diclofenac sodium 100 mg suppositories | 10 suppository | P 7.75 DT price = £3.03
    - Voltarol® (Novartis Pharmaceuticals UK Ltd)
    - Diclofenac sodium 12.5 mg: Voltarol® 12.5mg suppositories | 10 suppository | P 0.58 DT price = £0.58
    - Diclofenac sodium 25 mg: Voltarol® 25mg suppositories | 10 suppository | P 1.03 DT price = £1.03
    - Diclofenac sodium 50 mg: Voltarol® 50mg suppositories | 10 suppository | P 1.70 DT price = £1.70
    - Brands may include Econac Gel

  - **Exemptions:** May contain benzyl alcohol, fragrances, propylene glycol
    - **Dyloject** (Therabel Pharma UK Ltd)
      - Diclofenac diethylammonium 23.2 mg per 1 gram | 100 gram | P 5.63 NHS indicative price = £5.93
    - **MISOFEN** (Novartis Consumer Health UK Ltd)
      - Diclofenac diethylammonium 11.6 mg per 1 gram | 100 gram | P 5.63 NHS indicative price = £5.93
    - **VOLTAROL 12 HOUR EMULGEL** (Novartis Consumer Health UK Ltd)
      - Diclofenac diethylammonium 23.2 mg per 1 gram | 30 gram | P 10.70 NHS indicative price = £10.70
    - **SOLARAZE 3%GEL** (Almirall Ltd)
      - Diclofenac sodium 30 mg per 1 gram | 50 gram | P 10.80 NHS indicative price = £10.80

- **Diclofenac sodium with misoprostol**
  - The properties listed below are those particular to the combination only. For the properties of the components please consider, diclofenac sodium p. 921, misoprostol p. 709.

  - **INDICATIONS AND DOSE**
    - **Misofen® 50/200**
      - Prophylaxis against NSAID-induced gastroduodenal ulceration in patients requiring diclofenac for rheumatoid arthritis or osteoarthritis
        - **By mouth**
          - Adult: 1 tablet 2–3 times a day, take with food
          - **Misofen® 75/200**
            - Prophylaxis against NSAID-induced gastroduodenal ulceration in patients requiring diclofenac for rheumatoid arthritis or osteoarthritis
              - **By mouth**
                - Adult: 1 tablet twice daily, take with food
                - **Arthrotec® 50/200**
                  - Prophylaxis against NSAID-induced gastroduodenal ulceration in patients requiring diclofenac for rheumatoid arthritis or osteoarthritis
                    - Adult: 1 tablet 2–3 times a day, take with food

  - **Diclofenac sodium retention**
    - The properties listed below are those particular to the combination only. For the properties of the components please consider, diclofenac sodium p. 921, misoprostol p. 709.

    - **INDICATIONS AND DOSE**
      - **Misofen® 50/200**
        - Prophylaxis against NSAID-induced gastroduodenal ulceration in patients requiring diclofenac for rheumatoid arthritis or osteoarthritis
          - **By mouth**
            - Adult: 1 tablet 2–3 times a day, take with food
          - **Misofen® 75/200**
            - Prophylaxis against NSAID-induced gastroduodenal ulceration in patients requiring diclofenac for rheumatoid arthritis or osteoarthritis
              - **By mouth**
                - Adult: 1 tablet twice daily, take with food
                - **Arthrotec® 50/200**
                  - Prophylaxis against NSAID-induced gastroduodenal ulceration in patients requiring diclofenac for rheumatoid arthritis or osteoarthritis
                    - Adult: 1 tablet 2–3 times a day, take with food
924 Pain and inflammation in musculoskeletal disorders

**ARTHROTEC® 75/200**

Prophylaxis against NSAID-induced gastroduodenal ulceration in patients requiring diclofenac for rheumatoid arthritis or osteoarthritis

**BY MOUTH**

- Adult: 1 tablet twice daily, take with food

- **UNLICENSED USE** The BNF recommends a higher starting dose of misoprostol for prophylaxis against NSAID-induced gastroduodenal ulceration than that provided by the combination preparations of diclofenac and misoprostol.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  **GASTRO-RESISTANT TABLET**

  **CAUTIONARY AND ADVISORY LABELS 21, 25**

  - **DICLOFENAC SODIUM WITH MISOPROSTOL (Non-proprietary)**
    - Diclofenac sodium 50 mg, Misoprostol 200 microgram
      - Diclofenac sodium 50mg gastro-resistant / Misoprostol 200microgram tablets | 60 tablet [POD] £11.14 DT price = £11.98
      - Diclofenac sodium 75 mg, Misoprostol 200 microgram
        - Diclofenac sodium 75mg gastro-resistant / Misoprostol 200microgram tablets | 60 tablet [POD] £15.83 DT price = £15.83
      - [Arthrotec](https://www.pfizer.com) (Pfizer Ltd)
    - Diclofenac sodium 50 mg, Misoprostol 200 microgram
      - Arthrotec 50 gastro-resistant tablets | 60 tablet [POD] £11.98 DT price = £11.98
      - Diclofenac sodium 75 mg, Misoprostol 200 microgram
        - Arthrotec 75 gastro-resistant tablets | 60 tablet [POD] £15.83 DT price = £15.83
    - Misoprostol (Morningside Healthcare Ltd)
      - Diclofenac sodium 50 mg, Misoprostol 200 microgram
        - Misoprostol 50mg/200microgram gastro-resistant tablets | 60 tablet [POD] £11.98 DT price = £11.98
      - Diclofenac sodium 75 mg, Misoprostol 200 microgram
        - Misoprostol 75mg/200microgram gastro-resistant tablets | 60 tablet [POD] £15.83 DT price = £15.83
    - [Brands may include Misidecen](https://www.misidecen.com)
Etoricoxib

**INDICATIONS AND DOSE**

**Pain and inflammation in osteoarthritis**

- **BY MOUTH**
  - Child 16-17 years: 30 mg once daily, then increased if necessary to 60 mg once daily
  - Adult: 30 mg once daily, then increased if necessary to 60 mg once daily

**Pain and inflammation in rheumatoid arthritis | Ankylosing spondylitis**

- **BY MOUTH**
  - Child 16-17 years: 90 mg once daily
  - Adult: 90 mg once daily
  - Acute gout
    - Child 16-17 years: 120 mg once daily for maximum 8 days
    - Adult: 120 mg once daily for maximum 8 days

**CONTRA-INDICATIONS** Active gastro-intestinal bleeding · active gastro-intestinal ulceration · cerebrovascular disease · inflammatory bowel disease · ischaemic heart disease · mild to severe heart failure · peripheral arterial disease · uncontrolled hypertension (persistently above 140/90 mmHg)

**CAUTIONS**

**GENERAL CAUTIONS** Allergic disorders · cardiac impairment (NSAIDs may impair renal function) · coagulation defects · connective-tissue disorders · Crohn’s disease (may be exacerbated) · dehydration · history of cardiac failure · hypertension · left ventricular dysfunction · oedema · risk factors for cardiovascular events · ulcerative colitis (may be exacerbated)

**SPECIFIC CAUTIONS** Elderly (risk of serious side-effects and fatalities)

**INTERACTIONS** → Appendix 1 (NSAIDs).

**SIDE-EFFECTS**

- **Common or very common** Ecchymosis · fatigue · influenza-like symptoms · palpitation
- **Uncommon** Anxiety · appetite change · arthralgia · atrial fibrillation · chest pain · cough · dry mouth · dyspnoea · electrolyte disturbance · epistaxis · flushing · mental acuity impaired · mouth ulcer · myalgia · paraesthesia · taste disturbance · transient ischaemic attack · weight change
- **Rare** Alveolitis · aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) · hepatic damage · interstitial fibrosis associated with NSAIDs can lead to renal failure · pancreatitis · papillary necrosis associated with NSAIDs can lead to renal failure · pulmonary eosinophilia · Stevens-Johnson syndrome · toxic epidermal necrolysis · visual disturbances
- **Very rare** Confusion · hallucinations
- **Frequency not known** Angioedema · blood disorders · bronchospasm · colitis (induction of or exacerbation of) · Crohn’s disease (induction of or exacerbation of) · depression · diarrhoea · dizziness · drowsiness · fluid retention (rarely precipitating congestive heart failure) · gastro-intestinal bleeding · gastro-intestinal discomfort · gastro-intestinal ulceration · haematuria · headache · hearing disturbances · hypersensitivity reactions · insomnia · nausea · nervousness · photosensitivity · raised blood pressure · rashes · renal failure (especially in patients with pre-existing renal impairment) · tinnitus · vertigo

**SIDE-EFFECTS, FURTHER INFORMATION**

**Serious side-effects** For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 915.

**ALLERGY AND CROSS-SENSITIVITY** Contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

**CONCEPTION AND CONTRACEPTION** Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

**PREGNANCY** Manufacturer advises avoid (teratogenic in animal studies). Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

**BREAST FEEDING** Use with caution during breast-feeding. Manufacturer advises avoid—present in milk in animal studies.

**HEPATIC IMPAIRMENT** Max. 60 mg daily in mild impairment. Max. 60 mg on alternate days or 30 mg once daily in moderate impairment. Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

**RENAL IMPAIRMENT** Avoid if possible or use with caution. The lowest effective dose should be used for the shortest possible duration. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

- With systemic use in adults Avoid if eGFR less than 30 mL/minute/1.73 m².
- With systemic use in children Avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m².

**MONITORING REQUIREMENTS** Monitor blood pressure before treatment, 2 weeks after initiation and periodically during treatment.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Arcoxia** (Grunenthal Ltd)
  - Etoricoxib 30 mg Arcoxia 30 mg tablets | 28 tablet pack £13.99 DT price = £13.99
  - Etoricoxib 60 mg Arcoxia 60 mg tablets | 28 tablet pack £20.11 DT price = £20.11
  - Etoricoxib 90 mg Arcoxia 90 mg tablets | 5 tablet pack £4.10 |
  - 28 tablet pack £22.96 DT price = £22.96
  - Etoricoxib 120 mg Arcoxia 120 mg tablets | 7 tablet pack £6.03 |
  - 28 tablet pack £24.11 DT price = £24.11

Felbinac

**DRUG ACTION** Felbinac is an active metabolite of the NSAID fenbufen.

**INDICATIONS AND DOSE**

**Relief of pain in musculoskeletal conditions | Treatment in knee or hand osteoarthritis (adjunct)**

TO THE SKIN

- Adult: Apply 2–4 times a day, therapy should be reviewed after 14 days; maximum 25 g per day

**CAUTIONS** Avoid contact with eyes · avoid contact with inflamed or broken skin · avoid contact with mucous membranes · not for use with occlusive dressings · topical application of large amounts can result in systemic effects, including hypersensitivity and asthma (renal disease has also been reported)
Fenoprofen

**INDICATIONS AND DOSE**

Pain and inflammation in rheumatic disease and other musculoskeletal disease | Mild to moderate pain
---|---
**BY MOUTH**
* Adult: 300–600 mg 3–4 times a day; maximum 3 g per day

**CONTRA-INDICATIONS**

Active gastro-intestinal bleeding · active gastro-intestinal ulceration · history of gastro-intestinal bleeding related to previous NSAID therapy · history of gastro-intestinal perforation related to previous NSAID therapy · history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) · history of recurrent gastro-intestinal ulceration (two or more distinct episodes) · severe heart failure

**CAUTIONS**

Allergic disorders · cardiac impairment (NSAIDs may impair renal function) · cerebrovascular disease · coagulation defects · connective-tissue disorders · Crohn’s disease (may be exacerbated) · elderly (risk of serious side-effects and fatalities) · heart failure · ischaemic heart disease · peripheral arterial disease · risk factors for cardiovascular events · ulcerative colitis (may be exacerbated) · uncontrolled hypertension

**SIDE-EFFECTS**

Rash (discontinue use if develops)

**SIDE-EFFECTS, FURTHER INFORMATION**

**Serious side-effects** For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 915.

**Active gastro-intestinal bleeding** Related to previous NSAID therapy · history of gastro-intestinal perforation related to previous NSAID therapy · history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) · history of recurrent gastro-intestinal ulceration (two or more distinct episodes) · severe heart failure

**MEDICINAL FORMS**

<table>
<thead>
<tr>
<th>Foam</th>
<th>CAUTIONARY AND ADVISORY LABELS 15</th>
<th>EXCIPIENTS: May contain Caposteryl alcohol (including cetyl and stearyl alcohol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Felbinac 31.7 mg per 1 gram</td>
<td>Traxam (AMCo)</td>
<td>DT price = £8.41 DT price = £8.41</td>
</tr>
<tr>
<td>Gel</td>
<td>Traxam (AMCo)</td>
<td>DT price = £8.03</td>
</tr>
<tr>
<td>Felbinac 30 mg per 1 gram</td>
<td>Traxam % gel</td>
<td>100 gram POM £8.03</td>
</tr>
</tbody>
</table>

**MALIGNANT TUMOURS**

Carcinoma of the prostate; concurrent administration may increase the risk of bleeding due to antiplatelet effects

**RENAL IMPAIRMENT**

Deterioration in renal function has also been reported.

**SIDE-EFFECTS AND CROSS-SENSITIVITY**

**Rare** Allergic disorders · cardio-pulmonary disorders · haematological disorders · hepatic disorders · nervous system disorders · renal disorders · skin disorders · toxic epidermal necrolysis · uncontrolled hypertension

**SIDE-EFFECTS**

**Frequent** Rash (discontinue use if develops)

**BREAST FEEDING**

Use with caution during breast-feeding.

**PREPARING AND DISPENSING INFORMATION**

Caution—topical preparations not generally suitable for children.

**PATIENT AND CARER ADVICE**

For topical preparations patients and carers should be advised to wash hands immediately after use. Photosensitivity Patients should be advised against excessive exposure to sunlight of area treated in order to avoid possibility of photosensitivity.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Foam**

<table>
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</table>

**PANCREATITIS**

**Frequent** Pancreatitis

**BREAST FEEDING**

Use with caution during breast-feeding. Amount too small to be harmful.

**SIDE-EFFECTS**

**RENAIPMENT**

Avoid if possible or use with caution.

**SIDE-EFFECTS, FURTHER INFORMATION**

**Serious side-effects** For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 915.

**ALLERGY AND CROSS-SENSITIVITY**

Contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

**PREGNANCY**

Use with caution during breast-feeding.

**PREPARING AND DISPENSING INFORMATION**

Caution—topical preparations not generally suitable for children.

**PATIENT AND CARER ADVICE**

For topical preparations patients and carers should be advised to wash hands immediately after use. Photosensitivity Patients should be advised against excessive exposure to sunlight of area treated in order to avoid possibility of photosensitivity.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Foam**

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**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

<table>
<thead>
<tr>
<th>CAUTIONARY AND ADVISORY LABELS 21</th>
<th>FENOPRON (Typharm Ltd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FENOPRON (as Fenoprofen calcium) 300 mg</td>
<td>Fenoprofen 300 tablets</td>
</tr>
</tbody>
</table>
Flurbiprofen

INDICATIONS AND DOSE

Pain and inflammation in rheumatic disease and other musculoskeletal disorders | Migraine | Postoperative analgesia | Mild to moderate pain

BY MOUTH
- Child 12-17 years: 150–200 mg daily in 2–4 divided doses, then increased to 300 mg daily, dose to be increased only in acute conditions
- Adult: 150–200 mg daily in 2–4 divided doses, then increased to 300 mg daily, dose to be increased only in acute conditions

Dysmenorrhoea

BY MOUTH
- Child 12-17 years: Initially 100 mg, then 50–100 mg every 4–6 hours; maximum 300 mg per day
- Adult: Initially 100 mg, then 50–100 mg every 4–6 hours; maximum 300 mg per day

CONTRA-INDICATIONS
Active gastro-intestinal bleeding
- Active gastro-intestinal ulceration
- History of gastro-intestinal bleeding related to previous NSAID therapy
- History of gastro-intestinal perforation related to previous NSAID therapy
- History of recurrent gastro-intestinal haemorrhage (two or more distinct episodes)
- History of recurrent gastro-intestinal ulceration (two or more distinct episodes)
- Severe heart failure
- Ischaemic heart disease
- Peripheral arterial disease
- Risk factors for cardiovascular events
- Ulcerative colitis (may be exacerbated)
- Uncontrolled hypertension

INTERACTIONS
- Appendix 1 (NSAIDs).

SIDE-EFFECTS
- Common or very common
  - Stomatitis
- Uncommon
  - Confusion
  - Fatigue
  - Hallucinations
  - Parasomnia
- Rare
  - Alveolitis
  - Aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible)
  - Hepatic damage
  - Intestinal fibrosis associated with NSAIDs can lead to renal failure
  - Pancreatitis
  - Papillary necrosis
  - Pulmonary hypertension of the newborn
  - Stevens-Johnson syndrome
  - Stevens-Johnson syndrome in cases of severe heart failure
  - Toxic epidermal necrolysis
  - Vasculitis
  - Vasoconstriction
- Frequency not known
  - Angioedema
  - Blood disorders
  - Bronchospasm
  - Colitis (induction of or exacerbation of)
  - Cough
  - Depression
  - Dizziness
  - Drowsiness
  - Fluid retention (rarely precipitating congestive heart failure)
  - Gastro-intestinal bleeding
  - Gastro-intestinal discomfort
  - Gastro-intestinal disturbances
  - Haematuria
  - Headache
  - Hearing disturbances
  - Hypersensitivity reactions
  - Insomnia
  - Nausea
  - Nervousness
  - Photosensitivity
  - Raised blood pressure
  - Rash
  - Renal failure (especially in patients with pre-existing renal impairment)
  - Tinnitus
  - Vertigo

SIDE-EFFECTS, FURTHER INFORMATION

Serious side-effects
For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 915.

ALLERGY AND CROSS-SENSITIVITY

Contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

CONCEPTION AND CONTRACEPTION

Caution—Long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

PREGNANCY
Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

CREST FEEDING
Use with caution during breast-feeding.
Small amount present in milk—manufacturer advises avoid.

HEPATIC IMPAIRMENT
Use with caution; there is an increased risk of gastrointestinal bleeding and fluid retention. Avoid in severe liver disease.

RENAL IMPAIRMENT
Avoid if possible or use with caution.
The lowest effective dose should be used for the shortest possible duration. Avoid in severe impairment. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Tablet

CAUTIONARY AND ADVISORY LABELS 21
- FLURBIPROFEN (Non-proprietary)

Flurbiprofen 50 mg Flurbiprofen 50mg tablets | 100 tablet £21.30 DT price + £21.30
Flurbiprofen 100 mg Flurbiprofen 100mg tablets | 100 tablet £38.10 DT price + £38.10

Ibuprofen

INDICATIONS AND DOSE

Pain and inflammation in rheumatic disease and other musculoskeletal disorders | Migraine | Postoperative analgesia | Mild to moderate pain

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
- Adult: Initially 300–400 mg 3–4 times a day; increased if necessary up to 600 mg 4 times a day; maintenance 200–400 mg 3 times a day, may be adequate

BY MOUTH USING MODIFIED-RELEASE MEDICINES
- Adult: 1.6 g once daily, dose to be taken in the early evening, increased if necessary to 2.4 g daily in 2 divided doses, dose to be increased only in severe cases

Mild to moderate pain | Pain and inflammation of soft-tissue injuries | Pyrexia with discomfort

INITIALLY BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
- Child 3-5 months: 50 mg 3 times a day, maximum daily dose to be given in 3–4 divided doses; maximum 30 mg/kg per day
- Child 6-11 months: 50 mg 3–4 times a day, maximum daily dose to be given in 3–4 divided doses; maximum 30 mg/kg per day
- Child 1-3 years: 100 mg 3 times a day, maximum daily dose to be given in 3–4 divided doses; maximum 30 mg/kg per day
- Child 4-6 years: 150 mg 3 times a day, maximum daily dose to be given in 3–4 divided doses; maximum 30 mg/kg per day
- Child 7-9 years: 200 mg 3 times a day, maximum daily dose to be given in 3–4 divided doses; maximum 30 mg/kg per day; maximum 2.4 g per day
- Child 10-11 years: 300 mg 3 times a day, maximum daily dose to be given in 3–4 divided doses; maximum 30 mg/kg per day; maximum 2.4 g per day

continued →
Pain and inflammation in musculoskeletal disorders

- Child 12-17 years: Initially 300–400 mg 3–4 times a day; (by mouth) increased if necessary up to 600 mg 4 times a day; (by mouth) maintenance 200–400 mg 3 times a day, may be adequate

**Pain and inflammation**

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**
- Child 12-17 years: 1.6 g once daily, dose preferably taken in the early evening, increased to 2.4 g daily in 2 divided doses, dose to be increased only in severe cases

**Pain and inflammation in rheumatic disease including juvenile idiopathic arthritis**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
- Child 3-months-17 years: 30–40 mg/kg daily in 3–4 divided doses; maximum 2.4 g per day

**Pain and inflammation in systemic juvenile idiopathic arthritis**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**
- Child 3-months-17 years: Up to 60 mg/kg daily in 4–6 divided doses; maximum 2.4 g per day

**Post-immunisation pyrexia in infants** (on doctor's advice only)

**Side-effects**

- Rare
- With oral use Alveolitis - septic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) - hepatic damage - interstitial fibrosis associated with NSAIDs can lead to renal failure - pancreatitis - papillary necrosis associated with NSAIDs can lead to renal failure - pulmonary eosinophilia - Stevens-Johnson syndrome - toxic epidermal necrolysis - visual disturbances

**Frequency not known**

- With oral use Angioedema - blood disorders - bronchospasm - colitis (induction of or exacerbation of) - Crohn’s disease (induction of or exacerbation of) - depression - diarrhoea - dizziness - drowsiness - fluid retention (rarely precipitating congestive heart failure) - gastro-intestinal bleeding - gastro-intestinal discomfort - gastro-intestinal disturbances - gastro-intestinal ulceration - haematuria - headache - hearing disturbances - hypersensitivity reactions - insomnia - nausea - nervousness - photosensitivity - raised blood pressure - rashes - renal failure (especially in patients with pre-existing renal impairment) - tinnitus - vertigo

**With topical use** Photosensitivity - rash (discontinue use if develops)

**SIDE-EFFECTS, FURTHER INFORMATION**

**Serious side-effects** For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 915.

**With topical use in adults** Topical application of large amounts can result in systemic effects, including hypersensitivity and asthma (renal disease has also been reported).

**Overdose** Overdosage with ibuprofen may cause nausea, vomiting, epigastric pain, and tinnitus, but more serious toxicity is very uncommon. Charcoal, activated p. 1130 followed by symptomatic measures are indicated if more than 100 mg/kg has been ingested within the preceding hour. For details on the management of poisoning, see Emergency treatment of poisoning p. 1123.

**ALLERGY AND CROSS-SENSITIVITY** Contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

**CONCEPTION AND CONTRACEPTION** Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

**Pregnancy**

- With oral use Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.
- With topical use Patient packs for topical preparations carry a warning to avoid during pregnancy.

**Breast feeding**

- With oral use Use with caution during breast-feeding. Amount too small to be harmful but some manufacturers advise avoid.
- With topical use Patient packs for topical preparations carry a warning to avoid during breast-feeding.

**Hepatic impairment**

- With oral use Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

**Renal impairment**

- With oral use Avoid if possible or use with caution. Avoid in severe impairment. The lowest effective dose should be used for
**PATIENT AND CARER ADVICE**

Medicines for Children leaflet: Ibuprofen for pain and inflammation www.medicinesforchildren.org.uk/ibuprofen-for-pain-and-inflammation

For topical preparations, patients and their carers should be advised to wash hands immediately after use. Photosensitivity: For topical preparations, patients or their carers should be advised against excessive exposure to sunlight of area treated in order to avoid possibility of photosensitivity.

**PRESCRIBING AND DISPENSING INFORMATION**

Forms available from special-order preparations, apply with gentle massage only. For topical preparations, apply with gentle massage only.

**CAUTIONARY AND ADVISORY LABELS**

For topical preparations, apply with gentle massage only.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include:

<table>
<thead>
<tr>
<th>Oral suspension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ibuprofen (Non-proprietary)</strong></td>
</tr>
<tr>
<td>Ibuprofen 400 mg</td>
</tr>
<tr>
<td>Brands may include Nurofen Express</td>
</tr>
</tbody>
</table>

**Modified-release capsule**

| Brands may include Nurofen Express |
| Ibuprofen 200 mg | Lloydpharmacy Ibuprofen Long Lasting 200mg capsules | 16 capsule (P) no price available |
| Brands may include Nurofen Back Pain SR |

**Effervescent granules**

| CAUTIONARY AND ADVISORY LABELS 13, 21 |
| ELECTROLYTES: May contain Sodium |
| Brufen (BGP Products Ltd) |
| Ibuprofen 600 mg | Brufen 600mg effervescent granules sachets | 20 sachet (PO) £6.80 DT price = £6.80 |

**Oral suspension**

| **Ibuprofen (Non-proprietary)** |
| Ibuprofen 20 mg per 1 ml | Junior Ibuprofen 100mg/5ml oral suspension (sugar-free) | 100 ml (P) £0.86 DT price = £1.47 |
| Ibuprofen for Children 100mg/5ml oral suspension (sugar-free) | 100 ml (P) no price available DT price = £1.47 | Ibuprofen 100mg/5ml oral suspension sugar-free (sugar-free) |
| Brufen (BGP Products Ltd) |
| Ibuprofen 20 mg per 1 ml Brufen 100mg/5ml syrup | 500 ml (PO) £8.88 DT price = £8.88 |
| Brands may include Calprofen; Mandafen; Nurofen; Orifine |

**Solution for infusion**

| Pedea (Orphan Europe (UK) Ltd) |
| Ibuprofen 5 mg per 1 ml Pedea 10mg/2ml solution for infusion ampoules | 4 ampoule (PO) £288.00 (Hospital only) |

**Foam**

| **Ibumouse (Dermal Laboratories Ltd)** |
| **Ibuprofen 50 mg per 1 gram** |
| **Ibuprofen 50 mg per 1 gram** |
| Ibumouse 5% | 125 gram (P) £5.85 |

**Gel**

| **EJUCENTS:** May contain Benzyl alcohol |
| **Ibuprofen (Non-proprietary)** |
| Ibuprofen 50 mg per 1 gram Mentholatum Ibuprofen 5% gel | 100 gram (P) £5.01 DT price = £4.57 | Ibuprofen 5% gel | 30 gram (P) £1.36 | 50 gram (P) £2.27 DT price = £2.29 | 100 gram (P) £5.33 DT price = £4.57 |
| Ibuprofen 100 mg per 1 gram | Ibuprofen 10% gel | 30 gram (P) £1.74 | 50 gram (P) £3.32 | 100 gram (P) £5.79 DT price = £4.92 |
| Ibuprofen Pain Relief Maximum Strength 10% gel | 50 gram (P) £2.08 |
| Lloydpharmacy Maximum Strength Ibuprofen 10% gel | 30 gram (P) no price available |
| Brands may include Fenibid; Ibugele; Ibuleve; Phorpain |

**Spray**

| **Ibuprofen (Non-proprietary)** |
| Ibuprofen 50 mg per 1 ml | Ibuprofen 5% spray | 100 ml (P) no price available |
| Brands may include Ibupray |

**Powder**

| **Nurofen Express (Reckitt Benckiser Healthcare (UK) Ltd)** |
| **Ibuprofen (as ibuprofen lysine) 400 mg** |
| Nurofen Express Soluble 400mg oral powder sachets | 10 sachet (PO) £1.23 |

**Indomethacin**

**INDICATIONS AND DOSE**

**Pain and moderate to severe inflammation in rheumatic disease and other musculoskeletal disorders**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

- **Adult:** 50–200 mg daily in divided doses

**BY RECTUM**

- **Adult:** 100 mg twice daily if required, dose to be administered at night and in the morning, combined oral and rectal treatment, maximum total daily dose 150–200 mg

**BY MOUTH USING MODIFIED-RELEASE MEDICINES**

- **Adult:** 75 mg 1–2 times a day

**Acute gout**

**BY MOUTH USING IMMEDIATE-RELEASE MEDICINES**

- **Adult:** 150–200 mg daily in divided doses
930 Pain and inflammation in musculoskeletal disorders

BY MOUTH USING MODIFIED-RELEASE MEDICINES
- Adult: 75 mg 1–2 times a day


Dysmenorrhoea
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
- Adult: Up to 75 mg daily

BY MOUTH USING MODIFIED-RELEASE MEDICINES
- Adult: 75 mg daily

UNLICENSED USE Use of indomethacin in premature labour is an unlicensed indication.

CONTRA-INDICATIONS Active gastro-intestinal bleeding - active gastro-intestinal ulceration - history of gastro-intestinal bleeding related to previous NSAID therapy - history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) - history of recurrent gastro-intestinal ulceration (two or more distinct episodes) - severe heart failure

CAUTIONS

SPECIFIC SIDE-EFFECTS
- Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - cerebrovascular disease - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - elderly (risk of serious side-effects and fatalities) - epilepsy - ischaemic heart disease - parkinsonism - peripheral arterial disease - psychiatric disturbances - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated) - uncontrolled hypertension

INTERACTIONS Appendix 1 (NSAIDs).

SIDE-EFFECTS

GENERAL SIDE-EFFECTS
- Rare Arthritis - aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) - blood disorders - confusion - convulsions - hepatic damage - hyperglycaemia - interstitial fibrosis associated with NSAIDs can lead to renal failure - intestinal strictures - pancreatitis - papillary necrosis associated with NSAIDs can lead to renal failure - peripheral neuropathy - psychiatric disturbances - pulmonary eosinophilia - Stevens-Johnson syndrome - syncope - thrombocytopenia - toxic epidermal necrolysis - visual disturbances
- Frequency not known Angina - aseptic meningitis - bronchospasm - colitis (induction of or exacerbation of) - Crohn’s disease (induction of or exacerbation of) - depression - diarrhoea - dizziness - drowsiness - fluid retention (rarely precipitating congestive heart failure) - gastro-intestinal bleeding - gastro-intestinal discomfort - gastro-intestinal disturbances - gastro-intestinal ulceration - haematuria - headache - hearing disturbances - hyperkalaemia - hypersensitivity reactions - insomnia - nervousness - photosensitivity - raised blood pressure - rashes - renal failure (especially in patients with pre-existing renal impairment) - tinnitus - vertigo

SPECIFIC SIDE-EFFECTS
- With oral use Nausea
- With rectal use Suppositories may cause occasional bleeding - suppositories may cause rectal irritation

SIDE-EFFECTS, FURTHER INFORMATION
- Serious side-effects For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 915.
- ALLERGY AND CROSS-SENSITIVITY Contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

CONCEPTION AND CONTRACEPTION Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

PREGNANCY Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

BREAST FEEDING Amount probably too small to be harmful—manufacturers advise avoid. Use with caution during breast-feeding.

HEPATIC IMPAIRMENT Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

RENAL IMPAIRMENT Avoid if possible or use with caution. Avoid in severe impairment. The lowest effective dose should be used for the shortest possible duration. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

MONITORING REQUIREMENTS During prolonged therapy ophthalmic and blood examinations particularly advisable.

PATIENT AND CARER ADVICE Dizziness may affect performance of skilled tasks (e.g. driving).

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Capsule
CAUTIONARY AND ADVISORY LABELS 21
- INDOMETACIN (Non-proprietary) Indometacin 25 mg Indometacin 25mg capsules | 28 capsule £5.00 DT price = £1.31 Indometacin 50 mg Indometacin 50mg capsules | 28 capsule £7.50 DT price = £1.62

Modified-release capsule
CAUTIONARY AND ADVISORY LABELS 21, 25
- INDOMETACIN (Non-proprietary) Indometacin 75 mg Indometacin 75mg modified-release capsules | 100 capsule £9.00 DT price = £8.09
- Brands may include Berlind Retard; Indolar SR

Suppository
- INDOMETACIN (Non-proprietary) Indometacin 100 mg Indometacin 100mg suppositories | 10 suppository £13.25 DT price = £17.61
- Brands may include Indocid

Ketoprofen

INDICATIONS AND DOSE
Pain and mild inflammation in rheumatic disease
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
- Adult: 100–200 mg daily in 2–4 divided doses

BY MOUTH USING MODIFIED-RELEASE MEDICINES
- Adult: 100–200 mg once daily, dose to be taken with food

BY RECTUM
- Adult: 100 mg once daily, to be administered at bedtime, combined oral and rectal treatment, maximum total daily dose 200 mg

Pain in musculoskeletal disorders | Pain after orthopaedic surgery | Dysmenorrhoea | Acute gout
BY MOUTH USING IMMEDIATE-RELEASE MEDICINES
- Adult: 50 mg up to 3 times a day

BY MOUTH USING MODIFIED-RELEASE MEDICINES
- Adult: 100–200 mg once daily, dose to be taken with food
Relief of pain in musculoskeletal disorders | Treatment in knee or hand osteoarthritis (adjunct)

TO THE SKIN

- Adult: Apply 2–4 times a day for up to 7 days, ketoprofen 2.5% gel to be administered; maximum 15 g per day

POWERGEL®

Relief of pain in musculoskeletal conditions | Adjunctive treatment in knee or hand osteoarthritis

TO THE SKIN

- Adult: Apply 2–3 times a day for up to max. 10 days

- CONTRA-INDICATIONS
  - With systemic use Active gastro-intestinal bleeding - active gastro-intestinal ulceration - history of gastro-intestinal bleeding - history of gastro-intestinal perforation - history of gastro-intestinal ulceration - severe heart failure

- CAUTIONS
  - With systemic use Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - cerebrovascular disease - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - elderly (risk of serious side effects and fatalities) - heart failure - ischaemic heart disease - peripheral arterial disease - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated) - uncontrolled hypertension
  - With topical use Avoid contact with eyes - avoid contact with inflamed or broken skin - avoid contact with mucous membranes - not for use with occlusive dressings - topical application of large amounts can result in systemic effects, including hypersensitivity and asthma (renal disease has also been reported)

- INTERACTIONS → Appendix 1 (NSAIDs). Interactions do not generally apply to topical NSAIDs.

- SIDE-EFFECTS

  GENERAL SIDE-EFFECTS Photosensitivity

  SPECIFIC SIDE-EFFECTS

  Rare
  - With systemic use Alveolitis - aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) - hepatic damage - interstitial fibrosis associated with NSAIDs can lead to renal failure - pancreatitis - papillary necrosis associated with NSAIDs can lead to renal failure - pulmonary eosinophilia - Stevens-Johnson syndrome - toxic epidermal necrolysis - visual disturbances
  - Frequency not known
  - With rectal use Suppositories may cause rectal irritation
  - With systemic use Angioedema - blood disorders - bronchospasm - colitis (induction of or exacerbation of) - Crohn’s disease (induction of or exacerbation of) - depression - diarrhoea - dizziness - drowsiness - fluid retention (rarely precipitating congestive heart failure) - gastro-intestinal bleeding - gastro-intestinal discomfort - gastro-intestinal disturbances - gastro-intestinal ulceration - haematuria - headache - hearing disturbances - hypersensitivity reactions - insomnia - nausea - nervousness - raised blood pressure - rashes - renal failure (especially in patients with pre-existing renal impairment) - tinnitus - vertigo
  - With topical use Rash (discontinue use if develops)

- SIDE-EFFECTS, FURTHER INFORMATION

Serious side-effects For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 915. Topical application of large amounts can result in systemic effects, including hypersensitivity and asthma (renal disease has also been reported).

- ALLERGY AND CROSS-SENSITIVITY Contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

- CONCEPTION AND CONTRA CONCEPTION
  - With systemic use Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

- PREGNANCY
  - With systemic use Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.
  - With topical use Patient packs for topical preparations carry a warning to avoid during pregnancy.

- BREAST FEEDING
  - With systemic use Use with caution during breast-feeding. Amount probably too small to be harmful but manufacturers advise avoid.
  - With topical use Patient packs for topical preparations carry a warning to avoid during breast-feeding.

- HEPATIC IMPAIRMENT
  - With systemic use Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Should be avoided in severe liver disease.

- RENAL IMPAIRMENT
  - With systemic use Avoid if possible or use with caution. Avoid in severe impairment. The lowest effective dose should be used for the shortest possible duration. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.
  - With topical use Deterioration in renal function has also been reported after topical use.

- DIRECTIONS FOR ADMINISTRATION For topical preparations apply with gentle massage only.

- PRESCRIBING AND DISPENSING INFORMATION Caution—topical preparations not generally suitable for children. Flavours of oral liquid formulations may include strawberry.

- PATIENT AND CARER ADVICE For topical preparations, patients and their carers should be advised to wash hands immediately after use.
  - With topical use Photosensitivity Patients should be advised against excessive exposure to sunlight of area treated in order to avoid possibility of photosensitivity. Patients should be advised not to expose area treated to sunbeds or sunlight (even on a bright but cloudy day) during, and for two weeks after stopping treatment; treated areas should be protected with clothing.

- EXCEPTIONS TO LEGAL CATEGORY Smaller pack sizes of gel preparations may be available on sale to the public.

- MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Capsule

- CAUTIONARY AND ADVISORY LABELS 21
  - Tiloket (Tillomed Laboratories Ltd)
  - Ketoprofen 50 mg Tiloket 50mg capsules | 28 capsule £3.99 | 112 capsule £5.65 £17.20 DT price = £15.14
  - Modified-release capsule

- CAUTIONARY AND ADVISORY LABELS 21, 25
  - KETOPROFEN (Non-proprietary)
  - Ketoprofen 200 mg Tiloket CR 200mg capsules | 28 capsule £10.70 DT price = £23.85

  - Ketoprofen 200mg modified-release capsules | 28 capsule £23.85 DT price = £23.85
Ketoprofen with omeprazole

The properties listed below are those particular to the combination only. For the properties of the components please consider, ketoprofen p. 930, omeprazole p. 69.

**INDICATIONS AND DOSE**
Patients requiring ketoprofen for osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, who are at risk of NSAID associated duodenal or gastric ulcer or gastrroduodenal erosions

**BY MOUTH**
- Adult: Initially 100/20 mg daily, increased if necessary to 200/20 mg daily, depending on severity of symptoms, dose expressed as x/y mg ketoprofen/omeprazole

**PRESCRIBING AND DISPENSING INFORMATION**
Capsules enclose microgranules containing modified-release ketoprofen and gastro-resistant omeprazole.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Modified-release capsule**

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Formulation</th>
<th>Price*</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoprofen</td>
<td>100 mg</td>
<td>£23.93</td>
<td>DT price = £4.42</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>20 mg</td>
<td>£6.50</td>
<td>DT price = £4.42</td>
</tr>
</tbody>
</table>

*Brands may include Powergel; Toloket

**INTERACTIONS**

- **CAUTIONS**
  - Acute porphyrias p. 864 - allergic disorders - cardiac impairment (NSAIDs may impair renal function) - cerebrovascular disease - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - elderly (risk of serious side-effects and fatalities) - epilepsy - heart failure - ischaemic heart disease - peripheral arterial disease - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated) - uncontrolled hypertension

- **SIDE-EFFECTS**
  - Common or very common Diarrhoea (withdraw treatment) - rashes (withdraw treatment) - stomatitis
  - Uncommon Fatigue - paraesthesia
  - Rare Alveolitis - aplastic anaemia - aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) - glucose intolerance - haemolytic anaemia (positive Coombs’ test) - hepatic damage - hypotension - interstitial fibrosis associated with NSAIDs can lead to renal failure - palpititations - pancreatitis - papillary necrosis associated with NSAIDs can lead to renal failure - pulmonary eosinophilia - Stevens-Johnson syndrome - thrombocytopenia - toxic epidermal necrolysis - visual disturbances
  - Frequency not known Angioedema - blood disorders - bronchospasm - colitis (induction of or exacerbation of) - Crohn’s disease (induction of or exacerbation of) - depression - dizziness - drowsiness - fluid retention (rarely precipitating congestive heart failure) - gastro-intestinal bleeding - gastro-intestinal discomfort - gastro-intestinal disturbances - gastro-intestinal ulceration - haematuria - headache - hearing disturbances - hypersensitivity reactions - insomnia - nausea - nervousness - photosensitivity - raised blood pressure - renal failure (especially in patients with pre-existing renal impairment) - tinnitus - vertigo

SIDE-EFFECTS, FURTHER INFORMATION

Serious side-effects For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 915.

Overdose Mefenamic acid has important consequences in overdosage because it can cause convulsions, which if prolonged or recurrent, require treatment. For details on the management of poisoning, see Emergency treatment of poisoning p. 1123, in particular, Convolutions.

- **ALLERGY AND CROSS-SENSITIVITY** Contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rinitis have been precipitated by aspirin or any other NSAID.

- **CONCEPTION AND CONTRACTION** Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

- **PREGNANCY** Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

- **BREAST FEEDING** Use with caution during breast-feeding. Amount too small to be harmful but manufacturer advises avoid.

- **HEPATIC IMPAIRMENT** Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

- **RENAL IMPAIRMENT** The lowest effective dose should be used for the shortest possible duration. Avoid if possible or use with caution. Avoid in severe impairment. In renal impairment monitor renal function; sodium and water
retention may occur and renal function may deteriorate, possibly leading to renal failure.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

  **Tablet**
  CAUTIONARY AND ADVISED LABELS 21
  - MEFENAMIC ACID (Non-proprietary)
    - Mefenamic acid 500 mg Mefenamic acid 500mg tablets | 28 tablet (P) £18.00 DT price + £5.64 | 84 tablet (P) £18.00
    - Ponstan (Chemidex Pharma Ltd)
    - Mefenamic acid 500 mg Ponstan Forte 500mg tablets | 100 tablet (P) £15.72

  **Capsule**
  CAUTIONARY AND ADVISED LABELS 21
  - MEFENAMIC ACID (Non-proprietary)
    - Mefenamic acid 250 mg Mefenamic acid 250mg capsules | 100 capsule (P) £15.00 DT price + £8.49
    - Ponstan (Chemidex Pharma Ltd)
    - Mefenamic acid 250 mg Ponstan 250mg capsules | 100 capsule (P) £8.17 DT price + £8.49

  **Oral suspension**
  CAUTIONARY AND ADVISED LABELS 21
  EXCIPIENTS: May contain Ethanol
  - MEFENAMIC ACID (Non-proprietary)
    - Mefenamic acid 10 mg per 1 ml Mefenamic acid 50mg/5ml oral suspension | 125 ml (P) £79.98

**Meloxicam**

**INDICATIONS AND DOSE**

Exacerbation of osteoarthritis (short-term)
- **BY MOUTH**
  - Child 16-17 years: 7.5 mg once daily, then increased if necessary up to 15 mg once daily
  - Adult: 7.5 mg once daily, then increased if necessary up to 15 mg once daily

Pain and inflammation in rheumatic disease | Ankylosing spondylitis
- **BY MOUTH**
  - Child 16-17 years: 15 mg once daily, then reduced to 7.5 mg once daily if required
  - Adult: 15 mg once daily, then reduced to 7.5 mg once daily if required
  - Elderly: 7.5 mg once daily

Relief of pain and inflammation in juvenile idiopathic arthritis and other musculoskeletal disorders in children intolerant to other NSAIDs
- **BY MOUTH**
  - Child 16-17 years (body-weight up to 50 kg): 7.5 mg once daily
  - Child 16-17 years (body-weight 50 kg and above): 15 mg once daily

- **CONTRA-INDICATIONS**
  Active gastro-intestinal bleeding • active gastro-intestinal ulceration • history of gastro-intestinal bleeding related to previous NSAID therapy • history of gastro-intestinal perforation related to previous NSAID therapy • history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) • history of recurrent gastro-intestinal ulceration (two or more distinct episodes) • severe heart failure

- **CAUTIONS**
  Allergic disorders • cardiac impairment (NSAIDs may impair renal function) • cerebrovascular disease • coagulation defects • connective-tissue disorders • Crohn’s disease (may be exacerbated) • elderly (risk of serious side-effects and fatalities) • heart failure • ischaemic heart disease • peripheral arterial disease • risk factors for cardiovascular events • ulcerative colitis (may be exacerbated) • uncontrolled hypertension (in adults)

- **INTERACTIONS** → Appendix I (NSAIDs).

- **SIDE-EFFECTS**
  - Rare Alveolitis • aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) • hepatic damage • interstitial fibrosis associated with NSAIDs can lead to renal failure • pancreatitis • papillary necrosis associated with NSAIDs can lead to renal failure • pulmonary eosinophilia • Stevens-Johnson syndrome • toxic epidermal necrolysis • visual disturbances
  - Frequency not known Angioedema • blood disorders • bronchospasm • colitis (induction of or exacerbation of) • Crohn’s disease (induction of or exacerbation of) • depression • diarrhoea • dizziness • drowsiness • fluid retention (rarely precipitating congestive heart failure) • gastro-intestinal bleeding • gastro-intestinal discomfort • gastrointestinal disturbances • gastro-intestinal ulceration • haematuria • headache • heart failure • hypertension • hypersensitivity reactions • insomnia • nausea • nervousness • photosensitivity • raised blood pressure • rashes • renal failure (especially in patients with pre-existing renal impairment) • tinnitus • vertigo

**SIDE-EFFECTS, FURTHER INFORMATION**

**Serious side-effects** For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 915.

- **ALLERGY AND CROSS-SENSITIVITY**
  Contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

- **CONCEPTION AND CONCEPTION**
  Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

- **PREGNANCY**
  Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

- **BREAST FEEDING**
  Use with caution during breast-feeding. Present in milk in *animal* studies—manufacturer advises avoid.

- **HEPATIC IMPAIRMENT**
  Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

- **RENAL IMPAIRMENT**
  Avoid if possible or use with caution. The lowest effective dose should be used for the shortest possible duration. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.
  - In adults Avoid if eGFR less than 25 mL/minute/1.73 m².
  - In children Avoid if estimated glomerular filtration rate less than 25 mL/minute/1.73 m².

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

  **Tablet**
  CAUTIONARY AND ADVISED LABELS 21
  - MELOXICAM (Non-proprietary)
    - Meloxicam 7.5 mg Meloxicam 7.5mg tablets | 30 tablet (P) £8.20
      DT price + £1.16
    - Meloxicam 15 mg Meloxicam 15mg tablets | 30 tablet (P) £14.00
      DT price + £1.39
Musculoskeletal system

Allergy and cross-sensitivity

Frequency not known

Rare

Interactions

Appendix 1 (NSAIDs).

Contra-indications

Active gastro-intestinal bleeding - active gastro-intestinal ulceration - history of gastro-intestinal bleeding related to previous NSAID therapy - history of gastro-intestinal perforation related to previous NSAID therapy - history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) - history of recurrent gastro-intestinal ulceration (two or more distinct episodes) - severe heart failure

Caution

Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

Renal impairment

Avoid if possible or use with caution. Avoid in severe impairment. The lowest effective dose should be used for the shortest possible duration. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

Tablet

Cautionary and advisory labels 21

Nabumetone (Non-proprietary)

Nabumetone 500 mg Nabumetone 500mg tablets | 56 tablet £20.00 DT price = £8.56

Relifex (Meda Pharmaceuticals Ltd)

Nabumetone 500 mg Relifex 500mg tablets | 56 tablet £618 DT price = £8.56

Nabumetone

Indications and dose

Pain and inflammation in osteoarthritis and rheumatoid arthritis

By mouth

Adult: 1 g once daily, dose to be taken at night

Elderly: 0.5–1 g daily

Pain and inflammation in osteoarthritis and rheumatoid arthritis (severe and persistent symptoms)

By mouth

Adult: 0.5–1 g, dose to be taken in the morning and 1 g, dose to be taken at night

Contra-indications

Active gastro-intestinal bleeding - active gastro-intestinal ulceration - history of gastro-intestinal bleeding related to previous NSAID therapy - history of gastro-intestinal perforation related to previous NSAID therapy - history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) - history of recurrent gastro-intestinal ulceration (two or more distinct episodes) - severe heart failure

Caution

Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - cerebrovascular disease - coagulation defects - connective-tissue disorders - Crohn’s disease - elderly (risk of serious side-effects and fatalities) - heart failure - ischaemic heart disease - peripheral arterial disease - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated) - uncontrolled hypertension

Interactions

Appendix 1 (NSAIDs).

Side-effects

Rare

Alveolitis - aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) - hepatic damage - interstitial fibrosis associated with NSAIDs can lead to renal failure - pancreatitis - papillary necrosis associated with NSAIDs can lead to renal failure - pulmonary eosinophilia - Stevens-Johnson syndrome - toxic epidermal necrolysis - visual disturbances

Frequency not known


Side-effects, further information

Serious side-effects

For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 915.

Allergy and cross-sensitivity

Contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

contra-indications

Active gastro-intestinal bleeding - active gastro-intestinal ulceration - history of gastro-intestinal bleeding related to previous NSAID therapy - history of gastro-intestinal perforation related to previous NSAID therapy - history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) - history of recurrent gastro-intestinal ulceration (two or more distinct episodes) - severe heart failure

Caution

Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - cerebrovascular disease - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - elderly (risk of serious side-effects and fatalities) - heart failure - ischaemic heart disease - peripheral arterial disease - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated) - uncontrolled hypertension

Interactions

Appendix 1 (NSAIDs).

Side-effects

Rare

Alveolitis - aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) - hepatic
damage - interstitial fibrosis associated with NSAIDs can lead to renal failure - pancreatitis - papillary necrosis associated with NSAIDs can lead to renal failure - pulmonary eosinophilia - Stevens-Johnson syndrome - toxic epidermal necrolysis - visual disturbances

- **Frequency not known** Angioedema - blood disorders - bronchospasm - colitis (induction of or exacerbation of). - Crohn’s disease (induction of or exacerbation of) - depression - diarrhoea - dizziness - drowsiness - fluid retention (rarely precipitating congestive heart failure) - gastro-intestinal bleeding - gastro-intestinal discomfort - gastro-intestinal disturbances - gastro-intestinal ulceration - haematura - headache - hearing disturbances - hypersensitivity reactions - insomnia - nausea - nervousness - photosensitivity - raised blood pressure - rashes - renal failure (especially in patients with pre-existing renal impairment) - tinutius - vertigo

**SIDE-EFFECTS, FURTHER INFORMATION**

**Serious side-effects** For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 915.

- **ALLERGY AND CROSS-SENSITIVITY** Contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

- **CONCEPTION AND CONCEPTION** Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

- **PREGNANCY** Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and may be inadvisable for patients in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

- **BREAST FEEDING** Use with caution during breast-feeding. Amount too small to be harmful but manufacturer advises avoid.

- **HEPATIC IMPAIRMENT** Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

- **RENAL IMPAIRMENT** Avoid if possible or use with caution. The lowest effective dose should be used for the shortest possible duration. Avoid if eGFR less than 30 mL/minute/1.73 m². In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

- **EXCEPTIONS TO LEGAL CATEGORY** Can be sold to the public for the treatment of primary dysmenorrhoea in women aged 15–50 years subject to max. single dose of 500 mg, max. daily dose of 750 mg for max. 3 days, and a max. pack size of 9 x 250 mg tablets.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension

**Tablet**

**CAUTIONARY AND ADVISORY LABELS 21**

- **NAPROXEN (Non-proprietary)**
  - Naproxen 250 mg Naproxen 250mg tablets | 28 tablet | £6.98 DT price + £1.21 | 56 tablet | £2.46
  - Naproxen 500 mg Naproxen 500mg tablets | 28 tablet | £8.76 DT price + £1.67 | 56 tablet | £3.54
  - Naprosyn (Roche Products Ltd)
  - Naproxen 250 mg Naprosyn 250mg tablets | 56 tablet | £4.29
  - Naproxen 500 mg Naprosyn 500mg tablets | 56 tablet | £8.56

- **Gastro-resistant tablet**

  **CAUTIONARY AND ADVISORY LABELS 5, 25**

  - Naproxen 250 mg Naproxen 250mg gastro-resistant tablets | 56 tablet | £12.90 DT price + £4.03
  - Naproxen 375 mg Naproxen 375mg gastro-resistant tablets | 56 tablet | £6.82 DT price + £6.42
  - Naproxen 500 mg Naproxen 500mg gastro-resistant tablets | 56 tablet | £16.90 DT price + £3.78
  - Naprosyn (Roche Products Ltd)

  - Naproxen 250 mg Naprosyn EC 250mg tablets | 56 tablet | £4.29 DT price + £4.03
  - Naproxen 375 mg Naprosyn EC 375mg tablets | 56 tablet | £6.42 DT price + £6.42
  - Naproxen 500 mg Naprosyn EC 500mg tablets | 56 tablet | £8.56 DT price + £9.78
  - Brands may include Femina Ultra

**Naproxen with esomeprazole**

The properties listed below are those particular to the combination only. For the properties of the components please consider, esomeprazole p. 67, naproxen p. 934.

**INDICATIONS AND DOSE**

Patients requiring naproxen for osteoarthritis, rheumatoid arthritis, or ankylosing spondylitis, who are at risk of NSAID-associated duodenal or gastric ulcer and when treatment with lower doses of naproxen or other NSAIDs ineffective

**BY MOUTH**

- Adult: 1 tablet twice daily

**MEDICAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Modified-release tablet**

**CAUTIONARY AND ADVISORY LABELS 22, 25**

- Esomeprazole with Naproxen (Non-proprietary)
  - Esomeprazole (as Esomeprazole magnesium trihydrate) 20 mg, Naproxen 500 mg Naproxen 500mg / Esomeprazole 20mg modified-release tablets | 60 tablet | no price available
  - Vimovo (AstraZeneca UK Ltd)
  - Esomeprazole (as Esomeprazole magnesium trihydrate) 20 mg, Naproxen 500 mg Vimovo 500mg/20mg modified-release tablets | 60 tablet | £14.95

**Naproxen with misoprostol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, misoprostol p. 709, naproxen p. 934.

**INDICATIONS AND DOSE**

Patients requiring naproxen for rheumatoid arthritis, osteoarthritis, or ankylosing spondylitis, with prophylaxis against NSAID-induced gastroduodenal ulceration

**BY MOUTH**

- Adult: 500 mg twice daily, naproxen and 200 micrograms twice daily, misoprostol, taken together with food

**PRESCRIBING AND DISPENSING INFORMATION**

The BNF recommends a higher starting dose of misoprostol for prophylaxis against NSAID-induced gastroduodenal ulceration than that provided by the misoprostol with naproxen combination pack.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.
Tablet
- Napratec (Pfizer Ltd)
  Napratec OP tablets | 112 tablet £23.76 D7 price = £23.76

Piroxicam

INDICATIONS AND DOSE
Rheumatoid arthritis (initiated by a specialist) | Osteoarthritis (initiated by a specialist) | Ankylosing spondylitis (initiated by a specialist)

BY MOUTH
- Adult: Up to 20 mg once daily

Pain relief in musculoskeletal conditions | Treatment in knee or hand osteoarthritis (adjunct)

TO THE SKIN
- Adult: Apply 3–4 times a day, 0.5% gel to be applied; review treatment after 4 weeks

Important safety information

CHMP ADVICE—PIROXICAM (JUNE 2007)
The CHMP has recommended restrictions on the use of piroxicam because of the increased risk of gastro-intestinal side effects and serious skin reactions. The CHMP has advised that:
- piroxicam should be initiated only by physicians experienced in treating inflammatory or degenerative rheumatic diseases
- piroxicam should not be used as first-line treatment
- in adults, use of piroxicam should be limited to the symptomatic relief of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis
- piroxicam dose should not exceed 20 mg daily
- piroxicam should no longer be used for the treatment of acute painful and inflammatory conditions
- treatment should be reviewed 2 weeks after initiating piroxicam, and periodically thereafter
- concomitant administration of a gastro-protective agent should be considered. Topical preparations containing piroxicam are not affected by these restrictions.

CONTRA-INDICATIONS
- With systemic use Active gastro-intestinal bleeding | active gastro-intestinal ulceration | history of gastro-intestinal bleeding | history of gastro-intestinal perforation | history of gastro-intestinal ulceration | inflammatory bowel disease | severe heart failure
- WITH TOPICAL USE
- Frequency not known
- WITH TOPICAL USE
- ALLERGY AND CROSS-SENSITIVITY
- With systemic use Angioedema | blood disorders | bronchospasm | colitis (induction of or exacerbation of) | Crohn’s disease (induction of or exacerbation of) | depression | diarrhoea | dizziness | drowsiness | fluid retention (rarely precipitating congestive heart failure) | gastro-intestinal bleeding | gastro-intestinal discomfort | gastro-intestinal disturbances | gastro-intestinal ulceration | haematuria | headache | hearing disturbances | hypersensitivity reactions | insomnia | nausea | nervousness | photosensitivity | raised blood pressure | rash | renal failure (especially in patients with pre-existing renal impairment) | tinnitus | vertigo
- WITH TOPICAL USE
- Photosensitivity | rash (discontinue use if develops)

SIDE-EFFECTS, FURTHER INFORMATION

Serious side-effects
- For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 915. Topical application of large amounts can result in systemic effects, including hypersensitivity and asthma (renal disease has also been reported).
- ALLERGY AND CROSS-SENSITIVITY Contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.
- CONCEPTION AND CONTRACEPTION
- With systemic use Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.
- PREGNANCY
- With systemic use Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.
- WITH TOPICAL USE
- BREAST FEEDING
- With systemic use Use with caution during breast-feeding. Amount too small to be harmful.
- WITH TOPICAL USE
- PRESCRIBING AND DISPENSING INFORMATION
- Caution—topical preparations not generally suitable for children.
Sulindac

### INDICATIONS AND DOSE

**Pain and inflammation in rheumatic disease and other musculoskeletal disorders**  
*Acute gout*

**BY MOUTH**

- Adult: 200 mg twice daily for 7–10 days in peri-articular disorders; acute gout should respond within 7 days, dose may be reduced according to response; maximum 400 mg per day

- **CONTRA-INDICATIONS** Active gastro-intestinal bleeding - active gastro-intestinal ulceration - history of gastro-intestinal bleeding related to previous NSAID therapy - history of gastro-intestinal perforation related to previous NSAID therapy - history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) - history of recurrent gastro-intestinal ulceration (two or more distinct episodes) - severe heart failure

- **CAUTIONS** Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - cerebrovascular disease - coagulation defects - connective-tissue disorders  
  - Crohn’s disease (may be exacerbated) - elderly (risk of serious side-effects and fatalities) - ensure adequate hydration - heart failure - history of renal stones - ischaemic heart disease - peripheral arterial disease - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated) - uncontrolled hypertension

- **INTERACTIONS** → Appendix 1 (NSAIDs).

- **SIDE-EFFECTS**
  - Rare: Alveolitis - aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) - hepatic damage - interstitial fibrosis associated with NSAIDs can lead to renal failure - pancreatitis - papillary necrosis


**SIDE-EFFECTS, FURTHER INFORMATION**

**Serious side-effects** For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 915.

- **ALLERGY AND CROSS-SENSITIVITY** Contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

- **CONCEPTION AND CONTRAINDICATION**
  - Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

- **PREGNANCY** Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

- **BREAST FEEDING** Use with caution during breast-feeding.

- **HEPATIC IMPAIRMENT** Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

- **RENAL IMPAIRMENT** Avoid if possible or use with caution. Avoid in severe impairment. The lowest effective dose should be used for the shortest possible duration. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Orodispersible tablet**

| CAUTIONARY AND ADVISORY LABELS | 10, 21 |
| EXCIPIENTS: May contain Aspartame |
| Piroxicam 20 mg Feldene Melt 20 mg tablets (sugar-free) |
| 30 tablet (Paf) £10.53 DT price = £10.53 |

| Capsule |
| CAUTIONARY AND ADVISORY LABELS | 21 |
| Piroxicam (Non-proprietary) |
| Piroxicam 10 mg Piroxicam 10 mg capsules | 56 capsule (Paf) £16.62 DT price = £4.59 |
| Piroxicam 20 mg Piroxicam 20 mg capsules | 28 capsule (Paf) £17.60 DT price = £4.30 |
| Feldene (Pfizer Ltd) |
| Piroxicam 10 mg Feldene 10 mg capsules | 30 capsule (Paf) £3.86 |
| Piroxicam 20 mg Feldene 20 mg capsules | 30 capsule (Paf) £7.71 |

| EXCIPIENTS: May contain Benzyl alcohol, propylene glycol |
| Piroxicam (Non-proprietary) |
| Piroxicam 5 mg per 1 gram Piroxicam 5% gel | 60 gram (Paf) £4.04 DT price = £4.04 | 112 gram (Paf) £8.47 DT price = £7.54 |
| Feldene (Pfizer Ltd) |
| Piroxicam 5 mg per 1 gram Feldene 0.5% gel | 60 gram (Paf) £6.00 DT price = £4.04 | 112 gram (Paf) £9.41 DT price = £7.54 |

**Tenoxicam**

### INDICATIONS AND DOSE

**Pain and inflammation in rheumatic disease**  
*By mouth*

- Adult: 20 mg daily

**BY INTRAVENOUS INJECTION OR BY INTRAMUSCULAR INJECTION**

- Adult: 20 mg daily as initial treatment for 1–2 days if oral administration not possible

continued →
Pain and inflammation in acute musculoskeletal disorders

**BY MOUTH**
- Adult: 20 mg daily for 7 days; maximum duration of treatment 14 days (including treatment by intravenous or intramuscular injection)

**BY INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INJECTION**
- Adult: 20 mg daily as initial treatment for 1–2 days if oral administration not possible

- **CONTRA-INDICATIONS** Active gastro-intestinal bleeding - active gastro-intestinal ulceration - history of gastro-intestinal bleeding related to previous NSAID therapy - history of gastro-intestinal perforation related to previous NSAID therapy - history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) - history of recurrent gastro-intestinal ulceration (two or more distinct episodes) - severe heart failure

- **CAUTIONS** Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - cerebrovascular disease - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - elderly (risk of serious side-effects and fatalities) - heart failure - ischaemic heart disease - peripheral arterial disease - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated) - uncontrolled hypertension

- **SIDE-EFFECTS**
  - Rare: Alveolitis - aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) - hepatic damage - interstitial fibrosis associated with NSAIDs can lead to renal failure - pancreatitis - papillary necrosis associated with NSAIDs can lead to renal failure - pulmonary eosinophilia - Stevens-Johnson syndrome - toxic epidermal necrolysis - visual disturbances
  - Frequency not known: Angioedema - blood disorders - bronchospasm - colitis (induction or exacerbation of) - Crohn’s disease (induction of or exacerbation of) - depression - diarrhea - dizziness - dryness - fluid retention (rarely precipitating congestive heart failure) - gastro-intestinal bleeding - gastro-intestinal discomfort - gastro-intestinal disturbances - gastro-intestinal ulceration - haematuria - headache - hearing disturbances - hypersensitivity reactions - insomnia - nausea - nervousness - photosensitivity - raised blood pressure - rashes - renal failure (especially in patients with pre-existing renal impairment) - tinnitus - vertigo

- **INTERACTIONS**

- **SIDE-EFFECTS. FURTHER INFORMATION**
  - Serious side-effects: For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 915.

- **ALLERGY AND CROSS-SENSITIVITY** Contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID - which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

- **CONCEPTION AND CONTRACEPTION** Caution - long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

- **PREGNANCY** Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

- **BREAST FEEDING** Use with caution during breast-feeding. Present in milk in animal studies.

- **HEPATIC IMPAIRMENT** Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

- **RENAL IMPAIRMENT** Avoid if possible or use with caution. Avoid in severe impairment. The lowest effective dose should be used for the shortest possible duration. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

- **MEDIcular forms** There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

| CAUTIONARY AND ADVISORY LABELS 21 |
| TENOXICAM (Non-proprietary) |
| Tenoxicam 20 mg Tenoxicam 20mg tablet | 28 tablet £16.16 |
| DT price | £16.16 |
| Mobilflex (Meda Pharmaceuticals Ltd) |
| Tenoxicam 20 mg Mobilflex 20mg tablets | 30 tablet £13.42 |

**Powder and solvent for solution for injection**

| TENOXICAM (Non-proprietary) |
| Tenoxicam 20 mg Tenoxicam 20mg powder and solvent for solution for injection vials | 1 vial £3.98 |

**Tiaprofenic acid**

**INDICATIONS AND DOSE**

Pain and inflammation in rheumatic disease and other musculoskeletal disorders

**BY MOUTH**
- Adult: 300 mg twice daily

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**Important safety information**

**CSM ADVICE**

Following reports of severe cystitis the CSM has recommended that tiaprofenic acid should not be given to patients with urinary-tract disorders and should be stopped if urinary symptoms develop. Patients should be advised to stop taking tiaprofenic acid and to report to their doctor promptly if they develop urinary-tract symptoms (such as increased frequency, nocturia, urgency, pain on urinating, or blood in urine).

- **CONTRA-INDICATIONS** Active bladder disease (or symptoms) - active gastro-intestinal bleeding - active gastro-intestinal ulceration - active prostate disease (or symptoms) - history of gastro-intestinal bleeding related to previous NSAID therapy - history of gastro-intestinal perforation related to previous NSAID therapy - history of recurrent gastro-intestinal haemorrhage (two or more distinct episodes) - history of recurrent gastro-intestinal ulceration (two or more distinct episodes) - history of recurrent urinary-tract disorders (if urinary symptoms develop) - interstitial fibrosis associated with NSAIDs can lead to renal failure - papillary necrosis associated with NSAIDs can lead to renal failure - pulmonary eosinophilia - Stevens-Johnson syndrome - toxic epidermal necrolysis - visual disturbances

- **CAUTIONS** Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - cerebrovascular disease - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - elderly (risk of serious side-effects and fatalities) - heart failure - ischaemic heart disease - peripheral arterial disease - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated) - uncontrolled hypertension

- **INTERACTIONS**

- **SIDE-EFFECTS**
  - Rare: Alveolitis - aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) - hepatic damage - interstitial fibrosis associated with NSAIDs can lead to renal failure - pancreatitis - papillary necrosis associated with NSAIDs can lead to renal failure -
Local inflammation of joints and soft tissue

5 Soft tissue and joint disorders

5.1 Local inflammation of joints and soft tissue

Corticosteroids, inflammatory disorders

Systemic corticosteroids

Short-term treatment with corticosteroids can help to rapidly improve symptoms of rheumatoid arthritis. Long-term treatment in rheumatoid arthritis should be considered only after evaluating the risks and all other treatment options have been considered. Corticosteroids can induce osteoporosis, and prophylaxis should be considered on long-term treatment.

In severe, possibly life-threatening, situations a high initial dose of corticosteroid is given to induce remission and the dose is then reduced gradually and discontinued altogether. Relapse may occur as the dose of corticosteroid is reduced, particularly if the reduction is too rapid. The tendency is therefore to increase the maintenance dose and consequently the patient becomes dependent on corticosteroids. For this reason pulse doses of corticosteroids (e.g. methylprednisolone p. 584 up to 1 g intravenously on 3 consecutive days) are used to suppress highly active inflammatory disease while longer-term treatment with a disease-modifying drug is commenced.

Prednisolone p. 585 may reduce the rate of joint destruction in moderate to severe rheumatoid arthritis of less than 2 years’ duration. The reduction in joint destruction must be distinguished from mere symptomatic improvement (which lasts only 6 to 12 months at this dose) and care should be taken to avoid increasing the dose above 7.5 mg daily. Evidence supports maintenance of this anti- erosive dose for 2–4 years only after which treatment should be tapered off to reduce long-term adverse effects. A modified-release preparation of prednisolone p. 586 is also available for the treatment of moderate to severe rheumatoid arthritis.

Polymyalgia rheumatica and giant cell (temporal) arteritis are always treated with corticosteroids. Relapse is common if therapy is stopped prematurely. Many patients require treatment for at least 2 years and in some patients it may be necessary to continue long-term low-dose corticosteroid treatment.

Polyarteritis nodosa and polymyositis are usually treated with corticosteroids.

Systemic lupus erythematosus is treated with corticosteroids when necessary using a similar dosage regimen to that for polyarteritis nodosa and polymyositis. Patients with pleurisy, pericarditis, or other systemic manifestations will respond to corticosteroids. It may then be possible to reduce the dosage; alternate-day treatment is sometimes adequate, and the drug may be gradually withdrawn. In some mild cases corticosteroid treatment may be stopped after a few months. Many mild cases of systemic lupus erythematosus do not require corticosteroid treatment. Alternative treatment with anti-inflammatory analgesics, and possibly chloroquine p. 536 or hydroxychloroquine sulfate p. 894, should be considered.

Ankylosing spondylitis should not be treated with long-term corticosteroids; rarely, pulse doses may be needed and may be useful in extremely active disease that does not respond to conventional treatment.
Local corticosteroid injections
Corticosteroids are injected locally for an anti-inflammatory effect. In inflammatory conditions of the joints, particularly in rheumatoid arthritis, they are given by intra-articular injection to relieve pain, increase mobility, and reduce deformity in one or a few joints; they can also provide symptomatic relief while waiting for DMARDs to take effect. Full aseptic precautions are essential; infected areas should be avoided. Occasionally an acute inflammatory reaction develops after an intra-articular or soft-tissue injection of a corticosteroid. This may be a reaction to the microcrystalline suspension of the corticosteroid used, but must be distinguished from sepsis introduced into the injection site.
Smaller amounts of corticosteroids may also be injected directly into soft tissues for the relief of inflammation in conditions such as tennis or golfer’s elbow or compression neuropathies. In tendinitis, injections should be made into the tendon sheath and not directly into the tendon (due to the absence of a true tendon sheath and a high risk of rupture, the Achilles tendon should not be injected). Hydrocortisone p. 583 acetate or one of the synthetic analogues is generally used for local injection. Intra-articular corticosteroid injections can cause flushing and may affect the hyaline cartilage. Each joint should not usually be treated more than 4 times in one year.
Corticosteroid injections are also injected into soft tissues for the treatment of skin lesions.

Corticosteroids

Methylprednisolone with lidocaine
The properties listed below are those particular to the combination only. For the properties of the components please consider, lidocaine hydrochloride p. 1116, methylprednisolone p. 584.

INDICATIONS AND DOSE
Local inflammation of joints
BY INTRA-ARTICULAR INJECTION
- Adult: 4–80 mg, dose adjusted according to size; where appropriate may be repeated at intervals of 7–35 days, for details consult product literature

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
Suspension for injection
EXCIPIENTS: May contain Benzy alcohol
- TRIAMCINOLONE HEXACETONIDE (Non-proprietary) Triamcinolone hexacetonide 20 mg per 1 ml Triamcinolone hexacetonide 20mg/ml suspension for injection ampoules | 10 ampoule £12.00

5.2 Soft tissue disorders

Soft-tissue disorders
Extravasation
Local guidelines for the management of extravasation should be followed where they exist or specialist advice sought.
Extravasation injury follows leakage of drugs or intravenous fluids from the veins or inadvertent administration into the subcutaneous or subdermal tissue. It must be dealt with promptly to prevent tissue necrosis. Acidic or alkaline preparations and those with an osmolarity greater than that of plasma can cause extravasation injury; excipients including alcohol and polyethylene glycol have also been implicated. Cytotoxic drugs commonly cause extravasation injury. In addition, certain patients such as the very young and the elderly are at increased risk. Those receiving anticogulants are more likely to lose blood into surrounding tissues if extravasation occurs, while those receiving sedatives or analgesics may not notice the early signs or symptoms of extravasation.
Prevention of extravasation
Precautions should be taken to avoid extravasation; ideally, drugs likely to cause extravasation injury should be given through a central line and patients receiving repeated doses of hazardous drugs peripherally should have the cannula resited at regular intervals. Attention should be paid to the manufacturers’ recommendations for administration. Placing a glyceryl trinitrate patch distal to the cannula may improve the patency of the vessel in patients with small veins or in those whose veins are prone to collapse.
Patients should be asked to report any pain or burning at the site of injection immediately.

Management of extravasation
If extravasation is suspected the infusion should be stopped immediately but the cannula should not be removed until after an attempt has been made to aspirate the area (through the cannula) in order to remove as much of the drug as possible. Aspiration is sometimes possible if the extravasation presents with a raised bleb or blister at the injection site and is surrounded by hardened tissue, but it is often unsuccessful if the tissue is soft or soggy.
Corticosteroids are usually given to treat inflammation, although there is little evidence to support their use in extravasation. Hydrocortisone p. 583 or dexamethasone p. 581 can be given either locally by subcutaneous injection or intravenously at a site distant from the injury. Antihistamines and analgesics may be required for symptom relief.
The management of extravasation beyond these measures is not well standardised and calls for specialist advice. Treatment depends on the nature of the offending substance; one approach is to localise and neutralise the substance whereas another is to spread and dilute it.

The first method may be appropriate following extravasation of vesicant drugs and involves administration of an antidote (if available) and the application of cold compresses 3–4 times a day (consult specialist literature for details of specific antidotes). Spreading and diluting the offending substance involves infiltrating the area with physiological saline, applying warm compresses, elevating the affected limb, and administering hyaluronidase below. A saline flush-out technique (involving flushing the subcutaneous tissue with physiological saline) may be effective but requires specialist advice. Hyaluronidase should not be administered following extravasation of vesicant drugs (unless it is either specifically indicated or used in the saline flush-out technique). Dexrazoxane p. 782 is licensed for the treatment of anthracycline-induced extravasation.

**Enzymes**

**Collagenase**

Collagenase below are proteolytic enzymes that are derived from the fermentation of *Clostridium histolyticum* and have the ability to break down collagen. A preparation containing a mixture of two collagenases is licensed for the treatment of Dupuytren’s contracture; the preparation should be injected into a palpable cord with a contracture of a metacarpophalangeal joint or proximal interphalangeal joint.

*Hyaluronidase*

Hyaluronidase is used to render the tissues more readily permeable to injected fluids, e.g. for introduction of fluids by subcutaneous infusion (termed hypodermoclysis).

**Rubefacients, topical NSAIDs, capsaicin, and poultices**

Rubefacients act by counter-irritation. Pain, whether superficial or deep-seated, is relieved by any method that itself produces irritation of the skin. Topical rubefacient preparations may contain nicotinate and salicylate compounds, essential oils, capsicum, and camphor. The evidence available does not support the use of topical rubefacients in acute or chronic musculoskeletal pain.

**Topical NSAIDs**

The use of a NSAID by mouth is effective for relieving musculoskeletal pain. *Topical NSAIDs* (e.g. felbinac p. 925, ibuprofen p. 927, ketoprofen p. 930, and piroxicam p. 936) may provide some relief of pain in musculoskeletal conditions; they can be considered as an adjunctive treatment in knee or hand osteoarthritis.

**Capsaicin**

A preparation containing capsaicin p. 383 0.025% can be considered as an adjunct in hand or knee osteoarthritis. It may need to be used for 1–2 weeks before pain is relieved.

A capsaicin 0.075% cream is licensed for the symptomatic relief of postherpetic neuralgia after lesions have healed, and for the relief of painful diabetic neuropathy.

A self-adhesive patch containing capsaicin 8% is licensed for the treatment of peripheral neuropathic pain in non-diabetic patients.
Hypodermoclysis
BY SUBCUTANEOUS INJECTION
▶ Adult: 1500 units, to be dissolved in 1 mL water for injections or 0.9% sodium chloride injection, administered before start of 500–1000 mL infusion fluid

Extravasation
BY LOCAL INFILTRATION
▶ Adult: 1500 units, to be dissolved in 1 mL water for injections or 0.9% sodium chloride and infiltrated into affected area as soon as possible after extravasation

Haematoma
BY LOCAL INFILTRATION
▶ Adult: 1500 units, to be dissolved in 1 mL water for injections or 0.9% sodium chloride and infiltrated into affected area

Enhance permeation of ophthalmic local anaesthetic TO THE EYE
▶ Adult: 15 units/mL, to be mixed with the local anaesthetic solution

UNLICENSED USE Licensed for use in children, but age range not specified by the manufacturer.
CONTRA-INDICATIONS Avoid sites where infection is present · avoid sites where malignancy is present · do not apply direct to cornea · not for anaesthesia in unexplained premature labour · not for intravenous administration · not to be used to enhance the absorption and dispersion of dopamine and/or alpha-adrenoceptor agonists · not to be used to reduce swelling of bites · not to be used to reduce swelling of stings

CAUTIONS Elderly (control speed and total volume and avoid overhydration especially in renal impairment) · infants (control speed and total volume and avoid overhydration especially in renal impairment)

SIDE-EFFECTS
▶ Common or very common Oedema
▶ Rare Bleeding · bruising · infection · local irritation
▶ Frequency not known Anaphylaxis · severe allergy

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Powder for solution for injection
▶ HYALURONIDASE (Non-proprietary)
Hyaluronidase 1500 unit Hyaluronidase 1,500 unit powder for solution for injection ampoules | 10 ampoule £104.24
Chapter 11

Eye

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Eye

Administration of drugs to the eye

Drugs are most commonly administered to the eye by topical application as eye drops or eye ointments. When a higher drug concentration is required within the eye, a local injection may be necessary.

Eye-drop dispenser devices are available to aid the instillation of eye drops from plastic bottles and some are prescribable on the NHS (consult Drug Tariff—see Appliances and Reagents). Product-specific devices may be supplied by manufacturers—consult individual manufacturers for information. They are particularly useful for the elderly, visually impaired, arthritic, or otherwise physically limited patients.

Eye drops and eye ointments

Eye drops are generally instilled into the pocket formed by gently pulling down the lower eyelid and keeping the eye closed for as long as possible after application; one drop is all that is needed. Instillation of more than one drop should be discouraged because it may increase systemic side-effects. A small amount of eye ointment is applied similarly; the ointment melts rapidly and blinking helps to spread it.

When two different eye-drop preparations are used at the same time of day, dilution and overflow may occur when one immediately follows the other. The patient should therefore leave an interval of at least 5 minutes between the two; the interval should be extended when eye drops with a prolonged contact time, such as gels and suspensions, are used. Eye ointment should be applied after drops.

Systemic effects may arise from absorption of drugs into the general circulation from conjunctival vessels or from the nasal mucosa after the excess preparation has drained down through the tear ducts. The extent of systemic absorption following ocular administration is highly variable; nasal drainage of drugs is associated with eye drops much more often than with eye ointments. Pressure on the lacrimal punctum for at least a minute after applying eye drops reduces nasolacrimal drainage and therefore decreases systemic absorption from the nasal mucosa.

After using eye drops or eye ointments, patients should be warned not to drive or perform other skilled tasks until vision is clear.

Also see warnings relating to eye drops and contact lenses.

Eye lotions

These are solutions for the irrigation of the conjunctival sac. They act mechanically to flush out irritants or foreign bodies as a first-aid treatment. Sterile sodium chloride 0.9% solution is usually used. Clean water will suffice in an emergency.

Other preparations administered to the eye

Subconjunctival injection may be used to administer anti-infective drugs, mydriatics, or corticosteroids for conditions not responding to topical therapy; intracameral and intravitreal routes can also be used to administer certain drugs, for example antibacterials. These injections should only be used under specialist supervision.

Drugs such as antimicrobials and corticosteroids may be administered systemically to treat susceptible eye conditions.

Ophthalmic Specials

Certain eye drops, e.g. amphotericin, ceftazidime, cefuroxime, colistimethate sodium, desferrioxamine mesilate, dexamethasone, gentamicin, and vancomycin can be prepared aseptically from material supplied for injection.

The Royal College of Ophthalmologists and the UK Ophthalmic Pharmacy Group have produced the Ophthalmic Specials Guidance to help prescribers and pharmacists manage and restrict the use of unlicensed eye preparations. ‘Specials’ should only be prescribed in situations where a licensed product is not suitable for a patient’s needs. The Ophthalmic Specials Guidance can be accessed on the Royal College of Ophthalmologists website (www.rcophth.ac.uk). The guidance will be reviewed every six months to ensure the most accurate and up-to-date information is available.

Preservatives and sensitisers

Information on preservatives and substances identified as skin sensitisers is provided under Excipients statements in preparation entries. Very rarely, cases of corneal calcification have been reported with the use of phosphate-containing eye drops in patients with significantly damaged corneas—consult product literature for further information.

Control of microbial contamination

Preparations for the eye should be sterile when issued. Care should be taken to avoid contamination of the contents during use.

Eye drops in multiple-application containers for domiciliary use should not be used for more than 4 weeks after first opening (unless otherwise stated by the manufacturer).

Multiple application eye drops for use in hospital wards are normally discarded 1 week after first opening—local
Contact lenses

For cosmetic reasons many people prefer to wear contact lenses rather than spectacles; contact lenses are also sometimes required for medical indications. Visual defects are corrected by either rigid ('hard' or gas permeable) lenses or soft (hydrogel or silicone hydrogel—in adults only) lenses; soft lenses are the most popular type, because they are initially the most comfortable, but they may not give the best vision. Lenses should usually be worn for a specified number of hours each day and removed for sleeping. The risk of infectious and non-infectious keratitis is increased by extended continuous contact lens wear, which is not recommended, except when medically indicated.

Contact lenses require meticulous care. Poor compliance with directions for use, and with daily cleaning and disinfection, the use of contaminated lens cases, or tap water coming into contact with the lenses. The condition is associated with ineffective lens cleaning and with disinfection, can result in complications including ulcerative keratitis or conjunctivitis. Acanthamoeba keratitis, a painful and sight-threatening condition, is associated with ineffective lens cleaning and disinfection, the use of contaminated lens cases, or tap water coming into contact with the lenses. The condition is especially associated with the use of soft lenses (including frequently replaced lenses) and should be treated by specialists.

Contact lenses and drug treatment

Special care is required in prescribing eye preparations for contact lens users. Some drugs and preservatives in eye preparations can accumulate in hydrogel lenses and may induce toxic and adverse reactions. Therefore, unless medically indicated, the lenses should be removed before instillation of the eye preparation and not worn during the period of treatment. Alternatively, unpreserved drops can be used. Eye drops may, however, be instilled while patients are wearing rigid corneal contact lenses. Ointment preparations should never be used in conjunction with contact lens wear; oily eye drops should also be avoided.

Many drugs given systemically can also have adverse effects on contact lens wear. These include oral contraceptives (particularly those with a higher oestrogen content), drugs which reduce blink rate (e.g. anxiolytics, hypnotics, antihistamines, and muscle relaxants), drugs which reduce lacrimation (e.g. antihistamines, antimuscarinics, phenothiazines and related drugs, some beta-blockers, diuretics, and tricyclic antidepressants), and drugs which increase lacrimation (including ephedrine hydrochloride and hydralazine hydrochloride). Other drugs that may affect contact lens wear are isotretinoin (can cause conjunctival inflammation), aspirin (salicylic acid appears in tears and can be absorbed by contact lenses—leading to irritation), and rifampicin and sulfasalazine (can discolor lenses).

1 Allergic and inflammatory eye conditions

Eye, allergy and inflammation

Corticosteroids

Corticosteroids administered locally to the eye or given by mouth are effective for treating anterior segment inflammation, including that which results from surgery. Topical corticosteroids are applied frequently for the first 2–48 hours; once inflammation is controlled, the frequency of application is reduced. They should normally only be used under expert supervision; three main dangers are associated with their use:

- A 'red eye', when the diagnosis is unconfirmed, may be due to herpes simplex virus, and a corticosteroid may aggravate the condition, leading to corneal ulceration, with possible damage to vision and even loss of the eye.
- Bacterial, fungal, and amoebic infections pose a similar hazard;
- 'Steroid glaucoma' can follow the use of corticosteroid eye preparations in susceptible individuals;
- A 'steroid cataract' can follow prolonged use.

Combination products containing a corticosteroid with an anti-infective drug are sometimes used after ocular surgery to reduce inflammation and prevent infection; use of combination products is otherwise rarely justified.

Systemic corticosteroids may be useful for ocular conditions. The risk of producing a 'steroid cataract' increases with the dose and duration of corticosteroid use.

Intravitreal corticosteroids

An intravitreal implant containing dexamethasone p. 947 (Ozurdex®) is licensed for the treatment of adults with macular oedema following either branch retinal vein occlusion or central retinal vein occlusion; it is also licensed for the treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis.

An intravitreal implant containing fluocinolone acetonide p. 974 (Iluvien®) is licensed for the treatment of visual impairment associated with chronic diabetic macular oedema which is insufficiently responsive to available therapies. It should be administered by specialists experienced in the use of intravitreal injections.

Other anti-inflammatory preparations

Other preparations used for the topical treatment of inflammation and allergic conjunctivitis include antihistamines, lodoxamide p. 946, and sodium cromoglicate p. 946.

Eye drops containing antihistamines, such as antazoline (with xylometazoline hydrochloride p. 983 as Otrivine-Antistin®), azelastine hydrochloride p. 945, epinastine hydrochloride p. 945, ketotifen p. 945, and olopatadine p. 946, can be used for allergic conjunctivitis.

Sodium cromoglicate p. 946 (sodium cromoglycate) and nedocromil sodium p. 946 eye drops can be useful for vernal
1.1 Allergic conjunctivitis

ANTIHISTAMINES

Antazoline with xylometazoline

**INDICATIONS AND DOSE**

**Allergic conjunctivitis**

TO THE EYE

- Child 12-17 years: Apply 2–3 times a day for maximum 7 days
- Adult: Apply 2–3 times a day for maximum 7 days

**SIDE-EFFECTS**

- Common or very common Transient stinging
- Frequency not known Blurred vision, eye irritation, mydriasis

**SIDE-EFFECTS, FURTHER INFORMATION**

Absorption of antazoline and xylometazoline may result in the possibility of interaction with other drugs.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate

- Otrivine Antistin (Spectrum Thea Pharmaceuticals Ltd)
  - Antazoline sulfate 5 mg per 1 ml, Xylometazoline hydrochloride 500 microgram per 1 ml
  - Otrivine Antistin 0.5%/0.05% eye drops | 10 ml £2.35 DT price = £2.35

Azelastine hydrochloride

**INDICATIONS AND DOSE**

**Seasonal allergic conjunctivitis**

TO THE EYE

- Child 4-17 years: Apply twice daily, increased if necessary to 4 times a day
- Adult: Apply twice daily, increased if necessary to 4 times a day

**PERENNIAL CONJUNCTIVITIS**

TO THE EYE

- Child 12-17 years: Apply twice daily; increased if necessary to 4 times a day, maximum duration of treatment 6 weeks
- Adult: Apply twice daily; increased if necessary to 4 times a day, maximum duration of treatment 6 weeks

**SIDE-EFFECTS**

Bitter taste, mild transient irritation

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate

- Optilast (Meda Pharmaceuticals Ltd)
  - Azelastine hydrochloride 500 microgram per 1 ml Optilast 0.05% eye drops | 8 ml £6.40

**Emedastine**

**INDICATIONS AND DOSE**

**Seasonal allergic conjunctivitis**

TO THE EYE

- Child 3-17 years: Apply twice daily
- Adult: Apply twice daily

**SIDE-EFFECTS**

Blurred vision, corneal infiltrates (discontinue), corneal staining, dry eye, headache, irritation, keratitis, lacrimation, local oedema, photophobia, rhinitis, transient burning, transient stinging

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

EXCIPIENTS: May contain Benzalkonium chloride

- Emadine (Alcon Laboratories (UK) Ltd)
  - Emadine (as Emedastine difumarate) 500 microgram per 1 ml
  - Emadine 0.5mg/ml eye drops | 5 ml £7.31 DT price = £7.31

**Epinastine hydrochloride**

**INDICATIONS AND DOSE**

**Seasonal allergic conjunctivitis**

TO THE EYE

- Child 12-17 years: Apply twice daily for maximum 8 weeks
- Adult: Apply twice daily for maximum 8 weeks

**SIDE-EFFECTS**

- Common or very common Burning
- Uncommon Conjunctival hyperaemia, dry eye, eye pain, eye pruritus, headache, increased lacrimation, nasal irritation, rhinitis, taste disturbance, visual disturbance

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate

- Relestat (Allergan Ltd)
  - Epinastine hydrochloride 500 microgram per 1 ml Relestat 500micrograms/ml eye drops | 5 ml £9.90 DT price = £9.90

**Ketotifen**

**INDICATIONS AND DOSE**

**Seasonal allergic conjunctivitis**

TO THE EYE

- Child 3-17 years: Apply twice daily
- Adult: Apply twice daily

**INTERACTIONS**

→ Appendix 1 (antihistamines).

Sedative antihistamine interactions apply to a lesser extent to the non-sedating antihistamines. Interactions do not generally apply to antihistamines used for topical action.
Olopatadine

INDICATIONS AND DOSE
Seasonal allergic conjunctivitis
TO THE EYE
▶ Child 3–17 years: Apply twice daily for maximum 4 months
▶ Adult: Apply twice daily for maximum 4 months

SIDE-EFFECTS
▶ Common or very common Local irritation
▶ Uncommon Asthenia - dizziness - dry eye - headache - keratitis - local oedema - photophobia
▶ Frequency not known Dry nose

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
Eye drops
EXCIPIENTS: May contain Benzalkonium chloride
▶ Zaditen (Spectrum Thea Pharmaceuticals Ltd)
Ketotifen (as Ketotifen fumarate) 250 microgram per 1 ml
Zaditen 250 micrograms/ml eye drops | 5 ml [P] £7.80 DT price = £7.80

Mast cell stabilisers

Lodoxamide

INDICATIONS AND DOSE
Allergic conjunctivitis
TO THE EYE
▶ Child 4–17 years: Apply 4 times a day, improvement of symptoms may sometimes require treatment for up to 4 weeks
▶ Adult: Apply 4 times a day, improvement of symptoms may sometimes require treatment for up to 4 weeks

SIDE-EFFECTS
▶ Common or very common Blurred vision - burning - itching - ocular discomfort - stinging - tear production disturbance
▶ Uncommon Blepharitis - dizziness - drowsiness - flushing - headache - keratitis - nasal dryness

EXCEPTIONS TO LEGAL CATEGORY
Lodoxamide 0.1% eye drops can be sold to the public for treatment of allergic conjunctivitis in adults and children over 4 years.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
Eye drops
EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate
▶ Alomide (Alcon Laboratories (UK) Ltd)
Lodoxamide (as Lodoxamide trometamol) 1 mg per 1 ml
Lodoxamide 0.1% eye drops | 10 ml [P] £5.21 DT price = £5.21
Alomidone Allergy 0.1% eye drops | 5 ml [P] £1.12

Nedocromil sodium

INDICATIONS AND DOSE
Seasonal and perennial conjunctivitis
TO THE EYE
▶ Child 6–17 years: Apply twice daily, increased if necessary to 4 times a day for maximum 12 weeks
Adapt: Apply twice daily, increased if necessary to 4 times a day for maximum 12 weeks

SIDE-EFFECTS
Distinctive taste - transient burning - transient stinging

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
Eye drops
EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate
▶ Rapitil (Sanofi)
Nedocromil sodium 20 mg per 1 ml
Rapitil 2% eye drops | 5 ml [P] £2.86 DT price = £2.86

Sodium cromoglicate
(Sodium cromoglycate)

INDICATIONS AND DOSE
Allergic conjunctivitis | Seasonal keratoconjunctivitis
TO THE EYE
▶ Child: Apply 4 times a day
▶ Adult: Apply 4 times a day

SIDE-EFFECTS
Transient burning - transient stinging

EXCEPTIONS TO LEGAL CATEGORY
Sodium cromoglicate 2% eye drops can be sold to the public (in max. pack size of 10 ml) for treatment of acute seasonal and perennial allergic conjunctivitis.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops
Eye drops
▶ SODIUM CROMOGLICATE (Non-proprietary)
Sodium cromoglicate 20 mg per 1 ml
Sodium cromoglicate 2% eye drops | 13.5 ml [P] £6.30 DT price = £1.86
Lloydspharmacy Allergy 2% eye drops | 10 ml [P] no price available
Numark Allergy 2% eye drops | 10 ml [P] £1.53
▶ Catacom (Moorfields Pharmaceuticals)
Sodium cromoglicate 20 mg per 1 ml
Catacom 2% eye drops 0.3 ml unit dose | 30 unit dose [P] £8.99 DT price = £8.99
Cromolux (Tubilux Pharma Ltd)
Sodium cromoglicate 20 mg per 1 ml
Sodium cromoglicate 2% eye drops | 13.5 ml [P] £3.20 DT price = £1.86
Opticrom (Sanofi)
Sodium cromoglicate 20 mg per 1 ml
Opticrom Allergy 2% eye drops | 5 ml [P] £2.74 | 10 ml [P] £3.35
Opticrom Aqueous 2% eye drops | 13.5 ml [P] £8.03 DT price = £1.86
▶ Optrex Allergy (Reckitt Benckiser Healthcare (UK) Ltd)
Sodium cromoglicate 20 mg per 1 ml
Optrex Allergy 2% eye drops | 10 ml [P] £3.88
▶ Pollenase (sodium cromoglicate) (Peach Ethical Ltd)
Sodium cromoglicate 20 mg per 1 ml
Pollenase Allergy 2% eye drops | 10 ml [P] £2.08
▶ Vividrin (Bausch & Lomb UK Ltd)
Sodium cromoglicate 20 mg per 1 ml
Vividrin 2% eye drops | 13.5 ml [P] £10.85 DT price = £1.86

Pollenase Allergy
(Pollenase (sodium cromoglicate))
1.2 Inflammatory eye conditions

CORTICOSTEROIDS

Betamethasone

INDICATIONS AND DOSE

Local treatment of inflammation (short term)
TO THE EYE USING EYE DROP
- Child: Apply every 1–2 hours until controlled then reduce frequency
- Adult: Apply every 1–2 hours until controlled then reduce frequency
TO THE EYE USING EYE OINTMENT
- Child: Apply 2–4 times a day, alternatively apply at night when used in combination with eye drops
- Adult: Apply 2–4 times a day, alternatively apply at night when used in combination with eye drops

SIDE-EFFECTS
Adrenal suppression following prolonged use in neonates - corneal thinning - scleral thinning

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Ear/eye/nose drops solution
EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate
- Betamethasone sodium phosphate 1 mg per 1 ml Betamethasone 0.1% eye/ear/nose drops | 5 ml | no price available
- Betnesol (Focus Pharmaceuticals Ltd)
- Betamethasone sodium phosphate 1 mg per 1 ml Betnesol 0.1% eye/ear/nose drops | 10 ml | £2.32 DT price = £2.32
- Vistamethasone (Martindale Pharmaceuticals Ltd)
- Betamethasone sodium phosphate 1 mg per 1 ml Vistamethasone 0.1% eye/ear/nose drops | 5 ml | £1.62 | 10 ml | £1.16 DT price = £2.32

Eye ointment
- Betnesol (Focus Pharmaceuticals Ltd)
- Betamethasone sodium phosphate 1 mg per 1 gram Betnesol 0.1% eye ointment | 1 gram | £1.41 DT price = £1.41

Betamethasone with neomycin

The properties listed below are those particular to the combination only. For the properties of the components please consider, betamethasone p. 947.

INDICATIONS AND DOSE

Local treatment of eye inflammation and bacterial infection (short-term)
TO THE EYE USING EYE DROP
- Adult: Apply up to 6 times a day

LESS SUITABLE FOR PRESCRIBING Betamethasone with neomycin eye-drops are less suitable for prescribing.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Ear/eye/nose drops solution
EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate
- Betnesol-N (Focus Pharmaceuticals Ltd)
- Betamethasone (as Betamethasone sodium phosphate) 1 mg per 1 ml, Neomycin sulfate 5 mg per 1 ml Betnesol-N ear/eye/nose drops | 10 ml | £2.39

Dexamethasone

INDICATIONS AND DOSE

Local treatment of inflammation (short term)
INITIALLY TO THE EYE USING EYE DROP
- Child: Apply 4–6 times a day
- Adult: Apply every 30–60 minutes until controlled, then (to the eye) reduced to 4–6 times a day

Short term local treatment of inflammation (severe conditions)
TO THE EYE USING EYE DROP
- Child: Apply every 30–60 minutes until controlled, reduce frequency when control achieved

Macular oedema following either branch retinal vein occlusion or central retinal vein occlusion (specialist use only)
| Visual impairment due to diabetic macular oedema in adults who are pseudophoric, or who are insufficiently responsive to, or unsuitable for non-corticosteroid therapy (specialist use only) | For the treatment of inflammation of the posterior segment of the eye presenting as non-infectious uveitis (specialist use only) |

BY INTRAVITREAL INJECTION
- Adult: 700 micrograms, to be administered into the affected eye, concurrent administration to both eyes not recommended. For further information on pretreatment, administration and repeat dosing, consult product literature


CONTRA-INDICATIONS
- With intravitreal use active ocular herpes simplex - active or suspected ocular infection - active or suspected periocular infection - rupture of the posterior lens capsule in patients with aphakia, iris or transcleral fixed intra-ocular lens or anterior chamber intra-ocular lens - uncontrolled advanced glaucoma

CAUTIONS
- With intravitreal use history of ocular viral infection (including herpes simplex) - posterior capsule tear or iris defect (risk of implant migration into the anterior chamber which may cause corneal oedema and, in persistent severe cases, the need for corneal transplantation) - retinal vein occlusion with significant retinal ischaemia

INTERACTIONS
- With intravitreal use Caution with concomitant administration of anticoagulant or antiplatelet drugs—increased risk of haemorrhagic events.

SIDE-EFFECTS
- With intravitreal use Eyelid pruritus - glaucoma - migraine - necrotising retinitis
- Frequency not known
- When used by eye Adrenal suppression following prolonged use in neonates - corneal thinning - scleral thinning
- With intravitreal use Blepharitis - cataract - headache - ocular hypertension - raised intra-ocular pressure - secondary ocular infection - visual disturbance

PREGNANCY
- With intravitreal use Manufacturer advises avoid unless potential benefit outweighs risk—no information available.

BREAST FEEDING
- With intravitreal use Manufacturer advises avoid unless potential benefit outweighs risk—no information available.
**MONITORING REQUIREMENTS**

- With intravitreal use: Monitor intra-ocular pressure and for signs of ocular infection. In patients with posterior capsule tear or iris defect monitor for implant migration to allow for; early diagnosis and management.

**PRESCRIBING AND DISPENSING INFORMATION**

- **With intravitreal use**
  - **MONITORING REQUIREMENTS**
    - preservatives, preservative-free unit dose vials may be available.

**NATIONAL FUNDING/ACCESS DECISIONS**

- **NICE technology appraisals (TAs)**
  - **Ozurdex**
  - **Maxidex**
  - **Dropodex**

**EXCIPIENTS:** May contain Hydroxybenzoates (parabens), wool fat and related substances including lanolin

**Eye ointment**

- **Dexafree** (Alcon Laboratories (UK) Ltd)
  - Dexamethasone 1 mg per 1 gram
  - framycetin 5 mg per 1 gram
  - neomycin 3.5 mg per 1 ml
  - polymyxin B 6000 unit per 1 ml

**Ear/eye drops solution**

- **Sofradex** (Sanofi)
  - Dexamethasone (as Dexamethasone sodium metasulphobezoate) 500 microgram per 1 ml
  - Framycetin sulfate 5 mg per 1 ml
  - Gramicidin 50 microgram per 1 ml

The properties listed below are those particular to the combination only. For the properties of the components please consider, dexamethasone p. 947, neomycin sulfate p. 451.

**INDICATIONS AND DOSE**

- Local treatment of inflammation (short-term)
  - **TO THE EYE USING EYE OINTMENT**
    - Child: Apply 4–6 times a day, may be administered every 30–60 minutes in severe conditions until controlled, then reduce frequency
    - Adult: Apply 4–6 times a day, may be administered every 30–60 minutes in severe conditions until controlled, then reduce frequency

**INDICATIONS AND DOSE**

- **Local treatment of inflammation (short-term)**
  - **TO THE EYE USING EYE DROPS**
    - Adult: Apply every 30–60 minutes until controlled then reduce frequency to, 4–6 times a day
  - Local treatment of inflammation (short-term)

**Dexamethasone with framycetin sulfate and gramicidin**

The properties listed below are those particular to the combination only. For the properties of the components please consider dexamethasone p. 947.

**INDICATIONS AND DOSE**

- Local treatment of inflammation (short-term)
  - **TO THE EYE USING EYE DROPS**
    - Adult: Apply 4–6 times a day, may be administered every 30–60 minutes in severe conditions until controlled, then reduce frequency

**LESS SUITABLE FOR PRESCRIBING**

- **Sofradex** is less suitable for prescribing.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.
  - **Ear/eye drops solution**
    - EXCIPIENTS: May contain Polysorbates
  - **Sofradex**
    - Dexamethasone (as Dexamethasone sodium metasulphobezoate) 500 microgram per 1 ml
    - Framycetin sulfate 5 mg per 1 ml
    - Gramicidin 50 microgram per 1 ml
  - **Sofradex®** ear/eye drops 10 ml

**Dexamethasone with tobramycin**

The properties listed below are those particular to the combination only. For the properties of the components please consider, dexamethasone p. 947, tobramycin p. 957.
Fluorometholone

**INDICATIONS AND DOSE**
Local treatment of inflammation (short term)

**TO THE EYE**
- Child 2-17 years: Apply every 1 hour for 24–48 hours, then reduced to 2–4 times a day
- Adult: Apply every 1 hour for 24–48 hours, then reduced to 2–4 times a day

**SIDE-EFFECTS**
Adrenal suppression following prolonged use in neonates • corneal thinning • scleral thinning

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**
*EXCIPIENTS*: May contain Benzalkonium chloride, disodium edetate, polysorbates

▸ **FML Liquifilm** (Allergan Ltd)
  Fluorometholone 1 mg per 1 ml FML Liquifilm 0.1% ophthalmic suspension | 5 ml (Pom) £1.71 DT price = £3.75

**Prednisolone**

**INDICATIONS AND DOSE**
Local treatment of inflammation (short-term)

**TO THE EYE**
- Child: Apply every 1–2 hours until controlled then reduce frequency
- Adult: Apply every 1–2 hours until controlled then reduce frequency

**UNLICENSED USE**
*Pred Forte®* not licensed for use in children (age range not specified by manufacturer).

**SIDE-EFFECTS**
Adrenal suppression following prolonged use in neonates • corneal thinning • scleral thinning

**PRESCRIBING AND DISPENSING INFORMATION**
Although multi-dose prednisolone eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops

**Ear/eye drops solution**
*EXCIPIENTS*: May contain Benzalkonium chloride, disodium edetate

▸ **Predsol** (Focus Pharmaceuticals Ltd)
  Prednisolone sodium phosphate 5 mg per 1 ml Predsol 0.5% ear/eye drops | 10 ml (Pom) £2.00 DT price = £2.00

**Eye drops**
*EXCIPIENTS*: May contain Benzalkonium chloride, disodium edetate, polysorbates

▸ **PREDNISOLONE (Non-proprietary)**
  Prednisolone sodium phosphate 300 microgram per 1 ml Prednisolone sodium phosphate 0.03% eye drops preservative free | 10 ml (Pom) £33.24
  Prednisolone sodium phosphate 1 mg per 1 ml Prednisolone sodium phosphate 0.1% eye drops preservative free | 10 ml (Pom) £30.41
  Prednisolone sodium phosphate 3 mg per 1 ml Prednisolone sodium phosphate 0.3% eye drops preservative free | 10 ml (Pom) £28.03

▸ **Pred Forte** (Allergan Ltd)
  Prednisolone acetate 10 mg per 1 ml Pred Forte 1% eye drops | 5 ml (Pom) £1.82 DT price = £1.82 | 10 ml (Pom) £3.66 DT price = £3.66

**Rimexolone**

**INDICATIONS AND DOSE**
Local treatment of postoperative inflammation (short term use)

**TO THE EYE**
- Adult: Apply 4 times a day for a week, treatment to begin 24 hours after surgery

Local treatment of steroid-responsive inflammation (short term use)

**TO THE EYE**
- Adult: Apply at least 4 times a day for up to 4 weeks

**Uveitis (short term use)**

**TO THE EYE**
- Adult: Apply every 1 hour during the day time for week 1, then apply every 2 hours for week 2, then apply 4 times a day for a week 3, then apply twice daily for the first 4 days of week 4, then apply once daily for the remaining 3 days of week 4

**SIDE-EFFECTS**
Corneal thinning • scleral thinning

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**
*EXCIPIENTS*: May contain Benzalkonium chloride, disodium edetate, polysorbates

▸ **Vexol** (Alcon Laboratories (UK) Ltd)
  Rimexolone 10 mg per 1 ml Vexol 10mg/ml eye drops | 5 ml (Pom) £3.37 DT price = £3.37

**1.3 Uveitis, anterior**

**ANTIMUSCARINICS**

**Antimuscarinics (eye)**

**CAUTIONS**
Darkly pigmented iris is more resistant to pupillary dilatation and caution should be exercised to avoid overdosage • mydriasis can precipitate acute angle-closure glaucoma (usually in those aged over 60 years and hypermetropic (long-sighted), who are predisposed to the condition because of a shallow anterior chamber)

**SIDE-EFFECTS**
Conjunctivitis (on prolonged administration) • contact dermatitis • eye oedema (on prolonged administration) • hyperaemia (on prolonged administration) • local irritation (on prolonged administration)
administration) - raised intraocular pressure - transient stinging

**PATIENT AND CARER ADVICE** Patients may not be able to undertake skilled tasks until vision clears after mydriasis.

### Cyclopentolate hydrochloride

#### INDICATIONS AND DOSE

**Cycloplegia**

- **Adult:** (consult product literature)
- **Anterior uveitis**

**TO THE EYE USING EYE DROP**

- Adult: 10 mg (consult product literature)

#### SIDE-EFFECTS

**SIDE-EFFECTS, FURTHER INFORMATION**

Systemic side-effects can occur, particularly in children and the elderly.

#### MEDICINAL FORMS

- **Eye drops**
  - **ATROPINE SULFATE (Non-proprietary)**
    - Atropine sulfate 10 mg per 1 ml (Intrapharm Laboratories Ltd)
      - Minims atropine sulfate 1% eye drops 0.5ml unit dose £15.10
      - Atropine 1% eye drops 10 ml (BNF) £13.36

- **Cyclopentolate hydrochloride**

**INDICATIONS AND DOSE**

**Cycloplegia**

- **Child 3 months–11 years:** Apply 1 drop 30–60 minutes before examination, using 1% eye drops
- **Child 12–17 years:** Apply 1 drop 30–60 minutes before examination, using 0.5% eye drops

**Uveitis**

- **Child 3 months–17 years:** Apply 1 drop 2–4 times a day, using 0.5% eye drops (1% for deeply pigmented eyes)

**Adult:** (consult product literature)

#### SIDE-EFFECTS

**SIDE-EFFECTS, FURTHER INFORMATION**

Toxic systemic reactions can occur in children. Systemic side-effects can occur, particularly in children and the elderly.

**PRESCRIBING AND DISPENSING INFORMATION**

Although multi-dose cyclopentolate eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

#### MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug.

- **Eye drops**
  - May contain Benzalkonium chloride

- **Cyclopentolate hydrochloride 5 mg per 1 ml**
  - Minims cyclopentolate hydrochloride 0.5% eye drops 0.5ml unit dose £10.97
  - Cyclopentolate hydrochloride 0.5% eye drops 5 ml unit dose £11.23

- **Cyclopentolate hydrochloride 10 mg per 1 ml**
  - Minims cyclopentolate hydrochloride 1% eye drops 0.5ml unit dose £10.97
  - Cyclopentolate hydrochloride 1% eye drops 5 ml unit dose £11.23

### Homatropine hydrobromide

#### INDICATIONS AND DOSE

**Anterior uveitis**

- **Adult:** (consult product literature)

#### MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops

### Dry eye conditions

#### Dry eye

**Tear deficiency, ocular lubricants, and astringents**

- Chronic soreness of the eyes associated with reduced or abnormal tear secretion (e.g. in Sjögren’s syndrome) often responds to tear replacement therapy or pilocarpine p. 988 given by mouth in adults. The severity of the condition and patient preference will often guide the choice of preparation.

- Hypromellose p. 952 is the traditional choice of treatment for tear deficiency. It may need to be instilled frequently (e.g. hourly) for adequate relief. Ocular surface mucin is often abnormal in tear deficiency and the combination of hypromellose p. 952 with a mucolytic such as acetylcysteine below can be helpful.

- The ability of carbomers to cling to the eye surface may help reduce frequency of application to 4 times daily.

- Polyvinyl alcohol p. 952 increases the persistence of the tear film and is useful when the ocular surface mucin is reduced.

- Sodium hyaluronate p. 953 eye drops are also used in the management of tear deficiency.

- Sodium chloride p. 953 0.9% drops are sometimes useful in tear deficiency, and can be used as ‘comfort drops’ by contact lens wearers, and to facilitate lens removal. They are also used to irritate the eye. Special presentations of sodium chloride p. 953 0.9% and other irrigation solutions are used routinely for intra-ocular surgery. Sodium chloride p. 953 5% eye drops are used for the short-term treatment of corneal oedema in adults.

- Eye ointments containing a paraffin can be used to lubricate the eye surface, especially in cases of recurrent corneal epithelial erosion. They may cause temporary visual disturbance and are best suited for application before sleeping. Ointments should not be used during contact lens wear.

#### Ocular lubricants

**Acetylcysteine**

#### INDICATIONS AND DOSE

**Tear deficiency | Impaired or abnormal mucus production**

- **TO THE EYE**

- **Adult:** Apply 3–4 times a day
■ MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops

Eye drops
EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate

- Ilube (Moorfields Pharmaceuticals)
  Acetylcysteine 50 mg per 1 ml I Ilube 5% eye drops | 10 ml [P/PA]
  £14.93 DT price = £10.09

Carbomers (Polyacrylic acid)

INDICATIONS AND DOSE
Dry eyes including keratoconjunctivitis sicca, unstable tear film

TO THE EYE
- Child: Apply 3–4 times a day or when required
- Adult: Apply 3–4 times a day or when required

■ UNLICENSED USE
Some preparations not licensed for use in children.

■ PRESCRIBING AND DISPENSING INFORMATION
Synthetic high molecular weight polymers of acrylic acid cross-linked with either allyl ethers of sucrose or allyl ethers of pentaerythritol.

■ MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Eye drops
- CARBOMERS (Non-proprietary)
  Carbomer 980 2 mg per 1 gram EyeGel 0.2% eye gel | 10 gram £2.80 DT price = £2.80
  Carbomer 980 0.2% eye drops | 10 gram [P] £2.80 DT price = £2.80
  Carbomer 0.2% eye gel | 10 gram £2.80 DT price = £2.80
- Artelac Nighttime (Bausch & Lomb UK Ltd)
  Carbomer 980 2 mg per 1 gram Artelac Nighttime 0.2% eye gel | 10 gram £2.96 DT price = £2.96
- Clinitas Carboram (Alcon Ltd)
  Carbomer 980 2 mg per 1 gram Clinitas Carboram 0.2% eye gel | 10 gram £1.49 DT price = £1.49
- GelTears (Bausch & Lomb UK Ltd)
  Carbomer 980 2 mg per 1 gram GelTears 0.2% gel | 10 gram [P] £2.80 DT price = £2.80
- Lumecare Long Lasting (Medicom Healthcare Ltd)
  Carbomer 980 2 mg per 1 gram Lumecare Carbomer 0.2% eye gel | 10 gram £1.51 DT price = £1.51
- Viscotecars (Alcon Laboratories (UK) Ltd)
  Carbomer 980 2 mg per 1 gram Viscotecars 2mg/g liquid gel | 10 gram [P] £1.59 DT price = £1.59
  Viscotecars 2mg/g eye gel 0.6ml unit dose | 30 unit dose [P] £0.42
- Xailin (Nicox Pharma)
  Carbomer 980 2 mg per 1 gram Xailin 0.2% eye gel | 10 gram £3.25 DT price = £2.80

Eye gel
EXCIPIENTS: May contain Benzalkonium chloride, cetrimide, disodium edetate

- Blephagel (Spectrum Thea Pharmaceuticals Ltd)
  Carbomer 3.5 mg per 1 gram Blephagel 0.35% eye gel | 40 gram £6.66
  Carbomer 3.6 mg per 1 gram Blephagel 0.36% eye gel preservative free | 30 gram £7.53
- Liquivisc (Spectrum Thea Pharmaceuticals Ltd)
  Carbomer 974P 2.5 mg per 1 gram Liquivisc 0.25% eye gel | 10 gram [P] £4.50 DT price = £4.50

Carmellose sodium

INDICATIONS AND DOSE
Dry eye conditions

TO THE EYE
- Child: Apply as required
- Adult: Apply as required

■ PRESCRIBING AND DISPENSING INFORMATION
Some preparations are contained units which are resealable and may be used for up to 12 hours.

■ MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Eye drops
- CARMELLOSE SODIUM (Non-proprietary)
  Carmellose sodium 5 mg per 1 ml Carmellose 0.5% eye drops 0.4ml unit dose preservative free | 30 unit dose [P] no price available DT price = £4.80 | 30 unit dose 5.75 DT price = £4.80 | 90 unit dose [P] no price available
  PF Doses Carmellose 0.5% eye drops preservative free | 10 ml £7.49
  LumeCare Advance Carmellose 0.5% eye drops | 10 ml £5.99
  Carmellose 0.5% eye drops | 10 ml £7.49
  PF Doses Carmellose 1% eye drops preservative free | 10 ml £7.49
  Carmellose 1% eye drops 0.4ml unit dose preservative free | 30 unit dose [P] no price available DT price = £3.00 | 30 unit dose [P] no price available DT price = £3.00 | 60 unit dose [P] no price available
  Carmellosesee (Martindale Pharmaceuticals Ltd)
  Carmellose sodium 5 mg per 1 ml Melophthal 0.5% eye drops 0.4ml unit dose | 30 unit dose £5.75 DT price = £4.80
  Melophthal 1% eye drops 0.4ml unit dose | 30 unit dose £3.00 DT price = £3.00
  Carmellose 0.5% eye drops | 10 ml £7.49
- Carmize (Aspire Pharma Ltd)
  Carmellose sodium 5 mg per 1 ml Carmize 0.5% eye drops 0.4ml unit dose preservative free | 30 unit dose £3.75 DT price = £4.80 | 90 unit dose £15.53
  Carmize 1% eye drops | 10 ml £8.49
  Carmize 1% eye drops 0.4ml unit dose preservative free | 30 unit dose £3.00 DT price = £3.00 | 60 unit dose £6.00
  Carmellose 0.5% eye drops | 10 ml £7.49
- Cellusan (Farmigea S.p.A.)
  Carmellose sodium 5 mg per 1 ml Cellusan Light 0.5% eye drops 0.4ml unit dose preservative free | 30 unit dose £5.75 DT price = £4.80
  Cellusan 1% eye drops 0.4ml unit dose preservative free | 30 unit dose £3.00 DT price = £3.00
  Cellusan 0.5% eye drops 0.4ml unit dose preservative free | 30 unit dose £3.00 DT price = £3.00
  Melophthal 1% eye drops 0.4ml unit dose | 30 unit dose £3.00 DT price = £3.00
  Cellulan (Farmigea S.p.A.)
  Cellulan Light 0.5% eye drops 0.4ml unit dose preservative free | 30 unit dose £5.75 DT price = £4.80
  Cellusan 1% eye drops 0.4ml unit dose preservative free | 30 unit dose £3.00 DT price = £3.00
  LumeCare (Medicom Healthcare Ltd)
  Carmellose sodium 5 mg per 1 ml LumeCare Singles Carmellose 0.5% eye drops 0.4ml unit dose | 30 unit dose £4.60 DT price = £4.80

Hydroxyethylcellulose

INDICATIONS AND DOSE
Tear deficiency

TO THE EYE
- Child: Apply as required
- Adult: Apply as required

■ MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Eye drops
- HYDROXYETHYLCELLULOSE (Non-proprietary)
  Hydroxyethylcellulose 4.4 mg per 1 ml Minims artificial tears 0.44% eye drops 0.5ml unit dose | 20 unit dose [P] £8.97

Hydroxypropyl guar with polyethylene glycol and propylene glycol

INDICATIONS AND DOSE
Dry eye conditions

TO THE EYE
- Child: Apply as required
- Adult: Apply as required
**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

- Systane (Alcon Laboratories (UK) Ltd)
  
  Systane Gel eye drops | 10 ml £7.49

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**Hypromellose**

**INDICATIONS AND DOSE**

**Tear deficiency**

- **TO THE EYE**
  
  - Child: Apply as required
  
  - Adult: Apply as required

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**PRESCRIBING AND DISPENSING INFORMATION**

The Royal Pharmaceutical Society has stated that where it is not possible to ascertain the strength intended, the prescriber should be contacted to clarify the strength intended. Although multi-dose hypromellose eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

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**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops

**Eye drops**

EXCIPIENTS: May contain Benzalkonium chloride, cetrimide, disodium edetate

- **HYPROMELLOSE (Non-proprietary)**
  
  Hypromellose 2.5 mg per 1 ml Hypromellose 0.25% eye drops preservative free | 10 ml | £1.46
 
  Hypromellose 3 mg per 1 ml Hypromellose 0.3% eye drops preservative free | 10 ml | £1.75

  PF Drops Hypromelose 0.3% eye drops preservative free | 10 ml | £0.75

  Hypromellose 0.3% eye drops | 10 ml | £1.00 DT price = £1.17

  Artelac (Bausch & Lomb UK Ltd)
  
  Hypromellose 3.2 mg per 1 ml Artelac Single Dose Unit 0.32% eye drops 0.5ml unit dose | 30 unit dose | £16.95 | 60 unit dose | £32.85

  Artelac 0.32% eye drops | 10 ml | £6.99

  **Hydrocomor** (Moorfields-Pharmaceuticals)
  
  Hydrocomor 0.3% eye drops 0.4ml unit dose preservative free | 30 unit dose | £0.75

  Hydrogel (Envogen Healthcare Ltd)
  
  Hypromellose 3 mg per 1 ml Hydrogel 0.3% eye drops preservative free | 10 ml | £2.50

  Isoprop Alkaline (Alcon Laboratories (UK) Ltd)
  
  Hypromellose 10 mg per 1 ml Isoptal Alkaline 1% eye drops | 10 ml | £0.94 DT price | £0.94

  **Isopto Plain** (Alcon Laboratories (UK) Ltd)
  
  Hypromellose 5 mg per 1 ml Isopto Plain 0.5% eye drops | 10 ml | £0.61 DT price | £0.61

  **Lumecare Tear Drops** (Medicom Healthcare Ltd)
  
  Hypromellose 3 mg per 1 ml Lumecare Hypromellose 0.3% eye drops | 10 ml | £1.67 DT price | £1.17

  **Mandanol** (Hydroxypropyl methylcellulose) (M & A Pharmachem Ltd)
  
  Hypromellose 3 mg per 1 ml Mandanol eye drops | 10 ml | £1.33 DT price | £1.17

  SoftDrops (Farmigea S.p.A.)
  
  Hypromellose 3 mg per 1 ml SoftDrops 0.3% eye drops | 10 ml | £0.67 DT price | £0.17

  SoftDrops 0.3% eye drops 0.5ml unit dose preservative free | 30 unit dose | £0.75

  **Tear-Lac** (Scope Ophthalmics Ltd)
  
  Hypromellose 3 mg per 1 ml Tear-Lac 0.3% eye drops preservative free | 10 ml | £0.75

  **Xalilin Hydrate** (Nicox Pharma)
  
  Hypromellose 3 mg per 1 ml Xalilin Hydrate 0.3% eye drops preservative free | 10 ml | £4.60

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**Hypromellose with dextran 70**

The properties listed below are those particular to the combination only. For the properties of the components please consider, hypromellose above.

**INDICATIONS AND DOSE**

**Tear deficiency**

- **TO THE EYE**
  
  - Child: Apply as required
  
  - Adult: Apply as required

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**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate

- Tears Naturale (Alcon Laboratories (UK) Ltd)
  
  Dextran 70 1 mg per 1 ml Hypromelose 3 mg per 1 ml Tears Naturale eye drops | 15 ml | £1.89

  Tears Naturale eye drops 0.4ml unit dose | 28 unit dose | £13.26

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**Polyvinyl alcohol**

**INDICATIONS AND DOSE**

**Tear deficiency**

- **TO THE EYE**
  
  - Child: Apply as required
  
  - Adult: Apply as required

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**PRESCRIBING AND DISPENSING INFORMATION**

Although multi-dose polyvinyl alcohol eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

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**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops

**Eye drops**

EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate

- **POLYVINYL ALCOHOL (Non-proprietary)**
  
  Polyvinyl alcohol 14 mg per 1 ml PVA 1.4% eye drops | 15 ml | £1.63

  Polyvinyl alcohol 1.4% eye drops 0.4ml unit dose preservative free | 30 unit dose | no price available

  Polyvinyl alcohol 1.4% eye drops | 10 ml | no price available | 15 ml | no price available

  **Liquifilm Tears** (Allergan Ltd)
  
  Polyvinyl alcohol 14 mg per 1 ml Liquifilm Tears 1.4% eye drops | 15 ml | £1.93

  Liquifilm Tears 1.4% eye drops 0.4ml unit dose preservative free | 30 unit dose | £3.35

  Refresh Ophthalmic (Allergan Ltd)
  
  Polyvinyl alcohol 14 mg per 1 ml Refresh Ophthalmic 1.4% eye drops 0.4ml unit dose | 30 unit dose | £2.25

  Sno Tears (Bausch & Lomb UK Ltd)
  
  Polyvinyl alcohol 14 mg per 1 ml Sno Tears 1.4% eye drops | 10 ml | £1.06

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**Retinol palmitate with white soft paraffin and light liquid paraffin and liquid paraffin and wool**

**INDICATIONS AND DOSE**

**Dry eye conditions**

- **TO THE EYE**
  
  - Adult: (consult product literature)

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**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.
Sodium chloride

**INDICATIONS AND DOSE**
Irrigation, including first-aid removal of harmful substances TO THE EYE
- Child: Apply as required
- Adult: Apply as required

Tear deficiency | Ocular lubricants and astringents | Irrigation of the eye | Intra-ocular or topical irrigation during surgical procedures | Corneal oedema TO THE EYE
- Child: Apply as required
- Adult: Apply as required

*PRESCRIBING AND DISPENSING INFORMATION*  Although multi-dose sodium chloride eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

*MEDICINAL FORMS*
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops, eye ointment

**Eye drops**
- **SODIUM CHLORIDE (Non-proprietary)**
  - Sodium chloride 9 mg per 1 ml
  - Sodium chloride 50 mg per 1 ml
  - Sodium chloride 5% eye drops preservative free
  - Sodium chloride 5% eye drops
  - Sodium chloride 0.45ml unit dose preservative free
  - Sodium chloride 5% eye drops
  - Sodium chloride 10 ml
- **Hylo-Comod** (Scope Ophthalmics Ltd)
  - Hylo-Comod 0.2% eye drops preservative free
- **Vismed** (TRB Chemidica (UK) Ltd)
  - Vismed Multi 0.18% eye drops preservative free
  - Vismed Multi 0.18% eye drops preservative free
- **Xailin HA** (Nicot Pharma)
  - Xailin HA 0.2% eye drops preservative free

*Eye ointment*
- **SODIUM CHLORIDE (Non-proprietary)**
  - Sodium chloride 5% eye ointment preservative free
  - Sodium chloride 5 gram

Sodium hyaluronate

**INDICATIONS AND DOSE**
Dry eye conditions TO THE EYE
- Adult: Apply as required

*PRESCRIBING AND DISPENSING INFORMATION*  Some preparations are contained in units which are resealable and may be used for up to 12 hours. Although multi-dose sodium hyaluronate eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

*MEDICINAL FORMS*
There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**
- **Artefac Rebalance** (Bausch & Lomb UK Ltd)
  - Artefac Rebalance 0.15% eye drops
- **Artelac Splash** (Bausch & Lomb UK Ltd)
  - Artelac Splash 0.2% eye drops
- **Blink Intensive** (AMO UK Ltd)
  - Blink Intensive Tears 0.2% eye drops
- **Clinitas** (AltaCor Ltd)
  - Clinitas Multi 0.4% eye drops preservative free
  - Clinitas 0.4% eye drops 0.5ml unit dose

**Soybean oil**

**INDICATIONS AND DOSE**
Dry eye conditions TO THE EYE
- Child: Apply up to 4 times a day
- Adult: Apply up to 4 times a day

*MEDICINAL FORMS*
There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**
- **Emustil** (Moorfields Pharmaceuticals)
  - Emustil eye drops 0.3ml unit dose preservative free

**Paraffins**

**Liquid paraffin with white soft paraffin and wool alcohols**

**INDICATIONS AND DOSE**
Dry eye conditions TO THE EYE
- Child: Apply as required, best suited for application before sleep
- Adult: Apply as required, best suited for application before sleep

*MEDICINAL FORMS*
There can be variation in the licensing of different medicines containing the same drug.
Eye infections

Eye infections are broadly categorized into:
- Bacterial
- Viral
- Fungal
- Allergic
- Other conditions

**Bacterial infections**

- **Staphylococcal infections**
  - Treated with antibiotics such as cephalosporins, clindamycin, or methicillin.
  - Tetracyclines are also active against a wide variety of bacteria.
- **Gonococcal conjunctivitis**
  - Treated with penicillin or cephalosporins.
- **Bacterial endophthalmitis**
  - Requires immediate treatment, often with intravitreal injection.
- **Ocular cicatricial pemphigoid**
  - Treated with corticosteroids and immunosuppressants.

**Viral infections**

- **Herpes simplex**
  - Treated with aciclovir, if infection is localized.
  - May require oral or intravenous aciclovir for severe cases.
- **Herpes zoster**
  - Treated with aciclovir, often with corticosteroids to reduce complications.
- **CMV retinitis**
  - Treated with antiviral agents such as ganciclovir or foscarnet.

**Fungal infections**

- **Epidermophyton**
  - Treated with oral griseofulvin.
- **Cryptococcus**
  - Treated with amphotericin B or fluconazole.
- **Aspergillus**
  - Treated with voriconazole or caspofungin.

**Allergic conditions**

- **Allergic conjunctivitis**
  - Treated with antihistamines and topical corticosteroids.

**Other conditions**

- **Trachoma**
  - A blinding bacterial infection caused by Chlamydia trachomatis.
  - Treated with doxycycline or azithromycin.
- **Acute conjunctivitis**
  - Usually viral in origin and self-limiting.
  - Treat with cold compresses or artificial tears.

**Systemic treatment**

- **Intravitreal injection** for some conditions such as endophthalmitis.
- **Corticosteroids** for severe inflammatory conditions.

**Antibacterial eye preparations**

- **Chloramphenicol**
  - Well tolerated and effective against a wide range of bacteria.
- **Gentamicin**
  - Used for more severe bacterial infections.
- **Moxifloxacin**
  - Effective against most bacterial strains.
- **Chlorhexidine**
  - Used for antiseptic wound care.

**Antifungal eye preparations**

- **Miconazole**
  - Used for fungal infections of the cornea.
- **Fluconazole**
  - Used for more severe fungal infections.

**Antiviral eye preparations**

- **Ganciclovir**
  - Used for CMV retinitis.
- **Aciclovir**
  - Used for herpes simplex infections.
- **Foscarnet**
  - Used for severe herpes zoster.

**Ophthalmic preparations**

- **Eye ointments**
  - Used for conditions requiring prolonged application.
- **Eye drops**
  - Used for conditions requiring frequent application.

**Indications and dosage**

- **Eye surface lubrication**
  - Apply every 2 hours as required.
  - For conditions such as dry eye syndrome.
- **Antibacterial eye ointment**
  - Apply every 2 hours as required.
  - For conditions requiring prolonged application.

**Patient and carer advice**

- **Contact lens wear**
  - Avoid using contact lenses during eye infections.
- **Wound care**
  - Cleanse wounds gently to avoid infection.

**Medicinal forms**

- **Ointment**
  - Available in various forms such as paraffin, yellow, soft.
- **Lacri-Lube**
  - A preservative-free eye drops.
- **Propamidine isetionate**
  - Used for treatment of corneal ulcer.

**Administration**

- **Frequency of application**
  - Adjusted based on severity and response.
  - For conditions such as corneal ulcer.

**References**

- **Chloramphenicol**
  - Available on a named-patient basis from specialist centres.
- **Moxifloxacin**
  - Used for treatment of bacterial infections.

**Further reading**

- **British National Formulary**
  - Provides detailed information on medications.
- **Moorfields Eye Hospital**
  - Offers specialist advice and treatment.

**Note**

- **Caution**
  - Avoid using eye medications if there is a history of allergy.
  - Discontinue medications if there is no improvement.

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- **Eye infections**
  - Bacterial, Viral, Fungal, Allergic
  - Systemic treatment
  - Antimicrobial sensitivity
  - Antimicrobial agents
  - Antibacterial eye preparations
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  - Antiviral eye preparations
  - Ophthalmic preparations
  - Indications and dosage
  - Patient and carer advice
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  - Administration
  - References

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**Key points**

- **Bacterial infections**
  - Treated with antibiotics.
  - Systemic treatment may be required.
- **Viral infections**
  - Treated with antiviral agents.
  - Systemic treatment may be needed.
- **Fungal infections**
  - Treated with antifungal agents.
  - Systemic treatment may be used.
- **Allergic conditions**
  - Treated with antihistamines and topical corticosteroids.
  - Systemic treatment may be used.
- **Other conditions**
  - Treated with specific medications.
  - Systemic treatment may be used.

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**Further information**

- **Moorfields Eye Hospital**
  - Provides specialist advice and treatment.
- **British National Formulary**
  - Provides detailed information on medications.
3.1 Bacterial eye infection

Azithromycin

**INDICATIONS AND DOSE**

Trachomatous conjunctivitis caused by *Chlamydia trachomatis* | Purulent bacterial conjunctivitis

TO THE EYE

- **Child:** Apply twice daily for 3 days, review if no improvement after 3 days of treatment
- **Adult:** Apply twice daily for 3 days, review if no improvement after 3 days of treatment

**SIDE-EFFECTS**

- **Common or very common** Blurred vision - ocular burning - ocular discomfort - ocular pruritus
- **Uncommon** Conjunctival hyperaemia - eyelid eczema - eyelid erythema - eyelid oedema - keratitis

**MEDIcINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

- **Azityer** (Spectrum Thea Pharmaceuticals Ltd)
  - Azithromycin dihydrate 15 mg per 1 gram
  - Azityer 15mg/g eye drops 0.25g unit dose | 6 unit dose [P] £6.99 DT price = £6.99

Cefuroxime

**INDICATIONS AND DOSE**

**APROKAM** INTRACAMERAL INJECTION

Prophylaxis of endophthalmitis after cataract surgery

**B**Y **IN**TRACAMERAL **I**NJECTION

- **Adult:** 1 mg, dose to be injected into the anterior chamber of the eye at the end of cataract surgery

**CAUTIONS**

- **APROKAM** INTRACAMERAL INJECTION
  - Combined operations with cataract surgery - complicated cataracts - reduced corneal endothelial cells (less than 2000) - severe risk of infection - severe thyroid disease
- **PREGNANCY** Not known to be harmful.
- **BREAST FEEDING** Present in milk in low concentration, but appropriate to use.

**MEDIcINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder for solution for injection**

- **Aprokam** (Spectrum Thea Pharmaceuticals Ltd)
  - Cefuroxime (as Cefuroxime sodium) 50 mg
  - Aprokam 50mg powder for solution for injection vials | 10 vial [P] £73.50

Chloramphenicol

- **DRUG ACTION** Chloramphenicol is a potent broad-spectrum antibiotic.

**INDICATIONS AND DOSE**

**TO THE EYE USING EYE DROP**

- **Child:** Apply 1 drop every 2 hours then reduce frequency as infection is controlled and continue for 48 hours after healing, frequency dependent on the severity of the infection. For less severe infection 3–4 times daily is generally sufficient
- **Adult:** Apply 1 drop every 2 hours then reduce frequency as infection is controlled and continue for

48 hours after healing, frequency dependent on the severity of the infection. For less severe infection 3–4 times daily is generally sufficient

**TO THE EYE USING EYE OINTMENT**

- **Child:** Apply daily, to be applied at night (if eye drops used during the day), alternatively apply 3–4 times a day, if ointment used alone
- **Adult:** Apply daily, to be applied at night (if eye drops used during the day), alternatively apply 3–4 times a day, if ointment used alone

**UNLICENSED USE** Oral azithromycin not licensed for trachoma which results from chronic infection with *Chlamydia trachomatis*.

**SIDE-EFFECTS** Transient stinging

**PREGNANCY** Avoid unless essential—no information on topical use but risk of ‘neonatal grey-baby syndrome’ with oral use in third trimester.

**BREAST FEEDING** Avoid unless essential—theoretical risk of bone-marrow toxicity.

**PRESCRIBING AND DISPENSING INFORMATION** Although multi-dose chloramphenicol eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**EXCEPTIONS TO LEGAL CATEGORY** Chloramphenicol 0.5% eye drops (in max. pack size 10 mL) and 1% eye ointment (in max. pack size 4 g) can be sold to the public for treatment of acute bacterial conjunctivitis in adults and children over 2 years; max. duration of treatment 5 days.

**MEDIcINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

**EXCIPIENTS:** May contain Phenylmercuric acetate

- **CHLORAMPHENICOL (Non-proprietary)**
  - Chloramphenicol 5 mg per 1 ml
  - Chloramphenicol Antibiotic 0.5% eye drops | 10 ml [P] £1.70 DT price = £1.50
  - Golden Eye Antibiotic 0.5% eye drops | 10 ml [P] £3.26 DT price = £1.50

- Minims chloramphenicol 0.5% eye drops 0.5ml unit dose | 20 unit dose [P] £10.99 DT price = £10.99

- Chloramphenicol 0.5% eye drops | 10 ml [P] £2.68 DT price = £1.50

- Tubilux Infected Eyes 0.5% eye drops | 10 ml [P] £2.75 DT price = £1.50

- **Brochlor** (Sanofi)
  - Chloramphenicol 5 mg per 1 ml
  - Brochlor 0.5% eye drops | 10 ml [P] £2.83 DT price = £1.50

- **Chloromycetin (AMCo)**
  - Chloramphenicol 5 mg per 1 ml
  - Chloromycetin Redidrops 0.5% | 5 ml [P] £1.65 | 10 ml [P] £9.90 DT price = £1.50

- **Optrex Infected Eyes** (Reckitt Benckiser Healthcare (UK) Ltd)
  - Chloramphenicol 5 mg per 1 ml
  - Optrex Infected Eyes 0.5% eye drops | 10 ml [P] £3.75 DT price = £1.50

**Eye ointment**

- **CHLORAMPHENICOL (Non-proprietary)**
  - Chloramphenicol 10 mg per 1 gram
  - Chloramphenicol 1% eye ointment | 4 gram [P] £4.26 DT price = £1.95

- Golden Eye Antibiotic 1% eye ointment | 4 gram [P] £3.49 DT price = £1.95

- **Brochlor** (Sanofi)
  - Chloramphenicol 10 mg per 1 gram
  - Brochlor 1% eye ointment | 4 gram [P] £2.95 DT price = £1.95

- **Chloromycetin (AMCo)**
  - Chloramphenicol 10 mg per 1 gram
  - Chloromycetin 1% eye ointment | 4 gram [P] £4.97 DT price = £1.95

- **Optrex Infected Eyes** (Reckitt Benckiser Healthcare (UK) Ltd)
  - Chloramphenicol 10 mg per 1 gram
  - Optrex Infected Eyes 1% eye ointment | 4 gram [P] £3.88 DT price = £1.95
Ciprofloxacin

**INDICATIONS AND DOSE**

**Superficial bacterial eye infection**

**TO THE EYE USING EYE DROP**

- **Child:** Apply 4 times a day for maximum duration of treatment 21 days
- **Adult:** Apply 4 times a day for maximum duration of treatment 21 days

**TO THE EYE USING EYE OINTMENT**

- **Child 1-17 years:** Apply 1.25 centimetres 3 times a day for 2 days, then apply 1.25 centimetres twice daily for 5 days
- **Adult:** Apply 1.25 centimetres 3 times a day for 2 days, then apply 1.25 centimetres twice daily for 5 days

**Superficial bacterial eye infection (severe infection)**

**TO THE EYE USING EYE DROP**

- **Child:** Apply every 2 hours during waking hours for 2 days, then apply 4 times a day for maximum duration of treatment 21 days
- **Adult:** Apply every 2 hours during waking hours for 2 days, then apply 4 times a day for maximum duration of treatment 21 days

**TO THE EYE USING EYE OINTMENT**

- **Child 1-17 years:** Apply 1.25 centimetres every 1–2 hours for 2 days, then apply 1.25 centimetres every 4 hours for the next 12 days, to be administered throughout the day and night
- **Adult:** Apply 1.25 centimetres every 1–2 hours for 2 days, then apply 1.25 centimetres every 4 hours for the next 12 days, to be administered throughout the day and night

**Corneal ulcer**

**TO THE EYE USING EYE DROP**

- **Child:** Apply every 15 minutes for 6 hours, then apply every 30 minutes for the remainder of day 1, then apply every 1 hour on day 2, then apply every 4 hours on days 3–14, maximum duration of treatment 21 days, to be administered throughout the day and night
- **Adult:** Apply every 15 minutes for 6 hours, then apply every 30 minutes for the remainder of day 1, then apply every 1 hour on day 2, then apply every 4 hours on days 3–14, maximum duration of treatment 21 days, to be administered throughout the day and night

**TO THE EYE USING EYE OINTMENT**

- **Child 1-17 years:** Apply 1.25 centimetres every 1–2 hours for 2 days, then apply 1.25 centimetres every 4 hours for the next 12 days, to be administered throughout the day and night
- **Adult:** Apply 1.25 centimetres every 1–2 hours for 2 days, then apply 1.25 centimetres every 4 hours for the next 12 days, to be administered throughout the day and night

**UNLICENSED USE**

Eye ointment not licensed for use in children under 1 year.

**SIDE-EFFECTS**

- **Common or very common** Corneal deposits (reversible after completion of treatment) · ocular discomfort · ocular hyperaemia · taste disturbance
- **Uncommon** Blurred vision · conjunctival hyperaemia · corneal infiltrates · corneal staining · eye dryness · eye irritation · eye pain · eye pruritus · eye swelling · eyelid disorders · eyelid erythema · eyelid exfoliation · eyelid oedema · headache · increased lacrimation · keratopathy · nausea · photophobia
- **Rare** Abdominal pain · asthenopia · corneal disorders · corneal epithelium defect · dermatitis · diarrhoea · diplopia · diziness · ear pain · eye hypoesthesia · keratitis · paranasal sinus hyperssecretion · rhinitis

**PREGNANCY**

Manufacturer advises use only if potential benefit outweighs risk.

**BREAST FEEDING**

Manufacturer advises caution.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops

**Eye drops**

EXCIPIENTS: May contain Benzalkonium chloride

- **Ciloxan** (Alcon Laboratories (UK) Ltd)
  - **Ciprofloxacin (as Ciprofloxacin hydrochloride) 3 mg per 1 ml**
  - **Gentamicin (as Gentamicin sulfate) 0.3% eye drops | 5 ml (PVP) £4.70 DT price = £4.70**

**Eye ointment**

- **Ciloxan** (Alcon Laboratories (UK) Ltd)
  - **Ciprofloxacin (as Ciprofloxacin hydrochloride) 3 mg per 1 gram**
  - **Gentamicin (as Gentamicin sulfate) 0.3% eye drops | 3.5 gram (PVP) £3.22**

**Fusidic acid**

**INDICATIONS AND DOSE**

Staphylococcal eye infections

**TO THE EYE**

- **Child:** Apply twice daily
- **Adult:** Apply twice daily

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Medicines not identified.

**Gentamicin**

**INDICATIONS AND DOSE**

Bacterial eye infections

**TO THE EYE**

- **Child:** Apply 1 drop every 2 hours, reduce frequency as infection is controlled and continue for 48 hours after healing, frequency of eye drops depends on the severity of the infection and the potential for irreversible ocular damage; for less severe infection 3–4 times daily is generally sufficient
- **Adult:** Apply 1 drop every 2 hours, reduce frequency as infection is controlled and continue for 48 hours after healing, frequency of eye drops depends on the severity of the infection and the potential for irreversible ocular damage; for less severe infection 3–4 times daily is generally sufficient

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops

**Ear/eye drops solution**

EXCIPIENTS: May contain Benzalkonium chloride

- **GENTAMICIN (Non-proprietary)**
  - **Gentamicin (as Gentamicin sulfate) 1 mg per 1 ml**
  - **Gentamicin 0.3% eye/ear drops | 10 ml (PVP) £2.13 DT price = £2.13**
  - **Gentamicin 0.3% eye/ear drops | 10 ml (PVP) £2.13 DT price = £2.13**
  - **Gentamicin (as Gentamicin sulfate) 3 mg per 1 ml**

**Levofloxacin**

**INDICATIONS AND DOSE**

Local treatment of eye infections

**TO THE EYE**

- **Child 1-17 years:** Apply every 2 hours for first 2 days, to be applied maximum 8 times a day, then apply 4 times a day for 3 days
- **Adult:** Apply every 2 hours for first 2 days, to be applied maximum 8 times a day, then apply 4 times a day for 3 days
Moxifloxacin

**INDICATIONS AND DOSE**
Local treatment of infections

**TO THE EYE**
- Child: Apply 3 times a day continue treatment for 2–3 days after infection improves; review if no improvement within 5 days
- Adult: Apply 3 times a day continue treatment for 2–3 days after infection improves; review if no improvement within 5 days

**CAUTIONS**
- Not recommended for neonates

**SIDE-EFFECTS**
- **Common or very common** Ocular burning - visual disturbances
- **Uncommon** Conjunctival follicles - headache - lid erythema - lid oedema - ocular discomfort - ocular dryness - ocular itching - ocular pain - photophobia - rhinitis

**PREGNANCY**
Manufacturer advises avoid unless benefit outweighs risk.

**BREAST FEEDING**
Manufacturer advises avoid.

**PRESCRIBING AND DISPENSING INFORMATION**
Although multi-dose levofloxacin eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

Eye drops
- **EXCIPIENTS:** May contain Benzalkonium chloride
  - **Oftaquix** (Santen)
    - Levofloxacin (as Levofloxacin hemihydrate) 5 mg per 1 ml
    - Oftaquix Smg/ml eye drops 0.5ml unit dose | 30 unit dose | DT price = £17.95
  - Oftaquix Smg/ml eye drops | 5 ml | DT price = £6.95

Ofloxacin

**INDICATIONS AND DOSE**
Local treatment of infections

**TO THE EYE**
- Child 1-17 years: Apply every 2–4 hours for the first 2 days, then reduced to 4 times a day for maximum 10 days treatment
- Adult: Apply every 2–4 hours for the first 2 days, then reduced to 4 times a day for maximum 10 days treatment

**CAUTIONS**
- Corneal ulcer (risk of corneal perforation) - epithelial defect (risk of corneal perforation)

**SIDE-EFFECTS**
- **Common or very common** Eye irritation - ocular discomfort
- **Frequency not known** Dry eyes - facial oedema - increased lacrimation - keratitis - ocular hyperaemia - ocular oedema - photophobia - visual disturbances

**PREGNANCY**
Manufacturer advises use only if benefit outweighs risk (systemic quinolones have caused arthropathy in animal studies).

**BREAST FEEDING**
Manufacturer advises avoid.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

Eye drops
- **EXCIPIENTS:** May contain Benzalkonium chloride
  - **Exocin** (Allergan Ltd)
    - Ofloxacin 3 mg per 1 ml
    - Exocin 0.3% eye drops | 5 ml | DT price = £2.17
    - DT price = £2.17

Propamidine isetionate

**INDICATIONS AND DOSE**
*Acanthamoeba keratitis* infections (specialist use only)
Local treatment of eye infections

**TO THE EYE USING EYE OINTMENT**
- Adult: Apply 1–2 times a day
- Child: Apply twice daily for first day, then apply up to 4 times a day

**UNLICENSED USE**
Not licensed for *Acanthamoeba keratitis* infections.

**SIDE-EFFECTS**
- Eye irritation - eye pain

**PREGNANCY**
Manufacturer advises avoid unless essential—no information available.

**BREAST FEEDING**
Manufacturer advises avoid unless essential—no information available.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

Eye drops
- **EXCIPIENTS:** May contain Benzalkonium chloride
  - **PROPAMIDINE ISETIONATE (Non-proprietary)**
    - Propamidine isetionate 1 mg per 1 ml
    - Golden Eye 0.1% drops | 10 ml | DT price = £3.26
    - Brolene (Propamidine) (Sanofi)
      - Propamidine isetionate 1 mg per 1 ml
      - Brolene 0.1% eye drops | 10 ml | DT price = £2.80
  - **PROPAMIDINE ISETIONATE (Non-proprietary)**
    - Dibrompropamidine isetionate 1.5 mg per 1 gram
    - Golden Eye 0.15% ointment | 5 gram | DT price = £3.49
    - Brolene (Dibrompropamide) (Sanofi)
    - Dibrompropamide isetionate 1.5 mg per 1 gram
    - Brolene 0.15% eye ointment | 5 gram | DT price = £2.92

Eye ointment
- **PROPAMIDINE ISETIONATE (Non-proprietary)**
  - Dibrompropamidine isetionate 1.5 mg per 1 gram
  - Golden Eye 0.15% ointment | 5 gram | DT price = £3.49

Tobramycin

**INDICATIONS AND DOSE**
Local treatment of infections

**TO THE EYE**
- Child 1-17 years: Apply twice daily for 6–8 days
- Adult: Apply twice daily for 6–8 days

Local treatment of infections (severe infection)

**TO THE EYE**
- Child 1-17 years: Apply 4 times a day for first day, then apply twice daily for 5–7 days
- Adult: Apply 4 times a day for first day, then apply twice daily for 5–7 days
3.2 Herpes simplex infection

Aciclovir

(Acyliclovir)

**INDICATIONS AND DOSE**

Herpes simplex infection (local treatment) TO THE EYE USING EYE OINTMENT
- Child: Apply 1 centimetre 5 times a day continue for at least 3 days after complete healing
- Adult: Apply 1 centimetre 5 times a day continue for at least 3 days after complete healing

**SIDE-EFFECTS**
- Common or very common Local inflammation - local irritation - superficial punctate keratopathy
- Rare Blepharitis
- Very rare Angioedema - hypersensitivity reactions

**PATIENT AND CARER ADVICE**
Medicines for Children leaflet: Aciclovir eye ointment for herpes simplex infections www.medicinesforchildren.org.uk/aciclovir-eye-ointment-for-herpes-simplex-infection

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Eye ointment**
- **Zovirax** (GlaxoSmithKline UK Ltd)
  - Aciclovir 30 mg per 1 gram Zovirax 3% ophthalmic ointment | 4.5 gram £6.13 70 DT price = £9.34

Ganciclovir

**INDICATIONS AND DOSE**

Local treatment of herpes simplex infections TO THE EYE
- Adult: Apply 5 times a day until healing complete, then apply 3 times a day for a further 7 days

**SIDE-EFFECTS**
- Burning sensation - superficial punctate keratitis - tingling

**ALLERGY AND CROSS-SENSITIVITY**
Contra-indicated in patients hypersensitive to valganciclovir, aciclovir, or valaciclovir.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Eye gel**
- **EXCipients**: May contain Benzalkonium chloride
- **Tobravir (Spectrum Thea Pharmaceuticals Ltd)**
  - Ganciclovir 1.5 mg per 1 gram Tobravir 0.15% eye gel | 5 gram £19.99 DT price = £19.99

4 Eye procedures

Mydriatics and cycloplegics

Antimuscarinics dilate the pupil and paralyse the ciliary muscle; they vary in potency and duration of action. Short-acting, relatively weak mydriatics, such as tropicamide below 0.5% (action lasts for 4–6 hours), facilitate the examination of the fundus of the eye. Longer-acting options include cyclopentolate hydrochloride p. 950 1% (action up to 24 hours) or atropine sulfate p. 950 (action up to 7 days).

Phenylephrine hydrochloride p. 959 is used for mydriasis in diagnostic or therapeutic procedures; mydriasis occurs within 60–90 minutes and lasts up to 5–7 hours.

Mydriatics and cycloplegics are used in the treatment of anterior uveitis, usually as an adjunct to corticosteroids. Atropine sulfate p. 950 is used in anterior uveitis mainly to prevent posterior synechiae and to relieve ciliary spasm; cyclopentolate hydrochloride p. 950 or homatropine hydrobromide p. 950 (action up to 3 days) can also be used and may be preferred because they have a shorter duration of action.

**Drugs used for Eye procedures not listed below:**
*Fluorescein with lidocaine, p. 960

ANTIMUSCARINICS

Tropicamide

The properties listed below are those particular to the drug only. For the properties common to the class, see Antimuscarinics (eye) p. 949.

**INDICATIONS AND DOSE**

Funduscopy TO THE EYE
- Child: 0.5% eye drops to be applied 20 minutes before examination
- Adult: (consult product literature)

**PRESCRIBING AND DISPENSING INFORMATION**
Although multi-dose tropicamide eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**
- **EXCipients**: May contain Benzalkonium chloride, edet acid (edta)
  - TROPICAMIDE (Non-proprietary)
    - Tropicamide 5 mg per 1 ml Tropicamide 5% drops 0.5ml unit dose | 20 unit dose | £10.75
    - Tropicamide 10 mg per 1 ml Tropicamide 10% drops 0.5ml unit dose | 20 unit dose | £10.77
  - **Mydriacyl** (Alcon Laboratories (UK) Ltd)
    - Tropicamide 5 mg per 1 ml Mydriacyl 0.5% eye drops | 5 ml | £1.29
    - Tropicamide 10 mg per 1 ml Mydriacyl 1% eye drops | 5 ml | £1.60

Phenylephrine with tropicamide

The properties listed below are those particular to the combination only. For the properties of the components please consider, phenylephrine hydrochloride p. 959, tropicamide above.
INDICATIONS AND DOSE
Pre-operative mydriasis | Diagnostic procedures when monotherapy insufficient
TO THE EYE
  ▶ Adult: One insert to be applied into the lower conjunctival sac up to max. 2 hours before procedure; remove insert within 30 minutes of satisfactory mydriasis, and within 2 hours of application

DIRECTIONS FOR ADMINISTRATION
Patients with severe dry eyes may require a drop of saline to improve insert tolerance.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
  ▶ Mydriaser (Spectrum Thea Pharmaceuticals Ltd)
    Phenylephrine hydrochloride 5.4 mg, Tropicamide 0.28 mg
    Mydriaser 5.4mg / 0.28mg ophthalmic inserts | 20 insert (PM) £84.00

DIAGNOSTIC DYES
Fluorescein sodium

INDICATIONS AND DOSE
Detection of lesions and foreign bodies
TO THE EYE USING EYE DROP
  ▶ Adult: Use sufficient amount to stain damaged areas

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Eye drops
  ▶ FLUORESCIN SODIUM (Non-proprietary)
    Fluorescein sodium 10 mg per 1 ml Minims fluorescein sodium 1% eye drops 0.5ml unit dose | 20 unit dose (P) £8.89
    Fluorescein sodium 20 mg per 1 ml Minims fluorescein sodium 2% eye drops 0.5ml unit dose | 20 unit dose (P) £18.89

MIOTICS
Acetylcholine chloride

INDICATIONS AND DOSE
Cataract surgery | Penetrating keratoplasty | Iridectomy | Anterior segment surgery requiring rapid complete miosis
TO THE EYE
  ▶ Adult: (consult product literature)

CAUTIONS
Asthma - gastro-intestinal spasm - heart failure - hyperthyroidism - parkinsonism - peptic ulcer - urinary-tract obstruction
SIDE-EFFECTS
Rare Bradycardia - breathing difficulty - flushing - hypotension - sweating
PREGNANCY
Avoid unless potential benefit outweighs risk—no information available.
BREAST FEEDING
Avoid unless potential benefit outweighs risk—no information available.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
  ▶ Irrigation
    Miochol-E (Bausch & Lomb UK Ltd)
    Acetylcholine chloride 20 mg Miochol-E 20mg powder and solvent for solution for intraocular irrigation vials | 1 vial (PM) £7.28
    Miphtel (Alain Pharmaceuticals)
    Acetylcholine chloride 20 mg Miphtel 20mg powder and solvent for solution for intraocular irrigation ampoules | 6 ampoule (PM) £6.55 (Hospital only)

SYMPATHOMIMETICS (VASOCONSTRICTOR)
Phenylephrine hydrochloride

INDICATIONS AND DOSE
Mydriasis
TO THE EYE
  ▶ Child: Apply 1 drop, to be administered before procedure, a drop of proxymetacaine topical anaesthetic may be applied to the eye a few minutes before using phenylephrine to prevent stinging
  ▶ Adult: Apply 1 drop, to be administered before procedure, then apply 1 drop after 60 minutes if required, a drop of topical anaesthetic may be applied to the eye a few minutes before using phenylephrine to prevent stinging

CONTRA-INDICATIONS
Hypertension - 10% strength eye drops in neonates, children and the elderly - aneurysms - cardiovascular disease - thyrotoxicosis

CAUTIONS
Asthma - cerebral arteriosclerosis (in adults) - corneal epithelial damage - darkly pigmented iris is more resistant to pupillary dilatation and caution should be exercised to avoid overdosage. - diabetes (avoid eye drops in long standing diabetes) - mydriasis can precipitate acute angle-closure glaucoma in a few patients, usually over 60 years and hypermetropic (long-sighted) or children, who are predisposed to the condition because of a shallow anterior chamber - mydriasis can precipitate acute angle-closure glaucoma in the very few children who are predisposed to the condition because of a shallow anterior chamber - ocular hyperaemia - susceptibility to angle-closure glaucoma
INTERACTIONS
→ Appendix 1 (sympathomimetics). Phenylephrine may interact with systemically administered monoamine-oxidase inhibitors.
SIDE-EFFECTS
Arrhythmias - blurred vision - conjunctivitis on prolonged administration - coronary artery spasm - extrasystoles - hyperaemia on prolonged administration - hypertension - local irritation on prolonged administration - myocardial infarction (usually after use of 10% strength in patients with pre-existing cardiovascular disease) - oedema on prolonged administration - palpitation - photophobia - raised intraocular pressure - tachycardia - transient stinging
PREGNANCY
Use only if potential benefit outweighs risk.
BREAST FEEDING
Use only if potential benefit outweighs risk—no information available.
PRESCRIBING AND DISPENSING INFORMATION
Although multi-dose phenylephrine eye drops commonly contain preservatives, preservative-free unit dose vials may be available.
PATIENT AND CARER ADVICE
Patients should be warned not to undertake skilled tasks (e.g. driving) until vision clears after mydriasis.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops

EXCipients: May contain Dismodium edetate, sodium metabisulfite

Eye drops
  ▶ PHENYLEPHRINE HYDROCHLORIDE (Non-proprietary)
    Phenylephrine hydrochloride 25 mg per 1 ml Minims phenylephrine hydrochloride 2.5% eye drops 0.5ml unit dose | 20 unit dose (P) £11.41
    Phenylephrine hydrochloride 100 mg per 1 ml Minims phenylephrine hydrochloride 10% eye drops 0.5ml unit dose | 20 unit dose (P) £11.41
4.1 Post-operative pain and inflammation

Eye, surgical and peri-operative drug use

Ocular peri-operative drugs

Drugs used to prepare the eye for surgery, drugs that are injected into the anterior chamber at the time of surgery, and those used after eye surgery, are included here.

Cefuroxime p. 955, administered by intra-ocular injection into the anterior chamber of the eye (intracameral use), is used for the prophylaxis of endophthalmitis after cataract surgery.

Non-steroidal anti-inflammatory eye drops such as diclofenac sodium p. 961, flurbiprofen p. 961, ketorolac trometamol p. 961, and nepafenac p. 961, are used for the prophylaxis and treatment of inflammation, pain, and other symptoms associated with ocular surgery or laser treatment of the eye. Bromfenac p. 961 is used for the treatment of postoperative inflammation following cataract surgery. Diclofenac sodium p. 961 and flurbiprofen are also used to prevent miosis during ocular surgery.

Apraclonidine p. 963, an alpha,-adrenoreceptor agonist, reduces intra-ocular pressure possibly by reducing the production of aqueous humour. It is used to control increases in intra-ocular pressure associated with ocular surgery and as short-term treatment to reduce intraocular pressure prior to surgery.

Acetylecholine chloride p. 959, administered into the anterior chamber of the eye during surgery, rapidly produces miosis which lasts approximately 20 minutes. If prolonged miosis is required, it can be applied again.

Intra-ocular sodium hyaluronate p. 953 and balanced salt solution are used during surgical procedures on the eye.

Povidone-iodine is used for peri-ocular and conjunctival antisepsis before ocular surgery to support postoperative infection control.

Local anaesthetics

Oxybuprocaine hydrochloride below and tetracaine p. 961 are widely used topical local anaesthetics. Proxymetacaine hydrochloride below causes less initial stinging and is useful for children. Oxybuprocaine hydrochloride below or a combined preparation of lidocaine hydrochloride and fluorescein sodium p. 961 is used for tonometry. Tetracaine produces a more profound anaesthesia and is suitable for use before minor surgical procedures, such as the removal of corneal sutures. It has a temporary disruptive effect on the corneal epithelium. Lidocaine hydrochloride, with or without adrenaline/epinephrine p. 196, is injected into the eyelids for minor surgery. Local anaesthetics should never be used for the management of ocular symptoms.

CORTICOSTEROIDS

Loteprednol etabonate

INDICATIONS AND DOSE

Treatment of post-operative inflammation following ocular surgery

TO THE EYE

Adult: Apply 4 times a day for maximum duration of treatment of 14 days, to be started 24 hours after surgery

SIDE-EFFECTS

Corneal thinning, scleral thinning

LOCAL ANAESTHETICS

Fluorescein with lidocaine

INDICATIONS AND DOSE

Local anaesthesia

TO THE EYE

Adult: Apply as required

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Eye drops

EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate

Lotemax (Bausch & Lomb UK Ltd)

Loteprednol etabonate 5 mg per 1 ml Lotemax 0.5% eye drops

5 ml (Disp) £5.50 QT price = £5.50

Oxybuprocaine hydrochloride (Benoxinate hydrochloride)

INDICATIONS AND DOSE

Local anaesthetic

TO THE EYE

Adult: As required

PRESCRIBING AND DISPENSING INFORMATION

Although multi-dose oxybuprocaine eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Eye drops

FLUORESEE WITH LIDOCAINE (Non-proprietary)

Fluorescein sodium 2.5 mg per 1 ml Lidocaine hydrochloride 40 mg per 1 ml Minims lidocaine and fluorescein eye drops 0.5ml unit dose 20 unit dose (Disp) £11.24

Proxymetacaine hydrochloride

INDICATIONS AND DOSE

Local anaesthetic

TO THE EYE

Adult: As required

PRESCRIBING AND DISPENSING INFORMATION

Although multi-dose proxymetacaine eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Eye drops

PROXYMETACAINE HYDROCHLORIDE (Non-proprietary)

Proxymetacaine hydrochloride 4 mg per 1 ml Minims proxymetacaine hydrochloride 0.4% eye drops 0.5ml unit dose 20 unit dose (Disp) £10.15

Proxymetacaine hydrochloride

INDICATIONS AND DOSE

Local anaesthetic

TO THE EYE

Adult: As required

PRESCRIBING AND DISPENSING INFORMATION

Although multi-dose proxymetacaine eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Eye drops

PROXYMETACAINE HYDROCHLORIDE (Non-proprietary)

Proxymetacaine hydrochloride 5 mg per 1 ml Minims proxymetacaine 0.5% eye drops 0.5ml unit dose 20 unit dose (Disp) £11.54
**Bromfenac**

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**
- **TETRACAINE (Non-proprietary)**
  - Tetracaine hydrochloride 5 mg per 1 ml Minims tetracaine hydrochloride 0.5% eye drops 0.5ml unit dose | 20 unit dose [Pom] £10.16
  - Tetracaine hydrochloride 10 mg per 1 ml Minims tetracaine hydrochloride 1% eye drops 0.5ml unit dose | 20 unit dose [Pom] £10.16
- **BROMOCAINO (Amethocaine)**
  - Yellox 0.5% eye drops | 5 ml [Pom] £3.64
- **Tetracaine**
  - Minims Tetracaine 0.5% eye drops 0.5 ml unit dose | 20 unit dose [Pom] £5.20

**Diclofenac sodium**

**INDICATIONS AND DOSE**
Inhibition of intra-operative miosis during cataract surgery | Postoperative inflammation in cataract surgery, strabismus surgery or argon laser trabeculoplasty | Pain in corneal epithelial defects after photorefractive keratectomy, radial keratotomy or accidental trauma | Seasonal allergic conjunctivitis

**TO THE EYE**
- Adult: (consult product literature)

**PRESCRIBING AND DISPENSING INFORMATION**
Although multi-dose diclofenac sodium eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**
- **VOLTAROL OPHTHA MULTIDOSE (Spectrum Thea Pharmaceuticals Ltd)**
  - Diclofenac sodium 1 mg per 1 ml Voltarol Ophtha Multidose 0.1% eye drops | 5 ml [Pom] £4.00 | 40 unit dose [Pom] £32.00

**Flurbiprofen**

**INDICATIONS AND DOSE**
Inhibition of intra-operative miosis (but does not possess intrinsic mydriatic properties) | Control of anterior segment inflammation following postoperative and post-laser trabeculoplasty when corticosteroids contra-indicated

**TO THE EYE**
- Adult: (consult product literature)

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**
- **OCUFEN (Allergan Ltd)**
  - Flurbiprofen sodium 300 microgram per 1 ml Ocufen 0.03% eye drops 0.4ml unit dose | 40 unit dose [Pom] £37.15

**Ketorolac trometamol**

**INDICATIONS AND DOSE**
Prophylaxis and reduction of inflammation and associated symptoms following ocular surgery

**TO THE EYE**
- Adult: (consult product literature)

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**
- **ACULAR (Allergan Ltd)**
  - Ketorolac trometamol 5 mg per 1 ml Acular 0.5% eye drops | 5 ml [Pom] £3.00 DT price = £3.00

**Nepafenac**

**INDICATIONS AND DOSE**
Prophylaxis and treatment of postoperative pain and inflammation associated with cataract surgery | Reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients

**TO THE EYE**
- Adult: (consult product literature)

**CAUTIONS**
Avoid sunlight - corneal epithelial breakdown (if evidence of, then discontinue immediately)

**SIDE-EFFECTS**
- **Common or very common** Punctate keratitis
- **Uncommon** Allergic conjunctivitis - blurred vision - choroidal effusion - conjunctival hyperaemia - corneal deposits - corneal epithelial defect - dry eye - eye pruritus - headache - increased lacrimation - iritis - keratitis - nausea - ocular discomfort - photophobia
- **Frequency not known** Corneal opacity - dermatochalasis - dizziness - eye swelling - impaired corneal healing - reduced visual acuity

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.
Eye drops
EXCIPIENTS: May contain benzalkonium chloride, disodium edetate
▶ Nevanan (Alcon Laboratories (UK) Ltd)
Nepafenac 1 mg per 1 ml Nevanan 1mg/ml eye drops | 5 ml £14.52

IODINE PRODUCTS
Povidone-iodine
INDICATIONS AND DOSE
Cutaneous peri-ocular and conjunctival antisepsis before surgical procedure
TO THE EYE
▶ Adult: Apply, leave for 2 minutes, then irrigate thoroughly with sodium chloride 0.9%

CONTRA-INDICATIONS
Concomitant use of ocular antimicrobial drugs - concomitant use of ocular formulations containing mercury-based preservatives - preterm neonates
SIDE-EFFECTS
▶ Rare Conjunctival hyperaemia - superficial punctate keratitis
▶ Frequency not known Cytotoxicity on deep tissue - cytotoxicity on mucous membranes - hypothyroidism in neonates - residual yellow coloration of the conjunctiva

PRESCRIBING AND DISPENSING INFORMATION
Although multi-dose povidone iodine eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops, eye lotion
Eye drops
▶ Povidone-iodine (Non-proprietary)
Povidone-iodine 50 mg per 1 ml Minims povidone iodine 5% eye drops 0.4ml unit dose | 20 unit dose (Pod) £16.00

5 Glaucoma and ocular hypertension

Glaucoma
Glaucoma describes a group of disorders characterised by a loss of visual field associated with cupping of the optic disc and optic nerve damage. While glaucoma is generally associated with raised intra-ocular pressure, it can occur when the intra-ocular pressure is within the normal range.

The most common form of glaucoma is primary open-angle glaucoma (chronic open-angle glaucoma), where drainage of the aqueous humour through the trabecular meshwork is restricted. The condition is often asymptomatic, but the patient may present with significant loss of visual field. Patients with ocular hypertension are at high risk of developing primary open-angle glaucoma.

Drugs that reduce intra-ocular pressure by different mechanisms are available for managing ocular hypertension and glaucoma. A topical beta-blocker or a prostaglandin analogue is usually the drug of first choice for the treatment of ocular hypertension. A prostaglandin analogue should be used to manage patients with early or moderate primary open-angle glaucoma. After checking compliance and eye drop instillation technique, it may be necessary to combine these drugs or add others, such as sympathomimetics, carbonic anhydrase inhibitors, or miotics to control intra-ocular pressure.

Acute angle-closure glaucoma
Acute angle-closure glaucoma occurs when the outflow of aqueous humour from the eye is obstructed by bowing of the iris against the trabecular meshwork; it is a medical emergency that requires urgent reduction of intra-ocular pressure to prevent loss of vision. Patients with acute angle-closure glaucoma should be referred immediately for specialist ophthalmology assessment and treatment.

Standard antiglaucoma therapy is used if supplementary treatment is required after iridotomy, iridectomy, laser treatment, or drainage surgery in either primary open-angle or acute angle-closure glaucoma.

Beta-blockers
Topical application of a beta-blocker to the eye reduces intra-ocular pressure effectively in primary open-angle glaucoma, probably by reducing the rate of production of aqueous humour. Administration by mouth also reduces intra-ocular pressure but this route is not used since side-effects may be troublesome.

Beta-blockers used as eye drops include betaxolol p. 964, carteolol hydrochloride p. 964, levobunolol hydrochloride p. 964, and timolol maleate p. 965.

Prostaglandin analogues and prostamides
The prostaglandin analogues latanoprost p. 969, tafroprost p. 969 and travoprost p. 970, and the synthetic prostamide, bimatoprost p. 968, increase uveoscleral outflow and subsequently reduce intra-ocular pressure. They are used to reduce intra-ocular pressure in ocular hypertension or open-angle glaucoma.

Sympathomimetics
Brimonidine tartrate p. 963, a selective alpha₂-adrenoceptor agonist, is thought to lower intra-ocular pressure by reducing aqueous humour formation and increasing uveoscleral outflow. It is licensed for the reduction of intra-ocular pressure in open-angle glaucoma or ocular hypertension in patients for whom beta-blockers are inappropriate; it may also be used as adjunctive therapy when intra-ocular pressure is inadequately controlled by other anti-glaucoma therapy.

Apraclonidine p. 963 is another alpha₂-adrenoceptor agonist that lowers intra-ocular pressure by reducing aqueous humour formation. Eye drops containing apraclonidine p. 963 0.5% are used short-term to delay laser treatment or surgery in patients with glaucoma not adequately controlled by another drug; eye drops containing 1% are used for control of intra-ocular pressure after anterior segment laser surgery.

Apraclonidine may not provide additional benefit in patients already using two drugs that suppress the production of aqueous humour.

Carbonic anhydrase inhibitors and systemic drugs
The carbonic anhydrase inhibitors, acetazolamide p. 965, brinzolamide p. 966, and dorzolamide p. 967, reduce intra-ocular pressure by reducing aqueous humour production.

Systemic use of acetazolamide also produces weak diuresis. Acetazolamide is given by mouth or by intravenous injection (intramuscular injections are painful because of the alkaline pH of the solution). It is used as an adjunct to other treatment for reducing intra-ocular pressure.

Acetazolamide is not generally recommended for long-term use.

Dorzolamide and brinzolamide are topical carbonic anhydrase inhibitors. They are licensed for use in patients resistant to beta-blockers or those in whom beta-blockers are contra-indicated. They are used alone or as an adjunct to a topical beta-blocker. Brinzolamide can also be used as an adjunct to a prostaglandin analogue. Systemic...
absorption can rarely cause sulfonamide-like side-effects and may require discontinuation if severe.

The osmotic diuretics, intravenous hypertonic mannitol p. 202 or glycerol by mouth are useful short-term ocular hypotensive drugs.

Miotics
Miotics act by opening the inefficient drainage channels in the trabecular meshwork.

Pilocarpine p. 967, a miotic, is not commonly used for the treatment of primary open-angle glaucoma because side-effects are poorly tolerated. It is used mainly in the treatment of primary angle-closure glaucoma and in some secondary glaucomas.

**ALPHA₂-ADRENOCEPTOR AGONISTS**

**Apraclonidine**

**DRUG ACTION** Apraclonidine is an alpha₂-adrenoceptor agonist that lowers intra-ocular pressure by reducing aqueous humour formation. It is a derivative of clonidine.

**INDICATIONS AND DOSE**
Control or prevention of postoperative elevation of intra-ocular pressure after anterior segment laser surgery

→ **TO THE EYE**
  → Adult: Apply 1 drop 1 hour before laser procedure, then 1 drop immediately after completion of procedure, 1% eye drops to be administered
  → Short-term adjunctive treatment of chronic glaucoma in patients not adequately controlled by another drug

→ **TO THE EYE**
  → Adult: Apply 1 drop 3 times a day usually for maximum 1 month, 0.5% eye drops to be administered, may not provide additional benefit if patient already using two drugs that suppress the production of aqueous humour

**CONTRA-INDICATIONS** History of severe or unstable and uncontrolled cardiovascular disease

**CAUTIONS** Cerebrovascular disease • depression • heart failure • history of angina • hypertension • loss of effect may occur over time • Parkinson’s syndrome • Raynaud’s syndrome • recent myocardial infarction • reduction in vision in end-stage glaucoma (suspend treatment) • severe coronary insufficiency • thromboangiitis obliterans • vasovagal attack

**INTERACTIONS** → Appendix 1 (apraclonidine).

**SIDE-EFFECTS**
- Common or very common Conjunctivitis • dry eye • ocular intolerance • rhinitis • taste disturbance
- Uncommon Asthma • blepharitis • blepharospasm • chest pain • conjunctival vascular disorders • corneal erosion and infiltrates • dysphoria • eyelid ptosis or retraction • impaired co-ordination • irritability • keratitis • keratopathy • myalgia • mydriasis • nervousness • parosmia • photophobia • rhinorrhoea • throat irritation • visual impairment

**SIDE-EFFECTS, FURTHER INFORMATION**
Ocular intolerance Withdraw if eye pruritus, ocular hyperaemia, increased lacrimation, or oedema of the eyelids and conjunctiva occur.

Systemic effects Since absorption may follow topical application, see clonidine hydrochloride p. 137.

**PREGNANCY** Manufacturer advises avoid—no information available.

**BREAST FEEDING** Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT** Manufacturer advises caution.

**RENAL IMPAIRMENT** Use with caution in chronic renal failure.

**MONITORING REQUIREMENTS**
- Monitor intra-ocular pressure and visual fields.
- Monitor for excessive reduction in intra-ocular pressure following peri-operative use.

**PATIENT AND CARER ADVICE**
Drowsiness may affect performance of skilled tasks (e.g. driving).

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**
EXCipients: May contain Benzalkonium chloride

- **Iopidine** (Alcon Laboratories (UK) Ltd)
  - Apraclonidine (as Apraclonidine hydrochloride) 5 mg per 1 ml
  - Iopidine 5mg/ml eye drops | 5 ml (POSt) £10.88 DT price = £10.88
  - Apraclonidine (as Apraclonidine hydrochloride) 10 mg per 1 ml
  - Iopidine 2% eye drops 0.25ml unit dose | 24 unit dose (POSt) £77.85 DT price = £77.85

**Brimonidine tartrate**

**DRUG ACTION** Brimonidine, an alpha₂-adrenoceptor agonist, is thought to lower intra-ocular pressure by reducing aqueous humour formation and increasing uveoscleral outflow.

**INDICATIONS AND DOSE**
Raised intra-ocular pressure in open-angle glaucoma in patients for whom beta-blockers are inappropriate | Ocular hypertension in patients for whom beta-blockers are inappropriate | Adjunctive therapy when intra-ocular pressure is inadequately controlled by other antiglaucoma therapy

→ **TO THE EYE**
  → Adult: Apply twice daily

**CONTRA-INDICATIONS** Neonates and children under 2 years (risk of severe systemic side-effects)

**CAUTIONS** Cerebral insufficiency • children 2–12 years (increased risk of drowsiness) • coronary insufficiency • depression • postural hypotension • Raynaud’s syndrome • severe cardiovascular disease • thromboangiitis obliterans

**INTERACTIONS** → Appendix 1 (brimonidine).

**SIDE-EFFECTS**
- Common or very common Burning sensation at application site • conjunctival blanching • conjunctival disturbances • conjunctival follicles • conjunctival infection • corneal erosion • corneal staining • dizziness • drowsiness • dry mouth • eyelid inflammation • gastro-intestinal disturbances • headache • malaise • ocular disturbances • ocular dryness • ocular hyperaemia • ocular pain • ocular pruritus • photophobia • stinging at application site • taste disturbances • upper respiratory symptoms • visual disturbances
- Uncommon Arrhythmia • bradycardia • depression • nasal dryness • palpitation • tachycardia
- Rare Dyspnoea
- Very rare Hypertension • hypotension • insomnia • irritis • miosis • syncope

**PREGNANCY** Limited information available; manufacturer advises use only if benefit outweighs risk (eye drops).

**BREAST FEEDING** Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT** Manufacturer advises use with caution.

**RENAL IMPAIRMENT** Manufacturer advises use with caution.
**Brimonidine with timolol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, bromidine tartrate p. 963, timolol maleate p. 965.

### INDICATIONS AND DOSE

Raised intraocular pressure in open-angle glaucoma and for ocular hypertension when beta-blocker alone not adequate

**TO THE EYE**

- **Adult:** Apply twice daily

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

#### Eye drops

**EXCIPIENTS:** May contain Benzalkonium chloride

- Bromonidine tartrate 2 mg per 1 ml Bromonidine 2% eye drops 5 ml £8.65 DT price = £2.32
- Alphagan (Allergan Ltd)
- Bromonidine tartrate 2 mg per 1 ml Alphagan 2% eye drops 5 ml £8.65 DT price = £2.32
- Brymont (Blumont Pharma Ltd)
- Bromonidine tartrate 2 mg per 1 ml Brymont 2mg/ml eye drops 5 ml £6.55 DT price = £2.32

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**Carteolol hydrochloride**

### INDICATIONS AND DOSE

Primary open-angle glaucoma

**TO THE EYE**

- **Adult:** Apply twice daily

#### CONTRA-INDICATIONS

Also consider contra-indications listed for systemically administered beta blockers - bradycardia - heart block

#### CAUTIONS

Patients with corneal disease

### CAUTIONS, FURTHER INFORMATION

Systemic absorption can follow topical application to the eyes; consider cautions listed for systemically administered beta blockers.

#### INTERACTIONS

→ Appendix 1 (beta-blockers).

Since systemic absorption may follow topical application the possibility of interactions, in particular, with drugs such as verapamil should be borne in mind.

#### SIDE-EFFECTS

Anaphylaxis - blepharoconjunctivitis - burning - corneal disorders - dry eyes - erythema - itching - ocular stinging - pain

### SIDE-EFFECTS, FURTHER INFORMATION

Systemic absorption can follow topical application to the eyes; consider side effects listed for systemically administered beta blockers.

#### PRESCRIBING AND DISPENSING INFORMATION

Although multi-dose betaxolol eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

#### Eye drops

**EXCIPIENTS:** May contain Benzalkonium chloride, disodium edetate

- Betaxolol (as Betaxolol hydrochloride) 5 mg per 1 ml Betaxolol 0.5% eye drops 5 ml £1.90 DT price = £1.90
- Betoptic (Alcon Laboratories (UK) Ltd)
- Betaxolol 0.25% suspension eye drops 5 ml £2.66 DT price = £2.66
- Betoptic 0.25% eye drops suspension 0.25ml unit dose 50 unit dose £11.77
- Betaxolol (as Betaxolol hydrochloride) 5 mg per 1 ml Betoptic 0.5% eye drops 5 ml £1.90 DT price = £1.90

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**Betaxolol**

### INDICATIONS AND DOSE

Primary open-angle glaucoma

**TO THE EYE**

- **Adult:** Apply twice daily

#### CONTRA-INDICATIONS

Also consider contra-indications listed for systemically administered beta blockers - bradycardia - heart block

#### CAUTIONS

Patients with corneal disease

### CAUTIONS, FURTHER INFORMATION

Systemic absorption can follow topical application to the eyes; consider cautions listed for systemically administered beta blockers.

#### INTERACTIONS

→ Appendix 1 (beta-blockers).

Since systemic absorption may follow topical application the possibility of interactions, in particular, with drugs such as verapamil should be borne in mind.

#### SIDE-EFFECTS

Anaphylaxis - blepharoconjunctivitis - burning - corneal disorders - dry eyes - erythema - itching - ocular stinging - pain

### SIDE-EFFECTS, FURTHER INFORMATION

Systemic absorption can follow topical application to the eyes; consider side effects listed for systemically administered beta blockers.

#### PRESCRIBING AND DISPENSING INFORMATION

Although multi-dose betaxolol eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

#### Eye drops

**EXCIPIENTS:** May contain Benzalkonium chloride

- Betaxolol (as Betaxolol hydrochloride) 5 mg per 1 ml Betaxolol 0.5% eye drops 5 ml £1.90 DT price = £1.90
- Betoptic (Alcon Laboratories (UK) Ltd)
- Betaxolol 0.25% suspension eye drops 5 ml £2.66 DT price = £2.66
- Betoptic 0.25% eye drops suspension 0.25ml unit dose 50 unit dose £11.77
- Betaxolol (as Betaxolol hydrochloride) 5 mg per 1 ml Betoptic 0.5% eye drops 5 ml £1.90 DT price = £1.90

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**Levobunolol hydrochloride**

### INDICATIONS AND DOSE

Primary open-angle glaucoma

**TO THE EYE**

- **Adult:** Apply 1–2 times a day

#### CONTRA-INDICATIONS

Also consider contra-indications listed for systemically administered beta blockers - bradycardia - heart block

#### CAUTIONS

Patients with corneal disease

### CAUTIONS, FURTHER INFORMATION

Systemic absorption can follow topical application to the eyes; consider cautions listed for systemically administered beta blockers.

#### INTERACTIONS

→ Appendix 1 (beta-blockers).

Since systemic absorption may follow topical application the possibility of interactions, in particular, with drugs such as verapamil should be borne in mind.

#### SIDE-EFFECTS

Anaphylaxis - blepharoconjunctivitis - burning - corneal disorders - dry eyes - erythema - itching - ocular stinging - pain

### SIDE-EFFECTS, FURTHER INFORMATION

Systemic absorption can follow topical application to the eyes; consider side effects listed for systemically administered beta blockers.

#### PRESCRIBING AND DISPENSING INFORMATION

Although multi-dose betaxolol eye drops commonly contain preservatives, preservative-free unit dose vials may be available.
CAUTIONS, FURTHER INFORMATION
Systemic absorption can follow topical application to the eyes; consider cautions listed for systemically administered beta blockers.

• INTERACTIONS → Appendix 1 (beta-blockers).
  Since systemic absorption may follow topical application the possibility of interactions, in particular, with drugs such as verapamil should be borne in mind.

• SIDE-EFFECTS
  Anaphylaxis, anterior uveitis, blepharoconjunctivitis, burning, corneal disorders, dry eyes, erythema, itching, ocular stinging, pain

SIDE-EFFECTS, FURTHER INFORMATION
Systemic absorption can follow topical application to the eyes; consider side effects listed for systemically administered beta blockers.

• PRESCRIBING AND DISPENSING INFORMATION
  Although multi-dose timolol eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

• MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.
  Eye drops
  EXCIPENTS: May contain Benzalkonium chloride, disodium edetate, sodium metabsulphite
  ▶ Betagan (Allergan Ltd)
  Levobunol hydrochloride 5 mg per 1 ml
  Betagan 0.5% eye drops | 5 ml (£1.85 DT price = £1.85)
  Betagan Unit Dose 0.5% eye drops 0.4ml unit dose | 30 unit dose (£1.98)

Timolol maleate

INDICATIONS AND DOSE
Reduction of intra-ocular pressure in primary open-angle glaucoma

TO THE EYE
  ▶ Adult: Apply twice daily

TIMOPTOL-LA
Reduction of intra-ocular pressure in primary open-angle glaucoma

TO THE EYE
  ▶ Adult: Apply once daily

TIOPLEX
Reduction of intra-ocular pressure in primary open-angle glaucoma

TO THE EYE
  ▶ Adult: Apply once daily, to be applied in the morning

• CONTRA-INDICATIONS
  Also consider contra-indications listed for systemically administered beta blockers
  bradycardia, heart block

• CAUTIONS
  Also consider cautions listed for systemically administered beta blockers

• INTERACTIONS → Appendix 1 (beta-blockers).
  Since systemic absorption may follow topical application the possibility of interactions, in particular, with drugs such as verapamil should be borne in mind.

• SIDE-EFFECTS
  Anaphylaxis, blepharoconjunctivitis, burning, corneal disorders, dry eyes, erythema, itching, ocular stinging, pain

SIDE-EFFECTS, FURTHER INFORMATION
Systemic absorption can follow topical application to the eyes; consider side effects listed for systemically administered beta blockers.

• PRESCRIBING AND DISPENSING INFORMATION
  Although multi-dose timolol eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

• NATIONAL FUNDING/ACCESS DECISIONS
  Scottish Medicines Consortium (SMC) Decisions
  The Scottish Medicines Consortium has advised (February 2014) that timolol gel eye drops (Tiopex®) are accepted for restricted use within NHS Scotland for the reduction of elevated intraocular pressure in patients with ocular hypertension or chronic open angle glaucoma who have proven sensitivity to preservatives.

• MEDICINAL FORMS
  There can be variation in the licensing of different medicines containing the same drug.
  Forms available from special-order manufacturers include: eye drops

Eye drops
  EXCIPENTS: May contain Benzalkonium chloride
  ▶ TIMOLOL MALEATE (Non-proprietary)
  Timolol (as Timolol maleate) 2.5 mg per 1 ml
  Timolol 0.25% eye drops | 5 ml (£1.80 DT price = £1.36)
  Timolol (as Timolol maleate) 5 mg per 1 ml
  Timolol 0.5% eye drops | 5 ml (£1.95 DT price = £1.33)
  ▶ Timoptol (Merck Sharp & Dohme Ltd)
  Timolol (as Timolol maleate) 5 mg per 1 ml
  Timolol 0.25% eye drops | 5 ml (£3.12 DT price = £1.36)
  Timoptol Unit Dose 0.25% ophthalmic solution 0.2ml unit dose | 30 unit dose (£8.45)
  Timolol (as Timolol maleate) 5 mg per 1 ml
  Timolol 0.5% eye drops | 5 ml (£3.12 DT price = £1.33)
  Timoptol Unit Dose 0.5% ophthalmic solution 0.2ml unit dose | 30 unit dose (£9.65 DT price = £6.65)
  ▶ Tiopex (Spectrum Thea Pharmaceuticals Ltd)
  Timolol (as Timolol maleate) 1 mg per 1 gram
  Timolol 0.01% eye gel 0.4g unit dose | 30 unit dose (£7.40 DT price = £7.40)

Eye gel
  EXCIPENTS: May contain Benzozodecinum bromide
  ▶ Timoptol-LA (Merck Sharp & Dohme Ltd)
  Timolol (as Timolol maleate) 2.5 mg per 1 ml
  Timolol-LA 0.25% ophthalmic gel-forming solution | 2.5 ml (£3.12 DT price = £3.12)
  Timolol (as Timolol maleate) 5 mg per 1 ml
  Timolol-LA 0.5% ophthalmic gel-forming solution | 2.5 ml (£3.12 DT price = £3.12)

Also available in combination with Bimatoprost, p. 968: Brimonidine, p. 964: Brinzolamide, p. 966: Dorzolamide, p. 967: Latanoprost, p. 969: Travoprost, p. 970

CARBONIC ANHYDRASE INHIBITORS

Acetazolamide

INDICATIONS AND DOSE
Reduction of intra-ocular pressure in open-angle glaucoma | Reduction of intra-ocular pressure in secondary glaucoma | Reduction of intra-ocular pressure in angle-closure glaucoma

BY MOUTH USING IMMEDIATE-RELEASE MEDICINES OR BY INTRAVENOUS INJECTION OR BY INTRAMUSCULAR INJECTION
  Adult: 0.25–1 g daily in divided doses, intramuscular injection preferably avoided because of alkalinity

Glaucma

BY MOUTH USING MODIFIED-RELEASE MEDICINES
  Adult: 1–2 capsules daily

• CONTRA-INDICATIONS
  Adrenocortical insufficiency, hyperchloraemic acidosis, hypokalaemia, hyponatraemia, long-term administration in chronic angle-closure glaucoma

• CAUTIONS
  Avoid extravasation at injection site (risk of necrosis), diabetes mellitus, elderly, impaired alveolar ventilation (risk of acidosis), not generally recommended for long-term use, pulmonary obstruction (risk of acidosis), renal calculi

• INTERACTIONS → Appendix 1 (diuretics).

• SIDE-EFFECTS
  ▶ Common or very common
  Ataxia, depression, diarrhoea, dizziness, excitement, fatigue, flushing, headache, irritability, loss of appetite, nausea, paraesthesia...
### Glaucoma and ocular hypertension

**INDICATIONS AND DOSE**
Reduction of intra-ocular pressure in ocular hypertension and open-angle glaucoma either as adjunct to beta-blockers or prostaglandin analogues or used alone in patients unresponsive to beta-blockers or if beta-blockers contra-indicated

**TO THE EYE**
- Adult: Apply twice daily, then increased if necessary up to 3 times a day

**CONTRA-INDICATIONS**
- Hyperchloaraemic acidosis

**CAUTIONS**
- Renal tubular immaturity or abnormality - systemic absorption follows topical application

**INTERACTIONS**
- Appendix 1 (brinzolamide)

Since systemic absorption may follow topical application of brinzolamide to the eye, the possibility of interactions should be borne in mind.

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### Brinzolamide with timolol

The properties listed below are those particular to the combination only. For the properties of the components please consider, brinzolamide above, timolol maleate p. 965.

**INDICATIONS AND DOSE**
Raised intra-ocular pressure in open-angle glaucoma or ocular hypertension when beta-blocker alone not adequate

**TO THE EYE**
- Adult: Apply twice daily

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### Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**
- **Diameter:** May contain Benzalkonium chloride, disodium edetate

- **BRINZOLAMIDE (Non-proprietary)**
  - **Brinzolamide 10 mg per 1 ml**
  - Brinzolamide 10 mg/ml eye drops | 5 ml [PO](PO) £6.92 DT price + £6.92
  - **Azopt (Alcon Laboratories (UK) Ltd)**
  - **Azopt 10 mg per 1 ml**
  - Azopt 10mg/ml eye drops | 5 ml [PO](PO) £6.92 DT price + £6.92

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### Brinzolamide

**INDICATIONS AND DOSE**
Reduction of intra-ocular pressure in open-angle glaucoma or ocular hypertension when beta-blocker alone not adequate

**TO THE EYE**
- Adult: Apply twice daily

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.
Dorzolamide

**INDICATIONS AND DOSE**

Raised intra-ocular pressure in ocular hypertension used alone in patients unresponsive to beta-blockers or if beta-blockers contra-indicated | Open-angle glaucoma used alone in patients unresponsive to beta-blockers or if beta-blockers contra-indicated | Pseudo-exfoliative glaucoma used alone in patients unresponsive to beta-blockers or if beta-blockers contra-indicated

TO THE EYE

Adult: Apply 3 times a day

Raised intra-ocular pressure in ocular hypertension as adjunct to beta-blocker | Open-angle glaucoma as adjunct to beta-blocker | Pseudo-exfoliative glaucoma as adjunct to beta-blocker

TO THE EYE

Adult: Apply twice daily

**CONTRA-INDICATIONS**

Hyperchlorhaemic acidosis

**CAUTIONS**

Chronic corneal defects - history of intra-ocular surgery - history of renal calculus - low endothelial cell count - systemic absorption follows topical application

**INTERACTIONS**

Appendix 1 (dorzolamide).

Since systemic absorption may follow topical application of dorzolamide to the eye, the possibility of interactions should be borne in mind.

**SIDE-EFFECTS**

- **Common or very common**
  - Asthenia
  - Bitter taste
  - Blurred vision
  - Conjunctivitis
  - Eyelid crusting
  - Epistaxis
  - Eyelid inflammation
  - Eyelid oedema
  - Lacrimation
  - Nausea
  - Ocular irritation
  - Superficial punctate keratitis

- **Uncommon**
  - Iridocyclitis

- **Rare**
  - Contact dermatitis
  - Corneal oedema
  - Dizziness
  - Dry mouth
  - Epistaxis
  - Eyelid crusting
  - Paraesthesia
  - Stevens-Johnson syndrome
  - Throat irritation
  - Toxic epidermal necrolysis
  - Transient myopia
  - Urolithiasis

**SIDE-EFFECTS, FURTHER INFORMATION**

Systemic absorption can rarely cause sulfonamide-like side-effects and may require discontinuation if severe.

**ALLERGY AND CROSS-SENSITIVITY**

Contra-indicated if history of sulfonamide hypersensitivity.

**PREGNANCY**

Manufacturer advises avoid—toxicity in animal studies.

**BREAST FEEDING**

Manufacturer advises avoid—no information available.

**HEPATIC IMPAIRMENT**

Manufacturer advises caution—no information available.

**RENAL IMPAIRMENT**

Avoid if eGFR less than 30 mL/minute/1.73 m².

**PRESCRIBING AND DISPENSING INFORMATION**

Although multi-dose dorzolamide eye drops commonly contain preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

EXCIPIENTS: May contain Benzalkonium chloride

- **DORZOLAMIDE (Non-proprietary)**
  - Dorzolamide (as Dorzolamide hydrochloride) 20 mg per 1 ml
  - Dorzolamide 2% eye drops | 5 ml [P] £6.33 DT price = £2.33
  - Trusopt (Merck Sharp & Dohme Ltd)
  - Dorzolamide (as Dorzolamide hydrochloride) 20 mg per 1 ml
  - Trusopt 2% eye drops | 5 ml [P] £6.33 DT price = £2.33
  - Trusopt 2% eye drops 0.2ml unit dose preservative free | 60 unit dose [P] £24.18 DT price = £24.18

**Dorzolamide with timolol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, timolol maleate p. 965, dorzolamide above.

**INDICATIONS AND DOSE**

Raised intra-ocular pressure in ocular hypertension when beta-blockers alone not adequate | Raised intra-ocular pressure in open-angle glaucoma when beta-blockers alone not adequate | Raised intra-ocular pressure in pseudo-exfoliative glaucoma when beta-blockers alone not adequate

TO THE EYE

Adult: Apply twice daily

**PRESCRIBING AND DISPENSING INFORMATION**

Although multi-dose dorzolamide with timolol eye drops contain preservatives, preservative-free unit dose vials may be available.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Eye drops**

EXCIPIENTS: May contain Benzalkonium chloride

- **DORZOLAMIDE WITH TIMOLOL (Non-proprietary)**
  - Dorzolamide (as Dorzolamide hydrochloride) 20 mg per 1 ml
  - Timolol (as Timolol maleate) 5 mg per 1 ml
  - Dorzolamide 2% / Timolol 0.5% eye drops | 5 ml [P] £27.16 DT price = £2.58
  - Dorzolamide 2% / Timolol 0.5% eye drops 0.2ml unit dose preservative free | 60 unit dose [P] £27.16 DT price = £28.59
  - Cosopt (Merck Sharp & Dohme Ltd)
  - Dorzolamide (as Dorzolamide hydrochloride) 20 mg per 1 ml
  - Timolol (as Timolol maleate) 5 mg per 1 ml
  - Cosopt eye drops 0.2ml unit dose preservative free | 60 unit dose [P] £28.59 DT price = £28.59
  - Cosopt eye drops | 5 ml [P] £10.05 DT price = £2.58

**PARASYMPATHOMIMETICS**

Pilocarpine

**DRUG ACTION**

Pilocarpine acts by opening the inefficient drainage channels in the trabecular meshwork.

**INDICATIONS AND DOSE**

Primary angle-closure glaucoma | Some secondary glaucomas

TO THE EYE

Adult: Apply up to 4 times a day

**CONTRA-INDICATIONS**

Acute inflammatory disease of the anterior segment - acute iritis - anterior uveitis - conditions where pupillary constriction is undesirable - some forms of secondary glaucoma (where pupillary constriction is undesirable)

**CAUTIONS**

A darkly pigmented iris may require a higher concentration of the miotic or more frequent administration and care should be taken to avoid overdosage - asthma - cardiac disease - care in conjunctival damage - care in corneal damage - epilepsy - gastrointestinal spasm - hypertension - hyperthyroidism - hypotension - marked vasomotor instability - Parkinson’s disease - peptic ulceration - retinal detachment has occurred in susceptible individuals and those with retinal disease - urinary-tract obstruction

**INTERACTIONS**

Appendix 1 (parasympathomimetics).

Systemic effects rare after following application to the eye.

**SIDE-EFFECTS**

- **Rare**
  - Parasympathomimetics systemic side effects

- **Frequency not known**
  - Blurred vision - ciliary spasm (leads to headache and browache which may be more severe in

- **Pilocarpine**

- **TRUSOPT**

- **GLAUCOMA AND OCULAR HYPERTENSION**

- **BNF**

- **30%**
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the initial 2–4 weeks of treatment—a particular disadvantage in patients under 40 years of age) • conjunctival vascular congestion • lens changes (with chronic use) • myopia • ocular burning • ocular itching • pupillary block • smarting • vitreous haemorrhage

- PREGNANCY Avoid unless the potential benefit outweighs risk—limited information available.
- BREAST FEEDING Avoid unless the potential benefit outweighs risk—no information available.
- PRE-TREATMENT SCREENING Fundus examination is advised before starting treatment with a miotic (retinal detachment has occurred).
- MONITORING REQUIREMENTS Intra-ocular pressure and visual fields should be monitored in those with chronic simple glaucoma and those receiving long-term treatment with a miotic.
- PRESCRIBING AND DISPENSING INFORMATION Although multi-dose pilocarpine eye drops commonly contain preservatives, preservative-free unit dose vials may be available.
- PATIENT AND CARER ADVICE Blurred vision may affect performance of skilled tasks (e.g. driving) particularly at night or in reduced lighting.

- MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops

  **Eye drops**

  **EXCipients:** May contain Benzalkonium chloride

  - Pilocarpine (Non-proprietary)
    - Pilocarpine hydrochloride 10 mg per 1 ml
      - Pilocarpine hydrochloride 1% eye drops | 10 ml (Pst) £3.15 DT price = £2.92
    - Pilocarpine hydrochloride 20 mg per 1 ml
      - Pilocarpine hydrochloride 2% eye drops | 10 ml (Pst) £3.63 DT price = £3.63
    - Pilocarpine nitrate 20 mg per 1 ml
      - Minims pilocarpine nitrate 2% eye drops 0.5ml unit dose | 20 unit dose (Pst) £11.99
    - Pilocarpine hydrochloride 40 mg per 1 ml
      - Pilocarpine hydrochloride 4% eye drops | 10 ml (Pst) £5.40 DT price = £4.35

**PROSTAGLANDIN ANALOGUES AND PROSTAMIDES**

**Bimatoprost**

**INDICATIONS AND DOSE**

Raised intra-ocular pressure in open-angle glaucoma | Ocular hypertension TO THE EYE

- Adult: Apply once daily, to be administered preferably in the evening

- **CAUTIONS** Angle-closure glaucoma (no experience of use) • aphakia - astigmatism - chronic obstructive pulmonary disease • compromised respiratory function • congenital glaucoma (no experience of use) • contact lens wearers • history of significant ocular viral infections • inflammatory ocular conditions (no experience of use) • narrow-angle glaucoma (no experience of use) • neovascular glaucoma (no experience of use) • predisposition to bradycardia • predisposition to hypotension • pseudophakia with torn posterior lens capsule or anterior chamber lenses • risk factors for cystoid macular oedema • risk factors for iritis • risk factors for uveitis

- **SIDE-EFFECTS**

  - Common or very common Blepharitis • blood pressure changes • brown pigmentation particularly in those with mixed-colour irides • conjunctival disorders • corneal erosion • darkening, thickening and lengthening of eye lashes • eyelash and vellus hair changes • headache • ocular discomfort • photophobia • pigmentation of periocular skin • punctate keratitis • reduced visual acuity • transient punctate epithelial erosion

  - Uncommon Asthenopia • diziness • skin rash

  - Rare Arthralgia • darkening of palpebral skin • facial oedema • iritis • macular oedema • myalgia • uveitis

  - Very rare Chest pain • exacerbation of angina • palpitation • periorbital changes resulting in deepening of the eyelid sulcus

  - Frequency not known Asthma • blepharospasm • bradycardia • dyspnoea • exacerbation of asthma • exacerbation of COPD • eyelid retraction • malaise • nausea • ocular infection • reactivation of previous corneal infiltrates • retinal haemorrhage

- PREGNANCY Manufacturer advises use only if potential benefit outweighs risk.
- BREAST FEEDING Manufacturer advises avoid—present in milk in animal studies.
- HEPATIC IMPAIRMENT Use with caution in moderate to severe impairment—no information available.
- RESPIRATORY IMPAIRMENT Use with caution—no information available.
- PRESCRIBING AND DISPENSING INFORMATION Although multi-dose bimatoprost eye drops commonly contain preservatives, preservative-free unit dose vials may be available
- PATIENT AND CARER ADVICE Changes to eye colour Before initiating treatment, patients should be warned of a possible change in eye colour as an increase in the brown pigment in the iris can occur, which may be permanent; particular care is required in those with mixed coloured irides and those receiving treatment to one eye only. Changes in eyelashes and vellus hair can also occur, and patients should also be advised to avoid repeated contact of the eye drop solution with skin as this can lead to hair growth or skin pigmentation.

**NATIONAL FUNDING/ACCESS DECISIONS**

Scottish Medicines Consortium (SMC) Decisions The Scottish Medicines Consortium has advised (March 2013) that bimatoprost 300 micrograms/ml preservative-free eye drops (Lumigan® single-dose eye drops) are accepted for restricted use within NHS Scotland for the reduction of elevated intra-ocular pressure in chronic open-angle glaucoma and ocular hypertension (as monotherapy or as adjunctive therapy to beta-blockers) in adults who have proven sensitivity to benzalkonium chloride.

- MEDICINAL FORMS There can be variation in the licensing of different medicines containing the same drug.

  **Eye drops**

  **EXCipients:** May contain Benzalkonium chloride

  - Lumigan (Allergan Ltd)
    - Bimatoprost 100 microgram per 1 ml
      - Bimatoprost 100 microgram per 1 ml eye drops | 3 ml (Pst) £11.71 DT price = £11.71 | 9 ml (Pst) £35.13
    - Bimatoprost 300 microgram per 1 ml
      - Bimatoprost 300 microgram per 1 ml eye drops | 3 ml (Pst) £10.30 DT price = £10.30 | 9 ml (Pst) £30.90
      - Lumigan 300micrograms/ml eye drops 0.4ml unit dose | 30 unit dose (Pst) £13.75 DT price = £13.75

**Bimatoprost with timolol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, bimatoprost above, timolol maleate p. 965.

**INDICATIONS AND DOSE**

Raised intra-ocular pressure in patients with open-angle glaucoma or ocular hypertension when beta-blocker or prostaglandin analogue alone not adequate TO THE EYE

- Adult: Apply once daily
Glucoma and ocular hypertension

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **Scottish Medicines Consortium (SMC) Decisions**
    The Scottish Medicines Consortium has advised (October 2013) that Ganfort® unit dose eye drops are accepted for restricted use within NHS Scotland for the reduction of intra-ocular pressure in patents with open-angle glaucoma or ocular hypertension insufficiently responsive to topical beta-blockers or prostaglandin analogues who have proven sensitivity to preservatives.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
    - **Eye drops**
      - **EXCIPIENTS**: May contain Benzalkonium chloride
        - Ganfort (Allergan Ltd)
          - Bimatoprost 300 microgram per 1 ml, Timolol (as Timolol maleate) 5 mg per 1 ml
            - 3 ml (£31.95 DT price = £13.95) 9 ml (£87.59)
            - Ganfort 0.3mg/ml / 5mg/ml eye drops 0.4ml unit dose | 30 unit dose (£87.59)

- **Latanoprost**
  - **INDICATIONS AND DOSE**
    - Raised intra-ocular pressure in open-angle glaucoma | Ocular hypertension
      - TO THE EYE
        - Adult: Apply daily, to be administered preferably in the evening
    - **CONTRA-INDICATIONS**
      - Active herpes simplex keratitis - history of recurrent herpetic keratitis associated with prostaglandin analogues
    - **CAUTIONS**
      - Angle-closure glaucoma (no experience of use)
    - **SIDE-EFFECTS**
      - Common or very common: Blepharitis - blood pressure changes - brown pigmentation particularly in those with mixed-colour irides - conjunctival disorders - corneal erosion - darkening, thickening and lengthening of eye lashes - eyelash and vellus hair changes - headache - ocular discomfort - photophobia - pigmentation of periorical skin - punctate keratitis - reduced visual acuity - transient punctate epithelial erosion
      - Uncommon: Asthenopia - dizziness - skin rash
    - **Rare**
      - Arthralgia - darkening of palpebral skin - facial oedema - iritis - macular oedema - myalgia - uveitis
    - **Very rare**
      - Breast pain - exacerbation of angina - palpitation - periorbital changes resulting in deepening of the eyelid sulcus
    - **Frequency not known**
      - Asthma - dysphoena - exacerbation of asthma - exacerbation of COPD - iritis - nasopharyngitis - pyrexia
  - **PREGNANCY**
    - Manufacturer advises avoid.
  - **BREAST FEEDING**
    - May be present in milk—manufacturer advises avoid.
  - **PRESCRIBING AND DISPENSING INFORMATION**
    - Although multi-dose latanoprost eye drops commonly contain preservatives, preservative-free unit dose vials may be available

- **PATIENT AND CARER ADVICE**
  - Changes in eye colour: Before initiating treatment, patients should be warned of a possible change in eye colour as an increase in the brown pigmen in the iris can occur, which may be permanent; particular care is required in those with mixed coloured irides and those receiving treatment to one eye only. Changes in eyelashes and vellus hair can also occur, and patients should also be advised to avoid repeated contact of the eye drop solution with skin as this can lead to hair growth or skin pigmentation.

- **NATIONAL FUNDING/ACCESS DECISIONS**
  - **Scottish Medicines Consortium (SMC) Decisions**
    The Scottish Medicines Consortium has advised (June 2013) that Monopost® is accepted for restricted use within NHS Scotland for the reduction of elevated intra-ocular pressure in patients with open-angle glaucoma and ocular hypertension who have proven sensitivity to benzalkonium chloride.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
    - **Eye drops**
      - **Latanoprostone (Non-proprietary)**
        - Latanoprost 50 microgram per 1 ml
          - 2.5 ml (£12.48 DT price = £2.16)
      - Monopost (Spectrum Thea Pharmaceuticals Ltd)
        - Latanoprost 50 microgram per 1 ml
          - 0.2ml unit dose | 30 unit dose (£8.49 DT price = £8.49) 30 unit dose (£25.47 DT price = £25.47)
      - Xalatan (Pfizer Ltd)
        - Latanoprost 50 microgram per 1 ml
          - 2.5 ml (£12.48 DT price = £2.16)

- **Latanoprost with timolol**
  - The properties listed below are those particular to the combination only. For the properties of the components please consider, latanoprost above, timolol maleate p. 965.
  - **INDICATIONS AND DOSE**
    - Raised intra-ocular pressure in patients with open-angle glaucoma and ocular hypertension when beta-blocker or prostaglandin analogue alone not adequate
      - TO THE EYE
        - Adult: Apply once daily
  - **MEDICINAL FORMS**
    - There can be variation in the licensing of different medicines containing the same drug.
      - **Eye drops**
        - **Latanoprost with timolol (Non-proprietary)**
          - Latanoprost 50 microgram per 1 ml, Timolol (as Timolol maleate) 5 mg per 1 ml
            - 2.5 ml (£15.80 DT price = £3.88)
          - Xalacom (Pfizer Ltd)
            - Latanoprost 50 microgram per 1 ml, Timolol (as Timolol maleate) 5 mg per 1 ml
              - Xalacom eye drops | 2.5 ml (£14.32 DT price = £3.88)

- **Tafluprost**
  - **INDICATIONS AND DOSE**
    - Raised intra-ocular pressure in open-angle glaucoma | Ocular hypertension
      - TO THE EYE
        - Adult: Apply daily, to be administered preferably in the evening
Travoprost

INDICATIONS AND DOSE

Raised intra-ocular pressure in open-angle glaucoma | Ocular hypertension

TO THE EYE

Adult: Apply daily, to be administered preferably in the evening

Travoprost

INDICATIONS AND DOSE

Raised intra-ocular pressure in patients with open-angle glaucoma or ocular hypertension when beta-blocker or prostaglandin analogue alone not adequate

TO THE EYE

Adult: Apply once daily
6 Retinal disorders

6.1 Macular degeneration

Subfoveal choroidal neovascularisation

Aflibercept below, pegaptanib sodium p. 972 and ranibizumab p. 973 are vascular endothelial growth factor inhibitors licensed for the treatment of neovascular (wet) age-related macular degeneration. Aflibercept is also licensed for the treatment of macular oedema secondary to central retinal vein occlusion, and diabetic macular oedema; ranibizumab is also licensed for the treatment of visual impairment due to diabetic macular oedema, macular oedema secondary to branch or central retinal vein occlusion, and choroidal neovascularisation secondary to pathologic myopia. Ranibizumab can be administered concomitantly with laser photocoagulation for the treatment of diabetic macular oedema and for macular oedema secondary to branch retinal vein occlusion.

PHOTOSENSITISERS

Verteportin

DRUG ACTION Following intravenous infusion, verteportin is activated by local irradiation using non-thermal red light to produce cytotoxic derivatives.

INDICATIONS AND DOSE
Photodynamic treatment of age-related macular degeneration associated with predominantly classic subfoveal choroidal neovascularisation or with pathological myopia (specialist use only)

BY INTRAVENOUS INFUSION
Adult: 6 mg/m², dose to be given over 10 minutes

CONTRA-INDICATIONS Acute porphyria

CAUTIONS Avoid extravasation · biliary obstruction · photosensitivity

INTERACTIONS Caution on concomitant use with other photosensitising drugs.

SIDE-EFFECTS
Common or very common Back pain · flashing lights · hypercholesterolaemia · malaise · nausea · photosensitivity · reduced visual acuity · visual disturbances · visual-field defects

Uncommon Hyperaesthesia · hypertension · pyrexia · retinal detachment · subretinal, retinal or vitreous haemorrhage

Rare Retinal or choroidal vessel non-perfusion

Frequency not known Chest pain · macular oedema · myocardial infarction · retinal oedema · vasovagal reactions

PREGNANCY Manufacturer advises use only if potential benefit outweighs risk (teratogenic in animal studies).

Macular degeneration 971

Breastfeeding No information available—manufacturer advises avoid breast-feeding for 48 hours after administration.

Hepatic impairment Use with caution in moderate hepatic impairment. Avoid in severe hepatic impairment.

DIRECTIONS FOR ADMINISTRATION For information on administration and light activation, consult product literature. For intravenous infusion (Visudyne®), give intermittently in Glucose 5%· reconstitute each 15 mg with 7 ml water for injections to produce a 2 mg/ml solution then dilute requisite dose with infusion fluid to a final volume of 30 ml. Give over 10 minutes; protect infusion from light and administer within 4 hours of reconstitution. Incompatible with sodium chloride infusion.

PATIENT AND CARER ADVICE Photosensitivity—avoid exposure of unprotected skin and eyes to bright light during infusion and for 48 hours afterwards.

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)
Verteportin photodynamic therapy for wet age-related macular degeneration (September 2003) NICE TA68
Photodynamic therapy is recommended for wet age-related macular degeneration with a confirmed diagnosis of classic (no occult) subfoveal choroidal neovascularisation and best-corrected visual acuity of 6/60 or better.
Photodynamic therapy is not recommended for wet age-related macular degeneration with predominantly classic but partly occult subfoveal choroidal neovascularisation except in clinical studies. www.nice.org.uk/TA68

MEDICINAL FORMS

There can be variation in the licencing of different medicines containing the same drug.

Powder for solution for infusion
EXCipients: May contain Butylated hydroxytoluene
Verteportin 15 mg Visudyne 15mg powder for solution for infusion vials | 1 vial (PMS) £85.00 (Hospital only)

VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS

Aflibercept

DRUG ACTION Aflibercept is a recombinant fusion protein that acts as a soluble decoy receptor and binds to vascular endothelial growth factors A and B (VEGF-A, VEGF-B) and placental growth factor (PIGF). Aflibercept inhibits the activation of VEGF receptors and the proliferation of endothelial cells, thereby inhibiting the growth of new vessels that supply tumours with oxygen and nutrients.

INDICATIONS AND DOSE
Neovascular (wet) age-related macular degeneration (specialist use only)

BY INTRAVITREAL INJECTION
Adult: Initially 2 mg once a month for 3 months, to be injected into the affected eye, then 2 mg every 2 months, review treatment frequency after 12 months

Macular oedema secondary to central retinal vein occlusion (specialist use only)

BY INTRAVITREAL INJECTION
Adult: Initially 2 mg once a month, to be injected into the affected eye, monitor visual and anatomic outcomes monthly; continue treatment until visual and anatomic outcomes are stable for 3 monthly assessments (discontinue treatment if no improvement in visual and anatomic outcomes after initial 3 injections); if necessary subsequent doses may be given at least 1 month apart
Diabetic macular oedema (specialist use only)

**BY INTRAVITREAL INJECTION**

- Adult: Initially 2 mg once a month for 5 months, then maintenance 2 mg every 2 months, to be injected into the affected eye, review treatment frequency after 12 months (discontinue treatment if no improvement in visual and anatomic outcomes)

- **CONTRA-INDICATIONS** Clinical signs of irreversible ischaemic visual function loss - ocular or periocular infection - severe intra-ocular inflammation

- **CAUTIONS** Active systemic infection - diabetic patients with uncontrolled hypertension - discontinue treatment if stage 3 or 4 macular holes develop—consult product literature for full details - discontinue treatment in the event of a retinal break—consult product literature for full details - discontinue treatment in the event of retinal detachment - consult product literature for full details - patients at risk of retinal pigment epithelial tear - poorly controlled glaucoma - recent history of myocardial infarction - recent history of stroke - recent history of transient ischaemic attack

- **SIDE-EFFECTS**

  **SPECIFIC SIDE-EFFECTS**

  - Common or very common
  - **With intravitreal use** anterior chamber flare - blindness - corneal epithelium defect - eyelid irritation - iridocyclitis - iritis - lenticular opacities - retinal detachment - retinal tear - uveitis
  - Rare
  - **With intravitreal use** hypopyon - vitritis

  **CONCEPTION AND CONTRACEPTION**

  Manufacturer recommends women use effective contraception during and for at least 3 months after treatment.

- **PREGNANCY**

  Manufacturer advises avoid unless potential benefit outweighs risk.

- **BREAST FEEDING**

  Manufacturer advises avoid—no information available.

- **MONITORING REQUIREMENTS**

  Monitor intra-ocular pressure following injection.

- **DIRECTIONS FOR ADMINISTRATION**

  For further information on administration, consult product literature.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  **NICE technology appraisals (TAs)**

  - Afibercept solution for injection for treating wet age-related macular degeneration (July 2013) NICE TA294

  Afibercept solution for injection is recommended as an option for treating wet age-related macular degeneration only if:

  - it is used in accordance with the recommendations for ranibizumab in NICE TA 155

  - the manufacturer provides afibercept solution for injection with the discount agreed in the patient access scheme www.nice.org.uk/TA294

  - **Afibercept for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion (February 2014) NICE TA305**

  Afibercept solution for injection is recommended as an option for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion only if the manufacturer provides afibercept solution for injection with the discount agreed in the patient access scheme. www.nice.org.uk/TA305

- **MEDICINAL FORMS**

  - Solution for injection

  - Eylea (Bayer Plc) ▼

  Afibercept 40 mg per 1 ml Eylea 2mg/50microlitres solution for injection vials | 1 vial £816.00

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**Pegaptanib sodium**

**INDICATIONS AND DOSE**

Treatment of neovascular (wet) age-related macular degeneration (specialist use only)

**BY INTRAVITREAL INJECTION**

- Adult: 300 micrograms every 6 weeks, to be administered into the affected eye, review treatment if no benefit after 2 consecutive injections

- **CONTRA-INDICATIONS** Ocular or periocular infection

- **CAUTIONS**

  **CONATIONS, FURTHER INFORMATION**

  Pegaptanib is given by intravitreal injection by specialists experienced in the management of this condition. There is a potential risk of arterial thromboembolic events and non-ocular haemorrhage following the intravitreal injection of vascular endothelial growth factor inhibitors. Endophthalmitis can occur after intravitreal injections—patients should be advised to report any signs of infection immediately.

- **SIDE-EFFECTS**

  - Common or very common Anterior chamber inflammation - conjunctival hemorrhage - conjunctival hyperaemia - corneal abrasion or oedema - corneal erosion - eye pain - eyelid oedema - foreign body sensation in eye - increased lacrimation - injection-site haemorrhage - injection-site pain - ocular hyperaemia - punctate keratitis - raised intraocular pressure - reduced visual acuity - retinal degeneration - retinal pigment epithelium detachment - retinal pigment epithelium tear - vitreous detachment - vitreous floaters - vitreous haemorrhage

  - Uncommon

  - **With intravitreal use** anterior chamber flare - blindness - corneal epithelium defect - eyelid irritation - iridocyclitis - iritis - lenticular opacities - retinal detachment - retinal tear - uveitis

  - Rare

  - **With intravitreal use** hypopyon - vitritis

  **CONCEPTION AND CONTRACEPTION**

  Manufacturer recommends women use effective contraception during and for at least 3 months after treatment.

- **PREGNANCY**

  Manufacturer advises avoid unless potential benefit outweighs risk.

- **BREAST FEEDING**

  Manufacturer advises avoid—no information available.

- **MONITORING REQUIREMENTS** Monitor intra-ocular pressure following injection.

- **DIRECTIONS FOR ADMINISTRATION**

  For further information on administration, consult product literature.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  **NICE technology appraisals (TAs)**

  - Afibercept solution for injection for treating wet age-related macular degeneration (July 2013) NICE TA294

  Afibercept solution for injection is recommended as an option for treating wet age-related macular degeneration only if:

  - Aflibercept solution for injection with the discount agreed in the patient access scheme www.nice.org.uk/TA294

  - Pegaptanib solution for injection with the discount agreed in the patient access scheme www.nice.org.uk/TA305

  - There may be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Eylea (Bayer Plc) ▼

  Afibercept 40 mg per 1 ml Eylea 2mg/50microlitres solution for injection vials | 1 vial £816.00
**Ranibizumab**

**INDICATIONS AND DOSE**

Neovascular (wet) age-related macular degeneration (specialist use only)

- **BY INTRAVITREAL INJECTION**
  - Adult: 500 micrograms once a month, to be administered into the affected eye, monitor visual acuity monthly, continue treatment until visual acuity is stable for 3 consecutive months, thereafter monitor visual acuity monthly, if necessary subsequent doses may be given at least 1 month apart

Diabetic macular oedema / Macular oedema secondary to retinal vein occlusion (specialist use only)

- **BY INTRAVITREAL INJECTION**
  - Adult: Initially 500 micrograms once a month, to be administered into the affected eye, monitor visual acuity monthly, continue treatment until visual acuity is stable for 3 consecutive months (discontinue treatment if no improvement in visual acuity after initial 3 injections), thereafter monitor visual acuity monthly, if necessary subsequent doses may be given at least 1 month apart

Choroidal neovascularisation secondary to pathologic myopia (specialist use only)

- **BY INTRAVITREAL INJECTION**
  - Adult: Initially 500 micrograms, to be administered as a single injection into the affected eye, monitor for disease activity monthly for first 2 months, then at least every 3 months thereafter during the first year, then as required, if necessary subsequent doses may be given at least 1 month apart

Concomitant treatment of diabetic macular oedema, or macular oedema secondary to branch retinal vein occlusion, with laser photocoagulation (specialist use only)

- **BY INTRAVITREAL INJECTION**
  - Adult: 500 micrograms, to be administered at least 30 minutes after laser photocoagulation

**CONTRA-INDICATIONS**

- Ocular or periocular infection
- Severe intra-ocular inflammation
- Signs of irreversible ischaemic visual function loss in patients with retinal vein occlusion

**CAUTIONS**

- Active systemic infection
- Diabetic macular oedema due to type 1 diabetes (limited information available)
- Diabetic patients with HbA1c over 12%
- History of stroke
- History of transient ischaemic attack
- Patients at risk of retinal pigment epithelial tear
- Previous intravitreal injections
- Proliferative diabetic retinopathy
- Retinal detachment or macular hole
- Uncontrolled hypertension

CAUTIONS, FURTHER INFORMATION

Ranibizumab is given by intravitreal injection by specialists. There is a potential risk of arterial thromboembolic events and non-ocular haemorrhage following the intravitreal injection of vascular endothelial growth factor inhibitors. Endophthalmitis can occur after intravitreal injections—patients should be advised to report any signs of infection immediately.

**SIDE-EFFECTS**

- **Common or very common**
  - Allergic skin reactions
  - Anaemia
  - Anterior chamber flare
  - Anxiety
  - Arthralgia
  - Blepharitis
  - Cataract
  - Conjunctival disorders
  - Conjunctivitis
  - Cough
  - Eye haemorrhage
  - Eyelid oedema
  - Headache
  - Iridocyclitis
  - Irisitis
  - Nasopharyngitis
  - Nausea
  - Ocular discomfort
  - Photophobia
  - Photopsia
  - Posterior capsule opacification
  - Punctate keratitis
  - Raised intra-ocular pressure
  - Retinal disorders
  - Urinary tract infection
  - Uveitis
  - Visual disturbance
  - Vitreous disorders

- **Uncommon**
  - Blindness
  - Corneal disorders
  - Hyperaemia
  - Hypopyon
  - Iris adhesion
  - Keratopathy

- **CONCEPTION AND CONTRACEPTION**

  Manufacturer recommends women use effective contraception during and for at least 3 months after treatment.

- **PREGNANCY**

  Manufacturer advises avoid unless potential benefit outweighs risks.

- **BREAST FEEDING**

  Manufacturer advises avoid—no information available.

- **MONITORING REQUIREMENTS**

  - Monitor intra-ocular pressure, perfusion of the optic nerve head, and for signs of ocular infection following injection.
  - Monitor visual acuity, see individual indications and dose for frequency.

- **DIRECTIONS FOR ADMINISTRATION**

  For further information on administration, consult product literature.

**NATIONAL FUNDING/ACCESS DECISIONS**

- **NICE technology appraisals (TAs)**

  Ranibizumab and pegaptanib for the treatment of age-related macular degeneration (updated May 2012) NICE TA155

  Pegaptanib is not recommended for the treatment of wet age-related macular degeneration; patients currently receiving pegaptanib for any lesion type can continue treatment until they and their specialist consider it appropriate to stop. www.nice.org.uk/TA155

- **Macugen**

  Solution for injection (Pfizer Ltd)

  Micrograms once a month, to be administered as a single injection into the affected eye, monitor visual acuity monthly, continue treatment until visual acuity is stable for 3 consecutive months (discontinue treatment if no improvement in visual acuity after initial 3 injections), thereafter monitor visual acuity monthly, if necessary subsequent doses may be given at least 1 month apart

- **Ranibizumab and pegaptanib for the treatment of age-related macular degeneration (updated May 2012) NICE TA155**

  - Pegaptanib oligonucleotide (as Pegaptanib sodium) 3.3 mg per 1 ml Macugen 300micrograms/0.9ml injection pre-filled syringes | 1 pre-filled disposable injection (£20.00 per 1 ml)

  - Solution for injection pre-filled (Pfizer Ltd)

  - Solution for injection pre-filled (Pfizer Ltd)
Patients currently receiving ranibizumab for treating visual impairment due to diabetic macular oedema whose disease does not meet the criteria should be able to continue treatment until they and their clinician consider it appropriate to stop. www.nice.org.uk/TA274

- **Ranibizumab for the treatment of visual impairment caused by macular oedema secondary to retinal vein occlusion (May 2013)**

  - **NICE TA283**

  Ranibizumab is recommended as an option for treating visual impairment caused by macular oedema:
  - following central retinal vein occlusion or
  - following branch retinal vein occlusion only if treatment with laser photocoagulation has not been beneficial, or when laser photocoagulation is not suitable because of the extent of macular haemorrhage and
  - only if the manufacturer provides ranibizumab with the discount agreed in the patient access scheme in the context of NICE technology appraisal guidance 274. [www.nice.org.uk/TA283](http://www.nice.org.uk/TA283)

- **Ranibizumab for treating choroidal neovascularisation associated with pathological myopia (November 2013)**

  - **NICE TA298**

  Ranibizumab is recommended as an option for treating visual impairment due to choroidal neovascularisation secondary to pathological myopia when the manufacturer provides ranibizumab with the discount agreed in the patient access scheme. [www.nice.org.uk/TA298](http://www.nice.org.uk/TA298)

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (May 2007) that ranibizumab (Lucentis®) is accepted for use within NHS Scotland for the treatment of neovascular (wet) age-related macular degeneration. The Scottish Medicines Consortium has advised (October 2011 and April 2013) that ranibizumab (Lucentis®) is accepted for use within NHS Scotland for the treatment of macular oedema secondary to branch or central retinal vein occlusion, and (November 2012) for restricted use for the treatment of visual impairment due to diabetic macular oedema in adults with best corrected visual acuity 75 Early Treatment Diabetic Retinopathy Study letters or less at baseline, and (October 2013) for the treatment of visual impairment due to choroidal neovascularisation secondary to pathologic myopia in adults; SMC advice is contingent upon the continuing availability of ranibizumab at the price agreed in the patient access scheme.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  **Solution for injection**

  - Lucentis Novartis Pharmaceuticals UK Ltd

    Ranibizumab 10 mg per 1 ml Lucentis 2.3mg/0.23ml solution for injection vials | 1 vial (£42.00)
    - 1 ml prefilled syringe
    - 1 ml pre-filled disposable injection (£42.00)

6.2 Macular oedema

**Fluocinolone acetonide**

**INDICATIONS AND DOSE**

Treatment of visual impairment associated with chronic diabetic macular oedema which is insufficiently responsive to available therapies (specialist use only)

**BY INTRAVITREAL INJECTION**

- Adults: 190 micrograms, to be administered into the affected eye

- **CONTRA-INDICATIONS**

  - Active or suspected ocular infection
  - Active or suspected peri-ocular infection
  - Pre-existing glaucoma

- **CAUTIONS**

  - Raised baseline intra-ocular pressure

- **INTERACTIONS**

  - Caution with concomitant administration of anticoagulant or antithrombotic agents (higher incidence of conjunctival haemorrhage).

- **SIDE-EFFECTS**

  - Common or very common:
    - Blurred vision
    - Conjunctival haemorrhage
    - Iris adhesions
    - Iris neovascularisation
    - Maculopathy
    - Hypoesthesia
    - Optic atrophy
    - Optic nerve disorder
    - Retinal detachment
    - Retinal vascular occlusion
    - Sclera thinning
    - Vitreous degeneration
    - Vitreous haemorrhage

  - Uncommon:
    - Conjunctival ulcer
    - Endophthalmitis
    - Eye discharge
    - Eye pruritus
    - Headache
    - Iris atrophy
    - Iris neovascularisation
    - Maculopathy
    - Hypoesthesia
    - Optic atrophy
    - Optic nerve disorder
    - Retinal detachment
    - Retinal vascular occlusion
    - Sclera thinning
    - Vitreous degeneration
    - Vitreous haemorrhage
    - Sclera thinning
    - Vitreous detachment

  - Rare:
    - Active or suspected peri-ocular infection
    - Retinal detachment

- **PREGNANCY**

  - Manufacturer advises avoid unless potential benefit outweighs risk—no information available.

- **BREAST FEEDING**

  - Manufacturer advises avoid unless essential.

- **MONITORING REQUIREMENTS**

  - Monitor for raised intra-ocular pressure (particularly if raised at baseline), retinal detachment, endophthalmitis, vitreous haemorrhage or detachment within 2–7 days following the procedure.

- **DIRECTIONS FOR ADMINISTRATION**

  - Concurrent administration to both eyes not recommended. Further information on administration and repeat dosing, consult product literature.

- **NATIONAL FUNDING/ACCESS DECISIONS**

  - NICE technology appraisals (TAs)

    - Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy (November 2013) NICE TA301

    - Fluocinolone acetonide intravitreal implant is recommended as an option for treating chronic diabetic macular oedema that is insufficiently responsive to available therapies only if:
      - the implant is to be used in an eye with an intra-ocular (pseudophakic lens) and
      - the manufacturer provides fluocinolone acetonide intravitreal implant with the discount agreed in the patient access scheme. [www.nice.org.uk/TA301](http://www.nice.org.uk/TA301)

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (February 2014) that fluocinolone acetonide intravitreal implant (Iluvien®) is recommended for restricted use within NHS Scotland for the treatment of vision impairment associated with chronic diabetic macular oedema, considered insufficiently responsive to available therapies, only in patients in whom the affected eye is pseudophakic (has an artificial lens after cataract surgery), and retreatment would take place only if the patient had previously responded to treatment with...
fluocinolone acetonide and subsequently best corrected visual acuity had deteriorated to less than 20/32.

**MEDICAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Implant**

- **Iluvien (Alimera Sciences Ltd)**
  - Fluocinolone acetonide 190 microgram
  - ILUVIEN 190 microgram intravitreal implant in applicator | 1 device £5,500.00

**6.3 Vitreomacular traction**

**RECOMBINANT PROTEOLYTIC ENZYMES**

**Ocriplasmin**

**INDICATIONS AND DOSE**

Treatment of vitreomacular traction, including when associated with a macular hole of diameter less than or equal to 400 microns (specialist use only)

**BY INTRAVITREAL INJECTION**

- Adult: 125 micrograms for 1 dose, to be administered into the affected eye, concurrent administration to both eyes is not recommended

**CONTRA-INDICATIONS**

Active or suspected ocular or periocular infection · aphakia · exudative age-related macular degeneration · high myopia · history of rhegmatogenous retinal detachment · ischaemic retinopathies · large diameter macular hole (> 400 microns) · lens zonule instability · proliferative diabetic retinopathy · recent intra-ocular injection (including laser therapy) · recent ocular surgery · retinal vein occlusions · vitreous haemorrhage

**CAUTIONS**

History of uveitis (including severe active inflammation) · non-proliferative diabetic retinopathy · significant eye trauma

**SIDE-EFFECTS**

- Common or very common Abnormal retinograph · anterior chamber cell or flare · chromatopsia · conjunctival disorders · eyelid oedema · iritis · macular degeneration · macular hole · macular oedema · metamorphopsia · ocular discomfit · ocular hyperaemia · photophobia · photopsia · raised intra-ocular pressure · reduced visual acuity · retinal disorders · retinal pigment epitheliopathy · vitreous disorders

- Uncommon Anterior chamber inflammation · corneal abrasion · diplopia · eye inflammation · hyphaema · lens subluxation · miosis · scotoma · transient blindness · unequal pupils · visual field defect

**PREGNANCY**

Manufacturer advises use only if potential benefit outweighs risk—no information available.

**BREAST FEEDING**

Manufacturer advises use only if potential benefit outweighs risk—no information available.

**MONITORING REQUIREMENTS**

Monitor intra-ocular pressure, visual acuity, and for signs of intra-ocular inflammation or infection following injection.

**DIRECTIONS FOR ADMINISTRATION**

For further information on administration, consult product literature.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NICE technology appraisals (TAs)**

- Ocriplasmin for treating vitreomacular traction (October 2013) NICE TA297
  Ocriplasmin is recommended as an option for treating vitreomacular traction in adults, only if:
  - they have a stage II full-thickness macular hole with a diameter of 400 microns or less and/or
  - they have severe symptoms. [www.nice.org.uk/TA297](http://www.nice.org.uk/TA297)

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (July 2014) that ocriplasmin (Jetrea®) is accepted for restricted use within NHS Scotland for the treatment of patients with vitreomacular traction plus macular hole, regardless of whether they have epiretinal membrane formation, and in patients with vitreomacular traction alone (no epiretinal membrane and no macular hole).

**MEDICAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Jetrea (Alcon Laboratories (UK) Ltd)**
  - Ocriplasmin 2.5 mg per 1 ml Jetrea 0.5mg/0.2ml concentrate for solution for injection vials | 1 vial | £2,500.00
Chapter 12
Ear, nose and oropharynx

CONTENTS
1 Ear
  1.1 Otitis externa
  1.2 Removal of ear wax
2 Nose
  2.1 Nasal congestion
  2.2 Nasal inflammation, nasal polyps and rhinitis
  2.3 Nasal staphylococcal infection
3 Oropharynx

1 Ear

Otitis externa
Otitis externa is an inflammatory reaction of the meatal skin. It is important to exclude an underlying chronic otitis media before treatment is commenced. Many cases recover after thorough cleansing of the external ear canal by suction or dry mopping. A frequent problem in resistant cases is the difficulty in applying lotions and ointments satisfactorily to the relatively inaccessible affected skin. The most effective method is to introduce a ribbon gauze dressing or sponge wick soaked with corticosteroid ear drops or with an astringent such as aluminium acetate solution p. 451. When this is not practical, the ear should be gently cleansed with a probe covered in cotton wool and the patient encouraged to lie with the affected ear uppermost for ten minutes after the canal has been filled with a liberal quantity of the appropriate solution.

If infection is present, a topical anti-infective which is not used systemically (such as neomycin sulfate p. 451 or chlortetracycline) may be used, but for only about a week as excessive use may result in fungal infections; these may be difficult to treat and require expert advice. Sensitivity to the anti-infective or solvent may occur and resistance to antibacterials is a possibility with prolonged use. Aluminium acetate p. 979 ear drops are also effective against bacterial infection and inflammation of the ear. Chloramphenicol p. 955 may be used but the ear drops contain propylene glycol and cause hypersensitivity reactions in about 10% of patients. Solutions containing an anti-infective and a corticosteroid are used for treating cases where infection is present with inflammation and eczema.

In view of reports of ototoxicity, manufacturers contraindicate treatment with topical aminoglycosides or polymyxins in patients with a perforated tympanic membrane (eardrum) or patent grommet. However, some specialists do use these drops cautiously in the presence of a perforation or patent grommet in patients with chronic suppurrative otitis media and when other measures have failed for otitis externa; treatment should be considered only by specialists in the following circumstances:

- patients should be counselled on the risk of ototoxicity and given justification for the use of these topical antibiotics;
- baseline audiometry should be performed, if possible, before treatment is commenced.

Clinical expertise and judgement should be used to assess the risk of treatment versus the benefit to the patient in such circumstances.

A solution of acetic acid 2% acts as an antifungal and antibacterial in the external ear canal. It may be used to treat mild otitis externa but in severe cases an antiinflammatory preparation with or without an anti-infective drug is required. A proprietary preparation containing acetic acid 2% (EarCalm® spray) is on sale to the public.

For severe pain associated with otitis externa, a simple analgesic, such as paracetamol p. 354 or ibuprofen p. 927, can be used. A systemic antibacterial can be used if there is spreading cellulitis or if the patient is systemically unwell. When a resistant staphylococcal infection (a boil) is present, treatment should be for no longer than 2 weeks; when a resistant staphylococcal infection (a boil) is present, treatment should be for no longer than 2 weeks; when a resistant staphylococcal infection (a boil) is present, treatment should be for no longer than 2 weeks; a systemic antibacterial can be used if there is spreading cellulitis or if the patient is systemically unwell.

Otitis media
Acute otitis media
Acute otitis media is the commonest cause of severe aural pain in small children. Many infections, especially those accompanying coryza, are caused by viruses. Most uncomplicated cases resolve without antibacterial treatment and a simple analgesic, such as paracetamol p. 354, may be sufficient. In children without systemic features, a systemic antibacterial may be started after 72 hours if there is no improvement, or earlier if there is deterioration, if the patient is systemically unwell, if the patient is at high risk of serious complications (e.g. in immunosuppression, cystic fibrosis), if mastoiditis is present, or in children under 2 years of age with bilateral otitis media. Perforation of the tympanic membrane in patients with acute otitis media usually heals spontaneously without treatment; if there is no improvement, e.g. pain or discharge persists, a systemic antibacterial can be given. Topical treatment of acute otitis media is ineffective and there is no place for drops containing a local anaesthetic.
Otitis media with effusion
Otitis media with effusion (glue ear) occurs in about 10% of children and in 90% of children with cleft palates. Systemic antibacterials are not usually required. If glue ear persists for more than a month or two, the child should be referred for assessment and follow up because of the risk of long-term hearing impairment which can delay language development. Untreated or resistant glue ear may be responsible for some types of chronic otitis media.

Chronic otitis media
Opportunist organisms are often present in the debris, keratin, and necrotic bone of the middle ear and mastoid in patients with chronic otitis media. The mainstay of treatment is thorough cleansing with aural microsuction which may completely resolve long-standing infection. Local cleansing of the meatal and middle ear may be followed by treatment with a sponge wick or ribbon gauze dressing soaked with corticosteroid ear drops or with an astringent such as aluminium acetate p. 979 solution; this is particularly beneficial for discharging ears or infections of the mastoid cavity. An antibacterial ear ointment may also be used. Acute exacerbations of chronic infection may also require systemic treatment with amoxicillin p. 482 (or erythromycin p. 471 if penicillin-allergic); treatment is adjusted according to the results of sensitivity testing.

In view of reports of ototoxicity, manufacturers contraindicate topical treatment with ototoxic antibacterials in the presence of a tympanic perforation or patent grommet. Ciprofloxacin p. 956 or ofloxacin p. 957 eye drops used in the ear [unlicensed use] or ear drops [both unlicensed; available from ‘special-order’ manufacturers or specialist importing companies] are an effective alternative to such ototoxic ear drops for chronic otitis media in patients with perforation of the tympanic membrane.

However, some specialists do use ear drops containing aminoglycosides or polymyxins [unlicensed indications] cautiously in patients with chronic suppurrative otitis media and a perforation of the tympanic membrane, if the otitis media has failed to settle with systemic antibacterials; treatment should be considered only by specialists in the following circumstances:

- drops should only be used in the presence of obvious infection;
- treatment should be for no longer than 2 weeks;
- patients should be counselled on the risk of ototoxicity and given justification for the use of these topical antibacterials;
- baseline audiometry should be performed, if possible, before treatment is commenced.

Clinical expertise and judgement should be used to assess the risk of treatment versus the benefit to the patient in such circumstances. It is considered that the pus in the middle ear associated with otitis media also carries a risk of ototoxicity.

Removal of ear wax
Ear wax (cerumen) is a normal bodily secretion which provides a protective film on the meatal skin and need only be removed if it causes hearing loss or interferes with a proper view of the ear drum.

Ear wax can be softened using simple remedies such as olive oil ear drops or almond oil ear drops; sodium bicarbonate p. 979 ear drops are also effective, but may cause dryness of the ear canal. If the wax is hard and impacted, the drops can be used twice daily for several days and this may reduce the need for mechanical removal of the wax. The patient should lie with the affected ear uppermost for 5 to 10 minutes after a generous amount of the softening remedy has been introduced into the ear. Some proprietary preparations containing organic solvents can irritate the meatal skin, and in most cases the simple remedies indicated above are just as effective and less likely to cause irritation. Docosate sodium p. 980 or urea hydrogen peroxide p. 980 are ingredients in a number of proprietary preparations for softening ear wax.

If necessary, wax may be removed by irrigation with water (warmed to body temperature). Ear irrigation is generally best avoided in young children, in patients unable to cooperate with the procedure, in those with otitis media in the last six weeks, in otitis externa, in patients with cleft palate, a history of ear drum perforation, or previous ear surgery. A person who has hearing in one ear only should not have that ear irrigated because even a very slight risk of damage is unacceptable in this situation.

1.1 Otitis externa

ANTI-INFECTIVES

Chloramphenicol
- **DRUG ACTION** Chloramphenicol is a potent broad-spectrum antibiotic.

**INDICATIONS AND DOSE**

**Bacterial infection in otitis externa**

<table>
<thead>
<tr>
<th>TO THE EAR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child:</strong> Apply 2–3 drops 2–3 times a day</td>
</tr>
<tr>
<td><strong>Adult:</strong> Apply 2–3 drops 2–3 times a day</td>
</tr>
</tbody>
</table>

- **CAUTIONS** Avoid prolonged use
- **SIDE-EFFECTS**

- **Common or very common** High incidence of sensitivity reactions to vehicle

**PATIENT AND CARER ADVICE**

Medicines for children leaflet: Chloramphenicol ear drops for ear infections (otitis externa)

[www.medicinesforchildren.org.uk/](http://www.medicinesforchildren.org.uk/)

**LESS SUITABLE FOR PRESCRIBING** Chloramphenicol ear drops are less suitable for prescribing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Ear drops**

EXCIPIENTS: May contain Propylene glycol

- **CHLORAMPHENICOL (Non-proprietary)**
- **CHLORAMPHENICOL 50 mg per 1 ml Chloramphenicol 5% ear drops | 10 ml PMP £5.14 DT price = £5.14**
- **CHLORAMPHENICOL 100 mg per 1 ml Chloramphenicol 10% ear drops | 10 ml PMP £27.56**

**Clioquinol with flumetasone pivalate**

**INDICATIONS AND DOSE**

Eczematous inflammation in otitis externa | Mild bacterial or fungal infections in otitis externa

<table>
<thead>
<tr>
<th>TO THE EAR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child 2-17 years:</strong> 2–3 drops twice daily for 7–10 days, to be instilled into the ear</td>
</tr>
<tr>
<td><strong>Adult:</strong> 2–3 drops twice daily for 7–10 days, to be instilled into the ear</td>
</tr>
</tbody>
</table>

- **CONTRA-INDICATIONS** Iodine sensitivity
- **CAUTIONS** Avoid prolonged use - manufacturer advises avoid in perforated tympanic membrane (but used by specialists for short periods)
- **SIDE-EFFECTS** Local sensitivity
- **PATIENT AND CARER ADVICE** Clioquinol stains skin and clothing
Clotrimazole

**INDICATIONS AND DOSE**

Fungal infection in otitis externa

**TO THE EAR**
- Child: Apply 2–3 times a day continue for at least 14 days after disappearance of infection
- Adult: Apply 2–3 times a day continue for at least 14 days after disappearance of infection

**SIDE-EFFECTS** Local irritation · local sensitivity

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops, ear-drops-inflammatory-ear-infections www.medicinesforchildren.org.uk/gentamicin-and-hydrocortisone-ear-drops-inflamatory-ear-infections

**SIDE-EFFECTS** Local sensitivity

**CONTRA-INDICATIONS** Perforated tympanic membrane

**CAUTIONS** Avoid prolonged use

**Clotrimazole liquid**
- Canesten (clotrimazole) (Bayer Plc)
  - Clotrimazole 10 mg per 1 ml Canesten 1% solution | 20 ml $2.30 DT price = $2.30

**Framycetin sulfate with dexamethasone and gramicidin**

**INDICATIONS AND DOSE**

Eczematous inflammation in otitis externa

**TO THE EAR**
- Child: 2–3 drops 3–4 times a day
- Adult: 2–3 drops 3–4 times a day

**SIDE-EFFECTS** Local sensitivity

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: eye drops, ear-drops-inflammatory-ear-infections www.medicinesforchildren.org.uk/gentamicin-and-hydrocortisone-ear-drops-inflamitory-ear-infections

**SIDE-EFFECTS** Local sensitivity

**CONTRA-INDICATIONS** Perforated tympanic membrane

**CAUTIONS** Avoid prolonged use

**Neomycin with betamethasone**

**INDICATIONS AND DOSE**

Eczematous inflammation in otitis externa

**TO THE EAR USING EAR DROPS**
- Child: Apply 2–4 drops 4–5 times a day (including a dose at bedtime)
- Adult: Apply 2–4 drops 4–5 times a day (including a dose at bedtime)

**SIDE-EFFECTS** Local sensitivity

**CONTRA-INDICATIONS** Patent grommet (although may be used by specialists, see Ear p. 976) · perforated tympanic membrane (although may be used by specialists, see Ear p. 976)

**CAUTIONS** Avoid prolonged use

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**SIDE-EFFECTS** Local sensitivity

**CONTRA-INDICATIONS** Patent grommet (although may be used by specialists, see Ear p. 976) · perforated tympanic membrane (although may be used by specialists, see Ear p. 976)
**Neomycin sulfate with dexamethasone and glacial acetic acid**

**INDICATIONS AND DOSE**
Eczematous inflammation in otitis externa

**TO THE EAR**
- **Adult:** Apply 1 spray 3 times a day
- **Child:** Apply 1 spray 3 times a day

**CONTRA-INDICATIONS**
Patent grommet (although may be used by specialists, see Ear p. 976) • perforated tympanic membrane (although may be used by specialists, see Ear p. 976)

**CAUTIONS**
Avoid prolonged use

**SIDE-EFFECTS**
Local sensitivity reactions

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Ear/eye/nose drops solution**
EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate
- **BETAMETHASONE (Non-proprietary)**
  - Betamethasone sodium phosphate 1 mg per 1 ml
  - Betamethasone sodium phosphate 0.1% eye/ear/nose drops | 5 ml (PST) no price available
  - Betnesol (Focus Pharmaceuticals Ltd)
  - Betamethasone sodium phosphate 1 mg per 1 ml Betnesol 0.1% eye/ear/nose drops | 10 ml (PST) £2.32 DT price = £2.32

**Prednisolone**

**INDICATIONS AND DOSE**
Eczematous inflammation in otitis externa

**TO THE EAR**
- **Child:** Apply 2–3 drops every 2–3 hours, frequency to be reduced when relief obtained
- **Adult:** Apply 2–3 drops every 2–3 hours, frequency to be reduced when relief obtained

**CONTRA-INDICATIONS**
Avoid alone in the presence of untreated infection (combine with suitable anti-infective)

**CAUTIONS**
Avoid prolonged use

**SIDE-EFFECTS**
Local sensitivity reactions

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Ear/eye drops solution**
EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate
- **Predsol** (Focus Pharmaceuticals Ltd)
  - Prednisolone sodium phosphate 5 mg per 1 ml Predsol 0.5% eye/ear drops | 10 ml (PST) £2.00 DT price = £2.00

### 1.2 Removal of ear wax

**BICARBONATE**

**Sodium bicarbonate**

**INDICATIONS AND DOSE**
Removal of ear wax (with 5% ear drop solution)

**TO THE EAR**
- **Child:** (consult product literature)
- **Adult:** (consult product literature)

**SIDE-EFFECTS**
Dryness of the ear canal

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Ear drops**
- **SODIUM BICARBONATE (Non-proprietary)**
  - Sodium bicarbonate 50 mg per 1 ml Sodium bicarbonate 5% ear drops | 10 ml £1.25
**Ear, nose and oropharynx**

**SOFTENING DRUGS**

**Almond oil**

**INDICATIONS AND DOSE**
- **Removal of ear wax**
  - **TO THE EAR**
    - **Child:** Allow drops to warm to room temperature before use (consult product literature)
    - **Adult:** Allow drops to warm to room temperature before use (consult product literature)

**DIRECTIONS FOR ADMINISTRATION**
- The patient should lie with the affected ear uppermost for 5 to 10 minutes after a generous amount of the softening remedy has been introduced into the ear.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ear drops

**Liquid**
- **ALMOND OIL (Non-proprietary)**
- Almond oil 1 ml per 1 ml
- Almond oil liquid | 50 ml £0.76 DT price = £0.76 | 70 ml £0.73 | 200 ml £2.01 | 500 ml £11.56−£11.67 | 2000 ml (£50) £19.56 | 2000 ml £20.18–£20.38

**Arachis oil with chlorobutanol**

**INDICATIONS AND DOSE**
- **Removal of ear wax**
  - **TO THE EAR**
  - **Adult:** (consult product literature)
  - **Child:** (consult product literature)

**LESS SUITABLE FOR PRESCRIBING**
- Arachis (peanut) oil with chlorobutanol ear drops are less suitable for prescribing.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Ear drops**
- Cerumol (Thornton & Ross Ltd)
- Arachis oil 573 mg per 1 ml, Chlorobutanol 50 mg per 1 ml
- Cerumol ear drops | 11 ml | £2.05
- Earol olive oil ear drops | 1 ml | no price available
- Exterol
- Exterol % ear drops | 8 ml | £1.75
- Exterol 9% ear drops | 8 ml | £2.89

**Urea hydrogen peroxide**

**INDICATIONS AND DOSE**
- **Softening and removal of ear wax**
  - **TO THE EAR**
  - **Adult:** (consult product literature)

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Ear drops**
- Exterol (Dermal Laboratories Ltd)
- Urea hydrogen peroxide 50 mg per 1 gram
- Exterol 9% ear drops | 8 ml | £1.75
- Otex (Dendron Ltd)
- Urea hydrogen peroxide 50 mg per 1 gram
- Otex 9% ear drops | 8 ml | £2.89

**Docusate sodium**

(迪奥卡希纳印他烷酸)

**INDICATIONS AND DOSE**
- **Removal of ear wax**
  - **TO THE EAR**
  - **Adult:** (consult product literature)

**LESS SUITABLE FOR PRESCRIBING**
- Ear drops less suitable for prescribing.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Ear drops**
- Molcer (Wallace Manufacturing Chemists Ltd)
- Docusate sodium 50 mg per 1 ml
- Molcer ear drops | 15 ml | £8.08
- Waxsol (Meda Pharmaceuticals Ltd)
- Docusate sodium 5 mg per 1 ml
- Waxsol ear drops | 10 ml | £1.95
- DT price = £1.95

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**Olive oil**

**INDICATIONS AND DOSE**
- **Removal of ear wax**
  - **TO THE EAR**
  - **Child:** Apply twice daily for several days (if wax is hard and impacted)
  - **Adult:** Apply twice daily for several days (if wax is hard and impacted)

**DIRECTIONS FOR ADMINISTRATION**
- The patient should lie with the affected ear uppermost for 5 to 10 minutes after a generous amount of the softening remedy has been introduced into the ear. Allow ear drops to warm to room temperature before use.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Ear drops**
- OLIVE OIL (Non-proprietary)
- Care olive oil ear drops | 10 ml | £1.42
- Olive oil ear drops | 10 ml | £1.42 | 20 ml | £2.70
- Arjun ear drops | 10 ml | £1.25
- Cerumol (olive oil) (Thornton & Ross Ltd)
- Cerumol olive oil ear drops | 10 ml | no price available
- Spray
  - Earol (HL Healthcare Ltd)
  - Earol olive oil ear spray | 10 ml | no price available

**Urea hydrogen peroxide**

**INDICATIONS AND DOSE**
- Softening and removal of ear wax
  - **TO THE EAR**
  - **Adult:** (consult product literature)

**PATIENT AND CARER ADVICE**
- The patient should lie with the affected ear uppermost for 5 to 10 minutes after a generous amount of the softening remedy has been introduced into the ear.

**LESS SUITABLE FOR PRESCRIBING**
- Urea-hydrogen peroxide ear drops are less suitable for prescribing.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Ear drops**
- Exterol (Dermal Laboratories Ltd)
- Urea hydrogen peroxide 50 mg per 1 gram
- Exterol 9% ear drops | 8 ml | £1.75
- Otex (Dendron Ltd)
- Urea hydrogen peroxide 50 mg per 1 gram
- Otex 9% ear drops | 8 ml | £2.89

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**Nose**

Rhinitis is often self-limiting but bacterial sinusitis may require treatment with antibacterials. There are few indications for nasal sprays and drops except in allergic rhinitis and perennial rhinitis. Many nasal preparations contain sympathomimetic drugs which may damage the nasal cilia. Sodium chloride 0.9% solution may be used as a douche or ‘sniff’ following endonasal surgery.
Drugs used in nasal allergy

Mild allergic rhinitis is controlled by antihistamines (see under Antihistamines, allergen immunotherapy and allergic emergencies p. 241) or topical nasal corticosteroids; systemic nasal decongestants are of doubtful value. Topical nasal decongestants can be used for a short period to relieve congestion and allow penetration of a topical nasal corticosteroid.

More persistent symptoms and nasal congestion can be relieved by topical nasal corticosteroids. The topical antihistamine azelastine hydrochloride p. 945 is useful for controlling breakthrough symptoms in allergic rhinitis. Topical antihistamines are considered less effective than topical corticosteroids but probably more effective than Cromolyn. In seasonal allergic rhinitis (e.g. hay fever), treatment should begin 2 to 3 weeks before the season commences and may have to be continued for several months; continuous treatment may be required for years in perennial rhinitis.

Montelukast p. 233 is less effective than topical nasal corticosteroids; montelukast can be used in patients with seasonal allergic rhinitis and concomitant asthma.

Sometimes allergic rhinitis is accompanied by vasomotor rhinitis. In this situation, the addition of topical nasal ipratropium bromide can reduce watery rhinorrhea.

Very disabling symptoms occasionally justify the use of systemic corticosteroids for short periods, for example, in students taking important examinations. They may also be used at the beginning of a course of treatment with a corticosteroid spray to relieve severe mucosal oedema and allow the spray to penetrate the nasal cavity.

Corticosteroids

Corticosteroid nasal preparations should be avoided in the presence of untreated nasal infections, after nasal surgery (until healing has occurred), and in pulmonary tuberculosis. Patients transferred from systemic corticosteroids may experience exacerbation of some symptoms. Systemic absorption may follow nasal administration particularly if high doses are used or if treatment is prolonged; for cautions and side-effects of systemic corticosteroids. The risk of systemic effects may be greater with nasal drops than with nasal sprays; drops are administered incorrectly more often than sprays. The height of children receiving prolonged treatment with nasal corticosteroids should be monitored; if growth is slowed, referral to a paediatrician should be considered.

Nasal polyps

Short-term use of corticosteroid nasal drops helps to shrink nasal polyps; to be effective, the drops must be administered with the patient in the ‘head down’ position. A short course of a systemic corticosteroid may be required initially to shrink large polyps. A corticosteroid nasal spray can be used to maintain the reduction in swelling and also for the initial treatment of small polyps.

Pregnancy

If a pregnant woman cannot tolerate the symptoms of allergic rhinitis, treatment with nasal beclometasone dipropionate p. 984, budesonide p. 984, or fluticasone p. 985 may be considered.

Topical nasal decongestants

The nasal mucosa is sensitive to changes in atmospheric temperature and humidity and these alone may cause slight nasal congestion. The nose and nasal sinuses produce a litre of mucus in 24 hours and much of this finds its way silently into the stomach via the nasopharynx. Slight changes in the nasal airway, accompanied by an awareness of mucus passing along the nasopharynx causes some patients to be inaccurately diagnosed as suffering from chronic sinusitis. These symptoms are particularly noticeable in the later stages of the common cold. Sodium chloride 0.9% given as nasal drops or spray may relieve nasal congestion by helping to liquefy mucous secretions.

Inhalation of warm moist air is useful in the treatment of symptoms of acute infective conditions. The addition of volatile substances such as menthol and eucalyptus may encourage the use of warm moist air (see under Aromatic inhalations, cough preparations and systemic nasal decongestants p. 258).

Symptoms of nasal congestion associated with vasomotor rhinitis and the common cold can be relieved by the short-term use (usually not longer than 7 days) of decongestant nasal drops and sprays. These all contain sympathomimetic drugs which exert their effect by vasoconstriction of the mucosal blood vessels which in turn reduces oedema of the nasal mucosa. They are of limited value because they can give rise to a rebound congestion (rhinitis medicamentosa) on withdrawal, due to a secondary vasodilatation with a subsequent temporary increase in nasal congestion. This in turn tempts the further use of the decongestant, leading to a vicious cycle of events. Ephedrine hydrochloride p. 982 nasal drops is the safest sympathomimetic preparation and can give relief for several hours. The more potent sympathomimetic drugs oxymetazoline and xylometazoline hydrochloride p. 983 are more likely to cause a rebound effect.

Non-allergic watery rhinorrhea often responds well to treatment with the antimuscarinic ipratropium bromide p. 983.

Sinusitis and oral pain

Sinusitis affecting the maxillary antrum can cause pain in the upper jaw. Where this is associated with blockage of the opening from the sinus into the nasal cavity, it may be helpful to relieve the congestion with inhalation of warm moist air or with ephedrine hydrochloride p. 982 nasal drops.

Systemic antibacterials may sometimes be required for sinusitis (see under Nose infections, bacterial p. 446).

Nasal preparations for infection

There is no evidence that topical anti-infective nasal preparations have any therapeutic value in rhinitis or sinusitis; see elimination of nasal staphylococci.

Nasal staphylococci

Elimination of organisms such as staphylococci from the nasal vestibule can be achieved by the use of a cream containing chlorhexidine and neomycin (Noseptin®), but re-colonisation frequently occurs. Coagulase-positive staphylococci are present in the noses of 40% of the population. A nasal ointment containing mupirocin p. 987 is also available; it should probably be held in reserve for resistant infections. In hospitals or in care establishments, mupirocin nasal ointment should be reserved for the eradication (in both patients and staff) of nasal carriage of meticillin-resistant Staphylococcus aureus (MRSA). A sample should be taken 2 days after treatment to confirm eradication. The course may be repeated if the sample is positive (and the throat is not colonised). To avoid the development of resistance, the treatment course should not exceed 7 days and the course should not be repeated on more than one occasion. If the MRSA strain is mupirocin-resistant or does not respond after 2 courses, consider alternative products such as chlorhexidine and neomycin cream.
2.1 Nasal congestion

**SYMPATHOMIMETICS (VASOCONSTRICTOR)**

**Ephedrine hydrochloride**

**INDICATIONS AND DOSE**

- Nasal congestion: Sinusitis affecting the maxillary antrum
- Intranasal administration

- **Child 12–17 years**: Apply 1–2 drops up to 4 times a day as required for a maximum of 7 days, to be instilled into each nostril, administer ephedrine 0.5% nasal drops
- **Adult**: Apply 1–2 drops up to 4 times a day as required for a maximum of 7 days, to be instilled into each nostril

**CAUTIONS**

- Avoid excessive or prolonged use.
- Cardiovascular disease (in children).
- Diabetes mellitus.
- Elderly.
- Hypertension.
- Hypothyroidism.
- Ischaemic heart disease (in adults).
- Prostatic hypertrophy (risk of acute urinary retention) (in adults).

**INTERACTIONS**

- Appendix 1 (sympathomimetics).

**SIDE-EFFECTS**

- **Common or very common**
  - Headache.
  - Nausea.
- **Frequency not known**
  - After excessive use, tolerance with diminished effect.
  - Cardiovascular effect.
  - Local irritation.
  - Rebound congestion.

**PREGNANCY**

- Manufacturer advises avoid.

**BREAST FEEDING**

- Present in milk; manufacturer advises avoid—irritability and disturbed sleep reported.

**PRESCRIBING AND DISPENSING INFORMATION**

- For nasal drops, the BP directs that if no strength is specified, 0.5% drops should be supplied.

**PROFESSION SPECIFIC INFORMATION**

- **Dental practitioners’ formulary**
  - Ephedrine nasal drops may be prescribed.

**EXCEPTIONS TO LEGAL CATEGORY**

- Ephedrine nasal drops can be sold to the public provided no more than 180 mg of ephedrine base (or salts) are supplied at one time, and pseudoephedrine salts are not supplied at the same time; for conditions that apply to supplies made at the request of a patient, see Medicines, Ethics and Practice, London, Pharmaceutical Press (always consult latest edition).

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: spray, nasal drops.

**Nasal drops**

- **EPHEDRINE HYDROCHLORIDE (Non-proprietary)**
  - Ephedrine hydrochloride 5 mg per 1 ml Ephedrine 0.5% nasal drops | 10 ml | £1.53 DT price = £1.53
  - Ephedrine hydrochloride 10 mg per 1 ml Ephedrine 1% nasal drops | 10 ml | £1.58 DT price = £1.58

**Pseudoephedrine hydrochloride**

**INDICATIONS AND DOSE**

- Congestion of mucous membranes of upper respiratory tract
- **By mouth**
  - Child 6–11 years: 30 mg 3–4 times a day
  - Child 12–17 years: 60 mg 3–4 times a day

**Important safety information**

MHRA/CHM Advice (March 2008 and February 2009): Over-the-Counter Cough and Cold Medicines for Children

- Children under 6 years should not be given over-the-counter cough and cold medicines containing pseudoephedrine.

- **CAUTIONS**
  - Diabetes.
  - Heart disease.
  - Hypertension.
  - Hyperthyroidism.
  - Ischaemic heart disease (in adults).
  - Prostatic hypertrophy (in adults).
  - Raised intra-ocular pressure (in children).
  - Susceptibility to angle-closure glaucoma (in adults).

- **INTERACTIONS**
  - Appendix 1 (sympathomimetics).
  - Contra-indicated in patients taking monoamine oxidase inhibitors within the previous 2 weeks.

- **SIDE-EFFECTS**
  - **Common or very common**
    - Anxiety.
    - Headache.
    - Hypertension.
    - Insomnia.
    - Nausea.
    - Restlessness.
    - Tachycardia.
    - Vomiting.
  - **Rare**
    - Hallucinations - rash.
  - **Very rare**
    - Angle-closure glaucoma.
    - Urinary retention.

- **PREGNANCY**
  - Defective closure of the abdominal wall (gastroschisis) reported very rarely in newborns after first trimester exposure.

- **BREAST FEEDING**
  - May suppress lactation; avoid if lactation not well established or if milk production insufficient.

- **HEPATIC IMPAIRMENT**
  - Manufacturer advises use with caution in severe impairment.

- **RENAL IMPAIRMENT**
  - Use with caution in mild to moderate renal impairment. Manufacturer advises avoid in severe renal impairment.

- **LESS SUITABLE FOR PRESCRIBING**
  - Pseudoephedrine hydrochloride is less suitable for prescribing.

- **EXCEPTIONS TO LEGAL CATEGORY**
  - Galpseud® and Sudafed® can be sold to the public provided no more than 720 mg of pseudoephedrine salts are supplied, and ephedrine base (or salts) are not supplied at the same time; for details see Medicines, Ethics and Practice, London, Pharmaceutical Press (always consult latest edition).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- **Galpseud** (Thornton & Ross Ltd)
  - Pseudoephedrine hydrochloride 60 mg Galpseud 60 mg tablets | 24 tablet | £2.25 | 100 tablet | £5.42 DT price = £5.42
- **Sudafed Non-Drowsy Decongestant** (sudafed®) (McNeil Products Ltd)
  - Pseudoephedrine hydrochloride 60 mg Sudafed Decongestant 60 mg tablets | 12 tablet | £2.04

**Oral solution**

- **Galpseud** (Thornton & Ross Ltd)
  - Pseudoephedrine hydrochloride 6 mg per 1 ml Galpseud 30 mg/5 ml linctus (sugar-free) | 2000 ml | £4.00
- **Sudafed Non-Drowsy Decongestant** (pseudophedrine) (McNeil Products Ltd)
  - Pseudoephedrine hydrochloride 6 mg per 1 ml Sudafed Decongestant 30 mg/5 ml liquid | 100 ml | £1.92
Xylometazoline hydrochloride

**DRUG ACTION** Xylometazoline is a sympathomimetic.

### INDICATIONS AND DOSE

**Nasal congestion**
- **BY INTRanasAL ADMINISTRATION USING NASAL DROPS**
  - Child 6-11 years: 1–2 drops 1–2 times a day as required for maximum duration of 5 days, 0.05% solution to be administered into each nostril
  - Child 12–17 years: 2–3 drops 2–3 times a day as required for maximum duration of 7 days, 0.1% solution to be administered into each nostril
  - Adult: 2–3 drops 2–3 times a day as required for maximum duration of 7 days, 0.1% solution to be administered into each nostril

**BY INTRANASAL ADMINISTRATION USING NASAL SPRAY**
- Child 12–17 years: 1 spray 1–3 times a day as required for maximum duration of 7 days, to be administered into each nostril
- Adult: 1 spray 1–3 times a day as required for maximum duration of 7 days, to be administered into each nostril

### Important safety information
The CHM/MHRA has stated that non-prescription cough and cold medicines containing ephedrine, oxymetazoline, or xylometazoline can be considered for up to 5 days’ treatment in children aged 6–12 years after basic principles of best care have been tried; these medicines should not be used in children under 6 years of age.

### CAUTIONS
- Angle-closure glaucoma
- Avoid excessive or prolonged use
- Cardiovascular disease (in children)
- Diabetes mellitus
- Elderly
- Hypertension
- Hyperthyroidism
- Icaemic heart disease (in adults)
- Prostatic hypertrophy (risk of acute retention) (in adults)

### SIDE-EFFECTS
- Cardiovascular effects
- Hallucinations in small children
- Headache
- Local irritation
- Nausea
- Rebound congestion
- Restlessness in small children
- Sleep disturbances in small children
- Tolerance with diminished effect (after excessive use)
- Transient visual disturbances

### SIDE-EFFECTS, FURTHER INFORMATION
- Hallucinations (in small children)

### CAUTIONS, FURTHER INFORMATION
- **Rebound congestion** Symptomimetic drugs are of limited value in the treatment of nasal congestion because they can, following prolonged use (more than 7 days), give rise to a rebound congestion (rhinitis medicamentosa) on withdrawal, due to a secondary vasodilatation with a subsequent temporary increase in nasal congestion. This in turn tempts the further use of the decongestant, leading to a vicious cycle of events.
- **SIDE-EFFECTS** Cardiovascular effects
- Hallucinations in small children
- Headache
- Local irritation
- Nausea
- Rebound congestion
- Restlessness in small children
- Sleep disturbances in small children
- Tolerance with diminished effect (after excessive use)
- Transient visual disturbances

### MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.

#### Spray
- **Otrivine** (Novartis Consumer Health UK Ltd)
  - Xylometazoline hydrochloride 1 mg per 1 ml (Novartis Consumer Health UK Ltd)
  - Xylometazoline hydrochloride 500 microgram per 1 ml

### CAUTIONS
- Avoid excessive or prolonged use
- Cardiovascular disease (in children)
- Diabetes mellitus
- Elderly
- Hypertension
- Hyperthyroidism
- Icaemic heart disease (in adults)

### SIDE-EFFECTS
- Cardiovascular effects
- Hallucinations (in small children)

### MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.

#### Spray
- **Otrivine** (Novartis Consumer Health UK Ltd)
  - Xylometazoline hydrochloride 1 mg per 1 ml
  - Xylometazoline hydrochloride 500 microgram per 1 ml

### CAUTIONS
- Avoid spraying near eyes
- Bladder outflow obstruction
- Cystic fibrosis
- Prostatic hyperplasia (in adults)
- Risk of glaucoma (in children)
- Susceptibility to angle-closure glaucoma (in adults)

### SIDE-EFFECTS
- Common or very common
  - Epistaxis
  - Nasal dryness
  - Nasal irritation
- Uncommon
  - Headache
  - Nausea
  - Pharyngitis (in children)
- Very rare
  - Gastro-intestinal motility disturbances
  - Palpitations
  - Urinary retention

## ANTISMUSCARINICS

### Ipratropium bromide

### INDICATIONS AND DOSE
- Rhinorrhea associated with allergic and non-allergic rhinitis
- **BY INTRANASAL ADMINISTRATION**
  - Child 12-17 years: 2 sprays 2–3 times a day, dose to be sprayed into each nostril
  - Adult: 2 sprays 2–3 times a day, dose to be sprayed into each nostril

### Dose equivalence and conversion
- 1 metered spray of nasal spray = 21 micrograms.
CAUTIONS, FURTHER INFORMATION
Systemic absorption Systemic absorption may follow nasal administration particularly if high doses are used or if treatment is prolonged; therefore also consider the cautions and side-effects of systemic corticosteroids. The risk of systemic effects may be greater with nasal drops than with nasal sprays; drops are administered incorrectly more often than sprays.

SIDE-EFFECTS
- Rare Glaucoma - raised intra-ocular pressure
- Very rare Nasal septal perforation
- Frequency not known Aggression (particularly in children) - anxiety (particularly in children) - bronchospasm - depression (particularly in children) - dryness - epistaxis - headache - hyperactivity (particularly in children) - hypersensitivity reactions - nasal irritation - nasal ulceration - sleep disturbances (particularly in children) - smell disturbances - taste disturbances - throat irritation

SIDE-EFFECTS, FURTHER INFORMATION
Systemic absorption Systemic absorption may follow nasal administration particularly if high doses are used or if treatment is prolonged. Therefore also consider the side-effects of systemic corticosteroids. The risk of systemic effects may be greater with nasal drops than with nasal sprays; drops are administered incorrectly more often than sprays.

Medicinal forms

Beclometasone dipropionate (Beclometasone dipropionate)

INDICATIONS AND DOSE
Prophylaxis and treatment of allergic and vasomotor rhinitis

BY INTRANASAL ADMINISTRATION
- Child 6–17 years: 100 micrograms twice daily, dose to be administered into each nostril, reduced to 50 micrograms twice daily, dose to be administered into each nostril, dose to be reduced when symptoms controlled; maximum 400 micrograms per day
- Adult: 100 micrograms twice daily, dose to be administered into each nostril, reduced to 50 micrograms twice daily, dose to be administered into each nostril, dose to be reduced when symptoms controlled; maximum 400 micrograms per day

EXCEPTIONS TO LEGAL CATEGORY Preparations of beclometasone dipropionate can be sold to the public for nasal administration as a nasal spray if supplied for the prevention and treatment of allergic rhinitis in adults over 18 years subject to max. single dose of 100 micrograms per nostril, max. daily dose of 200 micrograms per nostril for max. 3 months, and a pack size of 20 mg.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Spray
EXCIPIENTS: May contain Benzalkonium chloride, polysorbates
- BECLOMETASONE DIPROPIONATE (Non-proprietary)
Beclometasone dipropionate 50 microgram per 1 dose Numark Hayfever Relief 50micrograms/dose nasal spray | 100 dose £3.84 | 200 dose £3.31 2.10
Beclometasone Hayfever Relief 50micrograms/dose nasal spray | 200 dose £3.56 DT price = £2.30
Beclometasone 50micrograms/dose nasal spray | 180 dose no price available | 200 dose £2.55 no price available DT price = £2.30 | 200 dose £2.10

Betamethasone

INDICATIONS AND DOSE
BETNESOL®
Non-infected inflammatory conditions of nose
BY INTRANASAL ADMINISTRATION
- Adult: Apply 2–3 drops 2–3 times a day, dose to be applied into each nostril

VISTAMETHASONE®
Non-infected inflammatory conditions of nose
BY INTRANASAL ADMINISTRATION
- Adult: Apply 2–3 drops twice daily, dose to be applied into each nostril

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Ear, eye/nose drops solution
EXCIPIENTS: May contain Benzalkonium chloride, disodium edetate
- BETAMETHASONE (Non-proprietary)
Betamethasone sodium phosphate 1 mg per 1 ml Betamethasone 0.1% eye/ear/nose drops | 5 ml £3.65 no price available
Betnesol (Focus Pharmaceuticals Ltd)
Betamethasone sodium phosphate 1 mg per 1 ml Betnesol 0.1% eye/ear/nose drops | 10 ml £3.22 DT price = £2.12
Vistamethasone (Martindale Pharmaceuticals Ltd)
Betamethasone sodium phosphate 1 mg per 1 ml Vistamethasone 0.1% eye/ear/nose drops | 5 ml £2.12 | 10 ml £4.16 DT price = £2.32

Budesonide

INDICATIONS AND DOSE
Prophylaxis and treatment of allergic and vasomotor rhinitis
BY INTRANASAL ADMINISTRATION
- Child 12-17 years: Initially 200 micrograms daily, dose to be administered into each nostril in the morning, alternatively initially 100 micrograms twice daily, dose to be administered to each nostril; reduced to 100 micrograms daily, dose to be administered into each nostril, dose can be reduced when control achieved
- Adult: Initially 200 micrograms daily, dose to be administered into each nostril in the morning, alternatively initially 100 micrograms twice daily, dose to be administered to each nostril; reduced to 100 micrograms daily, dose to be administered into each nostril, dose can be reduced when control achieved

Nasal polyps
BY INTRANASAL ADMINISTRATION
- Child 12-17 years: 100 micrograms twice daily for up to 3 months, dose to be administered into each nostril
- Adult: 100 micrograms twice daily for up to 3 months, dose to be administered into each nostril

RHINOCORT AQUA®
Rhinitis
BY INTRANASAL ADMINISTRATION
- Adult: 128 micrograms once daily, dose to be administered into each nostril in the morning,
Fluticasone

**INDICATIONS AND DOSE**

Prophylaxis and treatment of allergic rhinitis and perennial rhinitis

**BY INTRANASAL ADMINISTRATION USING NASAL SPRAY**

- **Child 4-11 years:** 50 micrograms once daily, to be administered into each nostril preferably in the morning, increased if necessary to 50 micrograms twice daily
- **Child 12-17 years:** 100 micrograms once daily, to be administered into each nostril preferably in the morning, increased if necessary to 100 micrograms twice daily; reduced to 50 micrograms once daily, dose to be administered into each nostril, dose to be reduced when control achieved
- **Adult:** 100 micrograms once daily, to be administered into each nostril preferably in the morning, increased if necessary to 100 micrograms twice daily; reduced to 50 micrograms once daily, to be administered into each nostril, dose to be reduced when control achieved

Nasal polyps

**BY INTRANASAL ADMINISTRATION USING NASAL DROPS**

- **Child 12-17 years:** 200 micrograms 1–2 times a day, to be administered into each nostril, dose of 200 micrograms approximately 6 drops, alternative treatment should be considered if no improvement after 4–6 weeks
- **Adult:** 200 micrograms 1–2 times a day, to be administered into each nostril, dose of 200 micrograms approximately 6 drops, alternative treatment should be considered if no improvement after 4–6 weeks

**AVAMYS® SPRAY**

Prophylaxis and treatment of allergic rhinitis

**BY INTRANASAL ADMINISTRATION**

- **Adult:** 55 micrograms once daily, dose to be sprayed into each nostril, reduced to 27.5 micrograms once daily, to be sprayed into each nostril, dose to be reduced once control achieved; use minimum effective dose

Dose equivalence and conversion

1 spray equivalent to 27.5 micrograms.

- **SIDE-EFFECTS**

**SIDE-EFFECTS, FURTHER INFORMATION**

Nasal ulceration

Nasal ulceration occurs commonly with nasal preparations containing fluticasone furoate.

**EXCEPTIONS TO LEGAL CATEGORY**

Preparations of budesonide can be sold to the public for nasal administration (other than by pressurised nasal spray) if supplied for the prevention and treatment of allergic rhinitis in adults over 18 years, subject to maximum single dose of 100 micrograms per nostril, max. daily dose of 200 micrograms per nostril for max. 3 months, and a pack size of 3 mg.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Spray**

EXCIPENTS: May contain Benzalkonium chloride, polysorbates, potassium sorbate

- FLUTICASONE (Non-proprietary)
  - Budesonide 64 microgram per 1 dose
  - Fluticasone furoate 27.5 microgram per 1 dose
    - Avamys 27.5 micrograms/dose nasal spray | 120 dose [P] £6.44 DT price = £6.44
  - Fluticasone propionate 50 microgram per 1 dose
    - Boots Pharmacy
      - Hayfever and Allergy 50 microgram/dose nasal spray | 60 dose [P] no price available
    - Fluticasone propionate 50 microgram/dose nasal spray
      - Flixonase 100 micrograms/dose nasal spray | 150 dose [P] £9.50 DT price = £11.01
    - Flixonase (GlaxoSmithKline UK Ltd)
      - Flixonase propionate 50 microgram per 1 dose
        - Flixonase 50 micrograms/dose nasal spray | 150 dose [P] £11.01 DT price = £11.01

**Fluticasone with azelastine**

The properties listed below are those particular to the combination only. For the properties of the components please consider, azelastine hydrochloride p. 945, fluticasone above.

**INDICATIONS AND DOSE**

Moderate to severe seasonal and perennial allergic rhinitis, if monotherapy with antihistamine or corticosteroid is inadequate

**BY INTRANASAL ADMINISTRATION**

- **Child 12-17 years:** 1 spray twice daily, dose to be administered into each nostril
- **Adult:** 1 spray twice daily, dose to be administered into each nostril

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Spray**

EXCIPENTS: May contain Benzalkonium chloride, polysorbates

- Dymista (Meda Pharmaceuticals Ltd)
  - Azelastine hydrochloride 137 microgram per 1 actuation,
    - Fluticasone propionate 50 microgram per 1 actuation
      - Dymista 137 micrograms/dose nasal spray | 50 micrograms/dose nasal spray | 120 dose [P] £14.80
Mometasone furoate

**INDICATIONS AND DOSE**

**Prophylaxis and treatment of allergic rhinitis**

**BY INTRANASAL ADMINISTRATION**

- Child 6–11 years: 50 micrograms daily, dose to be sprayed into each nostril
- Child 12–17 years: 100 micrograms daily, increased if necessary up to 200 micrograms daily, dose to be sprayed into each nostril; reduced to 50 micrograms daily, dose to be reduced when control achieved, dose to be sprayed into each nostril
- Adult: 100 micrograms daily, increased if necessary up to 200 micrograms daily, dose to be sprayed into each nostril; reduced to 50 micrograms daily, dose to be reduced when control achieved, dose to be sprayed into each nostril

**Nasal polyps**

**BY INTRANASAL ADMINISTRATION**

- Adult: Initially 100 micrograms daily for 5–6 weeks, dose to be sprayed into each nostril, then increased if necessary to 100 micrograms twice daily, dose to be sprayed into each nostril, consider alternative treatment if no improvement after further 5–6 weeks, reduce to the lowest effective dose when control achieved

**SIDE-EFFECTS**

**SIDE-EFFECTS, FURTHER INFORMATION**

**Nasal ulceration** Nasal ulceration occurs commonly with preparations containing mometasone furoate.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Spray**

**EXCIPIENTS:** May contain Benzalkonium chloride, polysorbates

**MOMETASONE FUROATE** (Non-proprietary)

- Mometasone furoate 50 microgram per 1 dose
  - Mometasone 50 micrograms/dose nasal spray | 140 dose [P] £7.30 DT price = £4.74
  - Nasonex (Merck Sharp & Dohme Ltd)
  - Mometasone furoate 50 microgram per 1 dose
  - Nasonex 50 micrograms/dose nasal spray | 140 dose [P] £7.68 DT price = £4.74

Triamcinolone acetonide

**INDICATIONS AND DOSE**

**Prophylaxis and treatment of allergic rhinitis**

**BY INTRANASAL ADMINISTRATION**

- Child 6–11 years: 55 micrograms once daily (sprayed into each nostril), increased if necessary to 110 micrograms once daily (sprayed into each nostril) when control achieved; max. duration 3 months
- Child 12–17 years: 110 micrograms once daily (sprayed into each nostril), reduced to 55 micrograms once daily (sprayed into each nostril) when control achieved; max. duration 3 months
- Adult: 110 micrograms once daily (sprayed into each nostril), reduced to 55 micrograms once daily (sprayed into each nostril) when control achieved

**EXCEPTIONS TO LEGAL CATEGORY** Preparations of triamcinolone acetonide can be sold to the public for nasal administration as a non-pressurised nasal spray if supplied for the symptomatic treatment of seasonal allergic rhinitis in adults over 18 years, subject to maximum daily dose of 110 micrograms per nostril for maximum 3 months, and a pack size of 3.75 mg.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: paste

**Spray**

**EXCIPIENTS:** May contain Benzalkonium chloride, disodium edetate, polysorbates

- Nasonex [P] 55 micrograms/dose nasal spray | 30 dose [P] £3.01
- Nasonex 55 micrograms/dose nasal spray | 120 dose [P] £7.39 DT price = £7.39

**MAST CELL STABILISERS**

**Sodium cromoglicate**

(Sodium cromoglicate)

**INDICATIONS AND DOSE**

**Prophylaxis of allergic rhinitis**

**BY INTRANASAL ADMINISTRATION**

- Child: 1 spray 2–4 times a day, to be administered into each nostril
- Adult: 1 spray 2–4 times a day, to be administered into each nostril

**SIDE-EFFECTS**

- Rare: Transient bronchospasm
- Frequency not known: Local irritation

**PREGNANCY** Not known to be harmful.

**BREAST FEEDING** Unlikely to be present in milk.

**MEDICINAL FORMS**

Medicines not identified.

2.3 **Nasal staphylococcal infection**

**ANTI-INFECTIVES**

**Betamethasone with neomycin**

The properties listed below are those particular to the combination only. For the properties of the components please consider, betamethasone p. 984, neomycin sulfate p. 451.

**INDICATIONS AND DOSE**

**Nasal infection**

**BY INTRANASAL ADMINISTRATION USING NASAL DROPS**

- Child: Apply 2–3 drops 2–3 times a day, to be applied into each nostril
- Adult: Apply 2–3 drops 2–3 times a day, to be applied into each nostril

**LESS SUITABLE FOR PRESCRIBING**

Betamethasone with neomycin nasal-drops are less suitable for prescribing; there is no evidence that topical anti-infective nasal preparations have any therapeutic value in rhinitis or sinusitis.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Drops solution**

**EXCIPIENTS:** May contain Benzalkonium chloride, disodium edetate

- Betnesol-N ear/eye/nose drops (Focus Pharmaceuticals)
  - Betamethasone (as Betamethasone sodium phosphate) 1 mg per 1 mL, Neomycin sulfate 5 mg per 1 mL | 10 mL [P] £2.39

**NTS**

- Neosporin 10 mL [P] £7.45
- Neosporin Otic Solution 10 mL [P] £7.45
- Neosporin Otic Solution 30 mL [P] £7.45
- Neosporin Otic Solution 60 mL [P] £7.45
- Neosporin Otic Solution 100 mL [P] £7.45
- Neosporin Otic Solution 150 mL [P] £7.45
- Neosporin Otic Solution 200 mL [P] £7.45
- Neosporin Otic Solution 250 mL [P] £7.45
- Neosporin Otic Solution 300 mL [P] £7.45
- Neosporin Otic Solution 350 mL [P] £7.45
- Neosporin Otic Solution 400 mL [P] £7.45
- Neosporin Otic Solution 450 mL [P] £7.45
- Neosporin Otic Solution 500 mL [P] £7.45
- Neosporin Otic Solution 550 mL [P] £7.45
- Neosporin Otic Solution 600 mL [P] £7.45
- Neosporin Otic Solution 650 mL [P] £7.45
- Neosporin Otic Solution 700 mL [P] £7.45
- Neosporin Otic Solution 750 mL [P] £7.45
- Neosporin Otic Solution 800 mL [P] £7.45
- Neosporin Otic Solution 850 mL [P] £7.45
- Neosporin Otic Solution 900 mL [P] £7.45
- Neosporin Otic Solution 950 mL [P] £7.45
- Neosporin Otic Solution 1000 mL [P] £7.45

**SERUM**

- Neosporin 10 mL [P] £7.45
- Neosporin Otic Solution 10 mL [P] £7.45
- Neosporin Otic Solution 30 mL [P] £7.45
- Neosporin Otic Solution 60 mL [P] £7.45
- Neosporin Otic Solution 100 mL [P] £7.45
- Neosporin Otic Solution 150 mL [P] £7.45
- Neosporin Otic Solution 200 mL [P] £7.45
- Neosporin Otic Solution 250 mL [P] £7.45
- Neosporin Otic Solution 300 mL [P] £7.45
- Neosporin Otic Solution 350 mL [P] £7.45
- Neosporin Otic Solution 400 mL [P] £7.45
- Neosporin Otic Solution 450 mL [P] £7.45
- Neosporin Otic Solution 500 mL [P] £7.45
- Neosporin Otic Solution 550 mL [P] £7.45
- Neosporin Otic Solution 600 mL [P] £7.45
- Neosporin Otic Solution 650 mL [P] £7.45
- Neosporin Otic Solution 700 mL [P] £7.45
- Neosporin Otic Solution 750 mL [P] £7.45
- Neosporin Otic Solution 800 mL [P] £7.45
- Neosporin Otic Solution 850 mL [P] £7.45
- Neosporin Otic Solution 900 mL [P] £7.45
- Neosporin Otic Solution 950 mL [P] £7.45
- Neosporin Otic Solution 1000 mL [P] £7.45
many patients by simple measures such as frequent sips of cool drinks or sucking pieces of ice or sugar-free fruit pastilles. Sugar-free chewing gum stimulates salivation in patients with residual salivary function.

Artificial saliva can provide useful relief of dry mouth. A properly balanced artificial saliva should be of a neutral pH and contain electrolytes (including fluoride) to correspond approximately to the composition of saliva. The acidic pH of some artificial saliva products may be inappropriate. Of the proprietary preparations, Aquoral®, Biotène Oralbalance® gel or Xerolin® can be used for any condition giving rise to a dry mouth. BioXtra®, Glandosane®, Saliva Orthana®, and Salivex®, have ACBS approval for dry mouth associated only with radiotherapy or sicsa syndrome. Salivix® pastilles, which act locally as salivary stimulants, are also available for any condition leading to a dry mouth and SST tablets may be prescribed for dry mouth in patients with salivary gland impairment (and patent salivary ducts).

Pilocarpine p. 988 tablets are licensed for the treatment of xerostomia following irradiation for head and neck cancer and for dry mouth and dry eyes (xerophthalmia) in Sjögren’s syndrome. They are effective only in patients who have some residual salivary gland function, and therefore should be withdrawn if there is no response.

### Artificial saliva products

- **ARTIFICIAL SALIVA PRODUCTS**
  - **AS SALIVA ORTHANA® LOZENGES**
    - Mucin 65 mg, xylitol 59 mg, in a sorbitol basis, pH neutral
  - **INDICATIONS AND DOSE**
    - Dry mouth as a result of having (or having undergone) radiotherapy | Sicsa syndrome
      - **BY MOUTH**
        - Adult: 1 lozenge as required, allow to dissolve slowly in the mouth
  - **PRESCRIBING AND DISPENSING INFORMATION**
    - Lozenges do not contain fluoride.
    - **AS Saliva Orthana lozenges (A S Pharma Ltd)**
      - 30 lozenge (ACBS) • NHS indicative price = £3.50
  - **AS SALIVA ORTHANA® SPRAY**
    - Gastric mucin (porcine) 3.5%, xylitol 2%, sodium fluoride 4.2 mg/litre, with preservatives and flavouring agents, pH neutral
  - **INDICATIONS AND DOSE**
    - Symptomatic treatment of dry mouth
      - **BY MOUTH**
        - Adult: Apply 2–3 sprays as required, spray onto oral and pharyngeal mucosa
  - **PROFESSION SPECIFIC INFORMATION**
    - Dental practitioners’ formulary
      - **AS Saliva Orthana® Oral Spray may be prescribed.**

### BioXtra Gel

- **INDICATIONS AND DOSE**
  - **Dry mouth as a result of having (or having undergone) radiotherapy (ACBS) | Dry mouth as a result of sicca syndrome (ACBS)**
    - **BY MOUTH**
      - Adult: Apply as required, apply to oral mucosa
  - **PROFESSION SPECIFIC INFORMATION**
    - Dental practitioners’ formulary
      - BioXtra® Gel may be prescribed.
INDICATIONS AND DOSE
Symptomatic treatment of dry mouth
BY MOUTH
- Adult: Apply as required, apply to gums and tongue

PATIENT AND CARER ADVICE
Avoid use with toothpastes containing detergents (including foaming agents).

PROFESSION SPECIFIC INFORMATION
Dental practitioners’ formulary

Glandosane®
Carmellose sodium 500 mg, sorbitol 1.5 g, potassium chloride 60 mg, sodium chloride 42.2 mg, magnesium chloride 2.6 mg, calcium chloride 7.3 mg, and dipotassium hydrogen phosphate 17.1 mg/50 g, pH 5.75.

INDICATIONS AND DOSE
Dry mouth as a result of having (or having undergone) radiotherapy (ACBS) | Sicca syndrome (ACBS)
BY MOUTH
- Adult: Apply as required, spray onto oral and pharyngeal mucosa

PROFESSION SPECIFIC INFORMATION
Dental practitioners’ formulary

Salivation spray lemon (Fresenius Kabi Ltd)
50 ml (ACBS) - NHS indicative price = £5.52

Salivation spray natural (Fresenius Kabi Ltd)
50 ml (ACBS) - NHS indicative price = £5.52

Salivation spray peppermint (Fresenius Kabi Ltd)
50 ml (ACBS) - NHS indicative price = £5.52

SST®
Sugar-free, citric acid, malic acid and other ingredients in a sorbitol base.

INDICATIONS AND DOSE
Symptomatic treatment of dry mouth in patients with impaired salivary gland function and patent salivary ducts
BY MOUTH
- Adult: 1 tablet as required, allow tablet to dissolve slowly in the mouth

PROFESSION SPECIFIC INFORMATION
Dental practitioners’ formulary

May be prescribed as Saliva Stimulating Tablets.

SST saliva stimulating tablets (Sinclair IS Pharma Plc)
100 tablet - NHS indicative price = £4.86

Parasympathomimetics

Pilocarpine

INDICATIONS AND DOSE
Xerostomia following irradiation for head and neck cancer
BY MOUTH
- Adult: 5 mg 3 times a day for 4 weeks, then increased if tolerated to up to 30 mg daily in divided doses if required, dose to be taken with or immediately after meals (last dose always with evening meal), maximum therapeutic effect normally within 4–8 weeks; discontinue if no improvement after 2–3 months

Dry mouth and dry eyes in Sjögren’s syndrome
BY MOUTH
- Adult: 5 mg 4 times a day; increased if tolerated to up to 30 mg daily in divided doses if required, dose to be taken with meals and at bedtime, discontinue if no improvement after 2–3 months

CONTRA-INDICATIONS
Acute iritis | chronic obstructive pulmonary disease (increased bronchial secretions and increased airways resistance) | uncontrolled asthma (increased bronchial secretions and increased airways resistance) | uncontrolled cardiorenal disease
Mouthwashes and other preparations for oropharyngeal use

Lozenges and sprays

There is no convincing evidence that antiseptic lozenges and sprays have a beneficial action and they sometimes irritate and cause sore tongue and sore lips. Some of these preparations also contain local anaesthetics which relieve pain but may cause sensitisation.

Mouthwashes, gargles, and dentifrices

Superficial infections of the mouth are often helped by warm mouthwashes which have a mechanical cleansing effect and cause some local hyperaemia. However, to be effective, they must be used frequently and vigorously. A warm saline mouthwash is ideal and can be prepared either by dissolving half a teaspoonful of salt in a glassful of warm water or by diluting compound sodium chloride mouthwash with an equal volume of warm water.

Mouthwashes containing an oxidising agent, such as hydrogen peroxide p. 980, may be useful in the treatment of acute ulcerative gingivitis (Vincent’s infection) since the organisms involved are anaerobes. It also has a mechanical cleansing effect arising from frothing when in contact with oral debris.

Chlorhexidine is an effective antiseptic which has the advantage of inhibiting plaque formation on the teeth. It does not, however, completely control plaque deposition and is not a substitute for effective toothbrushing. Moreover, chlorhexidine preparations do not penetrate significantly into stagnation areas and are therefore of little value in the control of dental caries or of periodontal disease once pocketing has developed.

Chlorhexidine mouthwash is used in the treatment of denture stomatitis. It is also used in the prevention of oral candidiasis in immunocompromised patients. Chlorhexidine mouthwash reduces the incidence of alveolar osteitis following tooth extraction. Chlorhexidine mouthwash should not be used for the prevention of endocarditis in patients undergoing dental procedures.

Chlorhexidine can be used as a mouthwash, spray or gel for secondary infection in mucosal ulceration and for controlling gingivitis, as an adjunct to other oral hygiene measures. These preparations may also be used instead of toothbrushing where there is a painful periodontal condition (e.g. primary herpetiform stomatitis) or if the patient has a haemorrhagic disorder, or is disabled.

Chlorhexidine preparations are of little value in the control of acute necrotising ulcerative gingivitis. With prolonged use, chlorhexidine causes reversible brown staining of teeth and tongue. Chlorhexidine may be incompatible with some ingredients in toothpaste, causing an unpleasant taste in the mouth; rinse the mouth thoroughly with water between using toothpaste and chlorhexidine-containing products.

There is no convincing evidence that gargles are effective in adults.

### Chlorhexidine

#### INDICATIONS AND DOSE

<table>
<thead>
<tr>
<th>Oral hygiene and plaque inhibition</th>
<th>Oral candidiasis</th>
<th>Gingivitis</th>
<th>Management of aphthous ulcers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BY MOUTH USING MOUTHWASH</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child: Rinse or gargle 10 mL twice daily (rinse or gargle for about 1 minute)</td>
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<tr>
<td>Adult: Rinse or gargle 10 mL twice daily (rinse or gargle for about 1 minute)</td>
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<tr>
<td><strong>Denture stomatitis</strong></td>
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<tr>
<td><strong>MOUTHWASH</strong></td>
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<tr>
<td>Adult: Cleanse and soak dentures in mouthwash solution for 15 minutes twice daily</td>
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</tr>
<tr>
<td><strong>Oral hygiene and plaque inhibition and gingivitis</strong></td>
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<tr>
<td><strong>BY MOUTH USING DENTAL GEL</strong></td>
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<tr>
<td>Child: Apply 1–2 times a day, to be brushed on the teeth</td>
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<tr>
<td>Adult: Apply 1–2 times a day, to be brushed on the teeth</td>
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<tr>
<td>**Oral candidiasis</td>
<td>Management of aphthous ulcers**</td>
<td></td>
<td></td>
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<tr>
<td><strong>BY MOUTH USING DENTAL GEL</strong></td>
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<tr>
<td>Child: Apply 1–2 times a day, to affected areas</td>
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<tr>
<td>Adult: Apply 1–2 times a day, to affected areas</td>
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</tr>
<tr>
<td>**Oral hygiene and plaque inhibition</td>
<td>Oral candidiasis</td>
<td>Gingivitis</td>
<td>Management of aphthous ulcers**</td>
</tr>
<tr>
<td><strong>BY MOUTH USING OROMUCOSAL SPRAY</strong></td>
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<tr>
<td>Child: Apply up to 12 sprays twice daily as required, to be applied to tooth, gingival, or ulcer surfaces</td>
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<tr>
<td>Adult: Apply up to 12 sprays twice daily as required, to be applied to tooth, gingival, or ulcer surfaces</td>
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</tbody>
</table>

#### SIDE-EFFECTS

Anaphylaxis - hypersensitivity - mucosal irritation - parotid gland swelling - reversible brown staining of composite restorations - reversible brown
Chlorhexidine with chlorobutanol

The properties listed below are those particular to the combination only. For the properties of the components please consider, chlorhexidine p. 389.

**INDICATIONS AND DOSE**

**Oral hygiene and plaque inhibition by mouth**
- Child 6–17 years: Rinse or gargle 10–15 mL 2–3 times a day, to be diluted with lukewarm water in measuring cup provided.
- Adult: Rinse or gargle 10–15 mL 2–3 times a day, to be diluted with lukewarm water in measuring cup provided.

**Dental practitioners’ formulary**
- Chlorhexidine gluconate 2 mg per 1 mL Corsodyl® 0.2% oral spray (sugar-free) 60 mL £4.28 DT price = £4.28

**Mouthwash**
- Corsodyl® (GlaxoSmithKline Consumer Healthcare)
  - Chlorhexidine gluconate 2 mg per 1 mL Corsodyl® 0.2% mouthwash | 300 mL GSS £2.50 DT price = £3.46
  - Chlorhexidine gluconate 0.2% mouthwash | 300 mL GSS £1.99–£2.09
  - Chlorhexidine gluconate 0.2% mouthwash plain | 300 mL GSS £3.46
  - Chlorhexidine gluconate 0.2% mouthwash peppermint | 300 mL GSS £3.46 DT price = £3.46
  - Chlorhexidine gluconate 0.2% mouthwash original | 300 mL GSS £3.48 DT price = £3.46

**Flavours of mouthwash may include mint.**

**Mouthwash**
- Eludril (Pierre Fabre Ltd)
  - Chlorhexidine gluconate 1 mg per 1 mL, Chlorobutanol 5 mg per 1 mL Eludril mouthwash (sugar-free) 90 mL GSS £1.36 (sugar-free) 250 mL GSS £2.83 (sugar-free) 500 mL GSS £5.06

**SIDE-EFFECTS, FURTHER INFORMATION**

- If desquamation occurs with mucosal irritation, discontinue treatment or dilute mouthwash with an equal volume of water.
- **PATIENT AND CARER ADVICE** Chlorhexidine gluconate may be incompatible with some ingredients in toothpaste; rinse the mouth thoroughly with water between using toothpaste and chlorhexidine-containing product.

**PROFESSION SPECIFIC INFORMATION**

- Dental practitioners’ formulary Corsodyl® dental gel may be prescribed as Chlorhexidine Gluconate Gel; Corsodyl® mouthwash may be prescribed as Chlorhexidine Dental Gel, Corsodyl® oral spray may be prescribed as Chlorhexidine Oral Spray.

**MOUTHWASH**

**Chlorhexidine (Non-proprietary)**

**Chlorhexidine gluconate 2 mg per 1 mL**
- Chlorhexidine gluconate 0.2% mouthwash natural | 300 mL GSS £2.50 DT price = £3.46
- Chlorhexidine gluconate 0.2% mouthwash | 300 mL GSS £1.99–£2.09
- Chlorhexidine gluconate 0.2% mouthwash plain | 300 mL GSS £3.46
- Chlorhexidine gluconate 0.2% mouthwash peppermint | 300 mL GSS £3.46 DT price = £3.46
- Chlorhexidine gluconate 0.2% mouthwash original | 300 mL GSS £3.48 DT price = £3.46
- Chlorhexidine gluconate 0.2% mouthwash alcohol free | 300 mL GSS no price available DT price = £3.46 500 mL GSS no price available
- Brands may include Corsodyl, Curasept

**Flavours of mouthwashes may include mint.**

**Mouthwash**
- Oraldene (McNeil Products Ltd)
  - Hexetidine 1 mg per 1 mL Oraldene (cermint 0.1% mouthwash (sugar-free) 200 mL GSS £2.21 DT price = £2.21
  - Oraldene 0.1% mouthwash peppermint (sugar-free) 100 mL GSS £1.43 (sugar-free) 200 mL GSS £2.21 DT price = £2.21

**SIDE-EFFECTS**
- Very rare: Taste disturbance; transient anaesthesia
- Frequency not known: Local irritation

**PRESCRIBING AND DISPENSING INFORMATION**

**Flavours of mouthwashes may include mint.**

**ANTI-INFECTION**

**Hexetidine**

**INDICATIONS AND DOSE**

**Oral hygiene**
- By mouth
  - Child 6–17 years: Rinse or gargle 15 mL 2–3 times a day, to be used undiluted
  - Adult: Rinse or gargle 15 mL 2–3 times a day, to be used undiluted

**SIDE-EFFECTS**
- Hypertrophy of papillae of tongue on prolonged use.

**PRESCRIBING AND DISPENSING INFORMATION**

- The BP directs that when hydrogen peroxide is prescribed, hydrogen peroxide solution 6% (20 vols) should be dispensed.
- Strong solutions of hydrogen peroxide which contain 27% (90 vols) and 30% (100 vols) are only for the preparation of weaker solutions.
- When prepared extemporaneously, the BP states that hydrogen peroxide mouthwash, BP consists of hydrogen peroxide 6% solution (+ approx. 20 volume) BP.

**HANDLING AND STORAGE**

- Hydrogen Peroxide Mouthwash may be prescribed.
Sodium bicarbonate with sodium chloride

**INDICATIONS AND DOSE**

**Oral hygiene**

**BY MOUTH USING MOUTHWASH**
- Adult: (consult product literature)

**DIRECTIONS FOR ADMINISTRATION** For mouthwash, extemporaneous preparations should be prepared according to the following formula: sodium chloride 1.5 g, sodium bicarbonate 1 g, concentrated peppermint emulsion 2.5 mL, double-strength chloroform water 50 mL, water to 100 mL. To be diluted with an equal volume of warm water prior to administration.

**PRESCRIBING AND DISPENSING INFORMATION** Flavours of mouthwash may include peppermint.

**PROFESSION SPECIFIC INFORMATION**
- Dental practitioners’ formulary
  - Compound sodium chloride mouthwash may be prescribed.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: mouthwash

3.3 Oral hygiene, dental caries

**Dental caries**

**Fluoride**

Availability of adequate fluoride confers significant resistance to dental caries. It is now considered that the topical action of fluoride on enamel and plaque is more important than the systemic effect.

When the fluoride content of drinking water is less than 700 micrograms per litre (0.7 parts per million), daily administration of fluoride tablets or drops provides suitable supplementation. Systemic fluoride supplements should not be prescribed without reference to the fluoride content of the local water supply. Infants need not receive fluoride supplementation. Systemic fluoride supplements should not be prescribed until the age of 6 months.

Dentifrices which incorporate sodium fluoride or monofluorophosphate are also a convenient source of fluoride.

Individuals who are either particularly caries prone or medically compromised may be given additional protection by use of fluoride rinses or by application of fluoride gels. Rinses may be used daily or weekly; daily use of a less concentrated rinse is more effective than weekly use of a more concentrated one. High-strength gels must be applied regularly under professional supervision; extreme caution is necessary to prevent children from swallowing any excess. Less concentrated gels are available for home use. Varnishes are also available and are particularly valuable for young or disabled children since they adhere to the teeth and set in the presence of moisture.

**FLUORIDE**

**Sodium fluoride**

**INDICATIONS AND DOSE**

Prophylaxis of dental caries for water content less than 300 micrograms/litre (0.3 parts per million) of fluoride ion

**BY MOUTH USING TABLETS**
- Child 6 months-2 years: 250 micrograms daily, doses expressed as fluoride ion (F-)
- Child 3-5 years: 500 micrograms daily, doses expressed as fluoride ion (F-)
- Child 6-17 years: 1 mg daily, doses expressed as fluoride ion (F-)
- Adult: 1 mg daily, doses expressed as fluoride ion (F-)

Prophylaxis of dental caries for water content between 300 and 700 micrograms/litre (0.3-0.7 parts per million) of fluoride ion

**BY MOUTH USING TABLETS**
- Child 3-5 years: 250 micrograms daily, doses expressed as fluoride ion (F-)
- Child 6-17 years: 500 micrograms daily, doses expressed as fluoride ion (F-)
- Adult: 500 micrograms daily, doses expressed as fluoride ion (F-)

Prophylaxis of dental caries for water content above 700 micrograms/litre (0.7 parts per million) of fluoride ion

**Child 6 months-7 years**: Supplements not advised
- **Adult**: Supplements not advised

Prophylaxis of dental caries for individuals who are caries prone or medically compromised

**BY MOUTH USING TABLETS**
- Child 6-17 years: Rinse or gargle 10 mL daily
- Adult: Rinse or gargle 10 mL daily

**Dose equivalence and conversion**

Sodium fluoride 2.2 mg provides approx. 1 mg fluoride ion.

These doses reflect the recommendations of the British Dental Association, the British Society of Paediatric Dentistry and the British Association for the Study of Community Dentistry (Br Dent J 1997; 182: 6–7).

**COLGATE DURAPHAT® 2800PPM FLUORIDE TOOTHPASTE**

**Prophylaxis of dental caries**

**BY MOUTH USING PASTE**
- Child 10-17 years: Apply 1 centimetre twice daily, to be applied using a toothbrush
- Adult: Apply 1 centimetre twice daily, to be applied using a toothbrush

**COLGATE DURAPHAT® 5000PPM FLUORIDE TOOTHPASTE**

**Prophylaxis of dental caries**

**BY MOUTH USING PASTE**
- Child 16-17 years: Apply 2 centimetres 3 times a day, to be applied after meals using a toothbrush
- Adult: Apply 2 centimetres 3 times a day, to be applied after meals using a toothbrush

**EN-DE-KAY® FLUORIRINSE**

**Prophylaxis of dental caries for individuals who are caries prone or medically compromised**

**INITIALLY BY MOUTH USING MOUTHWASH**
- Adult: 5 drops daily, dilute 5 drops to 10 mL of water, alternatively (by mouth) 20 drops once daily, dilute 20 drops to 10 mL

**CONTRA-INDICATIONS** Not for areas where drinking water is fluoridated

**SIDE-EFFECTS**
- **Uncommon** Occasional white flecks on teeth with recommended doses
- **Rare** Yellowish-brown discoloration if recommended doses are exceeded

**Ear, nose and oropharynx**
**DIRECTIONS FOR ADMINISTRATION**

- With oral use Tablets should be sucked or dissolved in the mouth and taken preferably in the evening.
- With oral (topical) use For mouthwash, rinse mouth for 1 minute and then spit out.

**COLGATE DURAPHAT® 2800PPM FLUORIDE TOOTHPASTE**
Brush teeth for 1 minute before spitting out.

**COLGATE DURAPHAT® 5000PPM FLUORIDE TOOTHPASTE**
Brush teeth for 3 minutes before spitting out.

**PRESCRIBING AND DISPENSING INFORMATION**

- **Flavours of oral tablet formulations may include orange.
- **DIRECTIONS FOR ADMINISTRATION**
  - With oral use Tablets should be sucked or dissolved in the mouth and taken preferably in the evening.
  - With oral (topical) use For mouthwash, rinse mouth for 1 minute and then spit out.

**COLGATE DURAPHAT® 2800PPM FLUORIDE TOOTHPASTE**
Brush teeth for 1 minute before spitting out.

**COLGATE DURAPHAT® 5000PPM FLUORIDE TOOTHPASTE**
Brush teeth for 3 minutes before spitting out.

**PROFESSION SPECIFIC INFORMATION**

- **Dental practitioners’ formulary** Tablets may be prescribed as Sodium Fluoride Tablets. Oral drops may be prescribed as Sodium Fluoride Oral Drops. Mouthwashes may be prescribed as Sodium Fluoride Mouthwash 0.05% or Sodium Fluoride Mouthwash 2%.
- **Dental information**
  - Fluoride mouthwash, oral drops, tablets and toothpaste are prescribable on form FP10D (GP14 in Scotland, WP10D in Wales). There are also arrangements for health authorities to supply fluoride tablets in the course of preschool dental schemes, and they may also be supplied in school dental schemes.
  - Fluoride gels are not prescribable on form FP10D (GP14 in Scotland, WP10D in Wales).
- **COLGATE DURAPHAT® 2800PPM FLUORIDE TOOTHPASTE**
  - Patients or carers should be given advice on how to administer Sodium Fluoride toothpaste. Avoid drinking or rinsing mouth for 30 minutes after use.
- **COLGATE DURAPHAT® 5000PPM FLUORIDE TOOTHPASTE**
  - Patients or carers should be given advice on how to administer Sodium Fluoride toothpaste.

**MEDICINAL FORMS**

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Manufacturer</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Fluoride 1 mg</td>
<td>Endekay (Manx Healthcare Ltd)</td>
<td>£2.38</td>
</tr>
<tr>
<td>Sodium Fluoride 2.2 mg</td>
<td>Endekay (Manx Healthcare Ltd)</td>
<td>£2.38</td>
</tr>
<tr>
<td>Sodium Fluoride 3.7 mg per 1 ml</td>
<td>Manx Healthcare Ltd</td>
<td>£2.38</td>
</tr>
<tr>
<td>Sodium Fluoride 0.11 mg</td>
<td>Dental Health Products Ltd</td>
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<tr>
<td>Sodium Fluoride 2.2 mg</td>
<td>Dental Health Products Ltd</td>
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</tr>
<tr>
<td>Sodium Fluoride 5 mg per 1 gram</td>
<td>Dental Health Products Ltd</td>
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</tr>
<tr>
<td>Sodium Fluoride 500 microgram per 1 ml</td>
<td>Dental Health Products Ltd</td>
<td>£2.38</td>
</tr>
</tbody>
</table>

**Oral ulceration and inflammation**

**Ulcercation and inflammation**

Ulcercation of the oral mucosa may be caused by trauma (physical or chemical), recurrent aphthae, infections, carcinoma, dermatological disorders, nutritional deficiencies, gastro-intestinal disease, haematopoietic disorders, and drug therapy (see also Chemotherapy induced mucositis and myelosuppression under Cytotoxic drugs p. 744). It is important to establish the diagnosis in each case as the majority of these lesions require specific management in addition to local treatment. Local treatment aims to protect the ulcerated area, to relieve pain, to reduce inflammation, or to control secondary infection. Patients with an unexplained mouth ulcer of more than 3 weeks’ duration require urgent referral to hospital to exclude oral cancer.

**Simple mouthwashes**

A saline mouthwash may relieve the pain of traumatic ulceration. The mouthwash is made up with warm water and used at frequent intervals until the discomfort and swelling subsides.

**Antiseptic mouthwashes**

Secondary bacterial infection may be a feature of any mucosal ulceration; it can increase discomfort and delay healing. Use of a chlorhexidine mouthwash p. 989 is often beneficial and may accelerate healing of recurrent aphthae.

**Corticosteroids**

Topical corticosteroid therapy may be used for some forms of oral ulceration. In the case of aphthous ulcers it is most effective if applied in the ‘prodromal’ phase. Thrush or other types of candidiasis are recognised complications of corticosteroid treatment.

**Hydrocortisone oromucosal tablets** p. 993 are allowed to dissolve next to an ulcer and are useful in recurrent aphthae and erosive lichenoid lesions.

**Beclometasone dipropionate inhaler** p. 993 sprayed on the oral mucosa is used to manage oral ulceration [unlicensed indication]. Alternatively, betamethasone soluble tablets p. 993 dissolved in water can be used as a mouthwash to treat oral ulceration [unlicensed indication].

**Systemic corticosteroid therapy** (see under Corticosteroids, inflammatory disorders p. 939), is reserved for severe conditions such as pemphigus vulgaris.

**Local anaesthetics**

Local anaesthetics have a limited role in the management of oral ulceration. When applied topically their action is of a relatively short duration so that anaesthesia cannot be maintained continuously throughout the day. The main indication for a topical local anaesthetic is to relieve the pain of otherwise intractable oral ulceration particularly when it is due to major aphthae. For this purpose lidocaine hydrochloride 5% p. 994 ointment or lozenges containing a local anaesthetic are applied to the ulcer. Lidocaine hydrochloride 10% p. 994 solution as spray can be applied...
thinly to the ulcer [unlicensed indication] using a cotton bud. When local anaesthetics are used in the mouth care must be taken not to produce anaesthesia of the pharynx before meals as this might lead to choking.

**Preparations on sale to the public:** many mouth ulcer preparations, throat lozenges, and throat sprays on sale to the public contain a local anaesthetic. To identify the active ingredients in such preparations, consult the product literature of the manufacturer—the correct proprietary name should be ascertained as many products have very similar names but different active ingredients.

Benzydamine hydrochloride below and flurbiprofen p. 994 are non-steroidal anti-inflammatory drugs (NSAIDs). Benzydamine hydrochloride below mouthwash or spray may be useful in reducing the discomfort associated with a variety of ulcerative conditions. It has also been found to be effective in reducing the discomfort of tonsillitis and post-irradiation mucositis. Some patients find the full-strength mouthwash causes some stinging and, for them, it should be diluted with an equal volume of water. Flurbiprofen lozenges are licensed for the relief of sore throat.

Choline salicylate p. 994 is a derivative of salicylic acid and has some analgesic action. The dental gel may provide relief for recurrent aphthae, but excessive application or confinement under a denture irritates the mucosa and can itself cause ulceration.

**Other preparations**

Doxycycline p. 995 rinsed in the mouth may be of value for recurrent aphthous ulceration.

**Periodontitis**

Low-dose doxycycline p. 995 (Periostar®) is licensed as an adjunct to scaling and root planing for the treatment of periodontitis; a low dose of doxycycline reduces collagenase activity without inhibiting bacteria associated with periodontitis.

For anti-infectives used in the treatment of destructive (refractory) forms of periodontal disease, see under Oropharynx infections, bacterial p. 995. See also Mouthwashes and other preparations for oropharyngeal use p. 989 for mouthwashes used for oral hygiene and plaque inhibition.

**CORTICOSTEROIDS**

**Beclometasone dipropionate**

*(Beclomethasone dipropionate)*

**INDICATIONS AND DOSE**

Management of oral ulceration

**BY BUCCAL ADMINISTRATION**

- Adult: 50–100 micrograms twice daily, use inhaler device to spray dose on to the oral mucosa

**UNLICENSED USE**

Use of soluble tablets and inhaler unlicensed in oral ulceration.

**MEDICINAL FORMS**

For preparations see inhaled beclomethasone p. 228.

**Betamethasone**

**INDICATIONS AND DOSE**

Oral ulceration

**BY MOUTH USING SOLUBLE TABLETS**

- Child 12–17 years: 500 micrograms 4 times a day, to be dissolved in 20 mL water and rinsed around the mouth; not to be swallowed

**UNLICENSED USE**

Betamethasone soluble tablets not licensed for use as mouthwash or oral ulceration.

**CONTRA-INDICATIONS**

Untreated local infection

**SIDE-EFFECTS**

Candidal infection • exacerbation of local infection

**PATIENT AND CARER ADVICE**

Patient counselling is advised for betamethasone soluble tablets (administration).

**PROFESSION SPECIFIC INFORMATION**

Dental practitioners’ formulary Betamethasone Soluble Tablets 500 micrograms may be prescribed for oral ulceration.

**Hydrocortisone**

**INDICATIONS AND DOSE**

Oral and perioral lesions

**BY BUCCAL ADMINISTRATION**

- Child 1 month–11 years: Only on medical advice
- Child 12–17 years: 1 lozenge 4 times a day, allowed to dissolve slowly in the mouth in contact with the ulcer
- Adult: 1 lozenge 4 times a day, allowed to dissolve slowly in the mouth in contact with the ulcer

**UNLICENSED USE**

Hydrocortisone mucosalhesive buccal tablets licensed for use in children (under 12 years—on medical advice only).

**CONTRA-INDICATIONS**

Untreated local infection

**SIDE-EFFECTS**

Candidal infection • exacerbation of local infection

**PROFESSION SPECIFIC INFORMATION**

Dental practitioners’ formulary Mucosalhesive buccal tablets may be prescribed as Hydrocortisone Oromucosal Tablets.

**Benzydamine hydrochloride**

**INDICATIONS AND DOSE**

Painful inflammatory conditions of oropharynx

**BY MOUTH USING MOUTHWASH**

- Child 12–17 years: Rinse or gargle 15 mL every 1.5–3 hours as required usually for not more than 7 days, dilute with an equal volume of water if stinging occurs
- Adult: Rinse or gargle 15 mL every 1.5–3 hours as required usually for not more than 7 days, dilute with an equal volume of water if stinging occurs

**ORAL ULCERATION 993**
**Medicinal Forms**

**Lidocaine hydrochloride** (Lignocaine hydrochloride)

**Indications and Dose**

Relief of pain in oral lesions

**To the lesion using ointment**

- Adult: Apply as required, rub sparingly and gently on affected areas

**Xylocaine**

Relief of pain in oral lesions

**To the lesion**

- Adult: Apply thinly to the ulcer using a cotton bud

**Local Anaesthetics**

**Choline salicylate**

**Indications and Dose**

Mild oral and perioral lesions

**To the lesion**

- Child 16–17 years: Apply 0.5 inch, apply with gentle massage, not more often than every 3 hours
- Adult: Apply 0.5 inch, apply with gentle massage, not more often than every 3 hours

**Contra-indications**

Children under 16 years

**Contra-indications, Further Information**

Reye’s syndrome The CHM has advised that topical oral pain relief products containing salicylate salts should not be used in children under 16 years, as a cautionary measure due to the theoretical risk of Reye’s syndrome.

**SALICYLATES**

**INDICATIONS AND DOSE**

Mild oral and perioral lesions

**To the lesion**

- Child 16–17 years: Apply 0.5 inch, apply with gentle massage, not more often than every 3 hours
- Adult: Apply 0.5 inch, apply with gentle massage, not more often than every 3 hours

**Contra-indications**

Children under 16 years

**Contra-indications, Further Information**

Reye’s syndrome The CHM has advised that topical oral pain relief products containing salicylate salts should not be used in children under 16 years, as a cautionary measure due to the theoretical risk of Reye’s syndrome.

**Flurbiprofen**

**Indications and Dose**

Relief of sore throat

**By mouth using lozenges**

- Child 12–17 years: 1 lozenge every 3–6 hours for maximum 3 days, allow lozenge to dissolve slowly in the mouth; maximum 5 lozenges per day
- Adult: 1 lozenge every 3–6 hours for maximum 3 days, allow lozenge to dissolve slowly in the mouth; maximum 5 lozenges per day

**Interactions**

See Appendix 1 (NSAIDs).

**Side-effects**

Mouth ulcers (move lozenge around mouth) - taste disturbance

**Allergy and Cross-sensitivity**

Contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID — which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

**Renal Impairment**

Deterioration in renal function has also been reported after topical use.

**Medicinal Forms**

There can be variation in the licensing of different medicines containing the same drug.

**Lozenges**

- Streffen (Beckitt Benckier Healthcare (UK) Ltd)

| Flurbiprofen 8.75 mg | Streffen 8.75 mg lozenges | 16 lozenge P | £2.58 DT price = £2.58

**LOCAL ANAESTHETICS**

**Lidocaine hydrochloride**

**Medicinal Forms**

**Spray**

- Benzydamine mouthwash may be prescribed as Benzydamine hydrochloride 1.5 mg per 1 ml

| Streffen 8.75 mg | Streffen 8.75 mg lozenges | 16 lozenge P | £2.58 DT price = £2.58

**Contra-indications**

Children under 16 years

**Contra-indications, Further Information**

Reye’s syndrome The CHM has advised that topical oral pain relief products containing salicylate salts should not be used in children under 16 years, as a cautionary measure due to the theoretical risk of Reye’s syndrome.
3.5 Oropharyngeal bacterial infections

Oropharyngeal bacterial infections

Antibacterial therapy for pericoronitis
Antibacterial required only in presence of systemic features of infection, or of trismus, or persistent swelling despite local treatment.
- Metronidazole p. 475, or alternatively, amoxicillin
  Suggested duration of treatment 3 days or until symptoms resolve.

Antibacterial therapy for gingivitis: acute necrotising ulcerative
Antibacterial required only if systemic features of infection.
- Metronidazole p. 475, or alternatively, amoxicillin
  Suggested duration of treatment 3 days or until symptoms resolve.

Antibacterial therapy for periapical or periodontal abscess
Antibacterial required only in severe disease with cellulitis or if systemic features of infection.
- Amoxicillin p. 482, or alternatively, metronidazole
  Suggested duration of treatment 5 days.

Antibacterial therapy for periodontitis
Antibacterial used as an adjunct to debridement in severe disease or disease unresponsive to local treatment alone.
- Metronidazole p. 475, or alternatively in adults and children over 12 years, doxycycline below

Antibacterial therapy for throat infections
Most throat infections are caused by viruses and many do not require antibacterial therapy. Consider antibacterial, if history of valvular heart disease, if marked systemic upset, if peritonsillar cellulitis or abscess, or if at increased risk from acute infection (e.g. in immunosuppression, cystic fibrosis); prescribe antibacterial for beta-haemolytic streptococcal pharyngitis.
- Phenoxymethylpenicillin
  In severe infection, initial parenteral therapy with benzylpenicillin sodium p. 480, then oral therapy with phenoxymethylpenicillin p. 481 or amoxicillin p. 482 (or ampicillin p. 483). Avoid amoxicillin if possibility of glandular fever.
  Suggested duration of treatment 10 days.
- If penicillin-allergic, clarithromycin p. 470 (or azithromycin p. 469 or erythromycin p. 471)
  Suggested duration of treatment 10 days

Doxycycline

INDICATIONS AND DOSE
Treatment of recurrent aphthous ulceration
BY MOUTH USING SOLUBLE TABLETS
- Child 12-17 years: 100 mg 4 times a day usually for 3 days, dispersible tablet can be stirred into a small amount of water then rinsed around the mouth for 2–3 minutes, it should preferably not be swallowed
- Adult: 100 mg 4 times a day usually for 3 days, dispersible tablet can be stirred into a small amount of water then rinsed around the mouth for 2–3 minutes, it should preferably not be swallowed
Ear, nose and oropharynx

Unlicensed use
Not licensed for severe recurrent aphthous ulceration.

Cautions
Alcohol dependence

Interactions
The metabolism of doxycycline may be influenced by antiepileptics.

Side-effects
Anorexia - anxiety - dry mouth - flushing - fungal superinfection (when used for periodontitis) - tinnitus

Renal impairment
Use with caution (avoid excessive doses).

Monitoring requirements
When used for periodontitis, monitor for superficial fungal infection, particularly if predisposition to oral candidiasis.

Patient and carer advice
Photosensitivity Patients should be advised to avoid exposure to sunlight or sunlamps.

Profession specific information
Dental practitioners’ formulary
Dispersible tablets may be prescribed as Dispersible Doxycycline Tablets.
Tablets may be prescribed as Doxycycline Tablets 20 mg.

Medicinal forms
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution

Tablet
CAUTIONARY AND ADVISORY LABELS 6, 11, 27
- Periostat (Alliance Pharmaceuticals Ltd)
- Doxycycline (as Doxycycline hyclate) 20 mg Periostat 20mg tablets
  | 56 tablet (PO) £17.30 DT price = £17.30
Dispersible tablet
CAUTIONARY AND ADVISORY LABELS 6, 9, 11, 13
- Vibramycin-D (Pfizer Ltd)
- Doxycycline (as Doxycycline monohydrate) 100 mg Vibramycin-D 100mg dispersible tablets (sugar-free) | 8 tablet (PO) £4.91 DT price = £4.91

3.6 Oropharyngeal fungal infections

Oropharyngeal fungal infections
Fungal infections of the mouth are usually caused by Candida spp. (candidiasis or candidosis). Different types of oropharyngeal candidiasis are managed as follows:

Thrush
Acute pseudemembranous candidiasis (thrush), is usually an acute infection but it may persist for months in patients receiving inhaled corticosteroids, cytotoxics or broad-spectrum antibacterials. Thrush also occurs in patients with serious systemic disease associated with reduced immunity such as leukaemia, other malignancies, and HIV infection. Any predisposing condition should be managed appropriately. When thrush is associated with corticosteroid inhalers, rinsing the mouth with water (or cleaning a child’s teeth) immediately after using the inhaler may avoid the problem. Treatment with nystatin p. 997 or miconazole p. 1011 may be needed. Fluconazole p. 518 is effective for unresponsive infections or if a topical antifungal drug cannot be used or if the patient has dry mouth. Topical therapy may not be adequate in immunocompromised patients and an oral triazole antifungal is preferred.

Acute erythematous candidiasis
Acute erythematous (atrophic) candidiasis is a relatively uncommon condition associated with corticosteroid and broad-spectrum antibacterial use and with HIV disease. It is usually treated with fluconazole p. 518.

Denture stomatitis
Patients with denture stomatitis (chronic atrophic candidiasis), should cleanse their dentures thoroughly and leave them out as often as possible during the treatment period. To prevent recurrence of the problem, dentures should not normally be worn at night. New dentures may be required if these measures fail despite good compliance.

Miconazole p. 1011 oral gel can be applied to the fitting surface of the denture before insertion (for short periods only). Denture stomatitis is not always associated with candidiasis and other factors such as mechanical or chemical irritation, bacterial infection, or rarely allergy to the dental base material, may be the cause.

Chronic hyperplastic candidiasis
Chronic hyperplastic candidiasis (candidal leucoplaquia) carries an increased risk of malignancy; biopsy is essential—this type of candidiasis may be associated with varying degrees of dysplasia, with oral cancer present in a high proportion of cases. Chronic hyperplastic candidiasis is treated with a systemic antifungal such as fluconazole p. 518 to eliminate candidal overlay. Patients should avoid the use of tobacco.

Angular cheilitis
Angular cheilitis (angular stomatitis) is characterised by soreness, erythema and fissuring at the angles of the mouth. It is commonly associated with denture stomatitis but may represent a nutritional deficiency or it may be related to oro-facial granulomatosis or HIV infection. Both yeasts (Candida spp.) and bacteria (Staphylococcus aureus and beta-haemolytic streptococci) are commonly involved as interacting, infective factors. A reduction in facial height related to ageing and tooth loss with maceration in the deep occlusive folds that may subsequently arise, predisposes to such infection. While the underlying cause is being identified and treated, it is often helpful to apply miconazole p. 1011 cream or fusidic acid p. 1008 ointment; if the angular cheilitis is unresponsive to treatment, hydrocortisone with miconazole p. 1011 cream or ointment can be used.

Immunocompromised patients
See advice on prevention of fungal infections in Immunocompromised patients under Antifungals, systemic use p. 512.

Drugs used in oropharyngeal candidiasis
Nystatin p. 997 is not absorbed from the gastro-intestinal tract and is applied locally (as a suspension) to the mouth for treating local fungal infections. Miconazole p. 1011 is applied locally (as an oral gel) in the mouth but it is absorbed to the extent that potential interactions need to be considered. Miconazole also has some activity against Gram-positive bacteria including streptococci and staphylococci. Fluconazole p. 518 is given by mouth for infections that do not respond to topical therapy or when topical therapy cannot be used. It is reliably absorbed and effective. Itraconazole p. 519 can be used for fluconazole-resistant infections.

If candidal infection fails to respond to 1 to 2 weeks of treatment with antifungal drugs the patient should be sent for investigation to eliminate the possibility of underlying disease. Persistent infection may also be caused by reinfection from the genito-urinary or gastro-intestinal tract. Infection can be eliminated from these sources by appropriate anticandidal therapy; the patient’s partner may also require treatment to prevent reinfection.

Antiseptic mouthwashes are used in the prevention of oral candidiasis in immunocompromised patients and in the treatment of denture stomatitis.
**IMIDAZOLE ANTIFUNGALS**

**Miconazole**

**INDICATIONS AND DOSE**
Prevention and treatment of oral candidiasis

**BY MOUTH USING ORAL GEL**
- Child 2-17 years: 2.5 mL 4 times a day treatment should be continued for at least 7 days after lesions have healed or symptoms have cleared, to be administered after meals, retain near oral lesions before swallowing (dental prostheses and orthodontic appliances should be removed at night and brushed with gel)
- Adult: 2.5 mL 4 times a day treatment should be continued for at least 7 days after lesions have healed or symptoms have cleared, to be administered after meals, retain near oral lesions before swallowing (dental prostheses and orthodontic appliances should be removed at night and brushed with gel)

**Prevention and treatment of intestinal candidiasis**
- Child 4 months-17 years: 5 mg/kg 4 times a day (max. per dose 250 mg (10 mL) 4 times a day), treatment should be continued for at least 7 days after lesions have healed or symptoms have cleared
- Adult: 5 mg/kg 4 times a day (max. per dose 250 mg (10 mL) 4 times a day), treatment should be continued for at least 7 days after lesions have healed or symptoms have cleared

**SIDE-EFFECTS**
- Common or very common Nausea, rash, vomiting
- Very rare diarrhoea (usually on long term treatment), hepatitis, rash (in children), Stevens-Johnson syndrome, toxic epidermal necrolysis
- **PREGNANCY** Manufacturer advises avoid if possible—toxicity at high doses in animal studies.
- **BREAST FEEDING** Manufacturer advises caution—no information available.
- **HEPATIC IMPAIRMENT** Avoid.
- **DIRECTIONS FOR ADMINISTRATION** Oral gel should be held in mouth, after food.
- **PRESCRIBING AND DISPENSING INFORMATION** Flavours of oral gel may include orange.
- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer miconazole oromucosal gel.
- **PROFESSION SPECIFIC INFORMATION** Dental practitioners’ formulary Miconazole Oromucosal Gel may be prescribed.
- **EXCEPTIONS TO LEGAL CATEGORY** 15-g tube of oral gel can be sold to the public.

**CONTRA-INDICATIONS** Infants with impaired swallowing reflex

**CAUTIONS** Avoid in Acute porphyrias p. 864

**INTERACTIONS** Appendix 1 (antifungals, imidazole).

**POLYENE ANTIFUNGALS**

**Nystatin**

**INDICATIONS AND DOSE**
Oral and perioral fungal infections

**BY MOUTH**
- Child: 100 000 units 4 times a day usually for 7 days, and continued for 48 hours after lesions have resolved, to be administered after food
- Adult: 100 000 units 4 times a day usually for 7 days, and continued for 48 hours after lesions have resolved, to be administered after food

**SIDE-EFFECTS** Local irritation, local sensitisation, nausea

**PATIENT AND CARER ADVICE**
Medicines for Children leaflet: Nystatin for Candida infection www.medicinesforchildren.org.uk/nystatin-for-candida-infection

Counselling advised with oral suspension (use of pipette, hold in mouth, after food).

**PROFESSION SPECIFIC INFORMATION**
Dental practitioners’ formulary Nystatin Oral Suspension may be prescribed.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Oral suspension**

**CAUTIONARY AND ADVISORY LABELS**

**EXCIPIENTS:** May contain Ethanol

**NYSTATIN (Non-proprietary)**
- Nystatin 100 000 unit per 1 ml Nystatin 100,000 units/ml oral suspension | 30 ml (sach) £22.44 DT price = £3.35
- Nystan (Bristol-Myers Squibb Pharmaceuticals Ltd) Nystatin 100 000 unit per 1 ml Nystan 100,000 units/ml oral suspension (ready mixed) | 30 ml (sach) £1.80 DT price = £3.35

**3.7 Oropharyngeal viral infections**

**Oropharyngeal viral infections**

Viral infections are the most common cause of a sore throat. They do not benefit from anti-infective treatment.

The management of primary herpetic gingivostomatitis is a soft diet, adequate fluid intake, and analgesics as required, including local use of benzylamine hydrochloride p. 993. The use of chlorhexidine p. 989 mouthwash will control plaque accumulation if toothbrushing is painful and will also help to control secondary infection in general.

In the case of severe herpetic stomatitis, a systemic antiviral such as aciclovir p. 550 is required. Valaciclovir p. 552 and famciclovir p. 552 are suitable alternatives for oral lesions associated with herpes zoster. Aciclovir and valaciclovir are also used for the prevention of frequently recurring herpes simplex lesions of the mouth, particularly when implicated in the initiation of erythema multiforme.
Skin conditions, management

Vehicles

The British Association of Dermatologists list of preferred unlicensed dermatological preparations (specials) is available at www.bad.org.uk/specials.

Both vehicle and active ingredients are important in the treatment of skin conditions; the vehicle alone may have more than a mere placebo effect. The vehicle affects the degree of hydration of the skin, has a mild anti-inflammatory effect, and aids the penetration of active drug.

Applications are usually viscous solutions, emulsions, or suspensions for application to the skin (including the scalp) or nails.

Collodions are painted on the skin and allowed to dry to leave a flexible film over the site of application.

Creams are emulsions of oil and water and are generally well absorbed into the skin. They may contain an antimicrobial preservative unless the active ingredient or basis is intrinsically bactericidal and fungicidal. Generally, creams are cosmetically more acceptable than ointments because they are less greasy and easier to apply.

Gels consist of active ingredients in suitable hydrophilic or hydrophobic bases; they generally have a high water content. Gels are particularly suitable for application to the face and scalp.

Lotions have a cooling effect and may be preferred to ointments or creams for application over a hairy area. Lotions in alcoholic basis can sting if used on broken skin. Shake lotions (such as calamine lotion) contain insoluble powders which leave a deposit on the skin surface.

Ointments are greasy preparations which are normally anhydrous and insoluble in water, and are more occlusive than creams. They are particularly suitable for chronic, dry lesions. The most commonly used ointment bases consist of soft paraffin or a combination of soft, liquid, and hard paraffin. Some ointment bases have both hydrophilic and lipophilic properties; they may have occlusive properties on the skin surface, encourage hydration, and also be miscible with water; they often have a mild anti-inflammatory effect. Water-soluble ointments contain macrogols which are freely soluble in water and are therefore readily washed off; they have a limited but useful role where ready removal is desirable.

Pastes are stiff preparations containing a high proportion of finely powdered solids such as zinc oxide and starch suspended in an ointment. They are used for circumscribed lesions such as those which occur in lichen simplex, chronic eczema, or psoriasis. They are less occlusive than ointments and can be used to protect inflamed, lichenified, or excoriated skin.

Dusting powders are used only rarely. They reduce friction between opposing skin surfaces. Dusting powders should not be applied to moist areas because they can cake and abrade the skin. Talc is a lubricant but it does not absorb moisture; it can cause respiratory irritation. Starch is less lubricant but absorbs water.

Dilution

The BP directs that creams and ointments should not normally be diluted but that should dilution be necessary care should be taken, in particular, to prevent microbial contamination. The appropriate diluent should be used and heating should be avoided during mixing; excessive dilution may affect the stability of some creams. Diluted creams should normally be used within 2 weeks of preparation.

### Suitable quantities of dermatological preparations to be prescribed for specific areas of the body

<table>
<thead>
<tr>
<th>Area of body</th>
<th>Creams and Ointments</th>
<th>Lotions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face</td>
<td>15–30 g</td>
<td>100 ml</td>
</tr>
<tr>
<td>Both hands</td>
<td>25–50 g</td>
<td>200 ml</td>
</tr>
<tr>
<td>Scalp</td>
<td>50–100 g</td>
<td>200 ml</td>
</tr>
<tr>
<td>Both arms or both legs</td>
<td>100–200 g</td>
<td>200 ml</td>
</tr>
<tr>
<td>Trunk</td>
<td>400 g</td>
<td>500 ml</td>
</tr>
<tr>
<td>Groins and genitalia</td>
<td>15–25 g</td>
<td>100 ml</td>
</tr>
</tbody>
</table>

These amounts are usually suitable for an adult for twice daily application for 1 week. The recommendations do not apply to corticosteroid preparations. For suitable quantities of corticosteroid preparations, see relevant table on p. 1021.
Excipients and sensitisation
Excipients in topical products rarely cause problems. If a patch test indicates allergy to an excipient, products containing the substance should be avoided. The following excipients in topical preparations are associated, rarely, with sensitisation; the presence of these excipients is indicated in the entries for topical products.

- Beeswax
- Benzyl alcohol
- Butylated hydroxyanisole
- Butylated hydroxytoluene
- Cetostearyl alcohol (including cetyl and stearyl alcohol)
- Chlorocresol
- Edetic acid (EDTA)
- Ethylenediamine
- Fragrances
- Hydroxybenzoates (parabens)
- Imidurea
- Isopropyl palmitate
- N-(3-Chloroallyl)hexaminium chloride (quaternium 15)
- Polyethylene glycol
- Sodium metabisulphite
- Sorbic acid
- Wool fat and related substances including lanolin (purified versions of wool fat have reduced the problem)

1 Dry and scaling skin disorders

Emollient and barrier preparations

Borderline substances
The preparations marked ‘ACBS’ are regarded as drugs when prescribed in accordance with the advice of the Advisory Committee on Borderline Substances for the clinical conditions listed. Prescriptions issued in accordance with this advice and endorsed ‘ACBS’ will normally not be investigated.

Emollients
Emollients soothe, smooth and hydrate the skin and are indicated for all dry or scaling disorders. Their effects are short lived and they should be applied frequently even after improvement occurs. They are useful in dry and eczematous disorders, and to a lesser extent in psoriasis. The choice of an appropriate emollient will depend on the severity of the condition, patient preference, and the site of application. Some ingredients rarely cause sensitisation and this should be suspected if an eczematous reaction occurs. The use of aqueous cream as a leave-on emollient may increase the hydration can be improved by soaking in the bath for 10–20 minutes. Some bath emollients can be applied to wet skin undiluted and rinsed off. In dry skin conditions soap should be avoided.

Emollient and barrier preparations

Emollient bath and shower preparations
Emollient bath additives should be added to bath water; hydration can be improved by soaking in the bath for 10–20 minutes. Some bath emollients can be applied to wet skin undiluted and rinsed off. In dry skin conditions soap should be avoided.

Barrier preparations
Barrier preparations often contain water-repellent substances such as dimeticone p. 1014 or other silicones. They are used on the skin around stomas, bedsores, and pressure areas in the elderly where the skin is intact. Where the skin has broken down, barrier preparations have a limited role in protecting adjacent skin. Barrier preparations are not a substitute for adequate nursing care.

Nappy rash
The first line of treatment is to ensure that nappies are changed frequently and that tightly fitting water-proof pants are avoided. The rash may clear when left exposed to the air and a barrier preparation, applied with each nappy change, can be helpful. A mild corticosteroid such as hydrocortisone 0.5% or 1% can be used if inflammation is causing discomfort, but it should be avoided in neonates. The barrier preparation should be applied after the corticosteroid preparation to prevent further damage. Preparations containing hydrocortisone should be applied for no more than a week; the hydrocortisone should be discontinued as soon as the inflammation subsides. The occlusive effect of nappies and waterproof pants may increase absorption of corticosteroids. If the rash is associated with candidal infection, a topical antifungal such as clotrimazole p. 1010 cream can be used. Topical antibacterial preparations can be used if bacterial infection is present; treatment with an oral antibacterial may occasionally be required in severe or recurrent infection. Hydrocortisone may be used in combination with antimicrobial preparations if there is considerable inflammation, erosion, and infection.

BARRIER PREPARATIONS

Emollients

Emollients

Dry and scaling skin disorders

The quantities of bath additives recommended for adults are suitable for an adult-size bath. Proportionately less should be used for a child-size bath or a washbasin; recommended bath additive quantities for children reflect this.

Barrier preparations

Barrier preparations often contain water-repellent substances such as dimeticone p. 1014 or other silicones. They are used on the skin around stomas, bedsores, and pressure areas in the elderly where the skin is intact. Where the skin has broken down, barrier preparations have a limited role in protecting adjacent skin. Barrier preparations are not a substitute for adequate nursing care.

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13
## Emollient bath and shower products, antimicrobial-containing

**INDICATIONS AND DOSE**

**DERMOL® 200 SHOWER EMOLLIENT**

Dry and pruritic skin conditions including eczema and dermatitis

**TO THE SKIN**

- **Adult:** To be applied to the skin or used as a soap substitute

**DERMOL® 600® BATH EMOLLIENT**

Dry and pruritic skin conditions including eczema and dermatitis

**TO THE SKIN**

- **Child 1-23 months:** 5–15 mL/bath, not to be used undiluted
- **Adult:** 15–30 mL/bath, not to be used undiluted

**DERMOL® WASH EMULSION**

Dry and pruritic skin conditions including eczema and dermatitis

**TO THE SKIN**

- **Adult:** To be applied to the skin or used as a soap substitute

**EMULSIDERM®**

Dry skin conditions including eczema and ichthyosis

**TO THE SKIN**

- **Adult:** 7–30 mL/bath, alternatively, to be rubbed into dry skin until absorbed

**OILATUM® PLUS**

Topical treatment of eczema, including eczema at risk from infection

**TO THE SKIN**

- **Child 6-11 months:** 1 mL/bath, not to be used undiluted
- **Adult:** 1–2 capfuls/bath, not to be used undiluted

### Important safety information

**FIRE HAZARD WITH PARAFFIN-BASED EMOLLIENTS**

Emulsifying ointment or 50% Liquid Paraffin and 50% White Soft Paraffin Ointment in contact with dressings and clothing is easily ignited by a naked flame. The risk is greater when these preparations are applied to large areas of the body, and clothing or dressings become soaked with the ointment. Patients should be told to keep away from fire or flames, and not to smoke when using these preparations. The risk of fire should be considered when using large quantities of any paraffin-based emollient. These preparations make skin and surfaces slippery—particular care is needed when bathing.

**DIRECTIONS FOR ADMINISTRATION**

Emollient bath additives should be added to bath water; hydration can be improved by soaking in the bath for 10–20 minutes. Some bath emollients can be applied to wet skin undiluted and rinsed off. Emollient preparations contained in tubs should be removed with a clean spoon or spatula to reduce bacterial contamination of the emollient. Emollients should be applied in the direction of hair growth to reduce the risk of folliculitis.

**PRESCRIBING AND DISPENSING INFORMATION**

Preparations containing an antibacterial should be avoided unless infection is present or is a frequent complication. When prepared extemporaneously, the BP states Aqueous Cream, BP consists of emulsifying ointment 30%, phenoxyethanol 1% in freshly boiled and cooled purified water. Hydros Ointment, BP consists of dried magnesium sulfate 0.5%, phenoxyethanol 1%, wool alcohols ointment 50%, in freshly boiled and cooled purified water.

### Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

**Liquid**

**EXCIPIENTS:** May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), hydroxybenzoates (parabens), wool fat and related substances including lanolin

- Spiron (Ayrton Saunders Ltd)

**Dimeticone 10.4 mg per 1 gram, Zinc oxide 125 mg per 1 gram**

**Spriron aerosol spray**

115 g £8.90 DT price = £8.90

**Emollient bath and shower products, colloidal oatmeal-containing**

**INDICATIONS AND DOSE**

**Endogenous and exogenous eczema | Xeroderma | Ichthyosis**

**TO THE SKIN**

- **Child 2-17 years:** 20–30 mL/bath, alternatively apply to wet skin and rinse
- **Adult:** 20–30 mL/bath, alternatively apply to wet skin and rinse
Pruritus of the elderly associated with dry skin

TO THE SKIN
- Elderly: 20–30 mL/bath, alternatively apply to wet skin and rinse

Important safety information
These preparations make skin and surfaces slippery—particular care is needed when bathing.

DIRECTIONS FOR ADMINISTRATION
Emollient bath additives should be added to bath water; hydration can be improved by soaking in the bath for 10–20 minutes. Some bath emollients can be applied to wet skin undiluted and rinsed off. Emollient preparations contained in tubs should be removed with a clean spoon or spatula to reduce bacterial contamination of the emollient. Emollients should be applied in the direction of hair growth to reduce the risk of folliculitis.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Bath additive
EXCIPIENTS: May contain Beeswax, fragrances
- EMOLLIENT BATH AND SHOWER PRODUCTS, COLLOIDAL OATMEAL-CONTAINING (Non-proprietary) 250 ml (ACBS) £4.49
- Brands may include Aveeno bath oil

Emollient bath and shower products, paraffin-containing

INDICATIONS AND DOSE

AQUAMAX® WASH
Dry skin conditions
TO THE SKIN
- Adult: To be applied to wet or dry skin and rinse

CETRABEN® BATH
Dry skin conditions, including eczema
TO THE SKIN
- Child 1 month-11 years: 0.5–1 capful/bath, alternatively, to be applied to wet skin and rinse
- Adult: 1–2 capfuls/bath, alternatively, to be applied to wet skin and rinse

DERMALO®
Dermatitis | Dry skin conditions including eczema
TO THE SKIN
- Child 1 month-11 years: 5–10 mL/bath, alternatively, to be applied to wet skin and rinse
- Child 12-17 years: 15–20 mL/bath, alternatively, to be applied to wet skin and rinse
- Adult: 15–20 mL/bath, alternatively, to be applied to wet skin and rinse

Pruritus of the elderly
TO THE SKIN
- Elderly: 15–20 mL/bath, alternatively, to be applied to wet skin and rinse

DOUBLEBASE® EMOLLIENT BATH ADDITIVE
Dry skin conditions including dermatitis and ichthyosis
TO THE SKIN
- Child 1 month-11 years: 5–10 mL/bath
- Child 12-17 years: 15–20 mL/bath
- Adult: 15–20 mL/bath

Pruritus of the elderly
TO THE SKIN
- Elderly: 15–20 mL/bath

DOUBBLEBASE® EMOLLIENT SHOWER GEL
Dry, chapped, or itchy skin conditions
TO THE SKIN
- Child: To be applied to wet or dry skin and rinse, or apply to dry skin after showering
- Adult: To be applied to wet or dry skin and rinse, or apply to dry skin after showering

E45® WASH CREAM
Endogenous and exogenous eczema, xeroderma, and ichthyosis
TO THE SKIN
- Child: To be used as a soap substitute
- Adult: To be used as a soap substitute

Pruritus of the elderly associated with dry skin

TO THE SKIN
- Elderly: To be used as a soap substitute

E45® BATH OIL
Endogenous and exogenous eczema, xeroderma, and ichthyosis
TO THE SKIN
- Elderly: 15 mL/bath, alternatively, to be applied to wet skin and rinse

HYDROMOL® BATH AND SHOWER EMOLLIENT
Dry skin conditions | Eczema | Ichthyosis
TO THE SKIN
- Child 1 month-11 years: 0.5–2 capfuls/bath, alternatively apply to wet skin and rinse
- Child 12-17 years: 1–3 capfuls/bath, alternatively apply to wet skin and rinse
- Adult: 1–3 capfuls/bath, alternatively apply to wet skin and rinse

Pruritus of the elderly
TO THE SKIN
- Elderly: 1–3 capfuls/bath, alternatively apply to wet skin and rinse

LPL 63.4®
Dry skin conditions
TO THE SKIN
- Child 1 month-11 years: 0.5–2 capfuls/bath, alternatively, to be applied to wet skin and rinse
- Child 12-17 years: 1–3 capfuls/bath, alternatively, to be applied to wet skin and rinse
- Adult: 1–3 capfuls/bath, alternatively, to be applied to wet skin and rinse

OILATUM® EMOLLIENT BATH ADDITIVE
Dry skin conditions including dermatitis, and ichthyosis
TO THE SKIN
- Child 1 month-11 years: Apply 0.5–2 capfuls/bath, alternatively, to be applied to wet skin and rinse
- Child 12-17 years: 1–3 capfuls/bath, alternatively, to be applied to wet skin and rinse
- Adult: 1–3 capfuls/bath, alternatively, to be applied to wet skin and rinse

Pruritus of the elderly
TO THE SKIN
- Elderly: 1–3 capfuls/bath, alternatively, to be applied to wet skin and rinse

OILATUM® JUNIOR BATH ADDITIVE
Dry skin conditions including dermatitis and ichthyosis
TO THE SKIN
- Child 1 month-11 years: 0.5–2 capfuls/bath, alternatively, apply to wet skin and rinse

continued →
• Child 12-17 years: 1–3 capfuls/bath, alternatively, apply to wet skin and rinse
• Adult: 1–3 capfuls/bath, alternatively, apply to wet skin and rinse

Pruritus of the elderly
TO THE SKIN
• Elderly: 1–3 capfuls/bath, alternatively, apply to wet skin and rinse

**QV® BATH OIL**

Dry skin conditions including eczema, psoriasis, ichthyosis, and pruritus
TO THE SKIN
• Child 1-11 months: 5 mL/bath, alternatively, to be applied to wet skin and rinse
• Child 1-17 years: 10 mL/bath, alternatively, to be applied to wet skin and rinse
• Adult: 10 mL/bath, alternatively, to be applied to wet skin and rinse

**QV® GENTLE WASH**

Dry skin conditions including eczema, psoriasis, ichthyosis, and pruritus
TO THE SKIN
• Child: To be used as a soap substitute
• Adult: To be used as a soap substitute

**ZEROLATUM®**

Dry skin conditions | Dermatitis | Ichthyosis
TO THE SKIN
• Child 1 month-11 years: 5–10 mL/bath
• Child 12-17 years: 15–20 mL/bath
• Adult: 15–20 mL/bath

Pruritus of the elderly
TO THE SKIN
• Elderly: 15–20 mL/bath

**INDICATIONS AND DOSE**

**BALNEUM® BATH OIL**

Dry skin conditions including those associated with dermatitis and eczema
TO THE SKIN
• Child 1-23 months: 5–15 mL/bath, not to be used undiluted
• Adult: 20–60 mL/bath, not to be used undiluted

**BALNEUM® PLUS BATH OIL**

Dry skin conditions including those associated with dermatitis and eczema where pruritus also experienced
TO THE SKIN
• Child 1-23 months: 5 mL/bath, alternatively, to be applied to wet skin and rinse
Emollients should be applied in the direction of hair growth to reduce the risk of folliculitis.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Bath additive**

- **EXCIPIENTS:** May contain Isopropyl palmitate, polysorbates
- **EMOLLIENT BATH AND SHOWER PRODUCTS, TAR-CONTAINING (Non-proprietary)**
  - Coal tar distilled 400 mg per 1 ml | 200 ml £2.74
  - Polytar (GlaxoSmithKline Consumer Healthcare)
    - Arachis oil extract of crude coal tar 75 mg per 1 gram, Cade oil 75 mg per 1 gram, Coal tar solution 25 mg per 1 gram. Liquid paraffin light 350 mg per 1 gram, Pine tar 75 mg per 1 gram Polytar Emollient | 500 ml £5.78
    - Brands may include Psoriderm Emulsion 40% bath additive

**Emollient creams and ointments, antimicrobial-containing**

**INDICATIONS AND DOSE**

Dry and pruritic skin conditions including eczema and dermatitis

- **TO THE SKIN**
  - **Child:** To be applied to the skin or used as a soap substitute
  - **Adult:** To be applied to the skin or used as a soap substitute

**DIRECTIONS FOR ADMINISTRATION**

Emollients should be applied immediately after washing or bathing to maximise the effect of skin hydration. Emollient preparations in tubes should be removed with a clean spoon or spatula to reduce bacterial contamination of the emollient. Emollients should be applied in the direction of hair growth to reduce the risk of folliculitis.

**PRESCRIBING AND DISPENSING INFORMATION**

Preparations containing an antibacterial should be avoided unless infection is present or is a frequent complication.

**Emollient bath and shower products, tar-containing**

**INDICATIONS AND DOSE**

**POLYTAR EMOLLIENT**

Psoriasis, eczema, atopic and pruritic dermatoses

- **TO THE SKIN**
  - **Adult:** 2–4 capfuls/bath, add 15–30 mL to an adult-size bath and proportionately less for a child’s bath; soak for 20 minutes

**PSORIDERM EMULSION**

Psoriasis

- **TO THE SKIN**
  - **Adult:** Up to 30 mL/bath, use 30 mL in adult-size bath, and proportionately less for a child’s bath, soak for 5 minutes

**Important safety information**

These preparations make skin and surfaces slippery—particular care is needed when bathing.

**DIRECTIONS FOR ADMINISTRATION**

Emollient bath additives should be added to bath water; hydration can be improved by soaking in the bath for 10–20 minutes. Some bath emollients can be applied to wet skin undiluted and rinsed off. Emollient preparations contained in tubs should be removed with a clean spoon or spatula to reduce bacterial contamination of the emollient.
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1004 Dry and scaling skin disorders

Senile pruritus (pruritus of the elderly) associated with dry skin

TO THE SKIN

Elderly: (consult product literature)

- DIRECTIONS FOR ADMINISTRATION Emollients should be applied immediately after washing or bathing to maximise the effect of skin hydration. Emollient preparations contained in tubes should be removed with a clean spoon or spatula to reduce bacterial contamination of the emollient. Emollients should be applied in the direction of hair growth to reduce the risk of folliculitis.

- MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Cream and lotion

EXCIPIENTS: May contain Benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol), hydroxybenzoates (parabens), isopropyl palmitate

- EMOLLIENT CREAMS AND OINTMENTS, COLLOIDAL OATMEAL-CONTAINING (Non-proprietary)
  500 ml (ACBS) £6.66 | 100 ml (ACBS) £3.97 | 300 ml (ACBS) £6.80
  Brands may include Aveeno

- EMOLLIENT CREAMS AND OINTMENTS, PARAFFIN-CONTAINING (Non-proprietary)
  White soft paraffin 50 mg per 1 gram | 250 ml £3.14 | 500 ml £5.24
  E4S (Forum Health Products Ltd)

- EMOLLIENT CREAMS AND OINTMENTS, PARAFFIN-CONTAINING
  E4S (Forum Health Products Ltd)
  Liquid paraffin 126 mg per 1 gram, White soft paraffin 145 mg per 1 gram
  150 mg per 1 gram | 50 gram (GSL) £1.63 | 150 gram (GSL) £2.46 | 500 ml (GSL) £4.99 | 1050 ml (GSL) £9.98

- Aquamol (Thornton & Ross Ltd)
  Aquamol cream | 50 gram £1.22 | 500 gram £6.40

- Aquamol (Thornton & Ross Ltd)
  Aquamol cream | 500 gram £1.65

- Lipomol (Dermal Laboratories Ltd)
  Lipomol cream | 50 gram £1.14

- Doublebase Dayleve gel
  Doublebase Dayleve gel | 100 gram (P) £2.65 DT price = £5.83

- ZeroAQS (Thornton & Ross Ltd)
  ZeroAQS emollient cream | 500 gram £3.29

- Zeroguent (Thornton & Ross Ltd)
  Liquid paraffin 110 mg per 1 gram, White soft paraffin 40 mg per 1 gram
  Zeroguent cream | 100 gram £2.23 | 500 gram £6.99

- Brands may include Aquamol, Cetraben, Diprobase, Hydromol, Ointcon, QV, Ultrasorb, Zerocream

- Gel

EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol)

- Doublebase (Dermal Laboratories Ltd)
  Isopropyl myristate 150 mg per 1 gram, Liquid paraffin 150 mg per 1 gram
  150 mg (GSL) £0.85 | 150 mg (GSL) £1.11 | 500 mg (GSL) £10.18 DT price = £10.18 | 4500 mg (GSL) £18.29

- Magnesium sulfate dried 5 mg per 1 gram, Phenoxyethanol 10 mg per 1 gram, Wool alcohols ointment 500 mg per 1 gram
  500 mg (GSL) £3.80 DT price = £4.89

- White soft paraffin 1 mg per 1 gram
  White soft paraffin 1 mg per 1 gram
  500 gram (GSL) £4.18 DT price = £3.23 | 4500 gram (GSL) £18.62–25.07

Emollient creams and ointments, paraffin-containing

INDICATIONS AND DOSE

Dry skin conditions | Eczema | Psoriasis | Ichthyosis | Pruritus

Adult: (consult product literature)

Important safety information

FIRE HAZARD WITH PARAFFIN-BASED EMOLLIENTS

Emulsifying ointment or 50% Liquid Paraffin and 50% White Soft Paraffin Ointment in contact with dressings and clothing is easily ignited by a naked flame. The risk is greater when these preparations are applied to large areas of the body, and clothing or dressings become soaked with the ointment. Patients should be told to keep away from fire or flames, and not to smoke when using these preparations. The risk of fire should be considered when using large quantities of any paraffin-based emollient.

- DIRECTIONS FOR ADMINISTRATION Emollients should be applied immediately after washing or bathing to maximise the effect of skin hydration. Emollient preparations contained in tubes should be removed with a clean spoon or spatula to reduce bacterial contamination of the emollient. Emollients should be applied in the direction of hair growth to reduce the risk of folliculitis.

- PRESCRIBING AND DISPENSING INFORMATION When prepared extemporaneously, the BP states Paraffin, Yellow Soft, BP consists of yellow petroleum jelly. Paraffin White Soft, BP consists of white petroleum jelly. Emulsifying ointment, BP consists of emulsifying wax 30%, white soft paraffin 50% and liquid paraffin 20%.

- MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Liquid

EXCIPIENTS: May contain Benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol), hydroxybenzoates (parabens), isopropyl palmitate

- EMOLLIENT CREAMS AND OINTMENTS, PARAFFIN-CONTAINING
  White soft paraffin 50 mg per 1 gram | 250 ml £3.14 | 500 ml £5.24
  E4S (Forum Health Products Ltd)

- EMOLLIENT CREAMS AND OINTMENTS, PARAFFIN-CONTAINING
  E4S (Forum Health Products Ltd)
  Liquid paraffin 126 mg per 1 gram, White soft paraffin 145 mg per 1 gram
  150 mg per 1 gram | 50 gram (GSL) £1.63 | 150 gram (GSL) £2.46 | 500 ml (GSL) £4.99 | 1050 ml (GSL) £9.98

- Aquamol (Thornton & Ross Ltd)
  Aquamol cream | 50 gram £1.22 | 500 gram £6.40

- Aquamol (Thornton & Ross Ltd)
  Aquamol cream | 500 gram £1.65

- Lipomol (Dermal Laboratories Ltd)
  Lipomol cream | 50 gram £1.14

- Doublebase Dayleve gel
  Doublebase Dayleve gel | 100 gram (P) £2.65 DT price = £5.83

- Zeroguent (Thornton & Ross Ltd)
  Zeroguent cream | 500 gram £3.29

- Zeroguent (Thornton & Ross Ltd)
  Liquid paraffin 110 mg per 1 gram, White soft paraffin 40 mg per 1 gram
  Zeroguent cream | 100 gram £2.23 | 500 gram £6.99

- Brands may include Aquamol, Cetraben, Diprobase, Hydromol, Ointcon, QV, Ultrasorb, Zerocream

- Gel

EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol)

- Doublebase (Dermal Laboratories Ltd)
  Isopropyl myristate 150 mg per 1 gram, Liquid paraffin 150 mg per 1 gram
  150 mg (GSL) £0.85 | 150 mg (GSL) £1.11 | 500 mg (GSL) £10.18 DT price = £10.18 | 4500 mg (GSL) £18.29

- Magnesium sulfate dried 5 mg per 1 gram, Phenoxyethanol 10 mg per 1 gram, Wool alcohols ointment 500 mg per 1 gram
  500 mg (GSL) £3.80 DT price = £4.89

- White soft paraffin 1 mg per 1 gram
  White soft paraffin 1 mg per 1 gram
  500 gram (GSL) £4.18 DT price = £3.23 | 4500 gram (GSL) £18.62–25.07
Emollients, urea-containing

- **DRUG ACTION** Urea is a keratin softener and hydrating agent used in the treatment of dry, scaling conditions (including ichthyosis) and may be useful in elderly patients.

**INDICATIONS AND DOSE**

AQUADRATETM

Dry, scaling and itching skin

**TO THE SKIN**

- Child: Apply twice daily, to be applied thinly
- Adult: Apply twice daily

BALNEUM® CREAM

Dry skin conditions

**TO THE SKIN**

- Child: Apply twice daily
- Adult: Apply twice daily

BALNEUM® PLUS CREAM

Dry, scaling and itching skin

**TO THE SKIN**

- Child: Apply twice daily
- Adult: Apply twice daily

CALMURID®

Dry, scaling and itching skin

**TO THE SKIN**

- Child: Apply twice daily, to be applied a thick layer for 3–5 minutes, massage into area, and remove excess. Can be diluted with aqueous cream (life of diluted cream is 14 days). Half-strength cream can be used for 1 week if stinging occurs
- Adult: Apply twice daily, to apply a thick layer for 3–5 minutes, massage into area, and remove excess. Can be diluted with aqueous cream (life of diluted cream is 14 days). Half-strength cream can be used for 1 week if stinging occurs

DERMATONICS ONCE HEEL BALM®

Dry skin on soles of feet

**TO THE SKIN**

- Child 12–17 years: Apply daily
- Adult: Apply daily

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**E45®ITCH RELIEF CREAM**

Dry, scaling, and itching skin

**TO THE SKIN**

- Child: Apply twice daily
- Adult: Apply twice daily

EUCERIN® INTENSIVE CREAM

Dry skin conditions including eczema, ichthyosis, xeroderma, and hyperkeratosis

**TO THE SKIN**

- Child: Apply twice daily, to be applied thinly and rubbed into area
- Adult: Apply twice daily, to be applied thinly and rubbed into area

EUCERIN® INTENSIVE LOTION

Dry skin conditions including eczema, ichthyosis, xeroderma, and hyperkeratosis

**TO THE SKIN**

- Child: Apply twice daily, to be applied sparingly and rubbed into area
- Adult: Apply twice daily, to be applied sparingly and rubbed into area

FLEXITOL®

Dry skin on soles of feet and heels

**TO THE SKIN**

- Child 12–17 years: Apply 1–2 times a day
- Adult: Apply 1–2 times a day

HYDROMOL® INTENSIVE

Dry, scaling and itching skin

**TO THE SKIN**

- Child: Apply twice daily, to be applied thinly
- Adult: Apply twice daily, to be applied thinly

NUTRAPLUS®

Dry, scaling and itching skin

**TO THE SKIN**

- Child: Apply 2–3 times a day
- Adult: Apply 2–3 times a day

**DIRECTIONS FOR ADMINISTRATION** Emollients should be applied immediately after washing or bathing to maximise the effect of skin hydration. Emollient preparations contained in tubs should be removed with a clean spoon or spatula to reduce bacterial contamination of the emollient. Emollients should be applied in the direction of hair growth to reduce the risk of folliculitis.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Liquid**

EXCIPIENTS: May contain Benzyl alcohol, isopropyl palmitate

- Eucerin (Beiersdorf UK Ltd)
- Urea 100 mg per 1 gram Eucerin Intensive 10% lotion | 250 ml | £7.93

**Cream**

EXCIPIENTS: May contain Benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol), hydroxybenzoates (parabens), isopropyl palmitate, polysorbates, propylene glycol, wool fat and related substances including lanolin

- EMOLLIENTS, UREA-CONTAINING (Non-proprietary)
  - Lauromacrogols 30 mg per 1 gram, Urea 50 mg per 1 gram | 100 gram | £3.29 | 500 gram | £14.99
  - Urea 100 mg per 1 gram | 50 mg | £2.85 | 500 gram | £9.97
  - Aquadrate (Alliance Pharmaceuticals Ltd)
  - Urea 100 mg per 1 gram Aquadrate 10% cream | 100 gram | £4.37
  - Calmurid (Galderma (UK) Ltd)
  - Lactic acid 50 mg per 1 gram, Urea 100 mg per 1 gram Calmurid cream | 100 gram | £9.27 DT price = £9.27 | 500 gram | £35.70 DT price = £35.70
2 Infections of the skin

Skin infections

Antibacterial preparations

Cellulitis, a rapidly spreading deeply seated inflammation of the skin and subcutaneous tissue, requires systemic antibacterial treatment. Lower leg infections or infections spreading around wounds are almost always cellulitis. Erysipelas, a superficial infection with clearly defined edges (and often affecting the face), is also treated with a systemic antibacterial.

In the community, acute impetigo on small areas of the skin may be treated by short-term topical application of mupirocin or fusidic acid p. In the community, acute impetigo on small areas of the skin may be treated by short-term topical application of mupirocin or fusidic acid p. Fusidic acid has a role in the treatment of impetigo.

An ointment containing fusidic acid is used in the fissures of the hands.

Antifungal preparations

Most localised fungal infections are treated with topical preparations. To prevent relapse, local antifungal treatment should be continued for 1–2 weeks after the disappearance of all signs of infection. Systemic therapy is necessary for scalp infection or if the skin infection is widespread, disseminated, or intractable; although topical therapy may be used to treat some nail infections, systemic therapy is more effective. Skin scrapings should be examined if systemic therapy is being considered or where there is doubt about the diagnosis.

Dermatophytes

Ringworm infection can affect the scalp (tinea capitis), body (tinea corporis), groin (tinea cruris), hand (tinea manuum), foot (tinea pedis, athlete’s foot), or nail (tinea unguium). Scalp infection requires systemic treatment; additional application of a topical antifungal, during the early stages of treatment, may reduce the risk of transmission. A topical antifungal can also be used to treat asymptomatic carriers of scalp ringworm. Most other local ringworm infections can be treated adequately with topical antifungal preparations (including shampoos). The imidazole antifungals clotrimazole p. 1010, econazole nitrate p. 1011, ketoconazole p. 1011, and miconazole p. 1011 are all effective. Terbinafine p. 1013 cream is also effective but it is more expensive. Other topical antifungals include griseofulvin p. 1012 and the undecenoates. Compound benzoic acid ointment (Whitfield’s ointment) has been used for ringworm infections but it is cosmetically less acceptable than proprietary preparations. Topical preparations for athlete’s foot containing tolnaftate are on sale to the public.

Antifungal dusting powders are of little therapeutic value in the treatment of fungal skin infections and may cause skin irritation; they may have some role in preventing re-infection.

Antifungal treatment may not be necessary in asymptomatic patients with tinea infection of the nails. If treatment is necessary, a systemic antifungal is more effective than topical therapy. However, topical application of amorolfine p. 1012 or tioconazole p. 1012 may be useful for treating early onychomycosis when involvement is limited to mild distal disease, or for superficial white onychomycosis, or where there are contra-indications to systemic therapy.
Pityriasis versicolor
Pityriasis (tinea) versicolor can be treated with ketoconazole shampoo p. 1011. Alternatively, selenium sulfide shampoo [unlicensed indication] can be used as a lotion (diluting with a small amount of water can reduce irritation) and left on the affected area for 10 minutes before rinsing off; it should be applied once daily for 7 days, and the course repeated if necessary.

Topical imidazole antifungals such as clotrimazole p. 1010, econazole nitrate p. 1011, ketoconazole p. 1011, and miconazole p. 997, or topical terbinafine p. 514 are alternatives, but large quantities may be required. If topical therapy fails, or if the infection is widespread, pityriasis versicolor is treated systemically with a triazole antifungal. Relapse is common, especially in the immunocompromised.

Candidiasis
Candidal skin infections can be treated with a topical imidazole antifungal, such as clotrimazole p. 1010, econazole nitrate p. 1011, ketoconazole p. 1011, or miconazole p. 1011; topical terbinafine p. 1013 is an alternative. Topical application of nystatin p. 997 is also effective for candidiasis but it is ineffective against dermatophytosis. Refractory candidiasis requires systemic treatment generally with a triazole such as fluconazole p. 518; systemic treatment with terbinafine is not appropriate for refractory candidiasis.

Angular cheilitis
Miconazole p. 1011 cream is used in the fissures of angular cheilitis when associated with Candida.

Compound topical preparations
Combination of an imidazole and a mild corticosteroid (such as hydrocortisone 1% p. 993) may be of value in the treatment of eczematous intertrigo and, in the first few days only, of a severely inflamed patch of ringworm.

Combination of a mild corticosteroid with either an imidazole antifungal, such as clotrimazole p. 1011 or miconazole p. 1011; topical terbinafine p. 1013 is an alternative. Topical application of nystatin p. 997 is also effective for candidiasis but it is ineffective against dermatophytosis. Refractory candidiasis requires systemic treatment generally with a triazole such as fluconazole p. 518; systemic treatment with terbinafine is not appropriate for refractory candidiasis.

Antiviral preparations
Aciclovir p. 1016 is licensed for the treatment of initial and recurrent labial and genital herpes simplex infections; treatment should begin as early as possible. Systemic treatment is necessary for buccal or vaginal infections and for herpes zoster (shingles).

Herpes labialis
Aciclovir cream can be used for the treatment of initial and recurrent labial herpes simplex infections (cold sores). It is best applied at the earliest possible stage, usually when prodromal changes of sensation are felt in the lip and before vesicles appear.

Penciclovir cream is also licensed for the treatment of herpes labialis; it needs to be applied more frequently than aciclovir cream.

Systemic treatment is necessary if cold sores recur frequently or for infections in the mouth.

Parasitical preparations

<table>
<thead>
<tr>
<th>Area of body</th>
<th>Skin creams</th>
<th>Lotions</th>
<th>Cream rinses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scalp (head lice)</td>
<td>50–100 mL</td>
<td>50–100 mL</td>
<td></td>
</tr>
<tr>
<td>Body (scabies)</td>
<td>30–60 g</td>
<td>100 mL</td>
<td></td>
</tr>
<tr>
<td>Body (crab lice)</td>
<td>30–60 g</td>
<td>100 mL</td>
<td></td>
</tr>
</tbody>
</table>

These amounts are usually suitable for an adult for single application.

Scabies
Permethrin p. 1015 is used for the treatment of scabies (Sarcoptes scabiei); malathion p. 1015 can be used if permethrin is inappropriate.

Benzyl benzoate p. 1014 is an irritant and should be avoided in children; it is less effective than malathion and permethrin.

Ivermectin p. 1015 (available on a named patient basis from ‘special-order’ manufacturers or specialist importing companies) by mouth has been used, in combination with topical drugs, for the treatment of hyperkeratotic (crusted or ‘Norwegian’) scabies that does not respond to topical treatment alone; further doses may be required.

Application
Although acaricides have traditionally been applied after a hot bath, this is not necessary and there is even evidence that a hot bath may increase absorption into the blood, removing them from their site of action on the skin.

All members of the affected household should be treated simultaneously. Treatment should be applied to the whole body including the scalp, neck, face, and ears. Particular attention should be paid to the webs of the fingers and toes and lotion brushed under the ends of nails. It is now recommended that malathion and permethrin should be applied twice, one week apart; in the case of benzyl benzoate in adults, up to 3 applications on consecutive days may be needed. It is important to warn users to reapply treatment to the hands if they are washed. Patients with hyperkeratotic scabies may require 2 or 3 applications of acaricide on consecutive days to ensure that enough penetrates the skin crusts to kill all the mites.

Itching
The itch and eczema of scabies persists for some weeks after the infestation has been eliminated and treatment for pruritus and eczema may be required. Application of crotamiton p. 1040 can be used to control itching after treatment with more effective acaricides. A topical corticosteroid may help to reduce itch and inflammation after scabies has been treated successfully; however, persistent symptoms suggest that scabies eradication was not successful. Oral administration of a sedating antihistamine at night may also be useful.

Head lice
Dimeticone p. 1014 is effective against head lice (Pediculus humanus capititis). It coats head lice and interferes with water balance in lice by preventing the excretion of water; it is less active against eggs and treatment should be repeated after 7 days. Malathion p. 1015, an organophosphorus insecticide, is an alternative, but resistance has been reported. Benzyl benzoate p. 1014 is licensed for the treatment of head lice but it is less effective than other drugs and not recommended for use in children. Permethrin is active against head lice but the formulation and licensed methods of application of the current products make them unsuitable for the treatment of head lice.

Head lice infestation (pediculosis) should be treated using lotion or liquid formulations only if live lice are present.

Shampoos are diluted too much in use to be effective. A contact time of 8–12 hours or overnight treatment is recommended for lotions and liquids; a 2-hour treatment is not sufficient to kill eggs.

In general, a course of treatment for head lice should be 2 applications of product 7 days apart to kill lice emerging from any eggs that survive the first application. All affected household members should be treated simultaneously.

Wet combing methods
Head lice can be mechanically removed by combing wet hair meticulously with a plastic detection comb (probably for at least 20 minutes each time) over the whole scalp at 4-day intervals for a minimum of 2 weeks, and continued until no
lice are found on 3 consecutive sessions; hair conditioner or vegetable oil can be used to facilitate the process. Several devices for the removal of head lice such as combs and topical solutions, are available and some are prescribable on the NHS.

The Drug Tariffs can be accessed online at:
- National Health Service Drug Tariff for England and Wales: www.ppa.org.uk/ppa/edt_intro.htm
- Health and Personal Social Services for Northern Ireland Drug Tariff: www.dhsspsni.gov.uk/pas-tariff
- Scottish Drug Tariff: www.isdscotland.org/Health-topics/Prescribing-and-Medicines/Scottish-Drug-Tariff/

Crab lice

Permethrin p. 1015 and malathion p. 1015 are used to eliminate crab lice (Phthirus pubis). An aqueous preparation should be applied, allowed to dry naturally and washed off after 12 hours; a second treatment is needed after 7 days to kill lice emerging from surviving eggs. All surfaces of the body should be treated, including the scalp, neck, and face (paying particular attention to the eyebrow and other facial hair). A different insecticide should be used if a course of treatment fails.

2.1 Bacterial skin infections

Bacitracin with polymyxin B

**INDICATIONS AND DOSE**

**Bacterial skin infections**

**TO THE SKIN**

- **Child:** Apply twice daily, can be applied more frequently if required
- **Adult:** Apply twice daily, can be applied more frequently if required

**CAUTIONS** Nephrotoxicity · neurotoxicity

**CAUTIONS, FURTHER INFORMATION**

If large areas of skin are being treated nephrotoxicity and neurotoxicity may be a hazard, particularly in children with renal impairment.

**SIDE-EFFECTS**

- Frequent not known Contact sensitisation

**RENAI IMPAIRMENT**

Renal impairment increases the risk of nephrotoxicity and neurotoxicity.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Ointment**

- **Polyfax** (Teva UK Ltd)
  - Bacitracin zinc 500 unit per 1 gram, Polymyxin B sulfate 10000 unit per 1 gram Polyfax ointment | 4 gram £0.92 | 20 gram £4.62 DT price = £4.62

Fusidic acid

**DRUG ACTION** Fusidic acid and its salts are narrow-spectrum antibiotics used for staphylococcal infections.

**INDICATIONS AND DOSE**

**Staphylococcal skin infection**

**TO THE SKIN**

- **Child:** Apply 3–4 times a day usually for 7 days
- **Adult:** Apply 3–4 times a day

**CAUTIONS** Avoid contact of cream or ointment with eyes
## Mupirocin

### INDICATIONS AND DOSE

**Bacterial skin infections**, particularly those caused by Gram-positive organisms (except pseudomonal infection) **TO THE SKIN**

- **Child:** Apply up to 3 times a day for up to 10 days
- **Adult:** Apply up to 3 times a day for up to 10 days

### SIDE-EFFECTS

- Burning sensation
- Local reactions
- Pruritus
- Rash
- Urticaria

### MEDICATION FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: gel, cream

**Cream**

- **EXCIPIENTS:** May contain Benzyl alcohol, isopropyl palmitate, propylene glycol
- **Rosedo (Pierre Fabre Dermo-Cosmetique)**
  - Metronidazole 7.5 mg per 1 gram Rosedo 0.75% cream | 30 gram (PDT) £15.00 DT price = £6.60
- **Rozex (Galdemura UK Ltd)**
  - Metronidazole 7.5 mg per 1 gram Rozex 0.75% cream | 30 gram (PDT) £6.60 DT price = £6.60 | 40 gram (PDT) £9.88 DT price = £9.88

**Gel**

- **EXCIPIENTS:** May contain Benzyl alcohol, disodium edetate, hydroxybenzoates (parabens), propylene glycol
- **METRONIDAZOLE (Non-proprietary)**
  - Metronidazole 7.5 mg per 1 gram Metronidazole 0.75% gel | 15 gram (PDT) no price available | 30 gram (PDT) £12.00 | 40 gram (PDT) £19.90
- **Ace (Ferndale Pharmaceuticals Ltd)**
  - Metronidazole 7.5 mg per 1 gram Acea 0.75% gel | 40 gram (PDT) £9.95
- **Anabact (Cambridge Healthcare Supplies Ltd)**
  - Metronidazole 7.5 mg per 1 gram Anabact 0.75% gel | 15 gram (PDT) £4.47 | 30 gram (PDT) £7.89
- **Metrogel (Galdemura UK Ltd)**
  - Metronidazole 7.5 mg per 1 gram Metrogel 0.75% gel | 40 gram (PDT) £22.63
- **Metrosa (Lindemara Ltd)**
  - Metronidazole 7.5 mg per 1 gram Metrosa 0.75% gel | 30 gram (PDT) £12.00 | 40 gram (PDT) £19.90
- **Rozex (Galdemura UK Ltd)**
  - Metronidazole 7.5 mg per 1 gram Rozex 0.75% gel | 30 gram (PDT) £6.60 | 40 gram (PDT) £9.88
- **Zyomet (AMCo)**
  - Metronidazole 7.5 mg per 1 gram Zyomet 0.75% gel | 30 gram (PDT) £12.00

**DT price = £**

- 9
- 47
- 60
- 40
- 6
- 7
- 88
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- 75
- 75
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- 75
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- 5
- 5
- 4
- 00

### CONTRA-INDICATIONS

- Neonates

### CAUTIONS

Large areas

- If large areas of skin are being treated

- Ototoxicity may be a hazard, particularly in children and the elderly, and in those with renal impairment.

### SIDE-EFFECTS

- Sensitisation (cross sensitivity with other aminoglycosides may occur)

### LESS SUITABLE FOR PRESCRIBING

- Neomycin sulfate cream is less suitable for prescribing.

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: cream

**Tablet**

- **NEOMYCIN SULFATE (Non-proprietary)**
  - Neomycin sulfate 500 mg Neomycin 500mg tablets | 100 tablet (PDT) £34.69

### Retapamulin

**INDICATIONS AND DOSE**

**Superficial bacterial skin infection caused by Staphylococcus aureus and Streptococcus pyogenes (if resistant to first line topical antibacterials)**

**TO THE SKIN**

- **Child 9 months-17 years:** Apply twice daily for 5 days, to be applied thinly, maximum area of skin treated 2% of body surface area, review treatment if no response within 2–3 days
- **Adult:** Apply twice daily for 5 days, to be applied thinly, maximum area of skin treated 100 cm² or lesion length 10 cm, review treatment if no response within 2–3 days

### CONTRA-INDICATIONS

- Contact with eyes
- Contact with mucous membranes

### SIDE-EFFECTS

- Contact dermatitis
- Localised erythema
- Localised irritation
- Localised pain
- Pruritus

### NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (March 2008) that retapamulin (Altargo®) is not recommended
for use within NHS Scotland for the treatment of superficial skin infections.

### MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

**Ointment**
- **CAUTIONARY AND ADVISORY LABELS**
  - **28**
  - **Altargo** (GlaxoSmithKline UK Ltd)
  - **Retapamulin** 10 mg per 1 gram
  - **Altargo** 10 mg/g ointment | 5 gram (P) £7.89

### Silver sulfadiazine

#### INDICATIONS AND DOSE
**Prophylaxis and treatment of infection in burn wounds**
- **To the skin**
  - **Child:** Apply daily, may be applied more frequently if very exudative
  - **Adult:** Apply daily, may be applied more frequently if very exudative

For conservative management of finger-tip injuries
- **To the skin**
  - **Child:** Apply every 2–3 days, consult product literature for details
  - **Adult:** Apply every 2–3 days, consult product literature for details

**Adjunct to prophylaxis of infection in skin graft donor sites and extensive abrasions**
- **To the skin**
  - **Adult:** (consult product literature)

**Adjunct to short-term treatment of infection in pressure sores**
- **To the skin**
  - **Adult:** Apply once daily or on alternate days

As an adjunct to short-term treatment of infection in leg ulcers
- **To the skin**
  - **Adult:** Apply once daily or on alternate days, not recommended if ulcer is very exudative

### CONTRA-INDICATIONS
Not recommended for neonates with severe PD deficiency.

### CAUTIONS
**G6PD deficiency**

**FURTHER INFORMATION**

**Large areas** Plasma-sulfadiazine concentrations may approach therapeutic levels with side-effects and interactions as for sulfonamides if large areas of skin are treated.

### INTERACTIONS
→ Appendix 1 (sulfonamides)—if large amounts given. May inactivate enzymatic debriding agents—concomitant use may be inappropriate.

### SIDE-EFFECTS
Allergic reactions - argyria (following treatment of large areas of skin or prolonged use) - burning - itching - leucopenia - rash

**SIDE-EFFECTS, FURTHER INFORMATION**

**Severe blood and skin disorders** Owing to the association of sulfonamides with severe blood and skin disorders, treatment should be stopped immediately if blood disorders or rashes develop. Leucopenia developing 2–3 days after starting treatment of burns patients is reported usually to be self-limiting and silver sulfadiazine need not usually be discontinued provided blood counts are monitored carefully to ensure return to normality within a few days.

### ALLERGY AND CROSS-SENSITIVITY
Contra-indicated in patients with sensitivity to sulfonamides.

### PREGNANCY
Risk of neonatal haemolysis and methaemoglobinemia in third trimester.

### BREAST FEEDING
Small risk of kernicterus in jaundiced infants and of haemolysis in G6PD-deficient infants.

### HEPATIC IMPAIRMENT
Manufacturer advises caution if significant impairment.

### RENAL IMPAIRMENT
Manufacturer advises caution if significant impairment.

### MONITORING REQUIREMENTS
Monitor for leucopenia.

### DIRECTIONS FOR ADMINISTRATION
Apply with sterile applicator.

### MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

**Cream**
- **EXCIPIENTS:** May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), polysorbates, propylene glycol
- **Flamazine** (Smith & Nephew Healthcare Ltd)
  - **Sulfadiazine silver 10 mg per 1 gram** Flamazine 1% cream | 20 gram (P) £2.91 | 50 gram (P) £3.85 DT price = £3.85 | 250 gram (P) £10.32 DT price = £10.32 | 500 gram (P) £18.27 DT price = £18.27

### 2.2 Fungal skin infections

#### IMIDAZOLE ANTIFUNGALS

**Clotrimazole**

#### INDICATIONS AND DOSE
**Fungal skin infections**
- **To the skin**
  - **Child:** Apply 2–3 times a day
  - **Adult:** Apply 2–3 times a day

#### CAUTIONS
Contact with eyes and mucus membranes should be avoided.

#### SIDE-EFFECTS
Local irritation - erythema - hypersensitivity reactions - itching - mild burning sensation

#### SIDE-EFFECTS, FURTHER INFORMATION
Treatment should be discontinued if side-effects are severe.

#### PREGNANCY
Minimal absorption from skin; not known to be harmful.

#### PRESCRIBING AND DISPENSING INFORMATION
Spray may be useful for application of clotrimazole to large or hairy areas of the skin.

### MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

**Liquid**
- **Canesten (clotrimazole)** (Bayer Plc)
  - **Clotrimazole 10 mg per 1 ml** Canesten 1% solution | 20 ml (P) £2.30 DT price = £2.30

**Cream**
- **EXCIPIENTS:** May contain Benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol), polysorbates
  - **CLOTRIMAZOLE (Non-proprietary)**
    - **Clotrimazole 10 mg per 1 gram** Clotrimazole 1% cream | 20 gram (P) £2.18 DT price = £2.18 | 50 gram (P) £3.50 DT price = £3.40
    - **Canesten Antifungal 1% cream** | 20 gram (P) £1.85 DT price = £1.85
    - **Clotrimazole 20 mg per 1 gram** Canesten 2% thrush cream | 10 gram (P) no price available | 20 gram (P) £4.46 DT price = £4.46
    - **Clotrimazole 100 mg per 1 gram** Canesten Internal 10% cream | 5 gram (P) £6.23 DT price = £6.23
      - **Canesten 10% VC cream** | 5 gram (P) £4.50 DT price = £6.23
Econazole nitrate

**INDICATIONS AND DOSE**

**Fungal skin infections**

**TO THE SKIN**

- Child: Apply twice daily
- Adult: Apply twice daily

**Fungal nail infections**

**BY TRANSGING NAIL APPLICATION**

- Child: Apply once daily, applied under occlusive dressing
- Adult: Apply once daily, applied under occlusive dressing

**SIDE-EFFECTS, FURTHER INFORMATION**

Treatment should be discontinued if side-effects are severe.

**PREGNANCY**

Minimal absorption from skin; not known to be harmful.

**EXCIPIENTS**

May contain Butylated hydroxyanisole, fragrances.

There can be variation in the licensing of different medicines containing the same drug.

Ketoconazole

**INDICATIONS AND DOSE**

**Tinea pedis**

**TO THE SKIN USING CREAM**

- Adult: Apply 1–2 times a day

**Treatment of seborrhoeic dermatitis and dandruff**

**TO THE SKIN**

- Child 12–17 years: Apply twice weekly for 2–4 weeks, leave preparation on for 3–5 minutes before rinsing
- Adult: Apply twice weekly for 2–4 weeks, leave preparation on for 3–5 minutes before rinsing

**Prophylaxis of seborrhoeic dermatitis and dandruff**

**TO THE SKIN**

- Child 12–17 years: Apply every 1–2 weeks, leave preparation on for 3–5 minutes before rinsing
- Adult: Apply every 1–2 weeks, leave preparation on for 3–5 minutes before rinsing

**Treatment of pityriasis versicolor**

**TO THE SKIN**

- Child 12–17 years: Apply once daily for maximum 5 days, leave preparation on for 3–5 minutes before rinsing

**SIDE-EFFECTS, FURTHER INFORMATION**

Treatment should be discontinued if side-effects are severe.

**NATIONAL FUNDING/ACCESS DECISIONS**

**NHS restrictions**

- Ketoconazole cream is not prescribable on the NHS except for seborrhoeic dermatitis and pityriasis versicolor endorsed ‘SLS’.

**EXCEPTIONS TO LEGAL CATEGORY**

- For Fungal skin infections in adults A 15-g tube is available for sale to the public for the treatment of tinea pedis, tinea cruris, and candidal intertrigo.
- For Seborrhoeic dermatitis and dandruff Can be sold to the public for the prevention and treatment of dandruff and seborrhoeic dermatitis of the scalp as a shampoo formulation containing ketoconazole maximum 2%, in a pack containing maximum 120 mL and labelled to show a maximum frequency of application of once every 3 days.

**EXCIPIENTS**

- May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), polysorbates, propylene glycol.
- May include Gyno-Pevaryl 1% cream.

Miconazole

**INDICATIONS AND DOSE**

**Fungal skin infections**

**TO THE SKIN**

- Child: Apply twice daily continuing for 10 days after lesions have healed
- Adult: Apply twice daily continuing for 10 days after lesions have healed

**Fungal nail infections**

**TO THE SKIN**

- Child: Apply 1–2 times a day
- Adult: Apply 1–2 times a day

**CAUTIONS**

Avoid in Acute porphyrias p. 664 - contact with eyes and mucous membranes should be avoided.
OTHER ANTIFUNGALS

**Amorolfin**

**INDICATIONS AND DOSE**

Fungal nail infections

**BY TRANSUNGUAL APPLICATION**

- **Child:** Apply 1–2 times a week for 6 months to treat finger nail and for toe nails 9–12 months (review at intervals of 3 months), apply to infected nails after filing and cleansing, allow to dry for approximately 3 minutes
- **Adult:** Apply 1–2 times a week for 6 months to treat finger nail and for toe nails 9–12 months (review at intervals of 3 months), apply to infected nails after filing and cleansing, allow to dry for approximately 3 minutes

**SIDE-EFFECTS**

- **Frequency not known**
  - Common or very common: Nausea, rash, vomiting
  - Frequency not known: Burning sensation, erythema, hypersensitivity reactions, itching, occasional local irritation

**SIDE-EFFECTS, FURTHER INFORMATION**

Treatment should be discontinued if side effects are severe.

**PREGNANCY**

Absorbed from the skin in small amounts; manufacturer advises caution.

**BREAST FEEDING**

Manufacturer advises caution—no information available.

**PROFESSION SPECIFIC INFORMATION**

Dental practitioners’ formulation

Miconazole cream may be prescribed.

**NATIONAL FUNDING/ACCESS DECISIONS**

NHS restrictions: Miconazole nitrate 2% powder is not prescribable on the NHS.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Cream**

- **Excipients:** May contain Butylated hydroxyanisole
  - **Daktarin** (McNeil Products Ltd, Janssen-Cilag Ltd)
    - Miconazole nitrate 20 mg per 1 gram
      - Daktarin 2% cream
        - 15 gram [P] £2.14 | 30 gram [P] £1.82 DT price = £1.62
      - Brands may include Gyno-Daktarin 2% vaginal cream

**Spray**

- **CAUTIONARY AND ADVISORY LABELS** 15
  - **Daktarin** (McNeil Products Ltd)
    - Miconazole nitrate 1.6 mg per 1 gram
      - Daktarin Aktiv 0.16% spray powder
        - 100 gram [GSS] £3.17 DT price = £3.17

**Powder**

- **Daktarin** (McNeil Products Ltd)
  - Miconazole nitrate 20 mg per 1 gram
    - Daktarin 2% powder
      - 20 gram [P] £2.58

**Tioconazole**

**INDICATIONS AND DOSE**

Fungal nail infection

**BY TRANUNGUAL APPLICATION**

- **Child:** Apply twice daily usually for up to 6 months (may be extended to 12 months), apply to nails and surrounding skin
- **Adult:** Apply twice daily usually for up to 6 months (may be extended to 12 months), apply to nails and surrounding skin

**SIDE-EFFECTS**

- **Common or very common:** Nausea, rash, vomiting
- **Frequency not known:** Burning sensation, erythema, hypersensitivity reactions, itching, occasional local irritation

**SIDE-EFFECTS, FURTHER INFORMATION**

Treatment should be discontinued if side effects are severe.

**PREGNANCY**

Manufacturer advises avoid.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Paint**

- **Tioconazole 283 mg per 1 ml**
  - Trosyl 283mg/ml nail solution
    - 12 ml [P] £27.38 DT price = £27.38

**Griseofulvin**

**INDICATIONS AND DOSE**

Tinea pedis

**TO THE SKIN**

- **Adult:** Apply 400 micrograms once daily, apply to an area approximately 13 cm², increased if necessary to 1.2 mg once daily for maximum treatment duration of 4 weeks, allow each spray to dry between application
SID Ef ECT S, FURTHER INFORMATION

Treatment should be discontinued if side-effects are severe.

• PREGNANCY Manufacturer advises avoid unless potential benefit outweighs risk.

• BREAST FEEDING Manufacturer advises avoid unless potential benefit outweighs risk.

• MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Spray

CAUTIONARY AND ADVISORY LABELS 15

EXCIPIENTS: May contain Benzyl alcohol

Griseofulvin 10 mg per 1 gram Grisol AF 1% spray | 20 ml

£1.35

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Terbinafine

INDICATIONS AND DOSE

Tinea pedis

TO THE SKIN USING CREAM

• Adult: Apply 1–2 times a day for up to 1 week, to be applied thinly

Tinea corporis

TO THE SKIN USING CREAM

• Adult: Apply 1–2 times a day for up to 1–2 weeks, to be applied thinly, review treatment after 2 weeks

Tinea cruris

TO THE SKIN USING CREAM

• Adult: Apply 1–2 times a day for up to 1–2 weeks, to be applied thinly, review treatment after 2 weeks

Cutaneous candidiasis | Pityriasis versicolor

TO THE SKIN USING CREAM

• Adult: Apply 1–2 times a day for 2 weeks, to be applied thinly, review treatment after 2 weeks

• CAUTIONS Contact with eyes and mucous membranes should be avoided

• SIDE-EFFECTS Erythema · hypersensitivity reactions · itching · mild burning sensation · occasional local irritation

SIDE-EFFECTS, FURTHER INFORMATION

Treatment should be discontinued if side effects are severe.

• PREGNANCY Manufacturer advises use only if potential benefit outweighs risk—animal studies suggest no adverse effects.

• BREAST FEEDING Manufacturer advises avoid—present in milk. Less than 5% of the dose is absorbed after topical application of terbinafine; avoid application to mother’s chest.

• EXCEPTIONS TO LEGAL CATEGORY Preparations of terbinafine hydrochloride (maximum 1%) can be sold to the public for use in those over 16 years for external use for the treatment of tinea pedis as a cream in a pack containing maximum 15 g, or for the treatment of tinea pedis and cruris as a cream in a pack containing maximum 15 g, or for the treatment of tinea pedis, cruris, and corporis as a spray in a pack containing maximum 30 mL spray or as a gel in a pack containing maximum 30 g gel.

• MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Cream

EXCIPIENTS: May contain Benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol), polysorbates

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TERBINAFINE (Non-proprietary)

Terbinafine hydrochloride 10 mg per 1 gram Terbinafine 1% cream | 7.5 gram (P) £0.95 | 7.5 gram (GSL) £0.95 | 15 gram (P) £4.86 DT price = £1.63 | 30 gram (P) £8.76 DT price = £3.38

Lamisil (Novartis Consumer Health UK Ltd)

Terbinafine hydrochloride 10 mg per 1 gram Lamisil 1% cream | 30 gram (P) £8.76 DT price = £3.38

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Benzoic acid with salicylic acid

INDICATIONS AND DOSE

Ringworm (tinea)

TO THE SKIN

• Child: Apply twice daily

• Adult: Apply twice daily

• CAUTIONS Avoid broken or inflamed skin · avoid contact with eyes · avoid contact with mucous membranes

CAUTIONS, FURTHER INFORMATION

Salicylate toxicity Salicylate toxicity may occur particularly if applied on large areas of skin.

SIDE-EFFECTS Erythema · hypersensitivity reactions · itching · mild burning sensation · occasional local irritation

SIDE-EFFECTS, FURTHER INFORMATION

Treatment should be discontinued if side effects are severe.

• PRESCRIBING AND DISPENSING INFORMATION Benzoic Acid Ointment, Compound, BP (a preparation containing benzoic acid and salicylic acid) has also been referred to as Whitfield’s ointment. When prepared extemporaneously, the BP states Benzoic Acid Ointment, Compound BP (Whitfield’s ointment) consists of benzoic acid 6%, salicylic acid 3%, in emulsifying ointment.

• MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ointment, cream

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Boric acid with salicylic acid and tannic acid

INDICATIONS AND DOSE

Fungal nail infection, particularly tinea

BY TRANSUNGUAL APPLICATION

• Child 5–17 years: Apply twice daily, and after washing

• Adult: Apply twice daily, and after washing

• CAUTIONS Avoid broken or inflamed skin · contact with eyes and mucous membranes should be avoided · use with caution in children likely to suck affected digits

CAUTIONS, FURTHER INFORMATION

Salicylate toxicity Salicylate toxicity can occur particularly if applied on large areas of skin.

SIDE-EFFECTS Burning sensation · erythema · hypersensitivity reactions · itching · occasional local irritation

SIDE-EFFECTS, FURTHER INFORMATION

Treatment should be discontinued if side effects are severe.

• PREGNANCY Avoid.

• LESS SUITABLE FOR PRESCRIBING Phytex® is less suitable for prescribing.

• MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.
Chlorhexidine with nystatin

**INDICATIONS AND DOSE**

Skin infections due to Candida spp.

**TO THE SKIN**
- **Child:** Apply 2–3 times a day, continuing for 7 days after lesions have healed
- **Adult:** Apply 2–3 times a day, continuing for 7 days after lesions have healed

**SIDE-EFFECTS**
- Avoid contact with eyes and mucous membranes
- Burning sensation, erythema, hypersensitivity reactions, itching, occasional local irritation

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Cream**
- Excipients: May contain Benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol), polysorbates
- Nystaform (Typharm Ltd)
  - Chlorhexidine hydrochloride 10 mg per 1 gram, Nystatin 100000 unit per 1 gram
  - Nystaform cream | 30 gram GSK £2.62 OT price = £2.62

**Undecenoic acid with zinc undecenoate**

**INDICATIONS AND DOSE**

Treatment of athlete’s foot

**TO THE SKIN**
- **Child:** Apply twice daily, continue use for seven days after lesions have healed
- **Adult:** Apply twice daily, continue use for seven days after lesions have healed

**PREVENTION OF ATHLETE’S FOOT**
- **Child:** Apply once daily
- **Adult:** Apply once daily

**SIDE-EFFECTS**
- Avoid broken skin - contact with eyes should be avoided - contact with mucous membranes should be avoided
- Erythema, hypersensitivity reactions, itching, local irritation, mild burning sensation

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Cream**
- Excipients: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), fragrances
- UNDECENOIC ACID WITH ZINC UNDECENOATE (Non-proprietary)
  - Undecenoic acid 50 mg per 1 gram, Zinc undecenoate 200 mg per 1 gram
  - Brands may include Mycota

2.3 Parasitic skin infections

**PARASITICIDES**

**Benzyl benzoate**

**INDICATIONS AND DOSE**

Scabies

**TO THE SKIN**
- **Child:** Apply over the whole body; repeat without bathing on the following day and wash off 24 hours later; a third application may be required in some cases

**SIDE-EFFECTS**
- Avoid contact with eyes and mucous membranes - children (not recommended) - do not use on broken or secondarily infected skin
- Burning sensation (especially on genitalia and excoriations) - rashes - skin irritation
- BREAST FEEDING: Suspend feeding until product has been washed off.

**PRESCRIBING AND DISPENSING INFORMATION**
Not recommended for children — dilution to reduce irritant effect also reduces efficacy. Some manufacturers recommend application to the body but to exclude the head and neck. However, application should be extended to the scalp, neck, face, and ears. When prepared extemporaneously, the BP states Benzyl Benzoate Application, BP consists of benzyl benzoate 25% in an emulsion basis.

**LESS SUITABLE FOR PRESCRIBING**
Benzyl benzoate is less suitable for prescribing.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Dimeticone**

**INDICATIONS AND DOSE**

Head lice

**TO THE SKIN**
- **Child:** Apply once weekly for 2 doses, rub into hair and scalp, allow to dry naturally, shampoo after minimum 8 hours (or overnight)
- **Adult:** Apply once weekly for 2 doses, rub into hair and scalp, allow to dry naturally, shampoo after minimum 8 hours (or overnight)

**UNLICENSED USE**
Not licensed for use in children under 6 months except under medical supervision.

**SIDE-EFFECTS**
- Skin irritation
- **PATIENT AND CARER ADVICE**
- Patients should be told to keep hair away from fire and flames during treatment.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.
Parasitic skin infections 1015

Malathion

INDICATIONS AND DOSE

Head lice

TO THE SKIN

> Child: Apply once weekly for 2 doses, apply 0.5% preparation over whole body, wash off after 12 hours or overnight

> Adult: Apply once weekly for 2 doses, apply 0.5% preparation over whole body, wash off after 12 hours or overnight

Crab lice

TO THE SKIN

> Child: Apply once weekly for 2 doses, apply 0.5% preparation over whole body, wash off after 12 hours or overnight

> Adult: Apply once weekly for 2 doses, apply 0.5% preparation over whole body, wash off after 12 hours or overnight

Scabies

TO THE SKIN

> Child: Apply once weekly for 2 doses, apply 0.5% preparation over whole body, wash off after 24 hours, if hands are washed with soap within 24 hours, they should be retreated

> Adult: Apply once weekly for 2 doses, apply 0.5% preparation over whole body, wash off after 24 hours, if hands are washed with soap within 24 hours, they should be retreated

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

- Liquid
  - EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), fragrances, hydroxybenzoates (parabens)
  - Derbac-M (G.R. Lane Health Products Ltd)
    - Malathion 5 mg per 1 gram Derbac-M 0.5% liquid | 50 ml | £3.23 DT price = £3.23 | 200 ml | £7.76 DT price = £7.76

Ivermectin

INDICATIONS AND DOSE

Scabies, in combination with topical drugs, for the treatment of hyperkeratotic (crusted or ‘Norwegian’) scabies that does not respond to topical treatment alone

HEAD LICE

> Adult: 200 micrograms/kg for 1 dose, further doses of 200 micrograms/kg may be required

SIDE-EFFECTS

Aggravation of itching · aggravation of rash

INDICATIONS AND DOSE

Crab lice

TO THE SKIN

> Child 2 months–17 years: Apply once weekly for 2 doses, apply 5% preparation over whole body including face, neck, scalp and ears then wash off after 8–12 hours. If hands are washed with soap they should be treated again with cream

> Adult: Apply once weekly for 2 doses, apply 5% preparation over whole body including face, neck, scalp and ears then wash off after 8–12 hours. If hands are washed with soap they should be treated again with cream

Head lice

TO THE SKIN

> Adult: Not recommended; no information given

SIDE-EFFECTS

Oedema · rashes · pruritus · stinging

PRESCRIBING AND DISPENSING INFORMATION

Manufacturer recommends application to the body but to exclude head and neck. However, application should be extended to the scalp, neck, face, and ears. Larger patients may require up to two 30-g packs for adequate treatment.

LESS SUITABLE FOR PRESCRIBING

Lyclear® Creme Rinse is less suitable for prescribing.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

- Liquid
  - EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol)
    - Lyclear (Omega Pharma Ltd)
      - Permethrin 10 mg per 1 gram Lyclear 1% cream rinse | 59 ml | £3.55 DT price = £3.55 | 118 ml | £6.46 DT price = £6.46

Cream

CAUTIONARY AND ADVISORY LABELS

EXCIPIENTS: May contain Butylated hydroxytoluene, wool fat and related substances including lanolin

- PERMETHRIN (Non-proprietary)
  - Permethrin 50 mg per 1 gram Permethrin 5% cream | 30 gram | £7.46 DT price = £7.46

Brands may include Lyclear 5% dermal cream

Liquid

- Hedrin (Thornton & Ross Ltd)
  - Dimeticonene 40 mg per 1 gram Hedrin 4% lotion | 50 ml | £2.98 DT price = £2.98 | 150 ml | £6.92 DT price = £6.92

- Hedrin (Thornton & Ross Ltd)
  - Dimeticonene 40 mg per 1 gram Hedrin 4% spray | 120 ml | £1.13

Malathion

INDICATIONS AND DOSE

TO THE SKIN

HEAD LICE

> Adult: 200 micrograms/kg for 1 dose, further doses of 200 micrograms/kg may be required

SIDE-EFFECTS

Aggravation of itching · aggravation of rash

CAUTIONS

Avoid contact with eyes · children aged 2 months–2 years, medical supervision required for dermal cream (scabies) · do not use on broken or secondarily infected skin

SIDE-EFFECTS

Rare Oedema · rashes · pruritus · stinging

PRESCRIBING AND DISPENSING INFORMATION

Manufacturer recommends application to the body but to exclude head and neck. However, application should be extended to the scalp, neck, face, and ears. Larger patients may require up to two 30-g packs for adequate treatment.

LESS SUITABLE FOR PRESCRIBING

Lyclear® Creme Rinse is less suitable for prescribing.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

- Liquid
  - EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol)
    - Lyclear (Omega Pharma Ltd)
      - Permethrin 10 mg per 1 gram Lyclear 1% cream rinse | 59 ml | £3.55 DT price = £3.55 | 118 ml | £6.46 DT price = £6.46

Cream

CAUTIONARY AND ADVISORY LABELS

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- PERMETHRIN (Non-proprietary)
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- Hedrin (Thornton & Ross Ltd)
  - Dimeticonene 40 mg per 1 gram Hedrin 4% lotion | 50 ml | £2.98 DT price = £2.98 | 150 ml | £6.92 DT price = £6.92

- Hedrin (Thornton & Ross Ltd)
  - Dimeticonene 40 mg per 1 gram Hedrin 4% spray | 120 ml | £1.13
2.4 Viral skin infections

NUCLEOSIDE ANALOGUES

Aciclovir (Acyclovir)

INDICATIONS AND DOSE
Herpes simplex infection (local treatment)

TO THE SKIN
- Child: Apply 5 times a day for 5–10 days, to be applied to lesions every 4 hours, starting at first sign of attack
- Adult: Apply 5 times a day for 5–10 days, to be applied to lesions every 4 hours, starting at first sign of attack

- CAUTIONS Avoid cream coming in to contact with eyes and mucous membranes
- SIDE-EFFECTS Drying of the skin, erythema, itching of the skin, transient burning, transient stinging
- PREGNANCY Limited absorption from topical aciclovir preparations.

PATIENT AND CARER ADVICE
Medicine for Children leaflet: Aciclovir cream for herpes
www.medicinesforchildren.org.uk/aciclovir-cream-for-herpes

PROFESSION SPECIFIC INFORMATION
Dental practitioners’ formulary

EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), propylene glycol

ACTIONS: Amphoteric. There can be variation in the licensing of different medicines containing the same drug.

ACICLOVIR (Non-proprietary)

Aciclovir 50 mg per 1 gram | 2 gram (£1.72)
£4.17 DT price + £1.33 | 10 gram (£1.96) £12.36 DT price + £6.65

Zovirax (GlaxoSmithKline UK Ltd)

Aciclovir 50 mg per 1 gram | 2 gram (£2.41)
£6.65 DT price + £1.33 | 10 gram (£2.41) £13.63 DT price + £6.65

3 Inflammatory skin conditions

3.1 Eczema and psoriasis

Eczema

Eczema (dermatitis) has several causes, which may influence treatment. The main types of eczema are irritant, allergic contact, atopic, venous and discoid; different types may co-exist. Lichenification, due to scratching and rubbing, may complicate any chronic eczema. Atopic eczema is the most common type and it usually involves dry skin as well as infection and lichenification.

Management of eczema involves the removal or treatment of contributory factors including occupational and domestic irritants. Known or suspected contact allergens should be avoided. Rarely, ingredients in topical medicinal products may sensitise the skin; the BNF lists active ingredients together with excipients that have been associated with skin sensitisation.

Skin dryness and the consequent irritant eczema requires emollients applied regularly (at least twice daily) and liberally to the affected area; this can be supplemented with bath or shower emollients. The use of emollients should continue even if the eczema improves or if other treatment is being used.

Topical corticosteroids are also required in the management of eczema; the potency of the corticosteroid should be appropriate to the severity and site of the condition. Mild corticosteroids are generally used on the face and on flexures; potent corticosteroids are generally required for use on adults with discoid or lichenified eczema or with eczema on the scalp, limbs, and trunk. Treatment should be reviewed regularly, especially if a potent corticosteroid is required. In patients with frequent flares (2–3 per month), a topical corticosteroid can be applied on 2 consecutive days each week to prevent further flares.

Bandages (including those containing ichthammol with zinc oxide p. 1019) are sometimes applied over topical corticosteroids or emollients to treat eczema of the limbs. Dry-wrap dressings can be used to provide a physical barrier to help prevent scratching and improve retention of emollients. See Wound management products and elasticated garments p. 1294 for details of elasticated viscose stockinette tubular bandages and garments, and silk clothing.

See Eczema and psoriasis, drugs affecting the immune response p. 1017 for the role of topical pimecrolimus p. 1019 and tacrolimus p. 1020 in atopic eczema.

Infection

Bacterial infection (commonly with Staphylococcus aureus and occasionally with Streptococcus pyogenes) can exacerbate eczema and requires treatment with topical or systemic antibacterial drugs. Antibacterial drugs should be used in short courses (typically 1 week) to reduce the risk of drug resistance or skin sensitisation. Associated eczema is treated simultaneously with a topical corticosteroid which can be combined with a topical antimicrobial.

Eczema involving widespread or recurrent infection requires the use of a systemic antibacterial that is active against the infecting organism. Products that combine an antiseptic with an emollient application and with a bath emollient can also be used; antiseptic shampoos can be used on the scalp.

Intertrigenous eczema commonly involves candida and bacteria; it is best treated with a mild or moderately potent topical corticosteroid and a suitable antimicrobial drug.

Widespread herpes simplex infection may complicate atopic eczema and treatment with a systemic antiviral drug is indicated.

Management of other features of eczema

Lichenification, which results from repeated scratching is treated initially with a potent corticosteroid. Bandages containing ichthammol paste p. 1019 (to reduce pruritus) and other substances such as zinc oxide can be applied over the corticosteroid or emollient. Coal tar and ichthammol can be useful in some cases of chronic eczema.

A non-sedating antihistamine may be of some value in relieving severe itching or urticaria associated with eczema. A sedating antihistamine can be used if itching causes sleep disturbance.

Exudative (weeping) eczema requires a potent corticosteroid initially; infection may also be present and require specific treatment. Potassium permanganate p. 1052 solution (1 in 10,000) can be used in exudating eczema for its antiseptic and astringent effects; treatment should be stopped when exudation stops.

Severe refractory eczema

Severe refractory eczema is best managed under specialist supervision; it may require phototherapy or drugs that act on the immune system. Alitretinoin p. 1033 is licensed for...
the treatment of severe chronic hand eczema refractory to potent topical corticosteroids; patients with hyperkeratotic features are more likely to respond to alitretinoin than those with pompholyx.

**Seborrhoeic dermatitis**

*Seborrhoeic dermatitis* (seborrhoeic eczema) is associated with species of the yeast *Malassezia* and affects the scalp, paranasal areas, and eyebrows. Shampoos active against the yeast (including those containing ketoconazole p. 1011 and coal tar) and combinations of mild corticosteroids with suitable antimicrobials are used.

### Eczema and psoriasis, drugs affecting the immune response

Drugs affecting the immune response are used for eczema or psoriasis. Systemic drugs acting on the immune system are used under specialist supervision.

**Pimecrolimus** p. 1019 by topical application is licensed for mild to moderate atopic eczema. Tacrolimus p. 1020 is licensed for topical use in moderate to severe atopic eczema. Both are drugs whose long-term safety is still being evaluated and they should not usually be considered first-line treatments unless there is a specific reason to avoid or reduce the use of topical corticosteroids. Treatment of atopic eczema with topical pimecrolimus or topical tacrolimus should be initiated only by prescribers experienced in managing the condition. Topical tacrolimus and pimecrolimus have a role in the treatment of psoriasis.

A short course of a systemic corticosteroid can be given for eczema flares that have not improved despite appropriate topical treatment.

**Ciclosporin** p. 717 by mouth can be used for severe psoriasis and for severe eczema. Azathioprine p. 716 or mycophenolate mofetil p. 725 are used for severe refractory eczema [unlicensed indication].

**Methotrexate** p. 762 can be used for severe psoriasis, the dose being adjusted according to severity of the condition and haematological and biochemical measurements. Folic acid p. 836 should be given to reduce the possibility of side-effects associated with methotrexate. Folic acid can be given once weekly [unlicensed indication], on a different day from the methotrexate; alternative regimens of folic acid may be used in some settings.

**Etanercept** p. 903, adalimumab p. 901, and infliximab p. 906 inhibit the activity of tumour necrosis factor (TNFα). They are used for severe plaque psoriasis either refractory to at least 2 standard systemic treatments and phototherapy, or when standard treatments cannot be used because of intolerance or contra-indications; while either etanercept or adalimumab is considered to be the first choice in stable disease, infliximab or adalimumab may be useful when rapid disease control is required. Ustekinumab p. 899 (a monoclonal antibody that inhibits interleukins 12 and 23) can be used for severe plaque psoriasis that has not responded to at least 2 standard systemic treatments and phototherapy, or when these treatments cannot be used because of intolerance or contra-indications. Adalimumab, etanercept, infliximab and ustekinumab are also licensed for psoriatic arthritis.

### Psoriasis

Psoriasis is characterised by epidermal thickening and scaling. It commonly affects extensor surfaces and the scalp.

Occasionally, psoriasis is provoked or exacerbated by drugs such as lithium, chloroquine and hydroxychloroquine, beta-blockers, non-steroidal anti-inflammatory drugs, and ACE inhibitors. Psoriasis may not be seen until the drug has been taken for weeks or months.

**Emollients**, in addition to their effects on dryness, scaling and cracking, may have an anti-proliferative effect in psoriasis, and may be the only treatment necessary for mild psoriasis. They are particularly useful in *inflammatory psoriasis* and in *plaque psoriasis of palms and soles*, in which irritant factors can perpetuate the condition. Emollients are useful adjuncts to other more specific treatments.

More specific topical treatment for *chronic stable plaque psoriasis* on extensor surfaces of trunk and limbs involves the use of vitamin D analogues, coal tar p. 1018, and the retinoid tazarotene p. 1034. However, they can irritate the skin and they are not suitable for the more inflammatory forms of psoriasis; their use should be suspended during an inflammatory phase of psoriasis. The efficacy and the irritancy of each substance varies between patients. If a substance irritates significantly, it should be stopped or the concentration reduced; if it is tolerated, its effects should be assessed after 4 to 6 weeks and treatment continued if it is effective.

**Scalp psoriasis** is usually scaly, and the scale may be thick and adherent; this will require softening with an emollient cream, ointment, or oil. A tar-based shampoo is first-line treatment for scalp psoriasis; a keratolytic, such as salicylic acid, should also be used if there is significant scaling, to allow other treatments to work.

Some preparations prescribed for psoriasis affecting the scalp, combine salicylic acid with coal tar or sulfur. The product should be applied generously, and an adequate quantity should be prescribed. It should be left on for at least an hour, often more conveniently overnight, before washing off. The use of scalp preparations containing a potent corticosteroid or a vitamin D analogue, either alone or in combination, can also be helpful.

**Facial, flexural and genital psoriasis** can be managed with short-term use of a mild or moderate potency topical corticosteroid (a mild potency topical corticosteroid is preferred for the initial treatment of facial psoriasis). Calcipotriol p. 1037 or tacalcitol p. 1037 can be used for longer-term treatment, or if the response to mild or moderate potency topical corticosteroid is inadequate; calcipotriol p. 1036 is more likely to cause irritation. Low strength tar preparations can also be used. Pimecrolimus p. 1019 or tacrolimus p. 1020 by topical application [unlicensed indication] can be used short-term, under specialist supervision, in patients whose condition has not responded adequately to other treatments, or who are intolerant of them.

Widespread *unstable psoriasis* of erythrodermic or generalised pustular type requires urgent specialist assessment. Initial topical treatment should be limited to using emollients frequently and generously; emollients should be prescribed in quantities of 1 kg or more. More localised acute or subacute *inflammatory psoriasis* with hot, spreading or itchy lesions, should be treated topically with emollients or with a corticosteroid of moderate potency.

Calcipotriol and tacalcitol are analogues of vitamin D that affect cell division and differentiation. Calcipotriol is an active form of vitamin D. Vitamin D and its analogues are used first-line for the long-term treatment of plaque psoriasis; they do not smell or stain and they may be more acceptable than tar or dithranol products. Of the vitamin D analogues, calcitriol and calcipotriol are less likely to irritate.

**Coal tar** has anti-inflammatory properties that are useful in chronic plaque psoriasis; it also has antiscaling properties. Crude coal tar (coal tar, BP) is the most effective form, typically in a concentration of 1 to 10% in a soft paraffin base, but few outpatients tolerate the smell and mess. Cleaner extracts of coal tar included in proprietary preparations, are more practicable for home use but they are less effective and improvement takes longer. Contact of
1018 Inflammatory skin conditions

Dithranol

(Anthralin)

**INDICATIONS AND DOSE**

**Subacute and chronic psoriasis**

**TO THE SKIN**

- Adult: (consult product literature)

**DITHROCREAM**

- Subacute and chronic psoriasis

**TO THE SKIN**

- Adult: For application to skin or scalp. 0.1–0.5% cream suitable for overnight treatment, 1–2% cream for maximum 1 hour (consult product literature)

**MICANOL**

- Subacute and chronic psoriasis

**TO THE SKIN**

- Adult: Apply once daily, for application to skin or scalp, to be applied for up to 30 minutes, apply 1% cream, if necessary 3% cream can be used under medical supervision

- **CONTRA-INDICATIONS** Acute and pustular psoriasis - hypersensitivity

- **CAUTIONS** Avoid sensitive areas of skin - avoid use near eyes

- **SIDE-EFFECTS** Local burning sensation - local irritation - stains hair - stains skin

- **PREGNANCY** No adverse effects reported.

- **BREAST FEEDING** No adverse effects reported.
**DIRECTIONS FOR ADMINISTRATION** When applying dithranol, hands should be protected by gloves or they should be washed thoroughly afterwards. Dithranol should be applied to chronic extensor plaques only, carefully avoiding normal skin.

**Micanol®** At the end of contact time, use plenty of lukewarm (not hot) water to rinse off cream; soap may be used after the cream has been rinsed off; use shampoo before applying cream to scalp and if necessary after cream has been rinsed off.

**PRESCRIBING AND DISPENSING INFORMATION** Treatment should be started with a low concentration such as dithranol 0.1%, and the strength increased gradually every few days up to 3%, according to tolerance. When prepared extemporaneously, the BP states Dithranol Paste, BP consists of dithranol in zinc and salicylic acid (Lassar’s) paste. Usual strengths 0.1–1% of dithranol. Dithranol Ointment BP, consists of dithranol, in yellow soft paraffin; usual strengths 0.1–2%. Part of basis may be replaced by hard paraffin if a stiffer preparation is required.

**PATIENT AND CARER ADVICE** Dithranol can stain the skin, hair and fabrics.

**EXCEPTIONS TO LEGAL CATEGORY** Prescription only medicine if dithranol content more than 1%, otherwise may be sold to the public.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ointment, cream, paste. The properties listed below are those particular to the combination only. For the properties of the components please consider, dithranol above.

**INDICATIONS AND DOSE**

**Adult:**
- Short-term treatment of facial, flexural, or genital psoriasis in patients unresponsive to, or intolerant of other topical therapy (initiated by a specialist)
- Apply twice daily until symptoms resolve (maximum duration of treatment 4 weeks)

**Child:**
- Subacute and chronic psoriasis
- Ichthammol: 1 mg per 1 mg
- Ichthammol 1 mg per 1 mg

**SIDE-EFFECTS** Skin irritation

**PRESCRIBING AND DISPENSING INFORMATION** When prepared extemporaneously, the BP states Ichthammol Ointment, BP 1980 consists of ichthammol 10%, white soft paraffin 45% and wool fat 45%.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: paste, ointment

**Liquid**
- Ichthammol (Non-proprietary)
- Ichthammol 1 mg per 1 mg: Ichthammol liquid | 100 gram £11.42
- Ichthammol 1 mg per 1 mg: Ichthammol liquid | 500 gram £34.27

**Ichthammol with zinc oxide**

The properties listed below are those particular to the combination only. For the properties of the components please consider, ichthammol above.

**INDICATIONS AND DOSE**

**Adult:** (consult product literature)

**PRESCRIBING AND DISPENSING INFORMATION** When prepared extemporaneously, the BP states Ichthammol Cream, BP consists of ichthammol 5%, cetostearyl alcohol 3%, wool fat 10%, in zinc cream.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ointment, cream

**Impregnated dressing**
- Ichthammol with zinc oxide (Non-proprietary)
- Ichthammol with zinc oxide

**CALCINEURIN INHIBITORS AND RELATED DRUGS**

**Pimecrolimus**

**INDICATIONS AND DOSE**

**Adult:** Short-term treatment of mild to moderate atopic eczema (including flares) when topical corticosteroids cannot be used (initiated by a specialist)

**TO THE SKIN**
- Apply twice daily until symptoms resolve (stop treatment if eczema worsens or no response after 6 weeks)

**Short-term treatment of facial, flexural, or genital psoriasis in patients unresponsive to, or intolerant of other topical therapy (initiated by a specialist)**

**TO THE SKIN**
- Apply twice daily until symptoms resolve (maximum duration of treatment 4 weeks)

**UNLICENSED USE** Pimecrolimus is not licensed for short-term treatment of facial, flexural, or genital psoriasis in patients unresponsive to, or intolerant of other topical therapy.
Tacrolimus

**DRUG ACTION** Tacrolimus is a calcineurin inhibitor.

**INDICATIONS AND DOSE**

Short-term treatment of moderate to severe atopic eczema (including flares) in patients unresponsive to or intolerant of conventional therapy

**TO THE SKIN**

- Adult: Apply twice daily until lesion clears (consider other treatment if eczema worsens or no improvement after 2 weeks), initially 0.1% ointment to be applied thinly, reduce frequency to once daily or strength of ointment to 0.03% if condition allows

**SIDE-EFFECTS**

Common or very common: Burning sensation, erythema, folliculitis, pruritus, skin infections

Uncommon: Herpes simplex, herpes zoster, impetigo, molluscum contagiosum

Rare: Dryness, local reactions including pain, oedema, papilloma, paraesthesia, peeling, skin discoloration, worsening of eczema

**CONTRA-INDICATIONS**

- Topical tacrolimus is recommended for moderate to severe atopic eczema on the face (particularly skin atrophy).
- Topical pimecrolimus is an option for atopic eczema not responding to initial treatment with topical tacrolimus.

**NATIONAL FUNDING/ACCESS DECISIONS**

NICE technology appraisals (TAs)

- Tacrolimus and pimecrolimus for atopic eczema (August 2004) NICE TA82
  
  Tacrolimus is an option for atopic eczema not controlled by topical corticosteroid treatment or if there is a risk of important corticosteroid side-effects (particularly skin atrophy). Topical pimecrolimus is recommended for moderate to severe atopic eczema on the face and neck of children aged 2–16 years. Pimecrolimus should be used within its licensed indications.

www.nice.org.uk/TA82

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Cream**

CAUTIONARY AND ADVISORY LABELS 4, 11, 28

EXCIPIENTS: May contain Benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol), propylene glycol

- Elidel (Meda Pharmaceuticals Ltd)

**Pimecrolimus 10 mg per 1 gram**

Elidel 1% cream | 30 gram £19.69 DT price | £13.69 | 60 gram £37.41 DT price | £37.41 | 100 gram £59.07 DT price | £59.07

**PREVENTION OF FLARES IN PATIENTS WITH MODERATE TO SEVERE ATOPIC ECZEMA AND 4 OR MORE FLARES A YEAR WHO HAVE RESPONDED TO INITIAL TREATMENT WITH TOPICAL TACROLIMUS**

TO THE SKIN

- Adult: Apply twice weekly, 0.1% ointment to be applied thinly, with an interval of 2–3 days between applications, use short-term treatment regimen during an acute flare; review need for preventative therapy after 1 year

**SHORT-TERM TREATMENT OF FACIAL, FLEXURAL, OR GENITAL PSORIASIS IN PATIENTS UNRESPONSIVE TO, OR INTOLERANT OF OTHER TOPICAL THERAPY**

TO THE SKIN

- Adult: Apply twice daily until symptoms resolve, 0.1% ointment to be applied thinly, reduce to once daily or switch to 0.03% ointment if condition allows, maximum duration of treatment 4 weeks

**UNLICENSED USE**

Short-term treatment of facial, flexural, or genital psoriasis is unlicensed.

**CONTRA-INDICATIONS**

Application to malignant or potentially malignant skin lesions, application under occlusion, avoid contact with eyes, avoid contact with mucous membranes, congenital epidermal barrier defects, generalised erythodema, immunodeficiency, infection at treatment site

**INTERACTIONS**

- Interactions do not generally apply to tacrolimus used topically. Concomitant use with drugs that cause immunosuppression (may be prescribed in exceptional circumstances by specialists).

**SIDE-EFFECTS**

- Common or very common: Burning sensation, erythema, folliculitis, pruritus, skin infections

- Uncommon: Herpes simplex, herpes zoster, impetigo, molluscum contagiosum

- Rare: Dryness, local reactions including pain, oedema, papilloma, paraesthesia, peeling, skin discoloration, worsening of eczema

- Frequency not known: Skin malignancy

**PREGNANCY**

Manufacturer advises caution; avoid unless essential; toxicity in animal studies following systemic administration.

**BREAST FEEDING**

Manufacturer advises caution; ensure infant does not come in contact with treated areas.

**NATIONAL FUNDING/ACCESS DECISIONS**

NICE technology appraisals (TAs)

- Tacrolimus and pimecrolimus for atopic eczema (August 2004) NICE TA82

  Topical tacrolimus is an option for atopic eczema not controlled by maximal topical corticosteroid treatment or if there is a risk of important corticosteroid side-effects (particularly skin atrophy). Topical pimecrolimus is recommended for moderate to severe atopic eczema on the face and neck of children aged 2–16 years. Pimecrolimus should be used within its licensed indications.

www.nice.org.uk/TA82

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Cream**

CAUTIONARY AND ADVISORY LABELS 4, 11, 28

EXCIPIENTS: May contain Benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol), propylene glycol

- Elidel (Meda Pharmaceuticals Ltd)

**Pimecrolimus 10 mg per 1 gram**

Elidel 1% cream | 30 gram £19.69 DT price | £13.69 | 60 gram £37.41 DT price | £37.41 | 100 gram £59.07 DT price | £59.07

**PREVENTION OF FLARES IN PATIENTS WITH MODERATE TO SEVERE ATOPIC ECZEMA AND 4 OR MORE FLARES A YEAR WHO HAVE RESPONDED TO INITIAL TREATMENT WITH TOPICAL TACROLIMUS**

TO THE SKIN

- Adult: Apply twice weekly, 0.1% ointment to be applied thinly, with an interval of 2–3 days between applications, use short-term treatment regimen during an acute flare; review need for preventative therapy after 1 year

**SHORT-TERM TREATMENT OF FACIAL, FLEXURAL, OR GENITAL PSORIASIS IN PATIENTS UNRESPONSIVE TO, OR INTOLERANT OF OTHER TOPICAL THERAPY**

TO THE SKIN

- Adult: Apply twice daily until symptoms resolve, 0.1% ointment to be applied thinly, reduce to once daily or switch to 0.03% ointment if condition allows, maximum duration of treatment 4 weeks

**UNLICENSED USE**

Short-term treatment of facial, flexural, or genital psoriasis is unlicensed.

**CONTRA-INDICATIONS**

Application to malignant or potentially malignant skin lesions, application under occlusion, avoid contact with eyes, avoid contact with mucous membranes, congenital epidermal barrier defects, generalised erythodema, immunodeficiency, infection at treatment site

**INTERACTIONS**

- Interactions do not generally apply to tacrolimus used topically. Concomitant use with drugs that cause immunosuppression (may be prescribed in exceptional circumstances by specialists).

**SIDE-EFFECTS**

- Common or very common: Burning sensation, erythema, folliculitis, pruritus, skin infections

- Uncommon: Herpes simplex, herpes zoster, impetigo, molluscum contagiosum

- Rare: Dryness, local reactions including pain, oedema, papilloma, paraesthesia, peeling, skin discoloration, worsening of eczema

- Frequency not known: Skin malignancy

**PREGNANCY**

Manufacturer advises caution; avoid unless essential; toxicity in animal studies following systemic administration.

**BREAST FEEDING**

Avoid—present in milk (following systemic administration).

**NATIONAL FUNDING/ACCESS DECISIONS**

NICE technology appraisals (TAs)

- Tacrolimus and pimecrolimus for atopic eczema (August 2004) NICE TA82

  Topical tacrolimus is an option for atopic eczema not controlled by maximal topical corticosteroid treatment or if there is a risk of important corticosteroid side-effects (particularly skin atrophy). Topical pimecrolimus is recommended for moderate to severe atopic eczema in adults and children over 2 years. Tacrolimus should be used within its licensed indications.

www.nice.org.uk/TA82

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (March 2010) that tacrolimus ointment (Protopic®) is accepted for restricted use within NHS Scotland for the prevention of flares in patients aged over 2 years with moderate to severe atopic eczema in accordance with the licensed indications; initiation of treatment is restricted to doctors (including general practitioners) with a specialist interest and experience in treating atopic eczema with immunomodulatory therapy.
**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: paste

**Ointment**

CAUTIONARY AND ADVISORY LABELS 4, 11, 28

**EXCIPIENTS:** May contain Beeswax

▶ **Protopic (Astellas Pharma Ltd)**

Tacrolimus (as Tacrolimus monohydrate) 300 microgram per 1 gram Protopic 0.03% ointment | 30 gram £19.44 DT price = £19.44 | 60 gram £35.46 DT price = £35.46

Tacrolimus (as Tacrolimus monohydrate) 1 mg per 1 gram Protopic 0.1% ointment | 30 gram £21.60 DT price = £21.60 | 60 gram £39.40 DT price = £39.40

**CORTICOSTEROIDS**

**Topical corticosteroids**

Topical corticosteroids are used for the treatment of inflammatory conditions of the skin (other than those arising from an infection), in particular eczema, contact dermatitis, insect stings, and eczema of scabies. Corticosteroids suppress the inflammatory reaction during use; they are not curative and on discontinuation a rebound exacerbation of the condition may occur. They are generally used to relieve symptoms and suppress signs of the disorder when other measures such as emollients are ineffective.

Topical corticosteroids are not recommended in the routine treatment of urticaria; treatment should only be initiated and supervised by a specialist. They should not be used indiscriminately in pruritus (where they will only benefit if inflammation is causing the itch) and are not recommended for acne vulgaris.

Systemic or very potent topical corticosteroids should be avoided or given only under specialist supervision in psoriasis because, although they may suppress the psoriasis in the short term, relapse or vigorous rebound occurs on withdrawal (sometimes precipitating severe pustular psoriasis). See the role of topical corticosteroids in the treatment of psoriasis.

In general, the most potent topical corticosteroids should be reserved for recalcitrant dermatoses such as *chronic discoid lupus erythematosus, lichen simplex chronicus, hypertrophic lichen planus,* and *palmoplantar pustulosis.* Potent corticosteroids should generally be avoided on the face and skin flexures, but specialists occasionally prescribe them for use on these areas in certain circumstances.

When topical treatment has failed, intralesional corticosteroid injections may be used. These are more effective than the very potent topical corticosteroid preparations and should be reserved for severe cases where there are localised lesions such as *lichen scars, hypertrophic lichen planus,* or localised alopecia areata.

**Perioral lesions**

Hydrocortisone cream 1% p. 993 can be used for up to 7 days to treat uninfected inflammatory lesions on the lips. Hydrocortisone with miconazole p. 1031 cream or ointment is useful where infection by susceptible organisms and inflammation co-exist, particularly for initial treatment (up to 7 days) e.g. in angular cheilitis. Organisms susceptible to miconazole include *Candida* spp. and many Gram-positive bacteria including streptococci and staphylococci.

**Choice of formulation**

Water-miscible corticosteroid creams are suitable for moist or weeping lesions whereas ointments are generally chosen for dry, lichenified or scaly lesions or where a more occlusive effect is required. **Lotions** may be useful when minimal application to a large or hair-bearing area is required or for the treatment of exudative lesions. **Oclusive polythene or hydrocolloid dressings** increase absorption, but also increase the risk of side effects; they are therefore used only under supervision on a short-term basis for areas of very thick skin (such as the palms and soles). The inclusion of urea or salicylic acid also increases the penetration of the corticosteroid.

In the BNF publications topical corticosteroids for the skin are categorised as ‘mild’, ‘moderately potent’, ‘potent’ or ‘very potent’; the **least potent** preparation which is effective should be chosen but dilution should be avoided whenever possible.

**Absorption through the skin**

*Mild and moderately potent* topical corticosteroids are associated with few side-effects but care is required in the use of *potent* and *very potent* corticosteroids. Absorption through the skin can rarely cause adrenal suppression and even Cushing’s syndrome, depending on the area of the body being treated and the duration of treatment.

Absorption is greatest where the skin is thin or raw, and from intertriginous areas; it is increased by occlusion.

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**Suitable quantities of corticosteroid preparations to be prescribed for specific areas of the body**

<table>
<thead>
<tr>
<th>Area of body</th>
<th>Creams and Ointments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face and neck</td>
<td>15 to 30 g</td>
</tr>
<tr>
<td>Both hands</td>
<td>15 to 30 g</td>
</tr>
<tr>
<td>Scalp</td>
<td>15 to 30 g</td>
</tr>
<tr>
<td>Both arms</td>
<td>30 to 60 g</td>
</tr>
<tr>
<td>Both legs</td>
<td>100 g</td>
</tr>
<tr>
<td>Trunk</td>
<td>100 g</td>
</tr>
<tr>
<td>Groins and genitalia</td>
<td>15 to 30 g</td>
</tr>
</tbody>
</table>

These amounts are usually suitable for an adult for a single daily application for 2 weeks.

**Compound preparations**

The advantages of including other substances (such as antibiotics or antifungals) with corticosteroids in topical preparations are uncertain, but such combinations may have a place where inflammatory skin conditions are associated with bacterial or fungal infection, such as infected eczema. In these cases the antimicrobial drug should be chosen according to the sensitivity of the infecting organism and used regularly for a short period (typically twice daily for 1 week). Longer use increases the likelihood of resistance and of sensitisation.

The keratolytic effect of salicylic acid p. 1057 facilitates the absorption of topical corticosteroids; however, excessive and prolonged use of topical preparations containing salicylic acid p. 1057 may cause salicylism.

**Topical corticosteroid preparation potencies**

Potency of a topical corticosteroid preparation is a result of the formulation as well as the corticosteroid. Therefore, proprietary names are shown.

- **Mild**
  - Hydrocortisone 0.1–2.5%
  - Dioderm
  - Mildison
  - Synalar

- **Mild with antifungals**
  - Canesten HC
  - Daktacort
  - Econacort
  - Fucidin H
  - Nystaform-HC
  - Terra-Cortril
  - Timodine

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Eczema and psoriasis 1021
Skin corticosteroid such as betamethasone condition. A mild corticosteroid such as hydrocortisone well as possible; inadequate treatment will perpetuate the being undertreated. The aim is to control the condition as corticosteroids in children should not result in the child

Children, especially infants, are particularly susceptible to

Use in children

Children, especially infants, are particularly susceptible to side-effects. However, concern about the safety of topical corticosteroids in children should not result in the child being undertreated. The aim is to control the condition as well as possible; inadequate treatment will perpetuate the condition. A mild corticosteroid such as hydrocortisone 0.5% or 1% p. 993 is useful for treating nappy rash and hydrocortisone 1% for atopic eczema in childhood. A moderately potent or potent corticosteroid may be appropriate for severe atopic eczema on the limbs, for 1–2 weeks only, switching to a less potent preparation as the condition improves. In an acute flare-up of atopic eczema, it may be appropriate to use more potent formulations of topical corticosteroids for a short period to regain control of the condition. A very potent corticosteroid should be initiated under the supervision of a specialist. Continuous daily application of a mild corticosteroid such as hydrocortisone 1% is equivalent to a potent corticosteroid such as betamethasone 0.1% p. 993 applied intermittently. Carers of young children should be advised that treatment should not necessarily be reserved to ‘treat only the worst areas’ and they may need to be advised that patient information leaflets may contain inappropriate advice for the patient’s condition.

Corticosteroids (topical)

CONTRA-INDICATIONS Acne • periocular dermatitis • potent corticosteroids in widespread plaque psoriasis • rosacea • untreated bacterial, fungal or viral skin lesions

CAUTIONS Avoid prolonged use (particularly on the face) - cautions applicable to systemic corticosteroids may also apply if absorption occurs following topical and local use - infection - keep away from eyes - use potent or very potent topical corticosteroids under specialist supervision in psoriasis (can result in rebound relapse, development of generalised pustular psoriasis, and local and systemic toxicity)

SIDE-EFFECTS

Rare Adrenal suppression - Cushing’s syndrome

Frequency not known Acne - contact dermatitis - hypertrichosis - irreversible striae atrophicae - irreversible telangiectasia - mild depigmentation (may be reversible) - periocular dermatitis - side-effects applicable to systemic corticosteroids may also apply if absorption occurs following topical and local use - spread and worsening of untreated infection - thinning of the skin (may be restored over a period after stopping treatment but the original structure may never return) - worsening of acne - worsening of rosacea

SIDE-EFFECTS, FURTHER INFORMATION

In order to minimise the side-effects of a topical corticosteroid, it is important to apply it thinly to affected areas only, no more frequently than twice daily, and to use the least potent formulation which is fully effective.

DIRECTIONS FOR ADMINISTRATION Topical corticosteroid preparations should be applied no more frequently than twice daily; once daily is often sufficient. Topical corticosteroids should be spread thinly on the skin but in sufficient quantity to cover the affected areas. The length of cream or ointment expelled from a tube may be used to specify the quantity to be applied to a given area of skin. This length can be measured in terms of a fingertip unit (the distance from the tip of the adult index finger to the first crease). One fingertip unit (approximately 500 mg from a tube with a standard 5 mm diameter nozzle) is sufficient to cover an area that is twice that of the flat adult handprint (palm and fingers). Mixing topical preparations on the skin should be avoided where possible; several minutes should elapse between application of different preparations.

PRESCRIBING AND DISPENSING INFORMATION The potency of each topical corticosteroid should be included on the label with the directions for use. The label should be attached to the container (for example, the tube) rather than the outer packaging.

PATIENT AND CARER ADVICE Patients or carers should be given advice on how to administer corticosteroid creams andointments. If a patient is using topical corticosteroids of different potencies, the patient should be told when to use each corticosteroid. Patients and their carers should be reassured that side effects such as skin thinning and systemic effects rarely occur when topical corticosteroids are used appropriately.

Alclometasone dipropionate

INDICATIONS AND DOSE

Inflammatory skin disorders such as eczemas

TO THE SKIN

Child: Apply 1–2 times a day, to be applied thinly
Adult: Apply 1–2 times a day, to be applied thinly
Beclometasone dipropionate
(Beclometasone dipropionate)

INDICATIONS AND DOSE
Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids | Psoriasis

TO THE SKIN
▶ Child 1–7 years: Apply 1–2 times a day, thin layer to be applied
▶ Adult: Apply 1–2 times a day, thin layer to be applied

Potency
Beclometasone dipropionate cream 0.05%: potent.

Chemical Name
Beclometasone dipropionate

PATIENT AND CARER ADVICE
Patients or carers should be counselled on the application of alclometasone dipropionate cream.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Cream

CAUTIONARY AND ADVISORY LABELS 28

EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), chlorocresol, propylene glycol

● ALCLOMETASONE DIPROPIONATE (Non-proprietary)
  Alclometasone dipropionate 500 microgram per 1 gram | 15 gram [P] no price available

● Modrasone (Teva UK Ltd)
  Alclometasone dipropionate 500 microgram per 1 gram Modrasone 0.05% cream | 50 gram [POT] £2.68 DT price = £2.68

PATIENT AND CARER ADVICE
Patient counselling is advised for betamethasone cream, ointment, scalp application and foam (application).

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: cream, ointment, liquid and foam.

Foam

CAUTIONARY AND ADVISORY LABELS 28, 15

EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), polyborates, propylene glycol

● Betamousse (Focus Pharmaceuticals Ltd)
  Betamethasone (as Betamethasone valerate) 1 mg per 1 gram Betamousse 0.1% cutaneous foam | 100 gram [POT] £9.75 DT price = £9.75

Liquids

CAUTIONARY AND ADVISORY LABELS 15, 28

EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), hydroxybenzoates (parabens)

● Betacap (Dermal Laboratories Ltd)
  Betamethasone (as Betamethasone valerate) 1 mg per 1 gram Betacap 0.1% scalp application | 100 ml [POT] £3.19 DT price = £3.19

● Betnovate (GlaxoSmithKline UK Ltd)
  Betamethasone (as Betamethasone valerate) 1 mg per 1 gram Betnovate 0.1% scalp application | 100 ml [POT] £4.99 DT price = £3.19
  Betnovate 0.1% lotion | 100 ml [POT] £4.58 DT price = £4.58

● Diprosone (Merck Sharp & Dohme Ltd)
  Betamethasone (as Betamethasone dipropionate) 500 microgram per 1 ml Diprosone 0.05% lotion | 30 ml [POT] £2.73 DT price = £2.73 | 100 ml [POT] £7.80 DT price = £7.80

Cream

CAUTIONARY AND ADVISORY LABELS 28

EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), chlorocresol

● Betacap (Dermal Laboratories Ltd)
  Betamethasone (as Betamethasone valerate) 1 mg per 1 gram Betacap 0.1% scalp application | 100 ml [POT] £3.19 DT price = £3.19

● Betnovate (GlaxoSmithKline UK Ltd)
  Betamethasone (as Betamethasone valerate) 1 mg per 1 gram Betnovate 0.1% scalp application | 100 ml [POT] £4.99 DT price = £3.19
  Betnovate 0.1% lotion | 100 ml [POT] £4.58 DT price = £4.58

● Diprosone (Merck Sharp & Dohme Ltd)
  Betamethasone (as Betamethasone dipropionate) 500 microgram per 1 ml Diprosone 0.05% lotion | 30 ml [POT] £2.73 DT price = £2.73 | 100 ml [POT] £7.80 DT price = £7.80

UNLICENSED USE
Betacap®, Betnovate® and Betnovate-RD® are not licensed for use in children under 1 year.
Betamethasone with clioquinol

The properties listed below are those particular to the combination only. For the properties of the components please consider, betamethasone p. 993.

**INDICATIONS AND DOSE**
Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids | Psoriasis TO THE SKIN
- Child 1-17 years: (consult product literature)
- Adult: (consult product literature)
**Potency**
Betamethasone (as valerate) 0.1% with clioquinol cream and ointment: potent.

- **PATIENT AND CARER ADVICE** Stains clothing. Patients or carers should be counselled on application of betamethasone with clioquinol preparations.

- **MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

  **Cream**
  CAUTIONARY AND ADVISORY LABELS 28
  EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), chlorocresol
  - BETAMETHASONE WITH CLIQUINOL (Non-proprietary)
    Betamethasone (as Betamethasone valerate) 1 mg per 1 gram, Clioquinol 30 mg per 1 gram Betamethasone valerate 0.1% / Clioquinol 3% cream | 30 gram [PTX] £18.88 DT price = £18.88
  **Ointment**
  CAUTIONARY AND ADVISORY LABELS 28
  - BETAMETHASONE WITH CLIQUINOL (Non-proprietary)
    Betamethasone (as Betamethasone valerate) 1 mg per 1 gram, Clioquinol 30 mg per 1 gram Betamethasone valerate 0.1% / Clioquinol 3% ointment | 30 gram [PTX] £18.88 DT price = £18.88

Betamethasone with clotrimazole

The properties listed below are those particular to the combination only. For the properties of the components please consider, betamethasone p. 993, clotrimazole p. 1010.

**INDICATIONS AND DOSE**
Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids | Psoriasis TO THE SKIN
- Child 12-17 years: (consult product literature)
- Adult: (consult product literature)
**Potency**
Betamethasone dipropionate 0.064% (=betamethasone 0.5%) with clotrimazole cream: potent.

- **PATIENT AND CARER ADVICE** Patients or carers should be given advice on how to administer betamethasone with clotrimazole cream.

- **MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

  **Cream**
  CAUTIONARY AND ADVISORY LABELS 28
  EXCIPIENTS: May contain Benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol), propylene glycol
  - Lotriderm (Lerva UK Ltd)
    Betamethasone dipropionate 640 microgram per 1 gram, Clotrimazole 10 mg per 1 gram Lotriderm cream | 30 gram [PTX] £6.34 DT price = £6.34
  **Ointment**
  CAUTIONARY AND ADVISORY LABELS 28
  - BETAMETHASONE WITH NEOMYCIN (Non-proprietary)
    Betamethasone (as Betamethasone valerate) 1 mg per 1 gram, Neomycin sulfate 5 mg per 1 gram Betamethasone valerate 0.1% / Neomycin 0.5% cream | 30 gram [PTX] £18.88 DT price = £18.88 | 100 gram [PTX] £38.00 DT price = £38.00

Betamethasone with fusidic acid

The properties listed below are those particular to the combination only. For the properties of the components please consider, betamethasone p. 993, fusidic acid p. 1009.

**INDICATIONS AND DOSE**
Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids | Psoriasis TO THE SKIN
- Child 6-17 years: (consult product literature)
- Adult: (consult product literature)
**Potency**
Betamethasone (as valerate) 0.1% with fusidic acid cream: potent.

- **PATIENT AND CARER ADVICE** Patients or carers should be counselled on application of betamethasone with fusidic acid preparations.

- **MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

  **Cream**
  CAUTIONARY AND ADVISORY LABELS 28
  EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), chlorocresol, hydroxybenzoates (parabens)
  - Fucibet (LEO Pharma)
    Betamethasone (as Betamethasone valerate) 1 mg per 1 gram, Fusidic acid 20 mg per 1 gram Fucibet cream | 30 gram [PTX] £6.38 DT price = £6.38 | 60 gram [PTX] £12.75 DT price = £12.75
    Fucibet Lipid cream | 30 gram [PTX] £6.74 DT price = £6.38

Betamethasone with neomycin

The properties listed below are those particular to the combination only. For the properties of the components please consider, betamethasone p. 993, neomycin sulfate p. 1009.

**INDICATIONS AND DOSE**
Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids | Psoriasis TO THE SKIN USING OINTMENT OR TO THE SKIN USING CREAM
- Child 2-17 years: Apply 1–2 times a day, to be applied thinly
- Adult: Apply 1–2 times a day, to be applied thinly
**Potency**
Betamethasone (as valerate) 0.1% with neomycin cream and ointment: potent.

- **PATIENT AND CARER ADVICE** Patient counselling is advised for betamethasone with neomycin cream and ointment (application).

- **MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

  **Cream**
  CAUTIONARY AND ADVISORY LABELS 28
  EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), chlorocresol
  - BETAMETHASONE WITH NEOMYCIN (Non-proprietary)
    Betamethasone (as Betamethasone valerate) 1 mg per 1 gram, Neomycin sulfate 5 mg per 1 gram Betamethasone valerate 0.1% / Neomycin 0.5% cream | 30 gram [PTX] £18.88 DT price = £18.88 | 100 gram [PTX] £38.00 DT price = £38.00
  **Ointment**
  CAUTIONARY AND ADVISORY LABELS 28
  - BETAMETHASONE WITH NEOMYCIN (Non-proprietary)
    Betamethasone (as Betamethasone valerate) 1 mg per 1 gram, Neomycin sulfate 5 mg per 1 gram Betamethasone valerate 0.1% / Neomycin 0.5% ointment | 30 gram [PTX] £18.88 DT price = £18.88 | 100 gram [PTX] £38.00 DT price = £38.00
Betamethasone with salicylic acid

The properties listed below are those particular to the combination only. For the properties of the components please consider, betamethasone p. 993, salicylic acid p. 1057.

INDICATIONS AND DOSE

DIPROSALIC® OINTMENT

Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids / Psoriasis

▶ TO THE SKIN

Child: Apply 1–2 times a day, max. 60 g per week

Adult: Apply 1–2 times a day, max. 60 g per week

Potency

Betamethasone (as dipropionate) 0.05% with salicylic acid 3%: potent.

DIPROSALIC® SCALP APPLICATION

Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids / Psoriasis

▶ TO THE SKIN

Child: Apply 1–2 times a day, apply a few drops

Adult: Apply 1–2 times a day, apply a few drops

Potency

Betamethasone (as dipropionate) 0.05% with salicylic acid 2%: potent.

PATIENT AND CARER ADVICE

Patients or carers should be counselled on application of betamethasone and salicylic acid preparations.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: cream, ointment

Foam

CAUTIONARY AND ADVISORY LABELS 15, 28

EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), polysorbates, propylene glycol

Clarelux (Pierre Fabre Dermo-Cosmetique)

Clobetasol propionate 500 microgram per 1 gram Clarelux

500micrograms/g foam | 100 gram (PFS) £11.06

Liquid

CAUTIONARY AND ADVISORY LABELS 15, 28

▶ Dermovate (GlaxoSmithKline UK Ltd)

Clobetasol propionate 500 microgram per 1 gram Dermovate

0.05% scalp application | 30 ml (PFS) £3.07 DT price = £3.07 | 100 ml (PFS) £10.42 DT price = £10.42

Cream

CAUTIONARY AND ADVISORY LABELS 28

EXCIPIENTS: May contain Beeswax, cetostearyl alcohol (including cetyl and stearyl alcohol), chlorocresol, propylene glycol

CLOBETASOL PROPIONATE (Non-proprietary)

Clobetasol propionate 500 microgram per 1 gram Clobetasol

0.05% cream | 30 gram (PFS) no price available DT price = £2.69 | 100 gram (PFS) no price available DT price = £7.90

Dermovate (GlaxoSmithKline UK Ltd)

Clobetasol propionate 500 microgram per 1 gram Dermovate

0.05% cream | 30 gram (PFS) £2.69 DT price = £2.69 | 100 gram (PFS) £7.90 DT price = £7.90

Brands may include ClobaDerm 0.05% cream

Ointment

CAUTIONARY AND ADVISORY LABELS 28

EXCIPIENTS: May contain Propylene glycol

CLOBETASOL PROPIONATE (Non-proprietary)

Clobetasol propionate 500 microgram per 1 gram Clobetasol

0.05% ointment | 30 gram (PFS) no price available DT price = £2.69 | 100 gram (PFS) no price available DT price = £7.90

Dermovate (GlaxoSmithKline UK Ltd)

Clobetasol propionate 500 microgram per 1 gram Dermovate

0.05% ointment | 30 gram (PFS) £2.69 DT price = £2.69 | 100 gram (PFS) £7.90 DT price = £7.90

Brands may include ClobaDerm 0.05% ointment

Shampoo

CAUTIONARY AND ADVISORY LABELS 28

▶ Etrivex (Gelderma (UK) Ltd)

Clobetasol propionate 500 microgram per 1 gram Etrivex

500micrograms/g shampoo | 125 ml (PFS) £10.29 DT price = £10.29

Clobetasol propionate with neomycin sulfate and nystatin

The properties listed below are those particular to the combination only. For the properties of the components please consider, clobetasol propionate above, neomycin sulfate p. 1009.

INDICATIONS AND DOSE

Short-term treatment only of severe resistant inflammatory skin disorders such as recalcitrant eczemas associated with infection and unresponsive to less potent corticosteroids / Psoriasis associated with infection

▶ TO THE SKIN

Adult: (consult product literature)
Clobetasone butyrate with nystatin and oxytetracycline

The properties listed below are those particular to the combination only. For the properties of the components please consider, clobetasone butyrate above, oxytetracycline p. 498.

**INDICATIONS AND DOSE**
Steroid-responsive dermatoses where candidal or bacterial infection is present

**TO THE SKIN**
- **Adult:** (consult product literature)
- **Potency**
  - Clobetasone butyrate 0.05% with nystatin and oxytetracycline cream: moderate.

**MEDICAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Cream**
**CAUTIONARY AND ADVISORY LABELS 28**
- **Clobetasol propionate with neomycin sulfate and nystatin (Non-proprietary)**
  - Clobetasol propionate 500 microgram per 1 gram, Neomycin sulfate 5 mg per 1 gram, Nystatin 100,000 unit per 1 gram
  - Clobetasol 500 microgram / Neomycin 5 mg / Nystatin 100,000 units / g ointment | 30 gram ($P30) $64.00

**Ointment**
**CAUTIONARY AND ADVISORY LABELS 28**
- **Clobetasol propionate with neomycin sulfate and nystatin (Non-proprietary)**
  - Clobetasol propionate 500 microgram per 1 gram, Neomycin sulfate 5 mg per 1 gram, Nystatin 100,000 unit per 1 gram
  - Clobetasol 500 microgram / Neomycin 5 mg / Nystatin 100,000 units / g ointment | 30 gram ($P30) $64.00

Clotetasone butyrate

**INDICATIONS AND DOSE**
Eczemas and dermatitis of all types | Maintenance between courses of more potent corticosteroids |

**TO THE SKIN**
- **Child:** Apply 1–2 times a day, to be applied thinly
- **Adult:** Apply 1–2 times a day, to be applied thinly

**Potency**
Clobetasone butyrate 0.05% cream and ointment: moderate.

**PATIENT AND CARER ADVICE**
Patients or carers should be advised on application of clobetasone butyrate containing preparations.

**EXCEPTIONS TO LEGAL CATEGORY**
Cream can be sold to the public for short-term symptomatic treatment and control of patches of eczema and dermatitis (but not seborrhoeic dermatitis) in adults and children over 12 years provided pack does not contain more than 15 g.

**MEDICAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ointment

**Cream**
**CAUTIONARY AND ADVISORY LABELS 28**
- **Trimovate** (GlaxoSmithKline Consumer Healthcare, GlaxoSmithKline UK Ltd)
  - Clobetasone butyrate 500 microgram per 1 gram, Nystatin 100,000 unit per 1 gram, Oxytetracycline (as Oxytetracycline calcium) 30 mg per 1 gram
  - Trimovate cream | 30 gram ($P30) £3.29

**Diflucortolone valerate**

**INDICATIONS AND DOSE**
Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids (using 0.3% diflucortolone valerate) | Short-term treatment of severe exacerbations (using 0.3% diflucortolone valerate) | Psoriasis (using 0.3% diflucortolone valerate)

**TO THE SKIN**
- **Child:** Apply 1–2 times a day for up to 2 weeks, reducing strength as condition responds, to be applied thinly; maximum 60 g per week
- **Adult:** Apply 1–2 times a day for up to 2 weeks, reducing strength as condition responds, to be applied thinly; maximum 60 g per week

Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids (using 0.1% diflucortolone valerate) | Psoriasis (using 0.1% diflucortolone valerate)

**TO THE SKIN**
- **Child:** Apply 1–2 times a day for up to 4 weeks, to be applied thinly
- **Adult:** Apply 1–2 times a day for up to 4 weeks, to be applied thinly

**Potency**
Diflucortolone valerate 0.1% cream and ointment: potent.
Diflucortolone valerate 0.3% cream and ointment: very potent.

**PATIENT AND CARER ADVICE**
Patients or carers should be advised on application of diflucortolone valerate containing preparations.

**MEDICAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Cream**
**CAUTIONARY AND ADVISORY LABELS 28**
- **Trimovate** (GlaxoSmithKline Consumer Healthcare, GlaxoSmithKline UK Ltd)
  - Diflucortolone valerate containing preparations.
Fludroxycortide (Flurandrenolone)

**INDICATIONS AND DOSE**
Inflammatory skin disorders such as eczemas

TO THE SKIN
- Child: Apply 1–2 times a day, to be applied thinly
- Adult: Apply 1–2 times a day, to be applied thinly

**Potency**
Fludroxycortide 0.0125% cream and ointment: moderate

HAELEN® TAPE
Chronic localised recalcitrant dermatoses (but not acute or weeping)

TO THE SKIN
- Child: Cut tape to fit lesion, apply to clean, dry skin shorn of hair, usually for 12 hours daily
- Adult: Cut tape to fit lesion, apply to clean, dry skin shorn of hair, usually for 12 hours daily

**PATIENT AND CARER ADVICE**
Patients or carers should be counselled on application of fludroxycortide cream and ointment.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Cream**

**CAUTIONARY AND ADVISORY LABELS**
- **EXCIPENTS:** May contain Benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol), polyethylene glycol
- **Nerisone (Meadow Laboratories Ltd)**
  - Fluocinolone acetonide 25 microgram per 1 gram Nerisone 1 in 10
    - Dilution 0.0025% cream | 50 gram (POD) £4.58 DT price = £4.58
  - Fluocinolone acetonide 62.5 microgram per 1 gram Nerisone 1 in 4
    - Dilution 0.00625% cream | 50 gram (POD) £4.84 DT price = £4.84
  - Fluocinolone acetonide 250 microgram per 1 gram Nerisone 0.025% cream | 30 gram (POD) £14.14 DT price = £14.14
    - 100 gram (POD) £11.75 DT price = £11.75

**Ointment**

**CAUTIONARY AND ADVISORY LABELS**
- **EXCIPENTS:** May contain Propylene glycol, wool fat and related substances including lanolin
- **Synalar (Derma UK Ltd)**
  - Fluocinolone acetonide 62.5 microgram per 1 gram Synalar 1 in 4
    - Dilution 0.00625% ointment | 50 gram (POD) £4.84 DT price = £4.84
  - Fluocinolone acetonide 250 microgram per 1 gram Synalar 0.025% ointment | 30 gram (POD) £14.14 DT price = £14.14
    - 100 gram (POD) £11.75 DT price = £11.75

**Gel**

**CAUTIONARY AND ADVISORY LABELS**
- **EXCIPENTS:** May contain Hydroxybenzoates (parabens), propylene glycol
- **Synalar (Derma UK Ltd)**
  - Fluocinolone acetonide 25 microgram per 1 gram Synalar 1 in 10
    - Dilution 0.0025% cream | 50 gram (POD) £2.60 DT price = £2.60

**Fluocinolone acetonide with clioquinol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, fluocinolone acetonide above.

**INDICATIONS AND DOSE**
Inflammatory skin disorders such as eczemas associated with infection | Psoriasis associated with infection

**TO THE SKIN**
- Adult: Apply 1–2 times a day, to be applied thinly, reducing strength as condition responds

**Potency**
Fluocinolone acetonide 0.025% cream, gel, and ointment: potent

**Fluocinolone acetonide**

**INDICATIONS AND DOSE**
Severe inflammatory skin disorders such as eczemas | Psoriasis

**TO THE SKIN**
- Child 1–17 years: Apply 1–2 times a day, to be applied thinly, reduce strength as condition responds
- Adult: Apply 1–2 times a day, to be applied thinly, reduce strength as condition responds

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Cream**

**CAUTIONARY AND ADVISORY LABELS**
- **EXCIPENTS:** May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), disodium edetate, hydroxybenzoates (parabens), polyethylene glycol
Fluocinolone acetonide with neomycin

The properties listed below are those particular to the combination only. For the properties of the components please consider, fluocinolone acetonide p. 1027, neomycin sulfate p. 1009.

**INDICATIONS AND DOSE**

Inflammatory skin disorders such as eczemas associated with infection | Psoriasis associated with infection

**TO THE SKIN**

- Child 1-17 years: Apply 1–2 times a day, to be applied thinly, reducing strength as condition responds
- Adult: Apply 1–2 times a day, to be applied thinly, reducing strength as condition responds

**Potency**

Fluocinolone acetonide 0.025% with neomycin 0.5% cream and ointment: potent.

**PATIENT AND CARER ADVICE**

Patients or carers should be counselled on the application of fluocinolone acetonide with neomycin preparations.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Cream**

| CAUTIONARY AND ADVISORY LABELS | 28 |
| EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), hydroxybenzoates (parabens), polysorbates, propylene glycol |
| **Synalar N** (Derma UK Ltd) |
| Fluocinolone acetonide 250 microgram per 1 gram, Neomycin sulfate 5 mg per 1 gram | **Synalar N cream** | 30 gram | **PBM** | £4.36 |

**Ointment**

| CAUTIONARY AND ADVISORY LABELS | 28 |
| EXCIPIENTS: May contain Propylene glycol, wool fat and related substances including lanolin |
| **Synalar N** (Derma UK Ltd) |
| Fluocinolone acetonide 250 microgram per 1 gram, Neomycin sulfate 5 mg per 1 gram | **Synalar N ointment** | 15 gram | **PBM** | £2.66 |

**Flucinonide**

**INDICATIONS AND DOSE**

Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids | Psoriasis

**TO THE SKIN**

- Child 1-17 years: Apply 1–2 times a day, to be applied thinly
- Adult: Apply 1–2 times a day, to be applied thinly

**Potency**

Flucinonide 0.05% cream and ointment: potent.

**PATIENT AND CARER ADVICE**

Patients or carers should be advised on the application of flucinonide preparations.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Cream**

| CAUTIONARY AND ADVISORY LABELS | 28 |
| EXCIPIENTS: May contain Propylene glycol |
| **Metosyn FAPG** (Derma UK Ltd) |
| Fluocinonide 500 microgram per 1 gram | **Metosyn FAPG 0.05% cream** | 25 gram | **PBM** | £3.96 DT price = £3.96 | 100 gram | **PBM** | £13.34 DT price = £13.34 |

**Ointment**

| CAUTIONARY AND ADVISORY LABELS | 28 |
| EXCIPIENTS: May contain Propylene glycol, wool fat and related substances including lanolin |
| **Metosyn** (Derma UK Ltd) |
| Fluocinonide 500 microgram per 1 gram | **Metosyn 0.05% ointment** | 25 gram | **PBM** | £3.50 DT price = £3.50 | 100 gram | **PBM** | £13.15 DT price = £13.15 |

**Flucortolone**

**INDICATIONS AND DOSE**

Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids | Psoriasis

**TO THE SKIN**

- Child 1-17 years: Apply 1–2 times a day, to be applied thinly, reducing strength as condition responds
- Adult: Apply 1–2 times a day, to be applied thinly, reducing strength as condition responds

**Potency**

Flucortolone hexanoate 0.25% cream and ointment; flucortolone pivalate 0.25% cream and flucortolone 0.25% ointment: moderate.

**PRESCRIBING AND DISPENSING INFORMATION**

Patients or carers should be counselled on the application of flucortolone preparations.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Cream**

| CAUTIONARY AND ADVISORY LABELS | 28 |
| EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), disodium edetate, fragrances, hydroxybenzoates (parabens) |
| **Ultralanum Plain** (Flucortolone hexanoate / Flucortolone pivalate) (Meadow Laboratories Ltd) |
| Flucortolone hexanoate 2.5 mg per 1 gram, Flucortolone pivalate 2.5 mg per 1 gram | **Ultralanum Plain cream** | 50 gram | **PBM** | £2.95 |

**Ointment**

| CAUTIONARY AND ADVISORY LABELS | 28 |
| EXCIPIENTS: May contain Fragrances, wool fat and related substances including lanolin |
| **Ultralanum Plain** (Flucortolone / Flucortolone hexanoate) (Meadow Laboratories Ltd) |
| Flucortolone 2.5 mg per 1 gram, Flucortolone hexanoate 2.5 mg per 1 gram | **Ultralanum Plain ointment** | 50 gram | **PBM** | £2.95 |

**Fluticasone**

**INDICATIONS AND DOSE**

Severe inflammatory skin disorders such as dermatitis and eczemas unresponsive to less potent corticosteroids | Psoriasis

**TO THE SKIN**

- Child 3 months–17 years: Apply 1–2 times a day, to be applied thinly
- Adult: Apply 1–2 times a day, to be applied thinly

**Potency**

Fluticasone cream 0.05%: potent. Fluticasone ointment 0.005%: potent.

**PATIENT AND CARER ADVICE**

Patients or carers should be given advice on application of fluticasone creams and ointments.
**Hydrocortisone**

**INDICATIONS AND DOSE**

Mild inflammatory skin disorders such as eczemas

**TO THE SKIN**
- Child: Apply 1–2 times a day, to be applied thinly
- Adult: Apply 1–2 times a day, to be applied thinly

**Nappy rash**
- Child: Apply as required for no more than 1 week, discontinued as soon as the inflammation subsides

**Potency**
- Hydrocortisone cream and ointment 0.5 to 2.5%: mild
- Hydrocortisone cream and ointment 1%: moderate
- Hydrocortisone cream and ointment 0.1%: high

**PRESCRIBING AND DISPENSING INFORMATION**

When hydrocortisone cream or ointment is prescribed and no strength is stated, the 1% strength should be supplied.

**DIODERM**

Although Dioderm® contains only 0.1% hydrocortisone, the formulation is designed to provide a clinical activity comparable to that of Hydrocortisone Cream 1% BP.

**PATIENT AND CARER ADVICE**

Medicines for children leaflet: Hydrocortisone (topical) for eczema

- www.medicinesforchildren.org.uk
  - Hydrocortisone-topical-for-eczema

Patient counselling is advised for hydrocortisone cream and ointment (application).

**PROFESSION SPECIFIC INFORMATION**

Dental practitioners’ formulary: Hydrocortisone Cream 1% 15g may be prescribed.

**EXCEPTIONS TO LEGAL CATEGORY**

- Over-the-counter hydrocortisone preparations: Skin creams and ointments containing hydrocortisone (alone or with other ingredients) can be sold to the public for the treatment of allergic contact dermatitis, irritant dermatitis, insect bite reactions and mild to moderate eczema in patients over 10 years, to be applied sparingly over the affected area 1–2 times daily for max. 1 week. Over-the-counter hydrocortisone preparations should not be sold without medical advice for children under 10 years or for pregnant women; they should not be sold for application to the face, anogenital region, broken or infected skin (including cold sores, acne, and athlete’s foot).
Hydrocortisone with benzalkonium chloride, dimeticone and nystatin

The properties listed below are those particular to the combination only. For the properties of the components please consider, dimeticone p. 1014, hydrocortisone p. 993.

**INDICATIONS AND DOSE**

Mild inflammatory skin disorders such as eczemas

- **TO THE SKIN**
  - Child: Apply 1–2 times a day, to be applied thinly
  - Adult: Apply 1–2 times a day, to be applied thinly

**Potency**

Benzalkonium with dimeticone, hydrocortisone acetate 1%, and nystatin cream: mild.

**PATIENT AND CARER ADVICE**

Patients or carers should be advised on application of benzalkonium with dimeticone and hydrocortisone and nystatin preparations.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Cream**
  - **CAUTIONARY AND ADVISORY LABELS 2B**
  - **EXCIPIENTS:** May contain Benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol), polysorbates
  - **Locoid (Astellas Pharma Ltd)**
    - Hydrocortisone butyrate 1 mg per 1 gram
    - Locoid 0.1% Lipocream | 30 gram £1.69 DT price = £1.60 | 100 gram £5.17 DT price = £4.93
  - **Ointment**
    - **CAUTIONARY AND ADVISORY LABELS 2B**
    - **Locoid (Astellas Pharma Ltd)**
      - Hydrocortisone butyrate 1 mg per 1 gram
      - Locoid 0.1% ointment | 30 gram £1.60 DT price = £1.60 | 100 gram £4.93 DT price = £4.93

Hydrocortisone with chlorhexidine hydrochloride and nystatin

The properties listed below are those particular to the combination only. For the properties of the components please consider, chlorhexidine p. 993.

**INDICATIONS AND DOSE**

Mild inflammatory skin disorders such as eczemas

- **TO THE SKIN**
  - Child: To be applied thinly (consult product literature)
  - Adult: To be applied thinly (consult product literature)

**Potency**

Chlorhexidine hydrochloride 1% with hydrocortisone 0.5% and nystatin cream: mild

Chlorhexidine hydrochloride 1% with hydrocortisone 1% and nystatin ointment: mild

**PATIENT AND CARER ADVICE**

Patients or carers should be given advice on application of chlorhexidine hydrochloride with hydrocortisone and nystatin preparations.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Cream**
  - **CAUTIONARY AND ADVISORY LABELS 2B**
  - **EXCIPIENTS:** May contain Benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol), polysorbates
  - **Locoid (Astellas Pharma Ltd)**
    - Chlorhexidine hydrochloride 10 mg per 1 gram, Hydrocortisone 5 mg per 1 gram, Nystatin 100000 iu per 1 gram
    - Nystaform HC cream | 30 gram £6.66
  - **Ointment**
    - **CAUTIONARY AND ADVISORY LABELS 2B**
    - **Nystaform HC (Thypharm Ltd)**
      - Chlorhexidine acetate 10 mg per 1 gram, Hydrocortisone 10 mg per 1 gram, Nystatin 100000 unit per 1 gram
      - Nystaform HC ointment | 30 gram £2.66

Hydrocortisone with clotrimazole

The properties listed below are those particular to the combination only. For the properties of the components please consider, clotrimazole p. 1010, hydrocortisone p. 993.

**INDICATIONS AND DOSE**

Mild inflammatory skin disorders such as eczemas (associated with fungal infection)

- **TO THE SKIN**
  - Child: (consult product literature)
  - Adult: (consult product literature)

**Potency**

Clotrimazole with hydrocortisone 1% cream: mild

**PATIENT AND CARER ADVICE**

Patients or carers should be given advice on how to administer clotrimazole with hydrocortisone cream.

**EXCEPTIONS TO LEGAL CATEGORY**

A 1.5-g tube is on sale to the public for the treatment of athlete’s foot and fungal infection of skin folds with associated inflammation in patients 10 years and over.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Cream**
  - **CAUTIONARY AND ADVISORY LABELS 2B**
  - **EXCIPIENTS:** May contain Benzyl alcohol, cetostearyl alcohol (including cetyl and stearyl alcohol)
  - **Canesten HC (Bayer Plc)**
    - Clotrimazole 10 mg per 1 gram, Hydrocortisone 10 mg per 1 gram
    - Canesten HC cream | 30 gram £2.42 DT price = £2.42
  - **Brands may include Canesten Hydrocortisone cream**

Hydrocortisone with fusidic acid

The properties listed below are those particular to the combination only. For the properties of the components please consider, fusidic acid p. 956, hydrocortisone p. 993.

**INDICATIONS AND DOSE**

Mild inflammatory skin disorders such as eczemas

- **TO THE SKIN**
  - Child: To be applied thinly (consult product literature)
  - Adult: To be applied thinly (consult product literature)

**Potency**

Hydrocortisone with fusidic acid cream: mild

**PATIENT AND CARER ADVICE**

Patients or carers should be advised on application of hydrocortisone with fusidic acid preparations.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.
Hydrocortisone with miconazole

The properties listed below are those particular to the combination only. For the properties of the components please consider, hydrocortisone p. 993, miconazole p. 1011.

**INDICATIONS AND DOSE**
Mild inflammatory skin disorders such as eczemas associated with infections

TO THE SKIN

- Adult: (consult product literature)
  - Potency
    - Hydrocortisone 1% with miconazole cream and ointment: mild

**INTERACTIONS** → Appendix 1 (antifungals, imidazole).

**PATIENT AND CARER ADVICE** Patients or carers should be advised on application of hydrocortisone with miconazole preparations.

**PROFESSION SPECIFIC INFORMATION**
Dental practitioners' formulary

May be prescribed as Miconazole and Hydrocortisone Cream or Ointment for max. 7 days.

**EXCEPTIONS TO LEGAL CATEGORY** A 15-g tube of hydrocortisone with miconazole cream is on sale to the public for the treatment of athlete's foot and candidal intertrigo.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Cream**

CAUTIONARY AND ADVISORY LABELS  28

EXCIPIENTS: May contain Butylated hydroxyanisole, cetostearyl alcohol (including cetyl and stearyl alcohol), polysorbates, potassium sorbate

- Fucidin H (Fusidic acid / Hydrocortisone) (LEO Pharma)
  - Fusidic acid 20 mg per 1 gram, Hydrocortisone acetate 10 mg per 1 gram Fucidin H cream | 30 gram [POD] £5.02 DT price = £5.02 | 60 gram [POD] £10.04 DT price = £10.04

**Ointment**

CAUTIONARY AND ADVISORY LABELS  28

- Terra-Cortril (Intrapharm Laboratories Ltd)
  - Hydrocortisone 10 mg per 1 gram, Oxytetracycline (as Oxytetracycline hydrochloride) 30 mg per 1 gram Terra-Cortril ointment | 30 gram [POD] £5.01

Hydrocortisone with oxytetracycline

The properties listed below are those particular to the combination only. For the properties of the components please consider, hydrocortisone p. 993, oxytetracycline p. 498.

**INDICATIONS AND DOSE**
Mild inflammatory skin disorders such as eczemas

TO THE SKIN

- Child 12-17 years: (consult product literature)
- Adult: (consult product literature)

**Potency**
Hydrocortisone 1% with oxytetracycline ointment: mild.

**CONTRA-INDICATIONS** Children under 12 years

**PREGNANCY** Tetracyclines should not be given to pregnant women. Effects on skeletal development have been documented when tetracyclines have been used in the first trimester in animal studies. Administration during the second or third trimester may cause discoloration of the child's teeth.

**BREAST FEEDING** Tetracyclines should not be given to women who are breast-feeding (although absorption and therefore discoloration of teeth in the infant is probably usually prevented by chelation with calcium in milk).

**PATIENT AND CARER ADVICE** Patients should be given advice on the application of hydrocortisone with oxytetracycline ointment.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Cream**

CAUTIONARY AND ADVISORY LABELS  28

- Alphaderm (Alliance Pharmaceuticals Ltd)
  - Hydrocortisone 10 mg per 1 gram, Urea 100 mg per 1 gram Alphaderm 1% / 10% cream | 30 gram [POD] £2.38 DT price = £2.38 | 100 gram [POD] £7.03 DT price = £7.03

Mometasone furoate

**INDICATIONS AND DOSE**
Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids | Psoriasis

TO THE SKIN

- Child 2-17 years: Apply once daily, to be applied thinly (to scalp in case of lotion)
- Adult: Apply once daily, to be applied thinly (to scalp in case of lotion)

**Potency**
Mometasone furoate 0.1% cream, ointment, and scalp lotion: potent.

**PATIENT AND CARER ADVICE** Patients and carers should be advised on application of topical mometasone.
Triamcinolone with chlortetracycline

INDICATIONS AND DOSE
Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids (associated with infection) | Psoriasis (associated with infection)

TO THE SKIN
- Child: 8-17 years: To be applied thinly (consult product literature)
- Adult: To be applied thinly (consult product literature)

Potency
Triamcinolone acetonide 0.1%, chlortetracycline hydrochloride 3% ointment: potent.

PATIENT AND CARER ADVICE
Stains clothing. Patients or carers should be counselled on the application of chlortetracycline with triamcinolone products.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Ointment
CAUTIONARY AND ADVISORY LABELS 28
EXCIPIENTS: May contain Wool fat and related substances including lanolin
- Aureocort (AMCo)
  Chlortetracycline hydrochloride 30.9 mg per 1 gram, Triamcinolone acetonide 1 mg per 1 gram Aureocort ointment | 15 gram POM £3.51

Severe Darier’s disease (keratosis follicularis) (under expert supervision)

BY MOUTH
- Adult: Initially 10 mg daily for 2–4 weeks, then adjusted according to response to 25–50 mg daily

CONTRA-INDICATIONS
Hyperlipidaemia

CAUTIONS
Avoid excessive exposure to sunlight and unsupervised use of sunlamps—diabetes (can alter glucose tolerance—initial frequent blood glucose checks) - do not donate blood during and for 2 years after stopping therapy (teratogenic risk) - in children use only in exceptional circumstances and monitor growth parameters and bone development (premature epiphyseal closure reported) - investigate atypical musculoskeletal symptoms

INTERACTIONS
Appendix 1 (retinoids).
Avoid concomitant use of keratolytics.

SIDE-EFFECTS
- Common or very common Abdominal pain - abnormal hair texture - alopecia (reversible on withdrawal) - arthralgia - brittle nails - dermatitis - diarrhoea - dryness and inflammation of mucous membranes - dryness of conjunctiva (causing conjunctivitis and decreased tolerance to contact lenses) - epidermal fragility - erythema - headache - myalgia - nausea - paronychia - peripheral oedema - pruritus - reversible increase in serum-cholesterol (with high doses) - reversible increase in serum-triglyceride concentrations (with high doses) - skin exfoliation - sticky skin - vomiting
- Uncommon Dizziness - hepatitis - photosensitivity - visual disturbances
- Rare Peripheral neuropathy
- Very rare Benign intracranial hypertension - bone pain - exostosis - night blindness - ulcerative keratitis
- Frequently not known Drowsiness - dry skin - flushing - granulomatous lesions - impaired hearing - initial worsening of psoriasis - malaise - rectal haemorrhage - sweating - taste disturbance - tinnitus

SIDE-EFFECTS, FURTHER INFORMATION
Exostosis Skeletal hyperostosis and extra-osseous calcification reported following long-term treatment with etretinate (of which Acitretin is a metabolite) and premature epiphyseal closure in children.

Benign intracranial hypertension Discontinue if severe headache, nausea, vomiting, or visual disturbances occur.

CONCEPTION AND CONTRACEPTION
Effective contraception must be used.

Pregnancy prevention In females of child-bearing potential (including those with a history of infertility), exclude pregnancy up to 3 days before treatment, every month during treatment, and every 1–3 months for 3 years after stopping treatment. Treatment should be started on day 2 or 3 of menstrual cycle. Females of child-bearing age must practise effective contraception for at least 1 month before starting treatment, during treatment, and for at least 3 years after stopping treatment. Females should be advised to use at least 1 method of contraception, but ideally they should use 2 methods of contraception. Oral progestogen-only contraceptives are not considered effective. Barrier methods should not be used alone but can be used in conjunction with other contraceptive methods. Females should be advised to seek medical attention immediately if they become pregnant during treatment or within 3 years of stopping treatment. They should also be advised to avoid alcohol during treatment and for 2 months after stopping treatment.

PREGNANCY
Avoid—teratogenic.

BREAST FEEDING
Avoid.

HEPATIC IMPAIRMENT
Avoid in severe impairment—risk of further impairment.
Alitretinoin

INDICATIONS AND DOSE

Severe chronic hand eczema refractory to potent topical corticosteroids

BY MOUTH

- Adult (prescribed by or under supervision of a consultant dermatologist): 30 mg once daily; reduced if not tolerated to 10 mg once daily for 12–24 weeks total duration of treatment, discontinue if no response after 12 weeks, course may be repeated in those who relapse

Severe chronic hand eczema refractory to potent topical corticosteroids in patients with diabetes, history of hyperlipidaemia, or risk factors for cardiovascular disease

BY MOUTH

- Adult (prescribed by or under supervision of a consultant dermatologist): Initially 10 mg once daily, increased if necessary up to 30 mg once daily for 12–24 weeks total duration of treatment, discontinue if no response after 12 weeks, course may be repeated in those who relapse

CONTRA-INDICATIONS Hypervitaminosis A · uncontrolled hyperlipidaemia · uncontrolled hypothyroidism

CAUTIONS Avoid blood donation during treatment and for at least 1 month after stopping treatment · dry eye syndrome · history of depression

INTERACTIONS → Appendix 1 (retinoids).

SIDE-EFFECTS

- Common or very common Alopecia · anaemia · arthralgia · changes in thyroid function tests · cheilitis · conjunctivitis · dry eyes · dryness of lips · dryness of skin · erythema · eye irritation · flushing · headache · myalgia · raised creatine kinase · raised serum concentration of triglycerides and of cholesterol (risk of pancreatitis if triglycerides above 9 mmol/litre)

- Uncommon Ankylosing spondylitis · asteyotic eczema · blurred vision · cataracts · epistaxis · hyperostosis · pruritus

- Rare Benign intracranial hypertension · vasculitis

- Frequency not known Decreased tolerance to contact lenses · depression · impaired night vision · keratitis · mood changes · suicidal ideation

SIDE-EFFECTS, FURTHER INFORMATION

Dry eyes Dry eyes may respond to lubricating eye ointment or tear replacement therapy.

Benign intracranial hypertension Discontinue treatment if severe headache, nausea, vomiting, papilloedema, or visual disturbances occur.

CONCEPTION AND CONTRACEPTION Effective contraception must be used.

Pregnancy prevention In women of child-bearing potential, exclude pregnancy 1 month before treatment, up to 3 days before treatment, every month during treatment (unless there are compelling reasons to indicate that there is no risk of pregnancy), and 5 weeks after stopping treatment—perform pregnancy test in the first 3 days of the menstrual cycle. Women must practise effective contraception for at least 1 month before starting treatment, during treatment, and for at least 1 month after stopping treatment. Women should be advised to use at least 1 method of contraception but ideally they should use 2 methods of contraception. Oral progestogen-only contraceptives are not considered effective. Barrier methods should not be used alone but can be used in conjunction with other contraceptive methods. Women should be advised to discontinue treatment and to seek prompt medical attention if they become pregnant during treatment or within 1 month of stopping treatment.

- BREAST FEEDING: Manufacturer advises avoid.

- HEPATIC IMPAIRMENT: Manufacturer advises avoid—no information available.

- RENAL IMPAIRMENT: Manufacturer advises avoid in severe impairment—no information available.

- MONITORING REQUIREMENTS: Monitor serum lipids (more frequently in those with diabetes, history of hyperlipidaemia, or risk factors for cardiovascular disease)—discontinue if uncontrolled hyperlipidaemia.

PRESCRIBING AND DISPENSING INFORMATION

Prescribing for women of child-bearing potential. Each prescription for alitretinoin should be limited to a supply of up to 30 days’ treatment and dispensed within 7 days of the date stated on the prescription. Alitretinoin is teratogenic and must not be given to women of child-bearing potential unless they practise effective contraception and then only after detailed assessment and explanation by the physician.

PATIENT AND CARER ADVICE A patient information leaflet should be provided. Females of child-bearing potential must be advised on pregnancy prevention.

NATIONAL FUNDING/ACCESS DECISIONS

NICE technology appraisals (TAs)

- Alitretinoin for the treatment of severe chronic hand eczema in adults (August 2009) NICE TA177

Alitretinoin is recommended for the treatment of severe chronic hand eczema that has not responded to potent topical corticosteroids. Treatment should be stopped as soon as an adequate response has been achieved (hands clear or almost clear), or if the eczema remains severe after 12 weeks, or if an adequate response has not been achieved by 24 weeks. www.nice.org.uk/TA177

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.
1034 Inflammatory skin conditions

Salicylic Acid Paste, BP (Lassar’s Paste), zinc oxide 24%, salicylic acid 2%, starch 24%, white soft paraffin 50%.

> MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ointment, paste

### TARS

#### Coal tar

**INDICATIONS AND DOSE**
Psoriasis | Seborrhoeic dermatitis | Scaling | Itching
TO THE SKIN
> Adult: Apply 2–3 times a day

**CONTRA-INDICATIONS**
Avoid broken or inflamed skin • avoid eye area • avoid genital area • avoid mucosal areas • avoid rectal area • infection • sore, acute, or pustular psoriasis

> MEDICATION FORMS
Application to face • application to skin flexures

**SIDE-EFFECTS**
Acne-like eruptions • photosensitivity • skin irritation

**PRESCRIBING AND DISPENSING INFORMATION**
When prepared extemporaneously, the BP states Coal Tar Solution: BP contains coal tar 20%; Strong Coal Tar Solution: BP contains coal tar 40%.

**HANDLING AND STORAGE**
Use suitable chemical protection gloves for extemporaneous preparation. May stain skin, hair and fabric.

> PATIENT AND CARER ADVICE
May stain skin, hair and fabric.

> MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: paste, cream, ointment

#### Bath additive
COAL TAR (Non-proprietary)
Coal tar distilled 400 mg per 1 ml Psoriderm Emulsion 40% bath additive | 200 ml £2.74

#### Shampoo
EXCIPIENTS: May contain Fragrances, hydroxybenzoates (parabens)
COAL TAR (Non-proprietary)
Coal tar extract 20 mg per 1 gram Coal tar extract 2% shampoo
125 ml GSK no price available
250 ml GSK no price available

Brands may include Alphosyl 2 in 1, Neutrogena T/Gel Therapeutic
**Cutaneous emulsion**

EXCIPIENTS: May contain Hydroxybenzoates (parabens)

- Exorex (Forest Laboratories UK Ltd)
  - Coal tar solution 50 mg per 1 gram. Exorex lotion | 100 ml £8.11  250 ml £16.24

**Coal tar with cade oil, arachis oil extract of coal tar, light liquid paraffin and tar**

The properties listed below are those particular to the combination only. For the properties of the components please consider, coal tar p. 1034.

*INDICATIONS AND DOSE*

Psoriasis | Eczema | Atopic dermatoses | Pruritic dermatoses

TO THE SKIN

- Child: 2–4 capfuls/bath, alternatively 15–30 mL, to be added in an adult-size bath and soak for 20 minutes (proportionally less for a child’s bath)
- Adult: 2–4 capfuls/bath, alternatively 15–30 mL, to be added in an adult-size bath and soak for 20 minutes (proportionally less for a child’s bath)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Bath additive**

EXCIPIENTS: May contain Isopropyl palmitate

- Polytar (GlaxoSmithKline Consumer Healthcare)
  - Arachis oil extract of crude coal tar 75 mg per 1 gram, Cade oil 75 mg per 1 gram, Coal tar solution 25 mg per 1 gram, Liquid paraffin light 350 mg per 1 gram, Pine tar 75 mg per 1 gram Polytar Emollient | 500 ml £5.78

**Coal tar with calamine**

The properties listed below are those particular to the combination only. For the properties of the components please consider, coal tar p. 1034.

*INDICATIONS AND DOSE*

Psoriasis | Chronic atopic eczema (occasionally)

TO THE SKIN

- Adult: Apply 1–2 times a day

**PRESCRIBING AND DISPENSING INFORMATION**

When prepared extemporaneously, the BP states Calamine and Coal Tar Ointment, BP consists of calamine 12.5 g, strong coal tar solution 2.5 g, zinc oxide 12.5 g, hydrous wool fat 25 g, white soft paraffin 47.5 g.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ointment

**Coal tar with coconut oil and salicylic acid**

The properties listed below are those particular to the combination only. For the properties of the components please consider, salicylic acid p. 1057, coal tar p. 1034.

*INDICATIONS AND DOSE*

Scaly scalp disorders | Psoriasis | Seborrhoeic dermatitis | Dandruff | Cradle cap

TO THE SKIN USING SHAMPOO

- Child: Apply daily as required
- Adult: Apply daily as required

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Shampoo**

- Capasal (Dermal Laboratories Ltd)
  - Coal tar distilled 10 mg per 1 gram, Coconut oil 10 mg per 1 gram, Salicylic acid 5 mg per 1 gram Capasal Therapeutic shampoo | 250 ml £4.69

**Coal tar with dithranol and salicylic acid**

The properties listed below are those particular to the combination only. For the properties of the components please consider, dithranol p. 1018, salicylic acid p. 1057, coal tar p. 1034.

*INDICATIONS AND DOSE*

Subacute and chronic psoriasis

TO THE SKIN

- Child: Apply up to twice daily
- Adult: Apply up to twice daily

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ointment

**Coal tar with lecithin**

The properties listed below are those particular to the combination only. For the properties of the components please consider, coal tar p. 1034.

*INDICATIONS AND DOSE*

PSORIDERM® CREAM

Psoriasis

TO THE SKIN

- Child: Apply 1–2 times a day, cream to be applied to the skin or scalp
- Adult: Apply 1–2 times a day, cream to be applied to the skin or scalp

PSORIDERM® SCALP LOTION

Scalp psoriasis

TO THE SKIN

- Child: Apply as required
- Adult: Apply as required

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Cream**

EXCIPIENTS: May contain Isopropyl palmitate, propylene glycol

- COAL TAR WITH LECITHIN (Non-proprietary)
  - Coal tar distilled 60 mg per 1 gram, Lecithin 4 mg per 1 gram Psoriderm cream | 225 ml £9.42

**Shampoo**

EXCIPIENTS: May contain Disodium edetate

- COAL TAR WITH LECITHIN (Non-proprietary)
  - Coal tar distilled 25 mg per 1 mL, Lecithin 3 mg per 1 mL Psoriderm scalp lotion | 250 ml £4.74

**Coal tar with salicylic acid**

The properties listed below are those particular to the combination only. For the properties of the components please consider, salicylic acid p. 1057, coal tar p. 1034.

*INDICATIONS AND DOSE*

Psoriasis | Chronic atopic eczema

TO THE SKIN USING OINTMENT

- Child: Apply 1–2 times a day
**Coal tar with salicylic acid and precipitated sulfur**

The properties listed below are those particular to the combination only. For the properties of the components please consider, salicylic acid p. 1034.

**INDICATIONS AND DOSE**

**COCOIS® OINTMENT**

Scaly scalp disorders including psoriasis, eczema, seborrhoeic dermatitis and dandruff

**INITIALLY TO THE SKIN USING SCALP OINTMENT**
- Child 6–11 years: Medical supervision required
- Child 12–17 years: Apply once weekly as required, alternatively (to the skin) apply daily for the first 3–7 days (if severe), shampoo off after 1 hour
- Adult: Apply once weekly as required, alternatively (to the skin) apply daily for the first 3–7 days (if severe), shampoo off after 1 hour

**SEBCO® OINTMENT**

Scaly scalp disorders including psoriasis, eczema, seborrhoeic dermatitis and dandruff

**INITIALLY TO THE SKIN USING SCALP OINTMENT**
- Adult: Apply as required, alternatively (to the skin) apply daily for the first 3–7 days (if severe), shampoo off after 1 hour

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: ointment, paste, liquid, shampoo, solution.

**Extract of coal tar with arachis oil**

The properties listed below are those particular to the combination only. For the properties of the components please consider, coal tar p. 1034.

**INDICATIONS AND DOSE**

**Scalp disorders** | **Psoriasis** | **Seborrhoea** | **Eczema** | **Pruritus** | **Dandruff**
--- | --- | --- | --- | --- | ---
**TO THE SKIN**
- Child: Apply 1–2 times a week, to the scalp
- Adult: Apply 1–2 times a week, to the scalp

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Shampoo**
- **Polytar** (GlaxoSmithKline Consumer Healthcare)
  - Arachis oil extract of crude coal tar 3 mg per 1 gram, Cade oil
  - Coal tar solution 1 mg per 1 gram, Pine tar
  - Polytar Plus (GlaxoSmithKline Consumer Healthcare)
  - Arachis oil extract of crude coal tar 3 mg per 1 gram, Cade oil
  - Coal tar solution 1 mg per 1 gram, Pine tar

**VITAMIN D AND ANALOGUES**

**Calcipotriol**

**INDICATIONS AND DOSE**

**Plaque psoriasis**

**TO THE SKIN USING OINTMENT**
- Adult: Apply 1–2 times a day, when preparations are used together maximum total calcipotriol 5 mg in any one week (e.g. scalp solution 60 ml with ointment 30 g or scalp solution 30 mL with ointment 60 g); maximum 100 g per week

**Scalp psoriasis**

**TO THE SKIN USING SCALP LOTION**
- Adult: Apply twice daily, when preparations are used together maximum total calcipotriol 5 mg in any one week (e.g. scalp solution 60 ml with ointment 30 g or scalp solution 30 mL with ointment 60 g); maximum 60 mL per week

**CONTRA-INDICATIONS**

Calcium metabolism disorders

**CAUTIONS**

Avoid excessive exposure to sunlight and sunlamps: avoid use on face · erythrodemic exfoliative psoriasis (enhanced risk of hypercalcaemia) · generalised pustular psoriasis (enhanced risk of hypercalcaemia)

**SIDE-EFFECTS**
- **Common or very common** Burning · dermatitis · erythema · itching · local skin reactions · paraesthesia
- **Rare** Facial dermatitis · perioral dermatitis
- **Frequency not known** Aggravation of psoriasis · dry skin · photosensitivity

**PREGNANCY**

Manufacturers advise avoid unless essential.

**BREAST FEEDING**

No information available.
Calcipotriol with betamethasone

The properties listed below are those particular to the combination only. For the properties of the components please consider, betamethasone p. 993, calcipotriol p. 1036.

INDICATIONS AND DOSE

DOVOBET® GEL

Scalp psoriasis

TO THE SKIN

► Adult: Apply 1–4 g once daily usual duration of therapy 4 weeks; if necessary, treatment may be continued beyond 4 weeks or repeated, on the advice of a specialist, shampoo off after leaving on scalp overnight or during day, when different preparations containing calcipotriol used together, maximum total calcipotriol 5 mg in any one week

Mild to moderate plaque psoriasis

TO THE SKIN

► Adult: Apply once daily for 8 weeks; if necessary, treatment may be continued beyond 8 weeks or repeated, on the advice of a specialist, apply to maximum 30% of body surface, when different preparations containing calcipotriol used together, max. total calcipotriol 5 mg in any one week; maximum 15 g per day

DOVOBET® OINTMENT

Stable plaque psoriasis

TO THE SKIN

► Adult: Apply once daily for 4 weeks; if necessary, treatment may be continued beyond 4 weeks or repeated, on the advice of a specialist, apply to a maximum 30% of body surface, when different preparations containing calcipotriol used together, max. total calcipotriol 5 mg in any one week; maximum 15 g per day

Calcitriol

(1,25-Dihydroxycholecalciferol)

INDICATIONS AND DOSE

Mild to moderate plaque psoriasis

TO THE SKIN

► Adult: Apply twice daily, not more than 35% of body surface to be treated daily; maximum 30 g per day

CONTRA-INDICATIONS

Do not apply under occlusion - patients with calcium metabolism disorders

CAUTIONS

Erythrodermic exfoliative psoriasis (enhanced risk of hypercalcemia) - generalised pustular psoriasis (enhanced risk of hypercalcemia)

SIDE-EFFECTS

► Common or very common Burning - dermatitis - erythema - itching - local skin reactions - paraesthesia

► Frequency not known Aggravation of psoriasis

PREGNANCY

Manufacturer advises use in restricted amounts only if clearly necessary. Monitor urine- and serum-calcium concentration in pregnancy.

BREAST FEEDING

Manufacturer advises avoid.

HANDLING AND STORAGE

Hands should be washed thoroughly after application to avoid inadvertent transfer to other body areas.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Ointment

CAUTIONARY AND ADVISORY LABELS 28

EXCIPIENTS: May contain Butylated hydroxytoluene

► Dovobet (LEO Pharma)

Betamethasone (as Betamethasone dipropionate) 500 microgram per 1 gram, Calcipotriol (as Calcipotriol monohydrate) 50 microgram per 1 gram Dovobet ointment | 30 gram (£8.99) £10.20 DT price = £10.95 | 60 gram (£8.26) £19.84 | 120 gram (£7.38) £37.86

Tacalcitol

INDICATIONS AND DOSE

Plaque psoriasis

TO THE SKIN

► Adult: Apply once daily, preferably at bedtime, maximum 10 g ointment or 10 mL lotion daily, when lotion and ointment used together, maximum total tacalcitol 280 micrograms in any one week (e.g. lotion 30 mL with ointment 40 g)

CONTRA-INDICATIONS

Calcium metabolism disorders

CAUTIONS

Avoid eyes - erythrodermic exfoliative psoriasis (enhanced risk of hypercalcemia) - generalised pustular psoriasis (enhanced risk of hypercalcemia) - if used in conjunction with UV treatment

CAUTIONS, FURTHER INFORMATION

UV treatment If tacalcitol is used in conjunction with UV treatment, UV radiation should be given in the morning and tacalcitol applied at bedtime.

SIDE-EFFECTS

► Common or very common Burning - dermatitis - erythema - itching - local skin reactions - paraesthesia

► Frequency not known Aggravation of psoriasis
4 Perspiration

Antiperspirants

Aluminium chloride hexahydrate below is a potent antiperspirant used in the treatment of hyperhidrosis. Aluminium salts are also incorporated in preparations used for minor fungal skin infections associated with hyperhidrosis.

In more severe cases specialists use glycopyrronium bromide as a 0.05% solution below in the iontophoretic treatment of hyperhidrosis of plantar and palmar areas. *Botox*® contains botulinum toxin type A complex p. 322 and is licensed for use intradermally for severe hyperhidrosis of the axillae unresponsive to topical antiperspirant or other antihidrotic treatment.

4.1 Hyperhidrosis

Aluminium chloride hexahydrate

**INDICATIONS AND DOSE**

Hyperhidrosis affecting axillae, hands or feet

**TO THE SKIN**

- Adult: Apply once daily, apply liquid formulation at night to dry skin, wash off the following morning, reduce frequency as condition improves—do not bathe immediately before use

Hyperhidrosis | Bromidrosis | Intertrigo | Prevention of tinea pedis and related conditions

**TO THE SKIN**

- Adult: Apply powder to dry skin

**SIDE-EFFECTS**

- Skin irritation

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Liquid**

- **Aluminium chloride hexahydrate (Non-proprietary)**
  - Aluminium chloride 200 mg per 1 ml
  - **Spray**
    - Driclor
    - Anhydrol

**Spray**

- **Aluminium chloride hexahydrate (Non-proprietary)**
  - Aluminium chloride 200 mg per 1 ml

**Ointment**

- **Curatoderm (Almirall Ltd)**
  - Tacalcitol (as Tacalcitol monohydrate) 4 microgram per 1 gram
  - **Liquid**
    - Curatoderm (Almirall Ltd)
      - Tacalcitol (as Tacalcitol monohydrate) 4 microgram per 1 gram

**Powder**

- **Odaban** (Bracey’s Pharmaceuticals Ltd)
  - Aluminium chloride 200 mg per 1 ml Odaban 20% spray | 30 ml | £6.69

**EXCEPTIONS TO LEGAL CATEGORY**

A 30 mL pack of aluminium chloride hexahydrate 20% is on sale to the public.

**CAUTIONS**

- Monitor serum calcium if the possibility of systemic side-effects should be considered; however, glycopyrronium is poorly absorbed and systemic effects unlikely with topical use.

**SIDE-EFFECTS**

- Tingling at administration site

**CONTRA-INDICATIONS, FURTHER INFORMATION**

The possibility of systemic side-effects should be considered; however, glycopyrronium is poorly absorbed and systemic effects unlikely with topical use.

**PATIENT AND CARER ADVICE**

Avoid contact with clothing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Liquid**

- **Aluminium chloride hexahydrate (Non-proprietary)**
  - Aluminium chloride 200 mg per 1 ml
  - **Spray**
    - Driclor
    - Anhydrol
  - **Ointment**
    - Curatoderm (Almirall Ltd)
      - Tacalcitol (as Tacalcitol monohydrate) 4 microgram per 1 gram

**Powder**

- **Odaban** (Bracey’s Pharmaceuticals Ltd)
  - Aluminium chloride 200 mg per 1 ml Odaban 20% spray | 30 ml | £6.69

**EXCEPTIONS TO LEGAL CATEGORY**

A 30 mL pack of aluminium chloride hexahydrate 20% is on sale to the public.

**CAUTIONS**

- Monitor serum calcium if the possibility of systemic side-effects should be considered; however, glycopyrronium is poorly absorbed and systemic effects unlikely with topical use.

**SIDE-EFFECTS**

- Tingling at administration site

**CONTRA-INDICATIONS, FURTHER INFORMATION**

The possibility of systemic side-effects should be considered; however, glycopyrronium is poorly absorbed and systemic effects unlikely with topical use.

**PATIENT AND CARER ADVICE**

Avoid contact with clothing.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Liquid**

- **Aluminium chloride hexahydrate (Non-proprietary)**
  - Aluminium chloride 200 mg per 1 ml
  - **Spray**
    - Driclor
    - Anhydrol
5 Photodamage

Photodamage

Patients should be advised to use a high-SPF sunscreen and to minimise exposure of the skin to direct sunlight or sun lamps.

Topical treatments can be used for actinic keratosis. An emollient may be sufficient for mild lesions. Diclofenac sodium p. 521 is suitable for the treatment of superficial lesions in mild disease. Fluorouracil cream p. 761 is effective against most types of non-hypertrophic actinic keratosis; a solution containing fluorouracil and salicylic acid is available for the treatment of low or moderately thick keratosis; a solution containing fluorouracil and salicylic acid is effective against most types of non-hypertrophic actinic keratosis. Imiquimod p. 1057 is used for lesions on the face and scalp when cryotherapy or other topical treatments cannot be used. Fluorouracil and imiquimod produce a more marked inflammatory reaction than diclofenac but lesions resolve faster. A short course of ingenol mebutate below is licensed for the treatment of non-hypertrophic actinic keratosis; response to treatment can usually be assessed 8 weeks after the course. Photodynamic therapy in combination with methyl-5-aminolevulinate cream (Metvix, available from Galderma) or 5-aminolevulinic acid gel (Ameluz, available from Spirit Healthcare) is used in specialist centres for treating superficial and confluent, non-hypertrophic actinic keratosis; when other treatments are inadequate or unsuitable; it is particularly suitable for multiple lesions, for periorbital lesions, or for lesions located at sites of poor healing.

Imiquimod or topical fluorouracil is used for treating superficial basal cell carcinomas. Photodynamic therapy in combination with methyl-5-aminolevulinate cream is used in specialist centres for treating superficial, nodular basal cell carcinomas where other treatments are unsuitable.

ANTIMETABOLITES

Fluorouracil

INDICATIONS AND DOSE

Superficial malignant and pre-malignant skin lesions

TO THE SKIN USING CREAM

Adult: Apply 1–2 times a day for 3–4 weeks (usual duration of initial therapy), apply thinly to the affected area, maximum area of skin 500 cm² (e.g. 23 cm x 23 cm) treated at one time, alternative regimens may be used in some settings.

• CAUTIONS Avoid contact with eyes and mucous membranes - do not apply to bleeding lesions
• SIDE-EFFECTS Erythema multiforme - local irritation (use a topical corticosteroid for severe discomfort associated with inflammatory reactions) - photosensitivity
• PREGNANCY Manufacturers advise avoid (teratogenic).
• BREAST FEEDING Manufacturers advise avoid.

• MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Cream

EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), hydroxybenzoates (parabens), polysorbates, propylene glycol

Efudix (Meda Pharmaceuticals Ltd)

Fluorouracil 50 mg per 1 gram Efudix 5% cream | 40 gram (£22.90, 750 mg/gram (£32.50))

Fluorouracil with salicylic acid

The properties listed below are those particular to the combination only. For the properties of the components please consider, fluorouracil p. 761, salicylic acid p. 1057.

INDICATIONS AND DOSE

Low or moderately thick hyperkeratotic actinic keratosis

TO THE SKIN

• Adult: Apply once daily for up to 12 weeks, reduced to 3 times a week if severe side effects occur and until side-effects improve, to be applied to the affected area, if treating area with thin epidermis, reduce frequency of application and monitor response more often; maximum area of skin treated at one time, 25 cm² (e.g. 5 cm x 5 cm)

• MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Cutaneous solution

CAUTIONARY AND ADVISORY LABELS 15

• Actikerall (Almirall Ltd)

Fluorouracil 5 mg/g, Salicylic acid 100 mg/g Actikerall 5mg/g / 100mg/g cutaneous solution | 25 ml (P)£38.30

PROTEIN KINASE C ACTIVATORS

Ingenol mebutate

INDICATIONS AND DOSE

Actinic keratosis on face and scalp

TO THE SKIN

• Adult: Apply once daily for 3 days, use the 150 microgram/g gel (Picato)

Actinic keratosis on trunk and extremities

TO THE SKIN

• Adult: Apply once daily for 2 days, use the 500 microgram/g gel (Picato)

• CAUTIONS Avoid contact with broken skin - avoid contact with inside of ears - avoid contact with inside of nostrils - avoid contact with lips - avoid occlusive dressings on treated area

• SIDE-EFFECTS

• Common or very common Blistering - crusting - erosion - erythema - exfoliation - headache - infection - local reactions - oedema - pain - pruritus

• Uncommon Local ulceration - paraesthesia

• PREGNANCY Not absorbed from skin, but manufacturer advises avoid.

• BREAST FEEDING Not absorbed from skin; ensure infant does not come in contact with treated area for 6 hours after application.

• DIRECTIONS FOR ADMINISTRATION One tube covers skin area of 25 cm². Allow gel to dry on treatment area for 15 minutes. Avoid washing or touching the treated area for 6 hours after application; after this time, area may be washed with mild soap and water. Avoid use immediately after shower or less than 2 hours before bedtime.

• MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Gel

CAUTIONARY AND ADVISORY LABELS 15

• Picato (LEO Pharma)

Ingenol mebutate 150 microgram per 1 gram Picato 150micrograms/g gel | 1.41 gram (P)£65.00

Ingenol mebutate 500 microgram per 1 gram Picato 500micrograms/g gel | .94 gram (P)£65.00
6 Pruritus

Topical local antipruritics

Pruritus may be caused by systemic disease (such as obstructive jaundice, endocrine disease, chronic renal disease, iron deficiency, and certain malignant diseases), skin disease (e.g. psoriasis, eczema, urticaria, and scabies), drug hypersensitivity, or as a side-effect of opioid analgesics. Where possible, the underlying causes should be treated. An emollient may be of value where the pruritus is associated with dry skin. Pruritus that occurs in otherwise healthy elderly people can also be treated with an emollient.

Levomenthol cream below can be used to relieve pruritus; it exerts a cooling effect on the skin. Local antipruritics have a role in the treatment of pruritus in palliative care.

Preparations containing crotamiton below are sometimes used but are of uncertain value. Preparations containing calamine are often ineffective.

A topical preparation containing doxepin 5% below is licensed for the relief of pruritus in eczema; it can cause drowsiness and there may be a risk of sensitisation.

Pruritus is common in biliary obstruction, especially in primary biliary cirrhosis and drug-induced cholestasis. Oral administration of colestyramine p. 173 is the treatment of choice.

Topical antihistamines and local anaesthetics are only marginally effective and occasionally cause hypersensitivity. For insect stings and insect bites, a short course of a topical corticosteroid is appropriate. Short-term treatment with a sedating antihistamine may help in insect stings and in intractable pruritus where sedation is desirable. Calamine preparations are of little value for the treatment of insect stings or bites and are no longer widely available.

Topical local anaesthetics are indicated for the relief of local pain. Preparations may be absorbed, especially through mucosal surfaces, therefore excessive application should be avoided and they should preferably not be used for more than 3 days; not generally suitable for young children and are less suitable for prescribing.

Topical antihistamines should be avoided in eczema and are not recommended for longer than 3 days. They are less suitable for prescribing.

Antipruritics

Crotamiton

INDICATIONS AND DOSE
Pruritus (including pruritus after scabies)

TO THE SKIN

▶ Child 1 month–2 years (on doctor’s advice only): Apply once daily
▶ Child 3–17 years: Apply 2–3 times a day
▶ Adult: Apply 2–3 times a day

CONTRA-INDICATIONS Acute exudative dermatoses

CAUTIONS Avoid use in buccal mucosa · avoid use near eyes · avoid use on broken skin · avoid use on very inflamed skin · use on doctor’s advice for children under 3 years

PREGNANCY Manufacturer advises avoid, especially during the first trimester—no information available.

BREAST FEEDING No information available; avoid application to nipple area.

MENDELC FORMS
There can be variation in the licensing of different medicines containing the same drug.

Doxepin

INDICATIONS AND DOSE
Pruritus in eczema

TO THE SKIN

▶ Child 12–17 years: Apply up to 3 g 3–4 times a day, apply thinly; coverage should be less than 10% of body surface area; maximum 12 g per day
▶ Adult: Apply up to 3 g 3–4 times a day, apply thinly; coverage should be less than 10% of body surface area; maximum 12 g per day

CAUTIONS Avoid application to large areas · cardiac arrhythmias · mania · severe heart disease · susceptibility to angle-closure glaucoma · urinary retention

SIDE-EFFECTS

▶ Common or very common Dizziness · drowsiness
▶ Frequency not known Antimuscarinic effects · fever · gastro-intestinal disturbances · headache · irritation · local burning · rash · stinging · tingling

PREGNANCY Manufacturer advises use only if potential benefit outweighs risk.

BREAST FEEDING Manufacturer advises use only if potential benefit outweighs risk.

HEPATIC IMPAIRMENT Manufacturer advises caution in severe liver disease.

PATIENT AND CARER ADVICE Drowsiness may affect performance of skilled tasks (e.g. driving). Effects of alcohol enhanced. A patient information leaflet should be provided.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Cream

CAUTIONARY AND ADVISORY LABELS 2, 10

EXCIPIENTS: May contain Benzyl alcohol

▶ Xepin (Cambridge Healthcare Supplies Ltd)

Doxepin hydrochloride 50 mg per 1 gram Xepin 5% cream 14 g

Menthyl and derivatives

Levomenthol

INDICATIONS AND DOSE
Pruritus

TO THE SKIN

▶ Adult: Apply 1–2 times a day

PRESCRIBING AND DISPENSING INFORMATION When prepared extemporaneously, the BP states Levomenthol cream, BP (Menthol in Aqueous Cream) consists of levomenthol 0.5%.

MENDELC FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: cream
Rosacea and acne

7 Rosacea and acne

Acne

Treatment of acne should be commenced early to prevent scarring. Patients should be counselled that an improvement may not be seen for at least a couple of months. The choice of treatment depends on whether the acne is predominantly inflammatory or comedonal and its severity.

Mild to moderate acne is generally treated with topical preparations. Systemic treatment with oral antibiotics is generally used for moderate to severe acne or where topical preparations are not tolerated or are ineffective or where application to the site is difficult. Another oral preparation used for acne is the hormone treatment co-cyprindiol (cyproterone acetate with ethinylestradiol p. 1042); it is for women only.

Severe acne, acne unresponsive to prolonged courses of oral antibacterials, scarring, or acne associated with psychological problems calls for early referral to a consultant dermatologist who may prescribe isotretinoin p. 1045 for administration by mouth.

Topical preparations for acne

In mild to moderate acne, comedones and inflamed lesions respond well to benzoyl peroxide p. 1044 or to a topical retinoid. Alternatively, topical application of an antibacterial such as erythromycin p. 1043 or clindamycin p. 467 may be effective for inflammatory acne. If topical preparations prove inadequate, oral preparations may be needed.

Benzoyl peroxide and azelaic acid

Benzoyl peroxide p. 1044 is effective in mild to moderate acne. Both comedones and inflamed lesions respond well to benzoyl peroxide. The lower concentrations seem to be as effective as higher concentrations in reducing inflammation. It is usual to start with a lower strength and to increase the concentration of benzoyl peroxide gradually. Adverse effects include local skin irritation, particularly when therapy is initiated, but the scaling and redness often subside with treatment continued at a reduced frequency of application. If the acne does not respond after 2 months then use of a topical antibacterial should be considered.

Azelaic acid p. 1043 has antimicrobial and anticomedonal properties. It may be an alternative to benzoyl peroxide or to a topical retinoid for treating mild to moderate comedonal acne, particularly of the face. Some patients prefer azelaic acid because it is less likely to cause local irritation than benzoyl peroxide.

Topical antibacterials for acne

For many patients with mild to moderate inflammatory acne, topical antibacterials may be no more effective than topical benzoyl peroxide or tretinoin. Topical antibacterials are probably best reserved for patients who wish to avoid oral antibacterials or who cannot tolerate them. Topical preparations of erythromycin p. 1043 and clindamycin p. 467 are effective for inflammatory acne. Topical antibacterials can produce mild irritation of the skin, and on rare occasions cause sensitisation; gastro-intestinal disturbances have been reported with topical clindamycin.

Antibacterial resistance of Propionibacterium acnes is increasing; there is cross-resistance between erythromycin and clindamycin. To avoid development of resistance:

- when possible use non-antibiotic antimicrobials (such as benzoyl peroxide or azelaic acid);
- avoid concomitant treatment with different oral and topical antibacterials;
- if a particular antibacterial is effective, use it for repeat courses if needed (short intervening courses of benzoyl peroxide or azelaic acid may eliminate any resistant propionibacteria);
- do not continue treatment for longer than necessary (however, treatment with a topical preparation should be continued for at least 6 months).

Some manufacturers of topical antibacterial preparations for acne advise that preparations containing alcohol are not suitable for use with benzoyl peroxide.

Topical retinoids and related preparations for acne

Topical tretinoin p. 765, its isomer isotretinoin p. 1045, and adapalene p. 1045 (a retinoid-like drug) are useful for treating comedones and inflammatory lesions in mild to moderate acne. Several months of treatment may be needed to achieve an optimal response and the treatment should be continued until no new lesions develop. Isotretinoin is given by mouth in severe acne.

Other topical preparations for acne

Preparations containing aluminium oxide p. 1042 are not considered beneficial in acne. A topical preparation of nicotinamide p. 1048 is available for inflammatory acne.

Oral preparations for acne

Systemic antibacterial treatment is useful for inflammatory acne if topical treatment is not adequately effective or if it is inappropriate. Anticomendonal treatment (e.g. with topical benzoyl peroxide p. 1044) may also be required. Either oxytetracycline p. 498 or tetracycline p. 498 is usually given for acne. If there is no improvement after the first 3 months another oral antibacterial should be used. Maximum improvement usually occurs after 4 to 6 months but in more severe cases treatment may need to be continued for 2 years or longer.

Doxycycline p. 995 and lymecycline p. 497 are alternatives to tetracycline.

Although minocycline p. 498 is as effective as other tetracyclines for acne, it is associated with a greater risk of lupus erythematosus-like syndrome. Minocycline sometimes causes irreversible pigmentation; it is given in a once or twice daily dose.

Erythromycin p. 1043 in a twice daily dose is an alternative for the management of acne but propionibacteria strains resistant to erythromycin are becoming widespread and this may explain poor response.

Trimethoprim p. 462 may be used for acne resistant to other antibacterials [unlicensed indication]. Prolonged treatment with trimethoprim may depress haematopoiesis; it should generally be initiated by specialists. Concomitant use of different topical and systemic antibacterials is undesirable owing to the increased likelihood of the development of bacterial resistance.

Hormone treatment for acne

Co-cyprindiol (cyproterone acetate with ethinylestradiol p. 1042) contains an anti-androgen. It is licensed for use in women with moderate to severe acne that has not...
responded to topical therapy or oral antibacterials, and for moderately severe hirsutism. Although it is an effective hormonal contraceptive, it should not be used solely for contraception.

Improvement of acne with co-cyprindiol probably occurs because of decreased sebum secretion which is under androgen control. Some women with moderately severe hirsutism may also benefit because hair growth is also androgen-dependent.

**Oral retinoid for acne**

The retinoid isotretinoin p. 1045 reduces sebum secretion. It is used for the systemic treatment of nodulo-cystic and conglobate acne, severe acne, scarring, acne which has not responded to an adequate course of a systemic antibacterial, or acne which is associated with psychological problems. It is also useful in women who develop acne in the third or fourth decades of life, since late onset acne is frequently unresponsive to antibacterials.

Isotretinoin is a toxic drug that should be prescribed only by, or under the supervision of, a consultant dermatologist. It is given for at least 15 weeks; repeat courses are not normally required.

Side-effects of isotretinoin include severe dryness of the skin and mucous membranes, nose bleeds, and joint pains. The drug is **teratogenic** and must not be given to women of child-bearing age unless they practise effective contraception (oral progestogen-only contraceptives not considered effective) and then only after detailed assessment and explanation by the physician. Women must also be registered with a pregnancy prevention programme.

Although a causal link between isotretinoin use and psychiatric changes (including suicidal ideation) has not been established, the possibility should be considered before initiating treatment; if psychiatric changes occur during treatment, isotretinoin should be stopped, the prescriber informed, and specialist psychiatric advice should be sought.

**Rosacea**

Rosacea is not comedonal (but may exist with acne which may be comedonal). Brimonidine tartrate p. 1048 is licensed for the treatment of facial erythema in rosacea. The pustules and papules of rosacea respond to topical metronidazole p. 1008 or to topical azelaic acid p. 1043. Alternatively oral administration of oxytetracycline p. 498 or tetracycline p. 498, or erythromycin p. 1043, can be used; courses usually last 6–12 weeks and are repeated intermittently. Doxycycline p. 995 can be used [unlicensed indication] if oxytetracycline or tetracycline is inappropriate (e.g. in renal impairment). A modified-release preparation of doxycycline is licensed in low daily doses for the treatment of facial rosacea. Isotretinoin p. 1045 is occasionally given in refractory cases [unlicensed indication]. Camouflagers may be required for the redness.

### 7.1 Acne

**ABRASIVE AGENTS**

**Aluminium oxide**

**INDICATIONS AND DOSE**

**Acne vulgaris**

**To the skin**

- **Adult:** Apply 1–3 times a day, to be used instead of soap

**SIDE-EFFECTS** Skin irritation (discontinue use temporarily)

**TREATMENT CESSATION** Discontinue use temporarily if skin becomes irritated.

**LESS SUITABLE FOR PRESCRIBING** Less suitable for prescribing (not considered beneficial).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Paste**

EXCIPIENTS: May contain Fragrances, n-(3-chloroallyl)hexaminium chloride (quaternium 15).

- Brasivol (GliaxSmithKline Consumer Healthcare)
  - Aluminium oxide 380 mg per 1 gram Brasivol Fine No.1 38% paste | 7 ggram Dice 12.76

**ANTI-ANDROGENS**

**Co-cyprindiol**

**INDICATIONS AND DOSE**

Moderate to severe acne in women of child-bearing age refractory to topical therapy or oral antibacterials

**Moderately severe hirsutism**

**BY MOUTH**

- Females of childbearing potential: 1 tablet daily for 21 days, to be started on day 1 of menstrual cycle; subsequent courses repeated after a 7–day interval (during which withdrawal bleeding occurs), time to symptom remission, at least 3 months; review need for treatment regularly

**CONTRA-INDICATIONS** Acute porphyria · gallstones · heart disease associated with pulmonary hypertension or risk of embolus · history during pregnancy of cholestatic jaundice · history during pregnancy of chorea · history during pregnancy of pemphigoid gestationis · history during pregnancy of pruritus · history of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal methods unacceptable · history of haemolytic uraemic syndrome · migraine with aura · personal history of venous or arterial thrombosis · sclerosing treatment for varicose veins · severe or multiple risk factors for arterial disease or for venous thromboembolism · systemic lupus erythematosus with (or unknown) antiphospholipid antibodies · transient cerebral ischaemic attacks without headaches · undiagnosed vaginal bleeding

**CAUTIONS** Active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration)—seek specialist advice · arterial disease · gene mutations associated with breast cancer (e.g. BRCA 1) · history of severe depression especially if induced by hormonal contraceptive · hyperprolactinaemia—seek specialist advice · inflammatory bowel disease including Crohn’s disease · migraine · personal or family history of hypertriglyceridaemia (increased risk of pancreatitis) · risk factors for venous thromboembolism · sickle-cell disease · undiagnosed breast mass

**CAUTIONS, FURTHER INFORMATION**

**Venous thromboembolism** There is an increased risk of venous thromboembolism in women taking co-cyprindiol, particularly during the first year of use. The incidence of venous thromboembolism is 1.5–2 times higher in women using co-cyprindiol than in women using combined oral contraceptives containing levonorgestrel, but the risk may be similar to that associated with use of combined oral contraceptives containing third generation progestogens (desogestrel and gestodene) or drospirenone. Women requiring co-cyprindiol may have an inherently increased risk of cardiovascular disease.

**INTERACTIONS** → Appendix 1 (oestrogens).
**SIDE-EFFECTS**

- **Rare** Rarely gallstones - systemic lupus erythematosus
- **Very rare** Photosensitivity
- **Frequency not known** Abdominal cramps - absence of withdrawal bleeding - amenorrhoea after discontinuation - breast enlargement - breast secretion - breast tenderness - cervical erosion - changes in libido - changes in lipid metabolism - changes in vaginal discharge - chloasma - cholesterolemia - contact lenses may irritate - depression - fluid retention - headache - hepatic tumours - hypertension - irritability - leg cramps - liver impairment - nausea - nervousness - reduced menstrual loss - skin reactions - thrombosis (more common when factor V Leiden present or in blood groups A, B, and AB - visual disturbances - vomiting - 'spotting' in early cycles
- **PREGNANCY** Avoid—risk of feminisation of male fetus by cyproterone.
- **BREAST FEEDING** Manufacturer advises avoid; possibility of anti-androgen effects in neonate with cyproterone.
- **HEPATIC IMPAIRMENT** Avoid in active liver disease including disorders of hepatic excretion (e.g. Dubin-Johnson or Rotor syndromes), infective hepatitis (until liver function returns to normal), and liver tumours.
- **PRESCRIBING AND DISPENSING INFORMATION** A mixture of cyproterone acetate and ethinylestradiol in the mass proportions 2000 parts to 35 parts, respectively.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Tablet**

- CD-CYPROPRINDOL (Non-proprietary) 
  Cyprioterone acetate 2 mg, Ethinylestradiol 35 microgram 
  Co-cyprindol 2000microgram/35microgram tablets | 63 tablet [PFA] 
  £5.65 DT price = £5.42
- Diianette (Mylan Ltd, Bayer Plc) ▼
  Cyprioterone acetate 2 mg, Ethinylestradiol 35 microgram 
  Diianette tablets | 63 tablet [PFA] £7.71-£11.10 DT price = £5.42
- Brands may include Clairette tablets

**Azelaic acid**

**INDICATIONS AND DOSE**

**FINACEA®**

**FACE**

- **Acne vulgaris** 
  TO THE SKIN
  - Adult: Apply twice daily, to be applied thinly
  - Child 12-17 years: Apply twice daily, to be applied thinly

**PAPULOPUSTULAR ROSACEA**

- **Acne vulgaris** 
  TO THE SKIN
  - Adult: Apply twice daily, to be applied thinly

**SKINOREN®**

- **Acne vulgaris** 
  TO THE SKIN
  - Adult: Apply twice daily, to be applied thinly

**CAUTIONS** Avoid contact with eyes - avoid contact with mouth - avoid contact with mucous membranes

**SIDE-EFFECTS**

- **Common or very common** Local irritation (reduce frequency or discontinue temporarily)
- **Uncommon** Skin discoloration
- **Frequency not known** Worsening of asthma

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Cream**

- EXCIPIENTS: May contain Propylene glycol 
  - Skinoren (Bayer Plc) 
  Azelaic acid 200 mg per 1 gram 
    Skinoren 200% cream | 30 gram [PFA] £3.74 DT price = £3.74
- Gel
  - EXCIPIENTS: May contain Disodium edetate, polysorbates, propylene glycol 
    - Finacea (Bayer Plc) 
    Azelaic acid 150 mg per 1 gram 
      Finacea 15% gel | 30 gram [PFA] £7.48 DT price = £7.48

**ANTI-INFECTIVES**

**Erythromycin**

The properties listed below are those particular to the drug only. For properties common to the class, see macrolides, p. 469.

**INDICATIONS AND DOSE**

**Rosacea**

- **BY MOUTH**
  - Adult: 500 mg twice daily courses usually last 6–12 weeks and are repeated intermittently
- **Acne**
  - **BY MOUTH**
    - Adult: 500 mg twice daily
- **STIEMYCIN®**
  - **Acne vulgaris** 
    - **TO THE SKIN**
      - Child 12-17 years: Apply twice daily, to be applied thinly
      - Adult: Apply twice daily, to be applied thinly

**CAUTIONS**

- With systemic use avoid in acute porphyrias p. 864
- **STIEMYCIN®**
  Some manufacturers advise preparations containing alcohol are not suitable for use with benzoyl peroxide

**INTERACTIONS**

- Appendix 1 (macrolides). 
  Caution with concomitant use of drugs that prolong the QT interval.
  - With topical use Interactions do not apply to small amounts of erythromycin used topically.

**PREGNANCY**

- With systemic use Not known to be harmful.

**BREAST FEEDING**

- With systemic use Only small amounts in milk—not known to be harmful.

**HEPATIC IMPAIRMENT**

- With systemic use May cause idiosyncratic hepatotoxicity.

**RENAL IMPAIRMENT**

- With systemic use in adults Max. 1.5 g daily in severe renal impairment (ototoxicity).
  - With systemic use in children Reduce dose in severe renal impairment (ototoxicity).

**PRESCRIBING AND DISPENSING INFORMATION**

- With oral use Flavours of oral liquid formulations may include banana

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: gel, ointment
Erythromycin with zinc acetate

INDICATIONS AND DOSE
Acne vulgaris
TO THE SKIN
▶ Child: Apply twice daily
▶ Adult: Apply twice daily

CAUTIONS
Some manufacturers advise preparations containing alcohol are not suitable for use with benzoyl peroxide

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Liquid
▶ Zineryt (Astellas Pharma Ltd)
Erythromycin 40 mg per 1 ml, Zinc acetate 12 mg per 1 ml Zineryt lotion | 30 ml (POD) £7.71 DT price = £7.71 | 90 ml (POD) £16.68 DT price = £16.68

PEROXIDES

Benzoyl peroxide

INDICATIONS AND DOSE
Acne vulgaris
TO THE SKIN
▶ Child 12-17 years: Apply 1–2 times a day, preferably after applying with soap and water, start treatment with lower-strength preparations
▶ Adult: Apply 1–2 times a day, preferably after applying with soap and water, start treatment with lower-strength preparations

CAUTIONS
Avoid contact with broken skin • avoid contact with eyes • avoid contact with mouth • avoid contact with mucous membranes • avoid excessive exposure to sunlight

SIDE-EFFECTS
Skin irritation

SIDE-EFFECTS, FURTHER INFORMATION
Skin irritation Reduce frequency or suspend use until irritation subsides and re-introduce at reduced frequency.

PATIENT AND CARER ADVICE
May bleach fabrics and hair.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Cream
EXCIPIENTS: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), fragrances, isopropyl palmitate, propylene glycol
▶ Brevoxyl (GlaxoSmithKline Consumer Healthcare)
Benzoyl peroxide 40 mg per 1 gram Brevoxyl 4% cream | 50 gram | £4.13 DT price = £4.13
▶ PanOxyl (GlaxoSmithKline Consumer Healthcare)
Benzoyl peroxide 50 mg per 1 gram PanOxyl 5 cream | 40 gram | £1.89 DT price = £1.89

Gel
EXCIPIENTS: May contain Fragrances, propylene glycol
▶ Acnecide (Galdenra (UK) Ltd)
Benzoyl peroxide 50 mg per 1 gram Acnecide 5% gel | 30 gram | £5.44 DT price = £5.44 | 60 gram | £12.56
▶ Acnecide Wash 5% gel | 50 gram | £5.44
▶ Brands may include PanOxyl Acnegel, PanOxyl Aquegel

Wash
EXCIPIENTS: May contain Imidurea
▶ PanOxyl (GlaxoSmithKline Consumer Healthcare)
Benzoyl peroxide 100 mg per 1 gram PanOxyl 10 wash | 150 ml | £4.00 DT price = £4.00

Benzoyl peroxide with clindamycin

The properties listed below are those particular to the combination only. For the properties of the components please consider, benzoyl peroxide above, clindamycin p. 467.

INDICATIONS AND DOSE
Acne vulgaris
TO THE SKIN
▶ Child 12-17 years: Apply once daily, dose to be applied in the evening
▶ Adult: Apply once daily, dose to be applied in the evening

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.
PATIENT AND CARER ADVICE

Gel may bleach clothing and hair.

NATIONAL FUNDING/ACCESS DECISIONS

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (March 2014) that Epiduo™ should be restricted for use in mild to moderate facial acne when monotherapy with benzoyl peroxide or adapalene is inappropriate.

MEDISET FORMS

There can be variation in the licensing of different medicines containing the same drug.

Gel

CAUTIONARY AND ADVISORY LABELS 11

EXCIPIENTS: May contain Disodium edetate, polysorbates, propylene glycol

Epiduo (Galderma (UK) Ltd)

Adapalene 1 mg per 1 gram, Benzoyl peroxide 25 mg per 1 gram Epiduo 0.1%/2.5% gel | 45 gram £17.91

Isotretinoin

INDICATIONS AND DOSE

Topical treatment of mild to moderate acne

TO THE SKIN

Adult: Apply 1–2 times a day, to be applied thinly

Severe acne (under expert supervision): Acne which is associated with psychological problems (under expert supervision). Acne which has not responded to an adequate course of a systemic antibacterial (under expert supervision). Acne with scarring (under expert supervision). Systemic treatment of nodulo-cystic and conglobate acne (under expert supervision).

BY MOUTH

Adult: Initially 500 micrograms/kg daily in 1–2 divided doses, increased if necessary to 1 mg/kg daily for 16–24 weeks, repeat treatment course after a period of at least 8 weeks if relapse after first course; maximum 150 mg/kg per course

CONTRA-INDICATIONS

With oral use: hyperlipidaemia, hypervitaminosis A

With topical use: perioral dermatitis, rosacea

CAUTIONS

With oral use: avoid blood donation during treatment and for at least 1 month after treatment; diabetes; dry eye syndrome (associated with risk of keratitis); history of depression; monitor for depression.

With topical use: allow peeling (resulting from other irritant treatments) to subside before using a topical retinoid; alternating a preparation that causes peeling with a topical retinoid may give rise to contact dermatitis (reduce frequency of retinoid application); avoid accumulation in angles of the nose; avoid contact with eyes, nostrils, mouth and mucous membranes, eczematous, broken or sunburned skin; avoid exposure to UV light (including sunlight, solariums); avoid in severe acne involving large areas; avoid use of topical retinoids with abrasive cleaners, comedogenic or astringent cosmetics; monitor for depression.

INTERACTIONS

With oral use: Appendix 1 (retinoids). Avoid keratolytics.

SIDE-EFFECTS

Common or very common

With oral use: anaemia, arthralgia, dryness of eyes (with blepharitis and conjunctivitis); dryness of lips (sometimes chelitis); dryness of nasal mucosa (with epiphactitis); dryness of pharyngeal mucosa (with hoarseness); dryness of skin (with dermatitis, scaling, thinning, erythema, pruritus); epidermal fragility (trauma may cause...
blistering), haematuria, headache, myalgia, neutropenia, proteinuria, raised blood-glucose concentration, raised plasma-triglyceride concentration, raised serum-cholesterol concentration (with reduced high-density lipoprotein concentration), raised serum-transaminase concentration, thrombocytopenia, thrombocytosis.

With oral use

Conception and contraception

Frequency not known

Very rare

With oral use

aggressive behaviour, alopecia, anxiety, depression, mood changes, skin reactions.

Rare

With oral use

Haemorrhagic diarrhoea develops.

Psychiatric side-effects require expert referral.

SIDE-EFFECTS, FURTHER INFORMATION

Management of side-effects

Risk of pancreatitis if triglycerides above 9 mmol/litre—discontinue if uncontrolled hypertriglyceridaemia or pancreatitis.

Psychiatric side-effects require expert referral.

Discontinue treatment if skin peeling severe or haemorrhagic diarrhoea develops.

Visual disturbances require expert referral and possible withdrawal.

Conception and contraception

With oral use

Effective contraception must be used. In women of child-bearing age, exclude pregnancy up to 3 days before treatment (start treatment on day 2 or 3 of menstrual cycle), every month during treatment (unless there are compelling reasons to indicate that there is no risk of pregnancy), and 5 weeks after stopping treatment—perform pregnancy test in the first 3 days of the menstrual cycle. Women must practise effective contraception for at least 1 month before starting treatment, during treatment, and for at least 1 month after stopping treatment. Women should be advised to use at least 1 method of contraception, but ideally they should use 2 methods of contraception. Oral progestogen-only contraceptives are considered ineffective. Barrier methods should not be used alone, but can be used in conjunction with other contraceptive methods. Each prescription for isotretinoin should be limited to a supply of up to 30 days’ treatment and dispensed within 7 days of the date stated on the prescription; repeat prescriptions or fixed prescriptions are not acceptable.

Women should be advised to discontinue treatment and to seek prompt medical attention if they become pregnant during treatment or within 1 month of stopping treatment.

With topical use

Females of child-bearing age must use effective contraception (oral progestogen-only contraceptives not considered sufficiently effective).

Pregnancy

Contra-indicated in pregnancy (teratogenic).

Breast feeding

Avoid.

Hepatic impairment

With oral use

Avoid—further impairment may occur.

Renal impairment

With oral use

In severe impairment, reduce initial dose (e.g. 10 mg daily) and increase gradually up to 1 mg/kg daily as tolerated.

Monitoring requirements

With oral use

Measure hepatic function and serum lipids before treatment, 1 month after starting and then every 3 months (reduce dose or discontinue if transaminase or serum lipids persistently raised).

Prescribing and dispensing information

Isotretinoin is an isomer of tretinoin.

Patient and carer advice

With oral use

Warn patient to avoid wax epilation (risk of epidermal stripping), dermabrasion, and laser skin treatments (risk of scarring) during treatment and for at least 6 months after stopping; patient should avoid exposure to UV light (including sunlight) and use sunscreen and emollient (including lip balm) preparations from the start of treatment. Patients and carers should be told how to recognise signs and symptoms of psychiatric disorders such as depression, anxiety, and rarely suicidal thoughts.

With topical use

Patients should be warned that some redness and skin peeling may occur initially but settles with time. If undue irritation occurs, the frequency of application should be reduced or treatment suspended until the reaction subsides; if irritation persists, discontinue treatment. Several months of treatment may be needed to achieve an optimal response and the treatment should be continued until no new lesions develop. If sun exposure is unavoidable, an appropriate sunscreen or protective clothing should be used.

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

Capsule

Isotretinoin (Non-proprietary)

Isotretinoin 5 mg |
Isotretinoin 10 mg |
Isotretinoin 20 mg |
Isotretinoin 40 mg |
Roaccutane (Roche Products Ltd)

Isotretinoin 10 mg |
Isotretinoin 20 mg |
Roaccutane 20mg capsules |

Gel

Isotretinoin 500 microgram per 1 gram

EXCIPIENTS: May contain Butylated hydroxytoluene

Isotrex (Stiefel Laboratories (UK) Ltd)

Isotrex 500 microgram per 1 gram
Isotretinoin with erythromycin

The properties listed below are those particular to the combination only. For the properties of the components please consider, erythromycin p. 1043, isotretinoin p. 1045.

**INDICATIONS AND DOSE**

Topical treatment of mild to moderate acne

**TO THE SKIN**

- **Adult:** (consult product literature)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Gel**

CAUTIONARY AND ADVISORY LABELS 11

**EXCIPIENTS:** May contain Butylated hydroxytoluene

- **Isotrexin** (Stiefel Laboratories (UK) Ltd)

  Erythromycin 20 mg per 1 gram, isotretinoin 500 microgram per 1 gram isotrexin gel | 30 gram (£10.08) DT price = £747

- **Treclin** (Meda Pharmaceuticals Ltd)

  Tretinoin 250 microgram per 1 gram Tretcin 1%/0.025% gel | 30 gram (£5.49) £11.94

**Tretinoin with clindamycin**

The properties listed below are those particular to the combination only. For the properties of the components please consider, clindamycin p. 467, tretinoin p. 769.

**INDICATIONS AND DOSE**

Facial acne

**TO THE SKIN**

- **Child 12-17 years:** Apply daily, (to be applied thinly at bedtime)
- **Adult:** Apply daily, (to be applied thinly at bedtime)

**CONTRA-INDICATIONS**

Perioral dermatitis · personal or familial history of non-melanoma skin cancer · rosacea

**CAUTIONS**

Allow peeling (resulting from other irritant treatments) to subside before using a topical retinoid · alternating a preparation that causes peeling with a topical retinoid may give rise to contact dermatitis (reduce frequency of retinoid application) · avoid accumulation in angles of the nose · avoid contact with eyes, nostrils, mouth and mucous membranes, eczematous, broken or sunburned skin · avoid exposure to UV light (including sunlight, solariums) · avoid in severe acne involving large areas · avoid use of topical retinoids with abrasive cleaners, comedogenic or astringent cosmetics · caution in sensitive areas such as the neck

**SIDE-EFFECTS**

Blistering of skin · burning · crusting of skin · dry or peeling skin (discontinue if severe) · erythema · eye irritation · increased sensitivity to UVB light or sunlight · oedema · pruritus · stinging · temporary changes of skin pigmentation

**CONCEPTION AND CONTRACEPTION**

Females of child-bearing age must use effective contraception (oral progestogen-only contraceptives not considered sufficiently effective).

**PREGNANCY**

Contra-indicated in pregnancy.

**BREAST FEEDING**

Amount of drug in milk after topical application probably too small to be harmful; ensure infant does not come in contact with treated areas.

**PATIENT AND CARER ADVICE**

Patients and carers should be warned that some redness and skin peeling can occur initially but settles with time. If undue irritation occurs, the frequency of application should be reduced or treatment suspended until the reaction subsides; if irritation persists, discontinue treatment. Several months of treatment may be needed to achieve an optimal response and the treatment should be continued until no new lesions develop.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Gel**

CAUTIONARY AND ADVISORY LABELS 11

**EXCIPIENTS:** May contain Butylated hydroxytoluene, hydroxybenzoates (parabens), polysorbates

- **Treclin** (Meda Pharmaceuticals Ltd)

  Tretinoin (as Tretinoin phosphate) 10 mg per 1 gram, clindamycin 15 mg per 1 gram 1% gel | 30 gram (£4.76) £11.94

Tretinoin with erythromycin

The properties listed below are those particular to the combination only. For the properties of the components please consider, erythromycin p. 1043, tretinoin p. 769.

**INDICATIONS AND DOSE**

**Acne**

**TO THE SKIN**

- **Child:** Apply 1–2 times a day, apply thinly
- **Adult:** Apply 1–2 times a day, apply thinly

**CONTRA-INDICATIONS**

Perioral dermatitis · personal or familial history of non-melanoma skin cancer · rosacea

**CAUTIONS**

Allow peeling (resulting from other irritant treatments) to subside before using a topical retinoid · alternating a preparation that causes peeling with a topical retinoid may give rise to contact dermatitis (reduce frequency of retinoid application) · avoid accumulation in angles of the nose · avoid contact with eyes, nostrils, mouth and mucous membranes, eczematous, broken or sunburned skin · avoid exposure to UV light (including sunlight, solariums) · avoid in severe acne involving large areas · avoid use of topical retinoids with abrasive cleaners, comedogenic or astringent cosmetics · caution in sensitive areas such as the neck

**SIDE-EFFECTS**

Blistering of skin · burning · crusting of skin · dry or peeling skin (discontinue if severe) · erythema · eye irritation · increased sensitivity to UVB light or sunlight · oedema · pruritus · stinging · temporary changes of skin pigmentation

**CONCEPTION AND CONTRACEPTION**

Females of child-bearing age must use effective contraception (oral progestogen-only contraceptives not considered sufficiently effective).

**PREGNANCY**

Contra-indicated in pregnancy.

**BREAST FEEDING**

Amount of drug in milk after topical application probably too small to be harmful; ensure infant does not come in contact with treated areas.

**PATIENT AND CARER ADVICE**

Patients and carers should be warned that some redness and skin peeling can occur initially but settles with time. If undue irritation occurs, the frequency of application should be reduced or treatment suspended until the reaction subsides; if irritation persists, discontinue treatment. Several months of treatment may be needed to achieve an optimal response and the treatment should be continued until no new lesions develop. If sun exposure is unavoidable, an appropriate sunscreen or protective clothing should be used.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.
Nicotinamide

INDICATIONS AND DOSE
Inflammatory acne vulgaris

TO THE SKIN
- Adult: Apply twice daily, reduced if not tolerated to once daily or on alternate days, reduced if irritation occurs

CAUTIONS
- Avoid contact with eyes - avoid contact with mucous membranes (including nose and mouth) - reduce frequency of application if excessive dryness, irritation or peeling

SIDE-EFFECTS
- Burning - dry skin - erythema - irritation - pruritus

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Gel
- Nicam (Derma Laboratories Ltd)
  Nicotinamide 40 mg per 1 gram Nicam 4% gel | 60 gram [P] £10.10
- Brands may include Freederm

7.2 Rosacea

Brimonidine tartrate

INDICATIONS AND DOSE
Facial erythema in rosacea

TO THE SKIN
- Adult: Apply once daily until erythema subsides, apply thinly, divide dose over forehead, chin, nose, and cheeks; maximum 5 mg per day

CAUTIONS
- Cerebral insufficiency - coronary insufficiency - depression - postural hypotension - Raynaud’s syndrome - severe cardiovascular disease - thromboangiitis obliterans

INTERACTIONS
- Appendix 1 (brimonidine).

SIDE-EFFECTS
- Common or very common - burning sensation at application site - stinging at application site
- Uncommon - dry mouth, headache, paraesthesia, skin irritation, dry skin
- PREGNANCY
  - Limited information available; manufacturer advises avoid.
- BREAST FEEDING
  - Manufacturer advises avoid — no information available.
- HEPATIC IMPAIRMENT
  - Manufacturer advises use with caution.
- RENAL IMPAIRMENT
  - Manufacturer advises use with caution.

DIRECTIONS FOR ADMINISTRATION
- Avoid contact with eyes, mouth, and mucous membranes; avoid use on irritated skin or open wounds; apply other topical preparations (including cosmetics) only after brimonidine gel has dried on skin.

PATIENT AND CARER ADVICE
- Drowsiness may affect performance of skilled tasks (e.g. driving). Patients should be advised on administration of gel.

NATIONAL FUNDING/ACCESS DECISIONS
Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (December 2014) that brimonidine (Mirvaso®) is accepted for restricted use within NHS Scotland for the symptomatic treatment of moderate to severe persistent facial erythema associated with rosacea in adult patients.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.

Gel
- Nicam (Dermal Laboratories Ltd)
  Nicotinamide 40 mg per 1 gram Nicam 4% gel | 60 gram [P] £10.10
- Brimonidine (as Brimonidine tartrate) 3 mg per 1 gram Mirvaso
  3mg/g gel | 30 gram [P] £33.69

8 Scalp and hair conditions

Scalp and hair conditions

Dandruff is considered to be a mild form of seborrhoeic dermatitis. Shampoos containing antimicrobial agents such as pyrithione zinc (which are widely available) and selenium p. 1049 may have beneficial effects. Shampoos containing tar extracts may be useful and they are also used in psoriasis. Ketoconazole shampoo p. 1011 should be considered for more persistent or severe dandruff or for seborrhoeic dermatitis of the scalp.

Corticosteroid gels and lotions can also be used. Shampoos containing coal tar with salicylic acid p. 1035 may also be useful. A cream or an ointment containing coal tar with salicylic acid p. 1035 is very helpful in psoriasis p. 1017 that affects the scalp. Patients who do not respond to these treatments may need to be referred to exclude the possibility of other skin conditions.

Cradle cap in infants may be treated with coconut oil or olive oil applications followed by shampooing.

Hirsutism

Hirsutism may result from hormonal disorders or as a side-effect of drugs such as minoxidil p. 1049, corticosteroids, anabolic steroids, androgens, danazol p. 636, and progestogens.

Weight loss can reduce hirsutism in obese women. Women should be advised about local methods of hair removal, and in the mildest cases this may be all that is required.

Efollinithine p. 1050 an antiprotozoal drug, inhibits the enzyme ornithine decarboxylase in hair follicles. Topical efollinithine can be used as an adjunct to laser therapy for facial hirsutism in women.

Co-cyprindiol p. 1042 may be effective for moderately severe hirsutism. Metformin hydrochloride p. 594 is an alternative in women with polycystic ovary syndrome [unlicensed indication]. Systemic treatment is required for 6–12 months before benefit is seen.

Androgenetic alopecia

Finasteride p. 676 is licensed for the treatment of androgenetic alopecia in men. Continuous use for 3–6 months is required before benefit is seen, and effects are reversed 6–12 months after treatment is discontinued.

Topical application of minoxidil p. 1049 may stimulate limited hair growth in a small proportion of adults but only for as long as it is used.
**ANTISEPTICS AND DISINFECTANTS**

**Benzalkonium chloride**

**INDICATIONS AND DOSE**

Seborrhoeic scalp conditions associated with dandruff and scaling  
**TO THE SKIN**  
▶ Child: Apply as required  
▶ Adult: Apply as required

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: liquid

**Shampoo**

- Dermax (Dermal Laboratories Ltd)
  - Benzalkonium chloride 5 mg per 1 ml  
  - Dermax Therapeutic 0.5% shampoo | 250 ml £5.69

**Cetrimide with undecenoic acid**

**INDICATIONS AND DOSE**

Scalp psoriasis | Seborrhoeic dermatitis | Dandruff  
**TO THE SKIN**  
▶ Child: Apply 3 times a week for 1 week, then apply twice weekly  
▶ Adult: Apply 3 times a week for 1 week, then apply twice weekly

**MEDITCINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: liquid

**Shampoo**

- Ceanel (Alliance Pharmaceuticals Ltd)
  - Cetrimide 100 mg per 1 ml, Phenylethyl alcohol 75 mg per 1 ml, Undecenoic acid 10 mg per 1 ml  
  - Ceanel Concentrate shampoo | 150 ml £3.40 | 500 ml £9.80

**ESSENTIAL TRACE ELEMENTS**

**Selenium**

**INDICATIONS AND DOSE**

Seborrhoeic dermatitis | Dandruff  
**TO THE SKIN**  
▶ Child 5-17 years: Apply twice weekly for 2 weeks, then apply once weekly for 2 weeks, then apply as required  
▶ Adult: Apply twice weekly for 2 weeks, then apply once weekly for 2 weeks, then apply as required

**Pityriasis versicolor**  
**TO THE SKIN**  
▶ Adult: Apply daily for 7 days, apply to the affected area and leave on for 10 minutes before rinsing off. The course may be repeated if necessary. Diluting with a small amount of water prior to application can reduce irritation

**UNLICENSED USE**

The use of selenium sulfide shampoo as a lotion for the treatment of pityriasis (tinea) versicolor is an unlicensed indication.

**PATIENT AND CARER ADVICE**  
Avoid using 48 hours before or after applying hair colouring, straightening or waving preparations.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

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**Shampoo**

**EXCIPIENTS:** May contain Fragrances  
- Selsun (Chattem (U.K.) Ltd)  
  - Selenium sulfide shampoo 25 mg per 1 ml  
  - Selsun 2.5% shampoo | 50 ml £1.44 | 100 ml £1.96 | 150 ml £2.75  
  - DT price = £1.96

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**8.1 Alopecia**

**PERIPHERAL VASODILATORS**

**Minoxidil**

**INDICATIONS AND DOSE**

**REGAINE® FOR MEN EXTRA STRENGTH FOAM**  
Androgenetic alopecia  
**TO THE SKIN**  
▶ Adult: Apply 0.5 capful twice daily, to be applied to the affected areas of scalp; discontinue if no improvement after 16 weeks

**REGAINE® FOR MEN EXTRA STRENGTH SOLUTION**  
Androgenetic alopecia  
**TO THE SKIN**  
▶ Adult: Apply 1 mL twice daily, to be applied to the affected areas of scalp; discontinue if no improvement after 1 year

**REGAINE® FOR WOMEN REGULAR STRENGTH**  
Androgenetic alopecia  
**TO THE SKIN**  
▶ Adult: Apply 1 mL twice daily, to be applied to the affected areas of scalp; discontinue if no improvement after 1 year

**CONTRA-INDICATIONS**

Phaeochromocytoma

**CAUTIONS**

Avoid contact with broken, infected, shaved, or inflamed skin - avoid contact with eyes - avoid contact with mouth - avoid contact with mucous membranes - avoid inhalation of spray mist - avoid occlusive dressings

**CAUTIONS, FURTHER INFORMATION**

When used topically systemic effects unlikely; only about 1–2% absorbed (greater absorption may occur with use on inflamed skin).

**INTERACTIONS**

Caution—avoid topical drugs which enhance absorption.

**SIDE-EFFECTS**

▶ Common or very common  
  - Headache  
  - Local irritation

▶ Uncommon  
  - Changes in hair colour or texture (discontinue if increased hair loss persists for more than 2 weeks) - hypotension

**SIDE-EFFECTS, FURTHER INFORMATION**

When used topically systemic effects unlikely; only about 1–2% absorbed (greater absorption may occur with use on inflamed skin).

**PREGNANCY**

Avoid—possible toxicity including reduced placental perfusion. Neonatal hirsutism reported.

**BREAST FEEDING**

Present in milk but not known to be harmful.

**PATIENT AND CARER ADVICE**

Ensure hair and scalp dry before application. Patients and their carers should be advised to wash hands after application of liquid or foam.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.
8.2 Hirsutism

Eflornithine

- **Drug action**: An antiparasitic drug that inhibits the enzyme ornithine decarboxylase in hair follicles.

**Indications and Dose**

Adjunct to laser therapy for facial hirsutism in women

- **Adult**: Apply twice daily, to be applied thinly, discontinue use if no improvement after 4 months of treatment.

**Side-effects**

- **Common or very common**: Acne, burning at application site, rash, stinging at application site.
- **Uncommon**: Abnormal hair growth, abnormal hair texture.
- **Pregnancy**: Toxicity in animal studies—manufacturer advises avoid.
- **Breast Feeding**: Manufacturer advises avoid—no information available.
- **Patient and Carer Advice**: Medicines must be rubbed in thoroughly. Cosmetics may be applied over treated area 5 minutes after eflornithine, do not wash treated area for 4 hours after application.

**National Funding/Access Decisions**

Scottish Medicines Consortium (SMC) Decisions

The Scottish Medicines Consortium has advised (September 2005) that eflornithine for facial hirsutism be restricted for use in women in whom alternative drug treatment cannot be used.

**Medicinal Forms**

There can be variation in the licensing of different medicines containing the same drug.

- **Cream**
  - **Excipients**: May contain Cetostearyl alcohol (including cetyl and stearyl alcohol), hydroxybenzoates (parabens)
  - **Vaniqa** (Almirall Ltd)
    - Eflornithine (as Eflornithine monohydrate chloride) 115 mg per 1 gram
      - Vaniqa 11.5% cream [60 gram (£19.84)] 180 ml (£39.71)

9 Skin cleansers, antiseptics and desloughing agents

**Skin cleansers, antiseptics and desloughing agents**

Soap or detergent is used with water to cleanse intact skin; emollient preparations such as aqueous cream or emulsifying ointment can be used in place of soap or detergent for cleansing dry skin.

An antiseptic is used for skin that is infected or that is susceptible to recurrent infection. Detergent preparations containing chlorhexidine p. 1051 or povidone-iodine p. 1053, which should be thoroughly rinsed off, are used. Emollients may also contain antiseptics.

Antiseptics such as chlorhexidine or povidone-iodine are used on intact skin before surgical procedures; their antiseptic effect is enhanced by an alcoholic solvent. Antiseptic solutions containing cetrimide can be used if a deterrent effect is also required.

Hydrogen peroxide p. 1052, an oxidising agent, can be used in solutions of up to 6% for skin disinfection, such as cleansing and deodorising wounds and ulcers. Hydrogen peroxide is also available as a cream for superficial bacterial skin infections.

For irrigating ulcers or wounds, lukewarm sterile sodium chloride 0.9% solution is used, but tap water is often appropriate.

Potassium permanganate solution 1 in 10000 p. 1052, a mild antiseptic with astrigent properties, can be used for exudative eczematous areas; treatment should be stopped when the skin becomes dry.

**Desloughing agents**

Alginate, hydrogel and hydrocolloid dressings are effective at wound debridement. Sterile larvae (maggots) (available from BioMondé) are also used for managing sloughing wounds and are prescribable on the NHS.

Desloughing solutions and creams are of little clinical value. Substances applied to an open area are easily absorbed and perilesional skin is easily sensitised. Gravitational dermatitis may be complicated by superimposed contact sensitivity to substances such as neomycin sulphate p. 1009 or lanolin.

**Alcohols**

**Industrial methylated spirit**

(Alcohol)

**Indications and Dose**

Skin preparation before injection

- **Child**: Apply as required
- **Adult**: Apply as required

**Contra-Indications**

- Neornates

**Caution**

- Avoid broken skin, flammable - patients have suffered severe burns when diathermy has been preceded by application of alcoholic skin disinfectants.

**Interactions**

For the interactions following the ingestion of alcohol, see Appendix 1 (alcohol).

**Side-Effects**

- Features of acute alcohol intoxication include ataxia, dysarthria, nyctagmus and drowsiness, which may progress to coma, with hypotension and acidosis.
For details on the management of poisoning, see Alcohol, under Emergency treatment of poisoning p. 1123.

**PRESCRIBING AND DISPENSING INFORMATION** When prepared extemporaneously, the BP states Surgical Spirit, BP consists of methyl salicylate 0.5 mL, diethylene phthalate 2%, castor oil 2.5%, in industrial methylated spirit.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Liquid**
- **ALCOHOL (Non-proprietary)**
- Industrial methylated spirit 70% | 600 mL £5.71
- Ethanol 950 mL per 1 litre, Wood naphtha 50 mL per 1 litre Industrial methylated spirit 95% | 600 mL £5.82 | 1000 mL £4.29-£6.02

**ANTISEPTICS AND DISINFECTANTS**

**Chlorhexidine**

**INDICATIONS AND DOSE**

**CEPTON® LOTION**
- For skin disinfection in acne
  - TO THE SKIN
    - Child: (consult product literature)
    - Adult: (consult product literature)

**CEPTON® SKIN WASH**
- For use as skin wash in acne
  - TO THE SKIN
    - Child: (consult product literature)
    - Adult: (consult product literature)

**CHLORAPREP®**
- For skin disinfection before invasive procedures
  - TO THE SKIN
    - Child 2 months-17 years: (consult product literature)
    - Adult: (consult product literature)

**CX ANTISEPTIC DUSTING POWDER**
- For skin disinfection
  - TO THE SKIN
    - Adult: (consult product literature)

**HIBICTANE® LIQUID HAND RUB+**
- Hand and skin disinfection
  - TO THE SKIN
    - Child: To be used undiluted (consult product literature)
    - Adult: To be used undiluted (consult product literature)

**HIBISCRUB®**
- Pre-operative hand and skin disinfection | General hand and skin disinfection
  - TO THE SKIN
    - Child: Use as alternative to soap (consult product literature)
    - Adult: Use as alternative to soap (consult product literature)

**HIBITANE® PLUS 5% CONCENTRATE SOLUTION**
- General and pre-operative skin disinfection
  - TO THE SKIN
    - Child: (consult product literature)

**HIBITANE OBSTETRIC®**
- For use in obstetrics and gynaecology as an antiseptic and lubricant
  - TO THE SKIN
    - Adult: To be applied to skin around vulva and perineum and to hands of midwife or doctor

**HYDREX® SOLUTION**
- For pre-operative skin disinfection
  - TO THE SKIN
    - Child: (consult product literature)
    - Adult: (consult product literature)

**HYDREX® SURGICAL SCRUB**
- For pre-operative hand and skin disinfection | General hand disinfection
  - TO THE SKIN
    - Child: (consult product literature)
    - Adult: (consult product literature)

**UNISEPT®**
- For cleansing and disinfecting wounds and burns and swabbing in obstetrics
  - TO THE SKIN
    - Child: (consult product literature)
    - Adult: (consult product literature)

**CONTRA-INDICATIONS**
- Alcohol solutions not suitable before diathermy · alcohol solutions not suitable for use on neonatal skin · not for use in body cavities

**CAUTIONS**
- Avoid contact with brain · avoid contact with eyes · avoid contact with meninges · avoid contact with middle ear

**SIDE-EFFECTS**
- Chemical burns in preterm neonates · sensitivity

**DIRECTIONS FOR ADMINISTRATION**

**HIBITANE® PLUS 5% CONCENTRATE SOLUTION**
- For pre-operative skin preparation, dilute 1 in 10 (0.5%) with alcohol 70%. For general skin disinfection, dilute 1 in 100 (0.05%) with water. Alcohol solutions not suitable for use before diathermy or on neonatal skin.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: liquid

**Liquid**
- CAUTIONARY AND ADVISORY LABELS 15
  - EXCIPIENTS: May contain Fragrances
- **CHLORHEXIDINE (Non-proprietary)**
  - Chlorhexidine gluconate 500 microgram per 1 ml Chlorhexidine gluconate 0.05% solution 100ml sachets | 10 sachet no price available
  - Cepton (Boston Healthcare Ltd)
  - Chlorhexidine gluconate 10 mg per 1 ml Cepton 1% medicated skin wash | 150 mL GSS £5.10
  - HiBiTane Plus (Molnlycke Health Care Ltd)
  - Chlorhexidine gluconate 50 mg per 1 ml HiBiTane Plus 5% concentrate solution | 5000 mL GSS £41.50
  - Hydrex (Ecolab Healthcare Division)
  - Chlorhexidine gluconate 5 mg per 1 ml Hydrex pink chlorhexidine gluconate 0.5% solution | 600 mL GSS £3.49
  - Chlorhexidine gluconate 40 mg per 1 ml Hydrex 4% Surgical Scrub | 250 mL GSS £3.39 | 500 mL GSS £3.59 | 5000 mL GSS £26.96

**Cream**
- **CHLORHEXIDINE (Non-proprietary)**
  - Chlorhexidine hydrochloride 5 mg per 1 gram | 30 gram GSS £2.07
  - Brands may include Acriflex, Eczmol, Hibitane

**Gel**
- **CEPTON (Boston Healthcare Ltd)**
  - Chlorhexidine gluconate 5 mg per 1 gram Cepton 0.5% medicated clear gel | 30 gram GSS £2.97
**Chlorhexidine gluconate with isopropyl alcohol**

The properties listed below are those particular to the combination only. For the properties of the components please consider, chlorhexidine p. 1051.

**INDICATIONS AND DOSE**
- **Skin disinfection before invasive procedures**
  - Child: 2 months–17 years: (consult product literature)
  - Adult: (consult product literature)

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Liquid**
- **CAUTIONARY AND ADVISORY LABELS** 15
- Chlorhexidine (CareFusion UK Ltd)
  - Chlorhexidine gluconate 20 mg per 1 ml, isopropyl alcohol 700 ml per 1 litre
    - Chloraprep with tint solution 10.5ml applicators | 25 applicator £67.65
    - Chloraprep with tint solution 26ml applicators | 25 applicator £170.75
    - Chloraprep solution 3ml applicators | 25 applicator £21.25
    - Chloraprep solution 1.5ml applicators | 20 applicator £13.00
    - Chloraprep with tint solution 3ml applicators | 25 applicator £22.31
    - Chloraprep solution 0.67ml applicators | 200 applicator £60.00
    - Chloraprep solution 10.5ml applicators | 25 applicator £73.00
    - Chloraprep solution 26ml applicators | 25 applicator £162.50

**Profavine**

**INDICATIONS AND DOSE**
- **Infected wounds | Infected burns**
  - Adult: (consult product literature)

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: liquid

**Potassium permanganate**

**INDICATIONS AND DOSE**
- **Cleansing and deodorising suppurating eczematous reactions and wounds**
  - Adult: For wet dressings or baths, use approximately 0.01% (1 in 10 000) solution

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: liquid

**Tablet for cutaneous solution**
- **POTASSIUM PERMANGANATE (Non-proprietary)**
  - Potassium permanganate 400 mg
    - Permivas 400mg tablets for cutaneous solution | 100 tablet £16.47
  - Potassium permanganate 800 mg
    - Permivas 800mg tablets for cutaneous solution | 50 tablet £31.95

**Prescribing and dispensing information**
- The BP directs that when hydrogen peroxide is prescribed, hydrogen peroxide solution 6% (20 vols) should be dispensed. Strong solutions of hydrogen peroxide which contain 27% (90 vols) and 30% (100 vols) are only for the preparation of weaker solutions. When prepared extemporaneously, the BP states Hydrogen Peroxide Solution, BP consists of hydrogen peroxide 6% (20 vols) or hydrogen peroxide 3% (10 vols).

**Handling and storage**
- Hydrogen peroxide bleaches fabric.
IODINE PRODUCTS

Povidone-iodine

INDICATIONS AND DOSE
Skin disinfection
TO THE SKIN
▶ Child: (consult product literature)
▶ Adult: (consult product literature)

BETADINE® DRY POWDER SPRAY
Skin disinfection, particularly minor wounds and infections
TO THE SKIN
▶ Adult: Not for use in serous cavities (consult product literature)

SAVLON® DRY
Skin disinfection of minor wounds
TO THE SKIN
▶ Adult: (consult product literature)

VIDENE® SOLUTION
Skin disinfection
TO THE SKIN
▶ Child: Apply undiluted in pre-operative skin disinfection and general antisepsis
▶ Adult: Apply undiluted in pre-operative skin disinfection and general antisepsis

VIDENE® SURGICAL SCRUB®
Skin disinfection
TO THE SKIN
▶ Child: Use as a pre-operative scrub for hand and skin disinfection
▶ Adult: Use as a pre-operative scrub for hand and skin disinfection

VIDENE® TINCTURE
Skin disinfection
TO THE SKIN
▶ Adult: Apply undiluted in pre-operative skin disinfection

CONTRA-INDICATIONS Avoid regular use in patients with thyroid disorders • concomitant use of lithium • corrected gestational age under 32 weeks • infants body-weight under 1.5 kg • regular use in neonates

CAUTIONS Broken skin • large open wounds

CAUTIONS, FURTHER INFORMATION
Large open wounds The application of povidone–iodine to large wounds or severe burns may produce systemic adverse effects such as metabolic acidosis, hypernatraemia and impairment of renal function.

VIDENE® TINCTURE
Procedures involving hot wire cautery and diathermy

SIDE-EFFECTS
▶ Rare: Sensitivity

PREGNANCY Sufficient iodine may be absorbed to affect the fetal thyroid in the second and third trimester.

BREAST FEEDING Avoid regular or excessive use.

RENAI IMPAIRMENT Avoid regular application to inflamed or broken skin or mucosa.

EFFECT ON LABORATORY TESTS May interfere with thyroid function tests.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: liquid

Liquid

CAUTIONARY AND ADVISORY LABELS 15
▶ Videne (Ecolab Healthcare Division)

Povidone-iodine 75 mg per 1 ml Videne 7.5% surgical scrub solution | 500 ml £15.43

Spray
▶ Betadine (J M Loveridge Ltd)
Povidone-iodine 25 mg per 1 gram Betadine 2.5% dry powder spray | 100 ml £3.05 DT price = £3.05
▶ Savlon Dry (Novartis Consumer Health UK Ltd)
Povidone-iodine 11.4 mg per 1 gram Savlon Dry 1.14% spray | 50 ml £2.51 DT price = £2.51

Impregnated dressing
▶ Povidone-iodine (Non-proprietary)
Povidone-iodine 100 mg per 1 gram Povitulle dressing 9.5cm x 9.5cm | 1 dressing £0.42 | 10 dressing no price available
Povitulle dressing 5cm x 5cm | 1 dressing £0.28 | 25 dressing no price available
▶ Inadine (Systagenix Wound Management Ltd)
Povidone-iodine 100 mg per 1 gram Inadine dressing 5cm x 5cm | 1 dressing £0.13 | 25 dressing no price available

SKIN CLEANSERS

Diethyl phthalate with methyl salicylate

INDICATIONS AND DOSE
Skin preparation before injection
TO THE SKIN
▶ Adult: Apply, to the area to be disinfected

MEDIcINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Liquid

CAUTIONARY AND ADVISORY LABELS 15
▶ DIETHYL PHTHALATE WITH METHYL SALICYLATE (Non-proprietary)

Castor oil 25 ml per 1 litre, Diethyl phthalate 20 ml per 1 litre, methyl salicylate 5 ml per 1 litre

IRRIGATION SOLUTIONS

FLOURASOR SODIUM CHLORIDE 0.9% irrigation solution 120ml bottles (Fresenius Kabi Ltd)
1 bottle • NHS indicative price = £1.53 • Drug Tariff (Part IXa)
Irriclens sodium chloride 0.9% irrigation solution aerosol spray (Convatec Ltd)
240 ml • NHS indicative price = £3.49 • Drug Tariff (Part IXa)
Normasol sodium chloride 0.9% irrigation solution 100ml sachets (Molyncke Health Care Ltd)
10 unit dose • NHS indicative price = £1.80 • Drug Tariff (Part IXa)
Normasol sodium chloride 0.9% irrigation solution 25ml sachets (Molyncke Health Care Ltd)
25 unit dose • NHS indicative price = £6.42 • Drug Tariff (Part IXa)
Sodium chloride 0.9% irrigation solution 20ml Clinipod unit dose (Mayors Healthcare Ltd)
25 unit dose • NHS indicative price = £4.95 • Drug Tariff (Part IXa)
Sodium chloride 0.9% irrigation solution 20ml ISO-POD unit dose (St Georges Medical Ltd)
25 unit dose • NHS indicative price = £4.95 • Drug Tariff (Part IXa)
Sodium chloride 0.9% irrigation solution 20ml Tropod unit dose (C D Medical Ltd)
25 unit dose • NHS indicative price = £5.94 • Drug Tariff (Part IXa)
Sodium chloride 0.9% irrigation solution 20ml Sal-e Pods unit dose (Ennogen Healthcare Ltd)
25 unit dose • NHS indicative price = £7.91 • Drug Tariff (Part IXa)
Sodium chloride 0.9% irrigation solution 20ml Steripod unit dose (Molyncke Health Care Ltd)
25 unit dose • NHS indicative price = £7.90 • Drug Tariff (Part IXa)
9.1 Minor cuts and abrasions

Minor cuts and abrasions

Many preparations traditionally used to manage minor burns, and abrasions have fallen out of favour. Preparations containing camphor and sulfonamides should be avoided. Preparations such as magnesium sulfate paste are now rarely used to treat carbuncles and boils as these are best treated with antibiotics.

Cetrimide is used to treat minor cuts and abrasions and profalvine p. 1052 may be used to treat infected wounds or burns, but its use has now been largely superseded by other antiseptics or suitable antibacterials. The effervescent effect of hydrogen peroxide p. 1052 is used to clean minor cuts and abrasions. When prepared extemporaneously, the BP states CETRIMIDE Cream 0.5% in a suitable water-miscible basis such as cetostearyl alcohol 5%, consists of liquid paraffin 50% in freshly boiled and cooled purified water.

Flexible collodion (see castor oil with collodion and colophony below) may be used to seal minor cuts and wounds that have partially healed; skin tissue adhesives are used similarly, and also for additional suture support.

ANTISEPTICS AND DISINFECTANTS

Cetrimide with chlorhexidine

The properties listed below are those particular to the combination only. For the properties of the components please consider, chlorhexidine p. 1051.

INDICATIONS AND DOSE

Skin disinfection such as wound cleansing and obstetrics

TO THE SKIN

Child: To be used undiluted

Adult: To be used undiluted

MAGNESIUM

Glycerol with magnesium sulfate and phenol

INDICATIONS AND DOSE

Treat carbuncles and boils

TO THE SKIN

Adult: To be applied under dressing

Skin adhesives

Skin adhesives

- DermaFlex skin adhesive (Chemence Ltd)
- Dermabond ProPen skin adhesive (Ethicon Ltd)
- Histoacryl L skin adhesive (B. Braun Medical Ltd)
- LiquiBand flow control tissue adhesive (MedLogic Global Ltd)
- Indermil skin adhesive (Covidien (UK) Commercial Ltd)

COLLIDIIONS

Castor oil with collodion and colophony

INDICATIONS AND DOSE

Used to seal minor cuts and wounds that have partially healed

TO THE SKIN

Child: (consult product literature)

Adult: (consult product literature)
10 Skin disfigurement

Camouflagers

Disfigurement of the skin can be very distressing to patients and may have a marked psychological effect. In skilled hands, or with experience, camouflage cosmetics can be very effective in concealing scars and birthmarks. The depigmented patches in vitiligo are also very disfiguring and camouflage creams are of great cosmetic value.

Opaque cover foundation or cream is used to mask skin pigment abnormalities; careful application using a combination of dark- and light-coloured cover creams set with powder helps to minimise the appearance of skin deformities.

Borderline substances

The preparations marked ‘ACBS’ cannot be prescribed on the NHS for postoperative scars and other deformities except as adjunctive therapy in the relief of emotional disturbances due to disfiguring skin disease, such as vitiligo.

Camouflages

- **CAMOUFLAGES**
  - Covermark classic foundation (Derma UK Ltd)
    - 15 ml (ACBS) - NHS indicative price = £11.86 (22 shades)
  - Covermark finishing powder (Derma UK Ltd)
    - 25 gram (ACBS) - NHS indicative price = £11.86
  - Covermark removing cream (Camouflage Cosmetics Ltd)
    - 200 ml - No NHS indicative price available
  - Dermablend Dermasmooth Corrective Foundation (Vichy)
    - 30 ml - No NHS indicative price available (12 shades)
  - Dermacolor Creme Effectiv (Charles H Fox Ltd)
    - 50 ml - NHS indicative price = £5.48
  - Dermacolor body cover (Charles H Fox Ltd)
    - 75 ml - No NHS indicative price available (51 shades)
  - Dermacolor camouflage creme (Charles H Fox Ltd)
    - 25 ml (ACBS) - NHS indicative price = £10.52 (150 shades)
  - Dermacolor cleansing cream (Charles H Fox Ltd)
    - 75 gram - No NHS indicative price available
  - Dermacolor fixing powder (Charles H Fox Ltd)
    - 60 gram (ACBS) - NHS indicative price = £3.05 (8 shades)
  - Keromask finishing powder (Bellava Ltd)
    - 20 gram (ACBS) - NHS indicative price = £5.68 (28 shades)
  - Veil cleansing cream (Thomas Blake Cosmetic Creams Ltd)
    - 50 gram - NHS indicative price = £2.45/100 gram - NHS indicative price = £4.00
  - Veil cover cream (Thomas Blake Cosmetic Creams Ltd)
    - 19 gram (ACBS) - NHS indicative price = £22.42/gram (ACBS) - NHS indicative price = £33.35/gram (ACBS) - NHS indicative price = £42.10 (40 shades)
  - Veil finishing powder (Thomas Blake Cosmetic Creams Ltd)
    - 35 gram (ACBS) - NHS indicative price = £24.58 (2 shades)

11 Superficial soft-tissue injuries and superficial thrombophlebitis

Topical circulatory preparations

These preparations are used to improve circulation in conditions such as bruising, superficial thrombophlebitis, chilblains and varicose veins but are of little value. Chilblains are best managed by avoidance of exposure to cold; neither systemic nor topical vasodilator therapy is established as being effective.

12 Warts and calluses

Warts and calluses

Warts (verrucas) are caused by a human papillomavirus, which most frequently affects the hands, feet (plantar warts), and the anogenital region; treatment usually relies on local tissue destruction. Warts may regress on their own and treatment is required only if the warts are painful, unsightly, persistent, or cause distress.

Preparations of salicylic acid p. 1057, formaldehyde, glutaraldehyde or silver nitrate p. 1056 are available for purchase by the public; they are suitable for the removal of warts on hands and feet. Salicylic acid is a useful keratolytic which may be considered first-line; it is also suitable for the removal of corns and calluses. Preparations of salicylic acid in a collodion basis are available but some patients may develop an allergy to colophony in the formulation; collodion should be avoided in children allergic to elastic adhesive plaster. Cryotherapy causes pain, swelling, and blistering, and may be no more effective than topical salicylic acid in the treatment of warts.

Anogenital warts

The treatment of anogenital warts (condylomata acuminata) should be accompanied by screening for other sexually transmitted infections. Podophyllotoxin (the major active ingredient of podophyllum) may be used for soft, non-keratinised external anogenital warts. Patients with a limited number of external warts or keratinised lesions may be better treated with cryotherapy or other forms of physical ablation.

Imiquimod cream p. 1057 is licensed for the treatment of external anogenital warts; it may be used for both keratinised and non-keratinised lesions. It is also licensed for the treatment of superficial basal cell carcinoma and actinic keratosis.

Inosine pranobex p. 550 is licensed for adjunctive treatment of genital warts but it has been superseded by more effective drugs.
ALDEHYDES AND DERIVATIVES

Formaldehyde

INDICATIONS AND DOSE
Warts, particularly plantar warts
TO THE SKIN
- Child: Apply twice daily
- Adult: Apply twice daily

CAUTIONS
- Impaired peripheral circulation - not suitable for application to anogenital region - not suitable for application to face - not suitable for application to large areas - patients with diabetes at risk of neuropathic ulcers - protect surrounding skin and avoid broken skin - significant peripheral neuropathy

SIDE-EFFECTS
- Skin irritation - skin ulceration (with high concentrations)

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: liquid
- FORMALDEHYDE (Non-proprietary)
  - Formaldehyde 40 mg per 1 ml
  - Formaldehyde (Buffered) 4% solution | 1000 ml £3.56-£3.90

Gel
- Veracur (Typharm Ltd)
  - Formaldehyde 7.5 mg per 1 gram
  - Veracur 0.75% gel | 15 gram | £2.41

Glutaraldehyde

INDICATIONS AND DOSE
Warts, particularly plantar warts
TO THE SKIN
- Child: Apply twice daily
- Adult: Apply twice daily

CAUTIONS
- Not for application to anogenital areas - not for application to face - not for application to mucosa - protect surrounding skin

SIDE-EFFECTS
- Rashes - skin irritation (discontinue if severe) - stains skin brown

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.
- Paint
  - Glutarol (Dermal Laboratories Ltd)
  - Glutaraldehyde 100 mg per 1 ml
    - Glutaral 10% cutaneous solution | 10 ml | £2.07

ANTIMITOTICS

Podophyllotoxin

INDICATIONS AND DOSE
CONDYLONE®
Condylomata acuminata affecting the penis or the female external genitalia
TO THE SKIN
- Adult: Apply twice daily for 3 consecutive days, treatment may be repeated at weekly intervals if necessary for a total of four 3-day treatment courses, direct medical supervision for lesions greater than 4 cm²

WARTICON® CREAM
Condylomata acuminata affecting the penis or the female external genitalia
TO THE SKIN
- Adult: Apply twice daily for 3 consecutive days, treatment may be repeated at weekly intervals if necessary for a total of four 3-day treatment courses, direct medical supervision for lesions greater than 4 cm², maximum 50 single applications (‘loops’) per session (consult product literature)

CAUTIONS
- Avoid normal skin - avoid open wounds - keep away from face - very irritant to eyes

SIDE-EFFECTS
- Local irritation

PREGNANCY
- Avoid.

BREAST FEEDING
- Avoid.

MEDICINAL FORMS
- There can be variation in the licensing of different medicines containing the same drug.
- Liquid
  - CONDYLINE (Takeda UK Ltd)
    - Podophyllotoxin 5 mg per 1 ml
      - Podophyllotoxin 5 mg per 1 ml | 3.5 ml | £14.49
  - WARTICON (Stiefel Laboratories (UK) Ltd)
    - Podophyllotoxin 5 mg per 1 ml
      - Warticon 0.5% solution | 3 ml | £14.86

Cream
- EXCIPIENTS: May contain Butylated hydroxyanisole, cetostearyl alcohol (including cetyl and stearyl alcohol), hydroxybenzoates (parabens), sorbic acid
  - WARTICON (Stiefel Laboratories (UK) Ltd)
    - Podophyllotoxin 1.5 mg per 1 gram
      - Warticon 0.15% cream | 5 gram | £17.83

CAUSTIC DRUGS

Silver nitrate

INDICATIONS AND DOSE
Common warts
TO THE SKIN
- Child: Apply every 24 hours for up to 3 applications, apply moistened caustic pencil tip for 1–2 minutes. Instructions in proprietary packs generally incorporate advice to remove dead skin before use by gentle filing and to cover with adhesive dressing after application
- Adult: Apply every 24 hours for up to 3 applications, apply moistened caustic pencil tip for 1–2 minutes. Instructions in proprietary packs generally incorporate advice to remove dead skin before use by gentle filing and to cover with adhesive dressing after application

Verrucas
TO THE SKIN
- Child: Apply every 24 hours for up to 6 applications, apply moistened caustic pencil tip for 1–2 minutes. Instructions in proprietary packs generally incorporate advice to remove dead skin before use by gentle filing and to cover with adhesive dressing after application
- Adult: Apply every 24 hours for up to 6 applications, apply moistened caustic pencil tip for 1–2 minutes.
Instructions in proprietary packs generally incorporate advice to remove dead skin before use by gentle filing and to cover with adhesive dressing after application.

**Umbilical granulomas**

**TO THE SKIN**

- **Child:** Apply moistened caustic pencil tip (usually containing silver nitrate 40%) for 1–2 minutes, protect surrounding skin with soft paraffin.
- **Adult:** Apply moistened caustic pencil tip (usually containing silver nitrate 40%) for 1–2 minutes, protect surrounding skin with soft paraffin.

**CAUTIONS** Avoid broken skin · not suitable for application to ano-genital region · not suitable for application to face · not suitable for application to large areas · protect surrounding skin.

**SIDE-EFFECTS** Chemical burns on surrounding skin · stains skin.

**PATIENT AND CARER ADVICE** Patients should be advised that silver nitrate may stain fabric.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: liquid stick.

- **Avoca** (Bray Group Ltd)
  - Silver nitrate 400 mg per 1 gram Avoca 40% silver nitrate pencils | 1 applicator | £1.01.
  - Silver nitrate 750 mg per 1 gram Avoca 75% silver nitrate applicators | 100 applicator | £43.73.
  - Avoca 75% silver nitrate applicators with thick handles | 50 applicator | £42.49.
  - Silver nitrate 950 mg per 1 gram Avoca 95% silver nitrate applicators | 100 applicator | £43.73.
  - Avoca 95% silver nitrate pencils | 1 applicator | £1.96 DT price = £2.44 | 12 applicator | £23.04.
  - Avoca wart and verruca treatment set | 1 applicator | £2.44 DT price = £2.44 | 6 applicator | £14.37.

**IMMUNE RESPONSE MODIFIERS**

**Imiquimod**

**INDICATIONS AND DOSE**

**ALDARA**

**Warts (external genital and perianal)**

**TO THE SKIN**

- **Adult:** Apply 3 times a week until lesions resolve (maximum 16 weeks), to be applied thinly at night.

**Superficial basal cell carcinoma**

**TO THE SKIN**

- **Adult:** Apply daily for 5 nights of each week for 6 weeks, to be applied to lesion and 1 cm beyond it, assess response 12 weeks after completing treatment.

**Actinic keratosis**

**TO THE SKIN**

- **Adult:** Apply 3 times a week for 4 weeks, to be applied to lesion at night, assess response after a 4 week treatment-free interval; repeat 4-week course if lesions persist, maximum 2 courses.

**ZYCLARA**

**Actinic keratosis**

**TO THE SKIN**

- **Adult:** Apply once daily for 2 weeks, to be applied at bedtime to lesion on face or balding scalp, repeat course after a 2-week treatment-free interval, assess response 8 weeks after second course; maximum 2 sachets per day.

**CAUTIONS** Autoimmune disease · avoid broken skin · avoid contact with eyes · avoid contact with lips · avoid contact with nostrils · avoid open wounds · immunosuppressed patients · not suitable for internal genital warts · uncircumcised males (risk of phimosis or stricture of foreskin).

**SIDE-EFFECTS**

- **Common or very common** Burning sensation · erosion · erythema · excoriation · headache · influenza-like symptoms · itching · local reactions · myalgia · oedema · scabbing.
- **Uncommon** Alopecia · local ulceration.
- **Rare** Cutaneous lupus erythematosus-like effect · Stevens-Johnson syndrome.
- **Very rare** Dysuria.
- **Frequency not known** Permanent hyperpigmentation · permanent hypopigmentation.

**CONCEPTION AND CONTRACEPTION** May damage latex condoms and diaphragms.

**PREGNANCY** No evidence of teratogenicity or toxicity in animal studies; manufacturer advises caution.

**BREAST FEEDING** No information available.

**DIRECTIONS FOR ADMINISTRATION**

**ALDARA**

**Important** Should be rubbed in and allowed to stay on the treated area for 6–10 hours for warts or for 8 hours for basal cell carcinoma and actinic keratosis, then washed off with mild soap and water (uncircumcised males treating warts under foreskin should wash the area daily). The cream should be washed off before sexual contact.

**ZYCLARA**

**Important** Should be rubbed in and allowed to stay on the treated area for 8 hours, then washed off with mild soap and water.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: liquid stick.

- **Aldara** (Meda Pharmaceuticals Ltd)
  - Imiquimod 50 mg per 1 gram Aldara 5% cream 250mg sachets | 12 sachet | £48.60 DT price = £48.60.
  - Zyclara (Meda Pharmaceuticals Ltd)
  - Imiquimod 37.5 mg per 1 gram Zyclara 3.75% cream 250mg sachets | 28 sachet | £113.00.

**SALICYLATES**

**Salicylic acid**

**INDICATIONS AND DOSE**

**OCCULARSAL**

**Common and plantar warts**

**TO THE SKIN**

- **Child:** Apply daily, treatment may need to be continued for up to 3 months.
- **Adult:** Apply daily, treatment may need to be continued for up to 3 months.

**VERRUGON**

**For plantar warts**

**TO THE SKIN**

- **Child:** Apply daily, treatment may need to be continued for up to 3 months.
- **Adult:** Apply daily, treatment may need to be continued for up to 3 months.

**UNLICENSED USE** Not licensed for use in children under 2 years.

**CAUTIONS** Avoid broken skin · impaired peripheral circulation · not suitable for application to ano-genital...
Skin

PRESCRIBING AND DISPENSING INFORMATION

Salicylic acid with lactic acid

The properties listed below are those particular to the combination only. For the properties of the components please consider, salicylic acid p. 1057.

INDICATIONS AND DOSE

CUPLEX®
Plantar and mosaic warts | Corns | Calluses
TO THE LESION
> Adult: Apply twice daily

DUOFILM®
Plantar and mosaic warts
TO THE LESION
> Adult: Apply daily

SALATAC®
Warts | Verrucas | Corns | Calluses
TO THE LESION
> Adult: Apply daily

SALACTOL®
Warts (particularly plantar warts) | Verrucas | Corns | Calluses
TO THE LESION
> Adult: Apply daily

PRESCRIBING AND DISPENSING INFORMATION

CUPLEX® AND SALACTOL®
Preparations of salicylic acid in a collodion basis are available but some patients may develop an allergy to colophony in the formulation.
Chapter 14

Vaccines

1 Immunoglobulin therapy

Immunoglobulins

Passive immunity

Immunoglobulins are available from the plasma of immune individuals with adequate levels of antibody to the disease for which protection is sought. The duration of this passive immunity varies according to the dose and the type of immunoglobulin. Passive immunity may last only a few weeks; when necessary, passive immunisation can be repeated. Antibodies of human origin are usually termed immunoglobulins. The term antisera is applied to material prepared in animals. Because of serum sickness and other allergic-type reactions that may follow injections of antisera, this therapy has been replaced wherever possible by the use of immunoglobulins. Reactions are theoretically possible after injection of human immunoglobulins but reports of such reactions are very rare.

Two types of human immunoglobulin preparation are available, normal immunoglobulin and disease-specific immunoglobulins.

Human immunoglobulin is a sterile preparation of concentrated antibodies (immune globulins) recovered from pooled human plasma or serum obtained from outside the UK, tested and found non-reactive for hepatitis B surface antigen and for antibodies against hepatitis C virus and human immunodeficiency virus (types 1 and 2). A global shortage of human immunoglobulin and the rapidly increasing range of clinical indications for treatment with immunoglobulins has resulted in the need for a Demand Management programme in the UK, for further information consult www.ivig.nhs.uk and Clinical Guidelines for Immunoglobulin Use (www.gov.uk/dh).

Further information on the use of immunoglobulins is included in Public Health England’s Immunoglobulin Handbook www.gov.uk/phe, and in the Department of Health’s publication, Immunisation against Infectious Disease, www.gov.uk/dh.

Availability

Normal immunoglobulin for intramuscular administration is available from some regional Public Health laboratories for protection of contacts and the control of outbreaks of hepatitis A, measles, and rubella only. For other indications, subcutaneous or intravenous normal immunoglobulin should be purchased from the manufacturer.

Disease-specific immunoglobulins are available from some regional Public Health laboratories, with the exception of tetanus immunoglobulin p. 1065 which is available from BPL, hospital pharmacies, or blood transfusion departments. Rabies immunoglobulin p. 1064 is available from the Specialist and Reference Microbiology Division, Public Health England, Colindale. Hepatitis B immunoglobulin p. 1062 required by transplant centres should be obtained commercially.

In Scotland all immunoglobulins are available from the Scottish National Blood Transfusion Service (SNBTS).

In Wales all immunoglobulins are available from the Welsh Blood Service (WBS).

In Northern Ireland all immunoglobulins are available from the Northern Ireland Blood Transfusion Service (NIBTS).

Normal immunoglobulin

Human normal immunoglobulin p. 1063 (‘HNIG’) is prepared from pools of at least 1000 donations of human plasma; it contains immunoglobulin G (IgG) and antibodies to hepatitis A, measles, mumps, rubella, varicella, and other viruses that are currently prevalent in the general population.

Uses

Normal immunoglobulin p. 1063 (containing 10%–18% protein) is administered by intramuscular injection for the protection of susceptible contacts against hepatitis A virus (infectious hepatitis), measles and, to a lesser extent, rubella. Injection of immunoglobulin produces immediate protection lasting several weeks.

Normal immunoglobulin p. 1063 (containing 3%–12% protein) for intravenous administration is used as replacement therapy for patients with congenital agammaglobulinaemia and hypogammaglobulinaemia, and for the short-term treatment of idiopathic thrombocytopenic purpura and Kawasaki disease; it is also used for the prophylaxis of infection following bone-marrow transplantation and in children with symptomatic HIV infection who have recurrent bacterial infections. Normal immunoglobulin for replacement therapy may also be given intramuscularly or subcutaneously, but intravenous formulations are normally preferred. Intravenous immunoglobulin is also used in the treatment of Guillain-Barré syndrome as an alternative to plasma exchange.

For guidance on the use of intravenous normal immunoglobulin and alternative therapies for certain conditions, consult Clinical Guidelines for Immunoglobulin Use (www.gov.uk/dh).

Hepatitis A

Hepatitis A vaccine p. 1081 is preferred for individuals at risk of infection including those visiting areas where the disease is highly endemic (all countries excluding Northern and Western Europe, North America, Japan, Australia, and New Zealand). In unimmunised individuals, transmission of hepatitis A is reduced by good hygiene. Intramuscular normal immunoglobulin p. 1063 is no longer recommended for routine prophylaxis in travellers, but it may be indicated for immunocompromised patients if their antibody response to the vaccine is unlikely to be adequate.

Intramuscular normal immunoglobulin is recommended for prevention of infection in close contacts (of confirmed cases of hepatitis A) who have chronic liver disease or HIV
infection, or who are immunosuppressed or over 50 years of age; normal immunoglobulin should be given as soon as possible, preferably within 14 days of exposure to the primary case. However, normal immunoglobulin can still be given to contacts at risk of severe disease up to 28 days after exposure to the primary case. Hepatitis A vaccine p. 1081 can be given at the same time, but it should be given at a separate injection site.

**Measles**

Intravenous or subcutaneous normal immunoglobulin p. 1063 may be given to prevent or attenuate an attack of measles in individuals who do not have adequate immunity. Patients with compromised immunity who have come into contact with measles should receive intravenous or subcutaneous normal immunoglobulin as soon as possible after exposure. It is most effective if given within 72 hours but can be effective if given within 6 days.

Subcutaneous or intramuscular normal immunoglobulin should also be considered for the following individuals if they have been in contact with a confirmed case of measles or with a person associated with a local outbreak:

- non-immune pregnant women
- infants under 9 months

Further advice should be sought from the Centre for Infections, Public Health England (tel. (020) 8200 6868). Individuals with normal immunity who are not in the above categories and who have not been fully immunised against measles, can be given measles, mumps and rubella vaccine, live p. 1087 for prophylaxis following exposure to measles.

**Rubella**

Intramuscular immunoglobulin after exposure to rubella does not prevent infection in non-immune contacts and is not recommended for protection of pregnant women exposed to rubella. It may, however, reduce the likelihood of a clinical attack which may possibly reduce the risk to the fetus. Risk of intra-uterine transmission is greatest in the first 11 weeks of pregnancy, between 16 and 20 weeks there is minimal risk of deafness only, after 20 weeks there is no increased risk. Intramuscular normal immunoglobulin p. 1063 should be used only if termination of pregnancy would be unacceptable to the pregnant woman—it should be given as soon as possible after exposure. Serological follow-up of recipients is essential to determine if the woman has become infected despite receiving immunoglobulin.

For routine prophylaxis against Rubella, see measles, mumps and rubella vaccine, live p. 1087.

**Disease-specific immunoglobulins**

Specific immunoglobulins are prepared by pooling the plasma of selected human donors with high levels of the specific antibody required. For further information, see Immunoglobulin Handbook (www.gov.uk/phe).

There are no specific immunoglobulins for hepatitis A, measles, or rubella—normal immunoglobulin p. 1063 is used in certain circumstances. There is no specific immunoglobulin for mumps; neither normal immunoglobulin nor measles, mumps and rubella vaccine, live is effective as post-exposure prophylaxis.

**Hepatitis B immunoglobulin**

Disease-specific hepatitis B immunoglobulin p. 1062 ('HBIG') is available for use in association with hepatitis B vaccine p. 1083 for the prevention of infection in laboratory and other personnel who have been accidentally inoculated with hepatitis B virus, and in infants born to mothers who have become infected with this virus in pregnancy or who are high-risk carriers. Hepatitis B immunoglobulin will not inhibit the antibody response when given at the same time as hepatitis B vaccine but should be given at different sites.

An intravenous and subcutaneous preparation of hepatitis B immunoglobulin is licensed for the prevention of hepatitis B recurrence in HBV-DNA negative patients who have undergone liver transplantation for liver failure caused by the virus.

**Rabies immunoglobulin**

Following exposure of an unimmunised individual to an animal in or from a country where the risk of rabies is high the site of the bite should be washed with soapy water and specific rabies immunoglobulin p. 1064 of human origin administered. All of the dose should be injected around the site of the wound; if this is difficult or the wound has completely healed it can be given in the anterolateral thigh (remote from the site used for vaccination). Rabies vaccine p. 1090 should also be given intramuscularly at a different site (for details see rabies vaccine). If there is delay in giving the rabies immunoglobulin p. 1064, it should be given within 7 days of starting the course of rabies vaccine.

**Tetanus immunoglobulin**

For the management of tetanus-prone wounds, tetanus immunoglobulin p. 1065 should be used in addition to wound cleaning and, when appropriate, antibacterial prophylaxis and a tetanus-containing vaccine. Tetanus immunoglobulin, together with metronidazole p. 1008 and wound cleansing, should also be used for the treatment of established cases of tetanus.

**Varicella-zoster immunoglobulin**

Varicella-zoster immunoglobulin p. 1065 (VZIG) is recommended for individuals who are at increased risk of severe varicella and who have no antibodies to varicella-zoster virus and who have significant exposure to chickenpox or herpes zoster. Those at increased risk include:

- neonates whose mothers develop chickenpox in the period 7 days before to 7 days after delivery;
- susceptible neonates exposed in the first 7 days of life;
- susceptible neonates or infants exposed whilst requiring intensive or prolonged special care nursing;
- susceptible women exposed at any stage of pregnancy (but when supplies of VZIG are short, may only be issued to those exposed in the first 20 weeks’ gestation or to those near term) providing VZIG is given within 10 days of contact;
- immunocompromised individuals including those who have received corticosteroids in the previous 3 months at the following dose equivalents of prednisolone: children 2 mg/kg daily for at least 1 week or 1 mg/kg daily for 1 month; adults about 40 mg daily for more than 1 week.

**Important:** for full details consult Immunisation against Infectious Disease. Varicella-zoster vaccine p. 1092 is available.

**Anti-D (Rh(D)) immunoglobulin**

Anti-D (Rh(D)) immunoglobulin p. 1061 is prepared from plasma taken from rhesus-negative donors who have been immunised against the anti-D-antigen. Anti-D (Rh(D)) immunoglobulin is used to prevent a rhesus-negative mother from forming antibodies to fetal rhesus-positive cells which may pass into the maternal circulation. The objective is to protect any subsequent child from the hazard of haemolytic disease of the newborn.

Anti-D (Rh(D)) immunoglobulin p. 1061 should be administered to the mother following any sensitising episode (e.g. abortion, miscarriage and birth); it should be injected within 72 hours of the episode but even if a longer period has elapsed it may still give protection and should be administered. Anti-D (Rh(D)) immunoglobulin p. 1061 is also given when significant feto-maternal haemorrhage occurs in rhesus-negative women during delivery. The dose of anti-
D (Rh\(_D\)) immunoglobulin below is determined according to the level of exposure to rhesus-positive blood.

Use of routine antenatal anti-D prophylaxis should be given irrespective of previous anti-D prophylaxis for a sensitising event early in the same pregnancy. Similarly, postpartum anti-D prophylaxis should be given irrespective of previous routine antenatal anti-D prophylaxis or antenatal anti-D prophylaxis for a sensitising event in the same pregnancy.

Anti-D (Rh\(_D\)) immunoglobulin below is also given to women of child-bearing potential after the inadvertent transfusion of rhesus-incompatible blood components and is used for the treatment of idiopathic thrombocytopenia purpura.

MMR vaccine
Measles, mumps and rubella vaccine, live p. 1087 may be given in the postpartum period with anti-D (Rh\(_D\)) immunoglobulin below injection provided that separate syringes are used and the products are administered into different limbs. If blood is transfused, the antibody response to the vaccine may be inhibited—measure rubella antibodies after 6–8 weeks and revaccinate if necessary.

IMMUNOGLOBULINS

Anti-D (Rh\(_D\)) immunoglobulin

### INDICATIONS AND DOSE

To rhesus-negative woman for prevention of Rh\(_D\) sensitisation, following birth of rhesus-positive infant

**BY DEEP INTRAMUSCULAR INJECTION**
- Females of childbearing potential: 500 units, dose to be administered immediately or within 72 hours; for transplacental bleed of over 4 mL fetal red cells, extra 100–125 units per mL fetal red cells, subcutaneous route used for patients with bleeding disorders

To rhesus-negative woman for prevention of Rh\(_D\) sensitisation, following any potentially sensitising episode (e.g. stillbirth, abortion, amniocentesis) up to 20 weeks’ gestation

**BY DEEP INTRAMUSCULAR INJECTION**
- Females of childbearing potential: 250 units per episode, dose to be administered immediately or within 72 hours, subcutaneous route used for patients with bleeding disorders

To rhesus-negative woman for prevention of Rh\(_D\) sensitisation, following any potentially sensitising episode (e.g. stillbirth, abortion, amniocentesis) after 20 weeks’ gestation

**BY DEEP INTRAMUSCULAR INJECTION**
- Females of childbearing potential: 500 units per episode, dose to be administered immediately or within 72 hours, subcutaneous route used for patients with bleeding disorders

To rhesus-negative woman for prevention of Rh\(_D\) sensitisation, antenatal prophylaxis

**BY DEEP INTRAMUSCULAR INJECTION**
- Females of childbearing potential: 500 units, dose to be given at weeks 28 and 34 of pregnancy, alternatively 1500 units for 1 dose, dose to be given between 28 and 34 weeks gestation

To rhesus-negative woman for prevention of Rh\(_D\) sensitisation, following Rh\(_D\) incompatible blood transfusion

**BY DEEP INTRAMUSCULAR INJECTION**
- Females of childbearing potential: 100–125 units/mL, dose per mL transfused rhesus-positive red cells given, subcutaneous route used for patients with bleeding disorders

**RHOPHYLAC\(^\text{®}\)**

To rhesus-negative woman for prevention of Rh\(_D\) sensitisation, following birth of rhesus-positive infant

**BY INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INJECTION**
- Females of childbearing potential: 1000 units per episode, dose to be administered immediately or within 72 hours, intravenous route recommended for patients with bleeding disorders, higher doses may be required after 12 weeks gestation

To rhesus-negative woman for prevention of Rh\(_D\) sensitisation, following any potentially sensitising episode (e.g. abortion, amniocentesis, chorionic villous sampling) up to 12 weeks’ gestation

**BY INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INJECTION**
- Females of childbearing potential: 1500 units, dose to be given between weeks 28–30 of pregnancy; if infant rhesus-positive, a further dose is still needed immediately or within 72 hours of delivery, intravenous route recommended for patients with bleeding disorders

To rhesus-negative woman for prevention of Rh\(_D\) sensitisation, following Rh\(_D\) incompatible blood transfusion

**BY INTRAVENOUS INJECTION**
- Females of childbearing potential: 50 units/mL, dose per mL of transfused rhesus-positive blood, alternatively 100 units/mL, dose per mL of erythrocyte concentrate, intravenous route recommended for patients with bleeding disorders

- **CONTRA-INDICATIONS** Treatment of idiopathic thrombocytopenia purpura in rhesus negative patients • treatment of idiopathic thrombocytopenia purpura in splenectomised patients

- **CAUTIONS** Immunoglobulin A deficiency • possible interference with live virus vaccines

CAUTIONS, FURTHER INFORMATION
MMR vaccine may be given in the postpartum period with anti-D (Rh\(_D\)) immunoglobulin injection provided that separate syringes are used and the products are administered into different limbs. If blood is transfused, the antibody response to the vaccine may be inhibited—measure rubella antibodies after 6–8 weeks and revaccinate if necessary.

- **INTERACTIONS** → Appendix 1 (immunoglobulins).

SIDE-EFFECTS

GENERAL SIDE-EFFECTS
- Rare Anaphylaxis • dyspnoea • hypotension • tachycardia • urticaria
- Frequency not known Abdominal pain • arthralgia • asthenia • back pain • diarrhoea • dizziness • drowsiness •
fever • headache • hypertension • hypotension • injection site pain • malaise • myalgia • nausea • pruritus • rash • sweating • vomiting

SPECIFIC SIDE-EFFECTS
- With intravenous use abdominal distension • abdominal pain • blood pressure fluctuations • deep vein thrombosis • haemolytic anaemia • injection site reactions • myocardial infarction • pulmonary embolism • stroke • thromboembolic events

HANDLING AND STORAGE Care must be taken to store all immunological products under the conditions recommended in the product literature, otherwise the preparation may become ineffective. Refrigerated storage is usually necessary; many immunoglobulins need to be stored at 2–8°C and not allowed to freeze. Immunoglobulins should be protected from light. Opened multidose vials must be used within the period recommended in the product literature.

NATIONAL FUNDING/ACCESS DECISIONS
NICE technology appraisals (TAs)
- Routine antenatal anti-D prophylaxis for rhesus-negative women (August 2008) NICE TA156

Vaccines

14

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
- D-Gam (Bio Products Laboratory Ltd)
  - Anti-D (RHO) immunoglobulin 250 unit solution for injection vials 1 vial £33.75
  - Anti-D (RHO) immunoglobulin 500 unit solution for injection vials 1 vial £68.00
  - Anti-D (RHO) immunoglobulin 1500 unit solution for injection vials 1 vial £156
- Rhophylac (CSL Behring UK Ltd)
  - Anti-D (RHO) immunoglobulin 750 unit per 1 ml solution for injection pre-filled syringes 1 vial £39.52

Hepatitis B immunoglobulin

INDICATIONS AND DOSE
Prophylaxis against hepatitis B infection

BY INTRAMUSCULAR INJECTION
- Adult: 500 units, dose to be administered as soon as possible after exposure; ideally within 12–48 hours, but no later than 7 days after exposure

Prophylaxis against hepatitis B infection, after exposure to hepatitis B virus-contaminated material

BY INTRAVENOUS INFUSION
- Adult: Dose to be administered as soon as possible after exposure, but no later than 72 hours (consult product literature)

Prevention of hepatitis B in haemodialysed patients

BY INTRAVENOUS INFUSION
- Adult: (consult product literature)

Prophylaxis against re-infection of transplanted liver

BY INTRAVENOUS INFUSION
- Adult: (consult product literature)

Prevention of hepatitis B re-infection more than 6 months after liver transplantation in stable HBV-DNA negative patients

BY SUBCUTANEOUS INJECTION
- Adult (body-weight up to 75 kg): 500 units once weekly, increased if necessary up to 1000 units once weekly, dose to be started 2–3 weeks after last dose of intravenous hepatitis B immunoglobulin
- Adult (body-weight 75 kg and above): 1000 units once weekly, dose to be started 2–3 weeks after last dose of intravenous hepatitis B immunoglobulin

CAUTIONS
- IgA deficiency • interference with live virus vaccines

SIDE-EFFECTS

GENERAL SIDE-EFFECTS
- Common or very common Injection site reactions
- Uncommon Abdominal pain • anaphylaxis • arthralgia • buccal ulceration • chest pain • dizziness • dyspnoea • glossitis • headache • tremor

SPECIFIC SIDE-EFFECTS
- With intravenous use abdominal distension • abdominal pain • blood pressure fluctuations • deep vein thrombosis • haemolytic anaemia • injection site reactions • myocardial infarction • pulmonary embolism • stroke • thromboembolic events

PRESCRIBING AND DISPENSING INFORMATION
Vials containing 200 units or 500 units (for intramuscular injection), available from selected Public Health England and NHS laboratories (except for Transplant Centres), also available from BPL.

HANDLING AND STORAGE Care must be taken to store all immunological products under the conditions recommended in the product literature, otherwise the preparation may become ineffective. Refrigerated storage is usually necessary; many immunoglobulins need to be stored at 2–8°C and not allowed to freeze. Immunoglobulins should be protected from light. Opened multidose vials must be used within the period recommended in the product literature.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
- HEPATITIS B IMMUNOGLOBULIN (Non-proprietary)
  - Hepatitis B immunoglobulin human 200 unit solution for injection vials 1 vial £122.44
  - Hepatitis B immunoglobulin human 500 unit solution for injection vials 1 vial £266.33
- Zutecra (Biotest (UK) Ltd)
  - Zutecra 500units/1ml solution for injection pre-filled syringes 5 syringe no price available

Solution for infusion
- Hepact CP (Biotest (UK) Ltd)
  - Hepatitis B immunoglobulin human 50 unit per 1 ml solution for infusion vials 1 vial no price available

BNF 70
Normal immunoglobulin

INDICATIONS AND DOSE

To control outbreaks of hepatitis A
By deep intramuscular injection
- Adult: 500 mg
Rubella in pregnancy, prevention of clinical attack
By deep intramuscular injection
- Females of childbearing potential: 750 mg
Antibody deficiency syndromes
By subcutaneous infusion
- Adult: (consult product literature)

SUBGAM®
Hepatitis A prophylaxis in outbreaks
By intramuscular injection
- Adult: 750 mg

UNLICENSED USE

SUBGAM® Subgam® is not licensed for prophylactic use, but due to difficulty in obtaining suitable immunoglobulin products, Public Health England recommends intramuscular use for prophylaxis against hepatitis A or rubella.

CONTRA-INDICATIONS
Patients with selective IgA deficiency who have known antibody against IgA

FLEBOGAMMA® DIF SOLUTION FOR INFUSION
Hereditary fructose intolerance (contains sorbitol)

GAMMAPLEX® SOLUTION FOR INFUSION
Hereditary fructose intolerance (contains sorbitol)

HIZENTRA® SOLUTION FOR INFUSION
Hyperprolinaemia (contains L-proline)

PRIVIGEN® SOLUTION FOR INFUSION
Hyperprolinaemia (contains L-proline)

CAUTIONS

GENERAL CAUTIONS
Agammaglobulinaemia with or without IgA deficiency - hypogammaglobulinaemia with or without IgA deficiency - interference with live virus vaccines

SPECIFIC CAUTIONS
- With intravenous use: ensure adequate hydration - obesity - renal insufficiency - risk factors for arterial thromboembolic events - risk factors for venous thromboembolic events - thrombophilic disorders

OCTAGAM® SOLUTION FOR INFUSION
Falsely elevated results with blood glucose testing systems (contains maltose)

CAUTIONS, FURTHER INFORMATION
Interference with live virus vaccines Normal immunoglobulin may interfere with the immune response to live virus vaccines which should therefore only be given at least 3 weeks before or 3 months after an injection of normal immunoglobulin (this does not apply to yellow fever vaccine since normal immunoglobulin does not contain antibody to this virus).

INTERACTIONS
- Appendix 1 (immunoglobulins).

SIDE-EFFECTS

GENERAL SIDE-EFFECTS
- Rare: Acute renal failure - anaphylaxis - aseptic meningitis - cutaneous skin reactions - hypotension
- Frequency not known: Arthralgia - chills - diarrhoea - dizziness - fever - headache - low back pain - muscle spasms - myalgia - nausea

SPECIFIC SIDE-EFFECTS
- With intravenous use: abdominal distension - abdominal pain - blood pressure fluctuations - deep vein thrombosis - haemolytic anaemia - injection site reactions - myocardial infarction - pulmonary embolism - stroke - thromboembolic events

SIDE-EFFECTS, FURTHER INFORMATION

Adverse reactions are more likely to occur in patients receiving normal immunoglobulin for the first time, or following a prolonged period between treatments, or when a different brand of normal immunoglobulin is administered.

MONITORING REQUIREMENTS
Monitor for acute renal failure; consider discontinuation if renal function deteriorates. Intravenous preparations with added sucrose have been associated with cases of renal dysfunction and acute renal failure.

DIRECTIONS FOR ADMINISTRATION
Preparations for subcutaneous use may be administered by intramuscular injection if subcutaneous route not possible; intramuscular route not for patients with thrombocytopenia or other bleeding disorders.

KIOVIC® SOLUTION FOR INFUSION
Use Glucose 5% intravenous infusion if dilution prior to infusion is required.

GAMUNEX® SOLUTION FOR INFUSION
Use Glucose 5% intravenous infusion if dilution prior to infusion is required.

PRESCRIBING AND DISPENSING INFORMATION
Antibody titres can vary widely between normal immunoglobulin preparations from different manufacturers—formulations are not interchangeable; patients should be maintained on the same formulation throughout long-term treatment to avoid adverse effects.

With intramuscular use
Available from the Centre for Infections and other regional Public Health England offices (for contacts and control of outbreaks only).

HANDLING AND STORAGE
Care must be taken to store all immunological products under the conditions recommended in the product literature, otherwise the preparation may become ineffective. Refrigerated storage is usually necessary; many immunoglobulins need to be stored at 2–8°C and not allowed to freeze. Immunoglobulins should be protected from light. Opened multidose vials must be used within the period recommended in the product literature.

MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

ELECTROLYTES: May contain Sodium
- Gammanorm (Octapharma Ltd)
  Normal immunoglobulin human 165 mg per 1 ml Gammanorm 3.3g/20ml solution for injection vials | 1 vial (£3) £13.55 Gammanorm 1.65g/10ml solution for injection vials | 1 vial (£3) £9.77
- Subcuvia (Baxter Healthcare Ltd)
  Normal immunoglobulin human 160 mg per 1 ml Subcuvia 800mg/5ml solution for injection vials | 1 vial (£4) no price available
- Subcuvia 1.6g/10ml solution for injection vials | 1 vial (£4) no price available
- Subgam (Bio Products Laboratory Ltd)
  Normal immunoglobulin human 150 mg per 1 ml Subgam 750mg/5ml solution for injection vials | 1 vial (£4) £34.20 Subgam 1.5g/10ml solution for injection vials | 1 vial (£4) £68.40

Powder and solvent for solution for injection
- Gammagard S/D (Baxter Healthcare Ltd)
  Normal immunoglobulin human 5 gram Gammagard S/D 5g powder and solvent for solution for injection bottles | 1 bottle (£3) no price available
- Normal immunoglobulin human 10 gram Gammagard S/D 10g powder and solvent for solution for injection bottles | 1 bottle (£3) no price available

Vaccines
### Solution for infusion

**EXCipients:** May contain Glucose, maltose, sorbitol, sucrose

- **NORMAL IMMUNOGLOBULIN (Non-proprietary)**
  - Normal immunoglobulin human 100 mg per 1 ml | Octaplas 100 mg/5 ml solution for infusion vials | 1 vial (Pfz) no price available
  - Normal immunoglobulin 2.5g/25ml solution for infusion vials | 1 vial (Pfz) no price available
  - Normal immunoglobulin human 20g/200ml solution for infusion vials | 1 vial (Pfz) no price available
  - Normal immunoglobulin human 100/100ml solution for infusion vials | 1 vial (Pfz) no price available
  - Normal immunoglobulin human 30g/300ml solution for infusion vials | 1 vial (Pfz) no price available

- **Aragram (Oxbridge Pharma Ltd)**
  - Normal immunoglobulin human 50 mg per 1 ml | Aragram 5g/100ml solution for infusion vials | 1 vial (Pfz) no price available
  - Aragram 2.5g/50ml solution for infusion vials | 1 vial (Pfz) no price available

- **Flebogammadif (Grifols UK Ltd)**
  - Normal immunoglobulin human 50 mg per 1 ml | Flebogamma DIF 10g/200ml solution for infusion vials | 1 vial (Pfz) £112.50
  - Flebogamma DIF 2.5g/50ml solution for infusion vials | 1 vial (Pfz) £27.50
  - Flebogamma DIF 5g/100ml solution for infusion vials | 1 vial (Pfz) £25.50
  - Flebogamma DIF 500mg/10ml solution for infusion vials | 1 vial (Pfz) £30.00
  - Flebogamma DIF 20g/400ml solution for infusion vials | 1 vial (Pfz) £1,020.00

- **Gammaplex (Bioproducts Laboratories Ltd)**
  - Normal immunoglobulin human 50 mg per 1 ml | Gammaplex 10g/200ml solution for infusion vials | 1 vial (Pfz) £48.00
  - Gammaplex 1g/10ml solution for infusion vials | 1 vial (Pfz) £42.50
  - Gammaplex 10g/100ml solution for infusion vials | 1 vial (Pfz) £425.00
  - Gamunex 10g/200ml solution for infusion vials | 1 vial (Pfz) £1,020.00
  - Gamunex 10g/100ml solution for infusion vials | 1 vial (Pfz) £50.00
  - Gamunex 10g/100ml solution for infusion vials | 1 vial (Pfz) £122.50

- **Hizentra (CSL Behring UK Ltd)**
  - Normal immunoglobulin human 200 mg per 1 ml | Hizentra 2g/10ml solution for infusion vials | 1 vial (Pfz) £91.80
  - Hizentra 1g/5ml solution for infusion vials | 1 vial (Pfz) £45.90
  - Hizentra 4g/20ml solution for infusion vials | 1 vial (Pfz) £183.60
  - Intratect (Biotest (UK) Ltd)
  - Normal immunoglobulin human 50 mg per 1 ml | Intratect 5g/100ml solution for infusion vials | 1 vial (Pfz) £22.50
  - Intratect 1g/20ml solution for infusion vials | 1 vial (Pfz) £45.00
  - Intratect 2.5g/50ml solution for infusion vials | 1 vial (Pfz) £112.50
  - Intratect 10g/200ml solution for infusion vials | 1 vial (Pfz) £450.00

- **Kiovig (Baxter Healthcare Ltd)**
  - Normal immunoglobulin human 100 mg per 1 ml | Kiovig 5g/50ml solution for infusion vials | 1 vial (Pfz) no price available
  - Kiovig 20g/200ml solution for infusion vials | 1 vial (Pfz) no price available
  - Kiovig 5g/50ml solution for infusion vials | 1 vial (Pfz) no price available
  - Kiovig 2.5g/25ml solution for infusion vials | 1 vial (Pfz) no price available
  - Kiovig 1g/10ml solution for infusion vials | 1 vial (Pfz) no price available

### Indications and Dose

**Post-exposure prophylaxis against rabies infection by local infiltration or by intramuscular injection**

- **Child:** 20 units/kg, dose administered by infiltration in and around the cleansed wound; if the wound not visible or healed or if infiltration of whole volume not possible, give remainder by intramuscular injection into anterolateral thigh (remote from vaccination site)

- **Adult:** 20 units/kg, dose administered by infiltration in and around the cleansed wound; if the wound not visible or healed or if infiltration of whole volume not possible, give remainder by intramuscular injection into anterolateral thigh (remote from vaccination site)

- **CAUTIONS** Iga deficiency - interference with live virus vaccines

- **SIDE-EFFECTS**
  - Rare: Anaphylaxis - arthralgia - buccal ulceration - chest tightness - dizziness - dysphoeea - glossitis - tremor
  - Frequency not known: Facial oedema - injection site pain - injection site swelling

**PRESCRIBING AND DISPENSING INFORMATION** The potency of individual batches of rabies immunoglobulin from the manufacturer may vary; potency may also be described differently by different manufacturers. It is therefore critical to know the potency of the batch to be used and the weight of the patient in order to calculate the specific volume required to provide the necessary dose. Available from Specialist and Reference Microbiology Division, Public Health England (also from BPL).

**HANDLING AND STORAGE** Care must be taken to store all immunological products under the conditions recommended in the product literature, otherwise the preparation may become ineffective. *Refrigerated storage* is usually necessary; many immunoglobulins need to be stored at 2–8°C and not allowed to freeze. Immunoglobulins should be protected from light. Opened multidose vials must be used within the period recommended in the product literature.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
2 Post-exposure prophylaxis

ANTITOXINS

Botulinum antitoxin

- **Drug Action** A preparation containing the specific antitoxin globulins that have the power of neutralising the toxins formed by types A, B, and E of Clostridium botulinum.

- **Indications and Dose**

  - **Post exposure prophylaxis of botulism**

  - **By Intramuscular Injection**

  - Adult: (consult product literature)

- **Side-effects** Hypersensitivity reactions

- **Further Information**

  - **Hypersensitivity reactions** It is essential to read the contra-indications, warnings, and details of sensitivity tests on the package insert. Prior to treatment checks should be made regarding previous administration of any antitoxin and history of any allergic condition, e.g. asthma, hay fever, etc.

- **Pre-treatment Screening** All patients should be tested for sensitivity (diluting the antitoxin if history of allergy).

- **Prescribing and Dispensing Information** Available from local designated centres, for details see TOXBASE (requires registration) [www.toxbase.org](http://www.toxbase.org). For supplies outside working hours apply to other designated centres or to the Public Health England Colindale duty doctor (Tel (020) 8200 6868). For major incidents, obtain supplies from the local blood bank.

  - The BP title Botulinum Antitoxin is not used because the preparation currently in use may have a different specification.

- **Medicinal Forms**

  - There can be variation in the licensing of different medicines containing the same drug.

  - **Solution for injection**

    - **Botulinum Antitoxin (Non-proprietary)**

      - Botulinum antitoxin type A 750 unit per 1 ml, Botulinum antitoxin type B 500 unit per 1 ml, Botulinum antitoxin type E
3 Tuberculosis diagnostic test

DIAGNOSTICS

Tuberculin purified protein derivative (Tuberculin PPD)

INDICATIONS AND DOSE

Mantoux test
BY INTRADERMAL INJECTION
- Child: 2 units for one dose
- Adult: 2 units for one dose

Mantoux test (if first test is negative and a further test is considered appropriate)
BY INTRADERMAL INJECTION
- Child: 10 units for 1 dose
- Adult: 10 units for 1 dose

Dose equivalence and conversion
2 units is equivalent to 0.1 mL of 20 units/mL strength. 10 units is equivalent to 0.1 mL of 100 units/mL strength.

CAUTIONS
Mantoux test Response to tuberculin may be suppressed by live viral vaccines, viral infection, sarcoidosis, corticosteroid therapy, or immunosuppression due to disease or treatment. Mantoux testing should not be carried out within 4 weeks of receiving a live viral vaccine.

PRESCRIBING AND DISPENSING INFORMATION
Available from ImmForm (SSI brand). The strength of tuberculin PPD in currently available products may be different to the strengths of products used previously for the Mantoux test; care is required to select the correct strength.

4 Vaccination

Vaccines

Active immunity
Active immunity can be acquired by natural disease or by vaccination. Vaccines stimulate production of antibodies and other components of the immune mechanism; they consist of either:
- a live attenuated form of a virus (e.g. measles, mumps and rubella vaccine) or bacteria (e.g. BCG vaccine), or
- inactivated preparations of the virus (e.g. influenza vaccine) or bacteria, or
- detoxified exotoxins produced by a micro-organism (e.g. tetanus vaccine), or
- extracts of a micro-organism, which may be derived from the organism (e.g. pneumococcal vaccine) or produced by recombinant DNA technology (e.g. hepatitis B vaccine).

Live attenuated vaccines usually produce a durable immunity, but not always as long-lasting as that resulting from natural infection.

Inactivated vaccines may require a primary series of injections of vaccine to produce an adequate antibody response, and in most cases booster (reinforcing) injections are required; the duration of immunity varies from months to many years. Some inactivated vaccines are adsorbed onto an adjuvant (such as aluminium hydroxide) to enhance the antibody response.

Advice reflects that in the handbook Immunisation against Infectious Disease (2006), which in turn reflects the guidance of the Joint Committee on Vaccination and Immunisation (JCVI).

Chapters from the handbook are available at www.immunisation.dh.gov.uk

The advice also incorporates changes announced by the Chief Medical Officer and Health Department Updates.

Immunisation schedule
Vaccines for the childhood immunisation schedule should be obtained from local health organisations or from ImmForm (www.immform.dh.gov.uk)—not to be prescribed on FP10 (HS21 in Northern Ireland; GP10 in Scotland; WP10 in Wales). For most up to date immunisation schedule consult The complete routine immunisation schedule available at (www.gov.uk)

Preterm birth
Babies born preterm should receive all routine immunisations based on their actual date of birth. The risk of apnoea following vaccination is increased in preterm babies, particularly in those born at or before 28 weeks gestational age. If babies at risk of apnoea are in hospital at the time of their first immunisation, they should be monitored for 48 hours after immunisation. If a baby develops apnoea, bradycardia, or desaturation after the first immunisation, the second immunisation should also be given in hospital with similar monitoring. Seroconversion may be unreliable in babies born earlier than 28 weeks’ gestation or in babies treated with corticosteroids for chronic lung disease; consideration should be given to testing for antibodies against Haemophilus influenzae type b, meningococcal C, and hepatitis B after primary immunisation.
### Immunisation Guidelines for HIV-Infected Adults

#### Vaccines and HIV infection

HIV-positive individuals with or without symptoms can receive the following live vaccines:

- MMR (but avoid if immunity significantly impaired; use of normal immunoglobulin should be considered after exposure to measles), varicella-zoster vaccine against chickenpox (but avoid if immunity significantly impaired—consult product literature; varicella—zoster immunoglobulin should be considered after exposure to chickenpox or herpes zoster), rotavirus; and the following inactivated vaccines:
  - anthrax, cholera (oral), diphtheria, haemophilus influenzae type b, hepatitis A, hepatitis B, human papillomavirus, influenza (injection), meningococcal, pertussis, pneumococcal, poliomyelitis, rabies, tetanus, tick-borne encephalitis, typhoid (injection).

HIV-positive individuals should not receive:

- BCG, influenza nasal spray (unless stable HIV infection and receiving antiretroviral therapy), typhoid (oral), yellow fever (if yellow fever risk is unavoidable, specialist advice should be sought)

The above advice differs from that for other immunocompromised patients; *Immunisation Guidelines for HIV-infected Adults* issued by British HIV Association (BHIVA) are available at [www.bhiva.org](http://www.bhiva.org)

#### Vaccines and asplenia

The following vaccines are recommended for asplenic patients or those with splenic dysfunction:

- haemophilus influenzae type b; influenza; pneumococcal A, C, W135, and Y conjugate; pneumococcal.

#### Vaccines and antiseras availability

- Anthrax vaccine p. 1078 and yellow fever vaccine, live p. 1092, botulism antitoxin p. 1065, diphtheria antitoxin p. 1066, and snake and spider venom antitoxins are available from local designated holding centres.

For antivenom, see *Emergency treatment of poisoning p. 1123.*

Enquiries for vaccines not available commercially can also be made to:

**Public Health England**

Vaccines and Countermeasures Response Department
Public Health England
Wellington House
133–155 Waterloo Road
London SE1 8UG
vaccinesupply@phe.gov.uk

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<tr>
<th>When to immunise</th>
<th>Vaccine given and dose schedule (for details of dose, see under individual vaccines)</th>
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| Neonates at risk only | Bacillus Calmette-Guérin vaccine p. 1078  
Hepatitis B vaccine p. 1083  
Diphtheria with haemophilus influenzae type b vaccine, pertussis, poliomyelitis and tetanus p. 1079 First dose  
Pneumococcal vaccine p. 1089 First dose  
Rotavirus vaccine p. 1090 First dose |
| 2 months | Influenza nasal spray (unless stable HIV infection and receiving antiretroviral therapy)  
Meningococcal group C vaccine p. 1088 First dose  
Pneumococcal vaccine p. 1089 Second dose |
| 3 months | Meningococcal group C vaccine p. 1088 First dose  
Pneumococcal vaccine p. 1089 Second dose |
| 4 months | Meningococcal group C vaccine p. 1088 Single booster dose  
Diphtheria with haemophilus influenzae type b vaccine, pertussis, poliomyelitis and tetanus p. 1079 Third dose  
Pneumococcal vaccine p. 1089 Second dose |
| 12-13 months | Diphtheria with pertussis, poliomyelitis vaccine and tetanus p. 1080 Single booster dose  
Measles, mumps and rubella vaccine, live p. 1087 First dose  
Pneumococcal vaccine p. 1089 First dose  
Haemophilus influenzae type b with meningococcal group C vaccine p. 1080 Single booster dose |
| Between 3 years and 4 months, and 5 years | Diphtheria with pertussis, poliomyelitis vaccine and tetanus p. 1080 Single booster dose  
Note: Preferably allow interval of at least 3 years after completing primary course  
Measles, mumps and rubella vaccine, live p. 1087 Second dose |
| 11-14 years (females only). First dose of HPV vaccine will be offered to females aged 12-13 years of age in England, Wales, and Northern Ireland, and 11-14 years of age in Scotland. | Human papillomavirus vaccines p. 1085 If a 3-dose course of HPV vaccine has been started under the 2013/2014 programme, where possible, the course should be completed. The two human papillomavirus vaccines are not interchangeable and, ideally, one vaccine product should be used for the entire course. However, for those females who started the schedule with Cervarix® under the national immunisation programme, but did not complete the vaccination course, the course can be completed with Gardasil®. |
| 13-15 years | Meningococcal group C vaccine p. 1088 Single booster dose |
| 13-18 years | Diphtheria with poliomyelitis and tetanus vaccine p. 1080 Single booster dose. Note: Can be given at the same time as the booster dose of meningococcal group C conjugate vaccine at 13-15 years of age. |
| During adult life, women of child-bearing age susceptible to rubella | Measles, mumps and rubella vaccine, live p. 1087 Women of child-bearing age who have not received 2 doses of a rubella-containing vaccine or who do not have a positive antibody test for rubella should be offered rubella immunisation (using the MMR vaccine)—exclude pregnancy before immunisation. |
| During adult life, those entering or being at university who are at risk of meningococcal group C disease | Meningococcal group C vaccine p. 1088 Single dose. Note: Should be offered to those of any age entering or being at university who have never been vaccinated against meningococcal group C disease, or those born after September 1995 who are entering university and only received meningococcal group C vaccine under the age of 10 years |
| During adult life, if not previously immunised | Diphtheria with poliomyelitis and tetanus vaccine p. 1080 |
| 70 years | Varicella-zoster vaccine p. 1092 Single dose |
In Scotland information about availability of vaccines can be obtained from a Specialist in Pharmaceutical Public Health.

In Wales enquiries for vaccines not available commercially should be directed to:

University Hospital of Wales
Welsh Medicines Information Centre
University Hospital of Wales
Cardiff CF14 4XW
(029) 2074 2979

In Northern Ireland:
Northern Health and Social Care Trust
Pharmacy and Medicines Management Centre
Northern Health and Social Care Trust
Beech House
Antrim Hospital Site
Bush Road
Antrim BT41 2RL
rphps.admin@northerntrust.hscni.net

For further details of availability, see under individual vaccines.

Anthrax vaccine
Anthrax vaccine p. 1078 is made from antigens from *B. anthracis*. Anthrax immunisation is indicated for individuals who handle infected animals, for those exposed to imported infected animal products, and for laboratory staff who work with *B. anthracis*. A 4-dose regimen is used for primary immunisation; booster doses should be given annually to workers at continued risk of exposure to anthrax.

In the event of possible contact with *B. anthracis*, post-exposure immunisation may be indicated, in addition to antimicrobial prophylaxis. Advice on the use of anthrax vaccine p. 1078 for post-exposure prophylaxis must be obtained from Public Health England Colindale (tel. 020 8200 4400).

BCG vaccine
BCG (Bacillus Calmette-Guérin) vaccine p. 1078 should be given intradermally by operators skilled in the technique. The expected reaction to successful BCG vaccine is induration at the site of injection followed by a local lesion which starts as a papule 2 or more weeks after vaccination; the lesion may ulcerate then subside over several weeks or months, leaving a small, flat scar. A dry dressing may be used if the ulcer discharges, but air should not be excluded.

BCG is recommended for the following groups if BCG immunisation has not previously been carried out and they are negative for tuberculin protein hypersensitivity:

- neonates with a family history of tuberculosis in the last 5 years;
- all neonates and infants (0–12 months) born in areas where the incidence of tuberculosis is greater than 40 per 100 000;
- neonates, infants, and children under 16 years with a parent or grandparent born in a country with an incidence of tuberculosis greater than 40 per 100 000;
- new immigrants aged under 16 years who were born in, or lived for more than 2 months in a country with an incidence of tuberculosis greater than 40 per 100 000;
- new immigrants aged 16–35 years from Sub-Saharan Africa or a country with an incidence of tuberculosis greater than 500 per 100 000;
- contacts aged under 36 years of those with active respiratory tuberculosis (for healthcare or laboratory workers who have had contact with clinical materials or patients with tuberculosis, age limit does not apply);
- healthcare workers and laboratory staff (irrespective of age) who are likely to have contact with patients, clinical materials, or derived isolates; other individuals under 35 years (there is inadequate evidence of protection by BCG vaccine in adults aged over 35 years; however, vaccination is recommended for healthcare workers irrespective of age because of the increased risk to them or their patients) at occupational risk including veterinary and other staff who handle animal species susceptible to tuberculosis, and staff working directly with prisoners, in care homes for the elderly, or in hostels or facilities for the homeless or refugees;
- individuals under 16 years intending to live with local people for more than 3 months in a country with an incidence of tuberculosis greater than 40 per 100 000.

List of countries or primary care trusts where the incidence of tuberculosis is greater than 40 cases per 100 000 is available at www.gov.uk/phe.

Bladder instillations of BCG are licensed for the management of bladder carcinoma.

See also Tuberculosis p. 501 for advice on chemoprophylaxis; for the treatment of infection following vaccination, seek expert advice.

Tuberculosis Diagnostic Agents
The Mantoux test is recommended for tuberculin skin testing, but no licensed preparation is currently available. Guidance for healthcare professionals is available at www.dh.gov.uk/immunisation.

In the Mantoux test, the diagnostic dose is administered by intradermal injection of tubercul purified protein derivative p. 1066 (PPD).

The Heaf test (involving the use of multiple-puncture apparatus) is no longer available.

Two interferon gamma release assay (IGRA) tests are also available as an aid in the diagnosis of tuberculosis infection: QuantiFERON® TB Gold and T-Spot®. Both tests measure T-cell mediated immune response to synthetic antigens. For further information on the use of interferon gamma release assay tests for tuberculosis, see www.gov.uk/phe.

Botulism antitoxin
A polyvalent botulism antitoxin p. 1065 is available for the post-exposure prophylaxis of botulism and for the treatment of persons thought to be suffering from botulism. It specifically neutralises the toxins produced by *Clostridium botulinum* types A, B, and E. It is not effective against infantile botulism as the toxin (type A) is seldom, if ever, found in the blood in this type of infection.

Cholera vaccine
Cholera vaccine p. 1079 (oral) contains inactivated Inaba (including El-Tor biotype) and Ogawa strains of *Vibrio cholerae*, serotype O1 together with recombinant B-subunit of the cholera toxin produced in Inaba strains of *V.cholerae*, serotype O1.

Oral cholera vaccine is licensed for travellers to endemic or epidemic areas on the basis of current recommendations. Immunisation should be completed at least 1 week before potential exposure. However, there is no requirement for cholera vaccination for international travel. Injectable cholera vaccine provides unreliable protection and is no longer available in the UK.

Diphtheria vaccine
Diphtheria-containing vaccines are prepared from the toxin of *Corynebacterium diphtheriae* and adsorption on aluminium hydroxide or aluminium phosphate improves antigenicity. The vaccine stimulates the production of the protective antibody. The quantity of diphtheria toxoid in a preparation determines whether the vaccine is defined as ‘high dose’ or ‘low dose’. Vaccines containing the higher dose of diphtheria toxoid are used for primary
immunisation of children under 10 years of age. Vaccines containing the lower dose of diphtheria toxoid are used for primary immunisation in adults and children over 10 years. Single-antigen diphtheria vaccine is not available and adsorbed diphtheria vaccine is given as a combination product containing other vaccines.

For primary immunisation of children aged between 2 months and 10 years vaccination is recommended usually in the form of 3 doses (separated by 1-month intervals) of diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed) (see Immunisation schedule). In unimmunised individuals aged over 10 years the primary course comprises of 3 doses of adsorbed diphtheria [low dose], tetanus and poliomyelitis (inactivated) vaccine.

A booster dose should be given 3 years after the primary course (this interval can be reduced to a minimum of 1 year if the primary course was delayed). Children under 10 years should receive either adsorbed diphtheria, tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine or adsorbed diphtheria [low dose], tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine. Individuals aged over 10 years should receive either adsorbed diphtheria [low dose], tetanus, and poliomyelitis (inactivated) vaccine.

A second booster dose, of adsorbed diphtheria [low dose], tetanus and poliomyelitis (inactivated) vaccine, should be given 10 years after the previous booster dose (this interval can be reduced to a minimum of 5 years if previous doses were delayed).

Diphtheria-containing vaccines for children over 10 years and adults

A low dose of diphtheria toxoid is sufficient to recall immunity in individuals previously immunised against diphtheria but whose immunity may have diminished with time; it is insufficient to cause serious reactions in an individual who is already immune. Preparations containing low dose diphtheria should be used for adults and children over 10 years, for both primary immunisation and booster doses.

Travel

Those intending to travel to areas with a risk of diphtheria infection should be fully immunised according to the UK schedule. If more than 10 years have lapsed since completion of the UK schedule, a dose of adsorbed diphtheria [low dose], tetanus and poliomyelitis (inactivated) vaccine should be administered.

Contacts

Staff in contact with diphtheria patients or with potentially pathogenic clinical specimens or working directly with C. diphtheriae or C. ulcerans should receive a booster dose if fully immunised (with 5 doses of diphtheria-containing vaccine given at appropriate intervals); further doses should be given at 10-year intervals if risk persists. Individuals at risk who are not fully immunised should complete the primary course; a booster dose should be given after 5 years and then at 10-year intervals. Adsorbed diphtheria [low dose], tetanus and poliomyelitis (inactivated) vaccine is used for this purpose; immunity should be checked by antibody testing at least 3 months after completion of immunisation.

Advice on the management of cases, carriers, contacts and outbreaks must be sought from health protection units. The immunisation history of infected individuals and their contacts should be determined; those who have been incompletely immunised should complete their immunisation and fully immunised individuals should receive a reinforcing dose. See advice on antibacterial treatment to prevent a secondary case of diphtheria in a non-immune individual.

Haemophilus influenzae type B conjugate vaccine

Haemophilus influenzae type b (Hib) vaccine is made from capsular polysaccharide; it is conjugated with a protein such as tetanus toxoid to increase immunogenicity, especially in young children. Haemophilus influenzae type b vaccine immunisation is given in combination with diphtheria, tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine, as a component of the primary course of childhood immunisation (see Immunisation schedule). For infants under 1 year, the course consists of 3 doses of a vaccine containing Haemophilus influenzae type b component with an interval of 1 month between doses. A booster dose of haemophilus influenzae type b vaccine (combined with meningococcal group C conjugate vaccine) should be given at 12–13 months of age.

Children 1–10 years who have not been immunised against Haemophilus influenzae type b need to receive only 1 dose of Haemophilus influenzae type b vaccine (combined with meningococcal group C conjugate vaccine). However, if a primary course of immunisation has not been completed, these children should be given 3 doses of diphtheria, tetanus, pertussis (acellular, component), and poliomyelitis (inactivated). The risk of infection falls sharply in older children and the vaccine is not normally required for children over 10 years.

Haemophilus influenzae type b vaccine may be given to those over 10 years who are considered to be at increased risk of invasive H. influenzae type b disease (such as those with sickle-cell disease or complement deficiency, or those receiving treatment for malignancy).

Invasive Haemophilus influenzae type b disease

After recovery from infection, unimmunised and partially immunised index cases under 10 years of age should complete their age-specific course of immunisation. Previously vaccinated cases under 10 years of age should be given an additional dose of haemophilus influenzae type b vaccine (combined with meningococcal group C conjugate vaccine) if Hib antibody concentrations are low or if it is not possible to measure antibody concentrations. Index cases of any age with asplenia or splenic dysfunction should complete their immunisation according to the recommendations below; fully vaccinated cases with asplenia or splenic dysfunction should be given an additional dose of haemophilus influenzae type b vaccine (combined with meningococcal group C conjugate vaccine) if they received their previous dose over 1 year ago.

See also use of rifampicin p. 508 in the prevention of secondary cases of Haemophilus influenzae type b disease.

Individuals diagnosed with asplenia, splenic dysfunction, or complement deficiency at:

- under 2 years of age should be vaccinated according to the Immunisation Schedule. The booster dose of haemophilus influenzae type b vaccine (combined with meningococcal group C conjugate vaccine), given at 12–13 months of age, should be followed at least 1 month later by one dose of meningococcal A, C, W135, and Y conjugate vaccine. An additional dose of haemophilus influenzae type b vaccine (combined with meningococcal group C conjugate vaccine) should be given after the second birthday;

- over 2 years of age should receive one dose of haemophilus influenzae type b vaccine (combined with meningococcal group C conjugate vaccine), followed 1 month later by one dose of meningococcal A, C, W135, and Y conjugate vaccine.

Hepatitis A vaccine

Hepatitis A vaccine p. 1081 is prepared from formaldehyde-inactivated hepatitis A virus grown in human diploid cells. Immunisation is recommended for:
Vaccines

However, children nappy changing are vaccinated against hepatitis A.

Hepatitis B vaccine

Hepatitis B vaccine is recombinant DNA technology. The vaccine is used in individuals at high risk of contracting hepatitis B. For rapid protection against hepatitis A after exposure or during an outbreak, in adults a single dose of a monovalent vaccine is recommended; for children under 16 years, a single dose of the combined vaccine Ambirix® can also be used.

Intramuscular normal immunoglobulin p. 1063 is recommended for use in addition to hepatitis A vaccine p. 1081 for close contacts (of confirmed cases of hepatitis A) who have chronic liver disease or HIV infection, or who are immunosuppressed or over 50 years of age.

Post-exposure prophylaxis is not required for healthy children under 1 year of age, so long as all those involved in nappy changing are vaccinated against hepatitis A. However, children 2–12 months of age can be given a dose of hepatitis A vaccine if it is not possible to vaccinate their carers, or if the child becomes a source of infection to others [unless they are unimmunised]. In these cases, if the child goes on to require long-term protection against hepatitis A after the first birthday, the full course of 2 doses should be given.

Hepatitis B vaccine

Hepatitis B vaccine p. 1083 contains inactivated hepatitis B virus surface antigen (HBsAg) adsorbed onto aluminium hydroxide adjuvant. It is made biosynthetically using recombinant DNA technology. The vaccine is used in individuals at high risk of contracting hepatitis B.

In the UK, groups at high-risk of hepatitis B include:

- Laboratory staff who work directly with the virus;
- Staff and residents of homes for those with severe learning difficulties;
- Workers at risk of exposure to untreated sewage;
- Individuals who work with primates;
- Patients with haemophilia or other conditions treated with plasma-derived clotting factors;
- Individuals who have direct contact with blood or blood-stained body fluids or with patients’ tissues;
- Laboratory staff who handle material that may contain the virus;
- Other occupational risk groups such as morticians and embalmers;
- Staff and patients of day-care or residential accommodation for those with severe learning difficulties;
- Staff and inmates of custodial institutions;
- Those travelling to areas of high or intermediate prevalence who are at increased risk or who plan to remain there for lengthy periods;
- Families adopting children from countries with a high or intermediate prevalence of hepatitis B;
- Foster carers and their families.

Different immunisation schedules for hepatitis B vaccine are recommended for specific circumstances. Generally, three or four doses are required for primary immunisation; an ‘accelerated schedule’ is recommended for pre-exposure prophylaxis in high-risk groups where rapid protection is required, and for post-exposure prophylaxis.

Immunisation may take up to 6 months to confer adequate protection; the duration of immunity is not known precisely, but a single booster 5 years after the primary course may be sufficient to maintain immunity for those who continue to be at risk.

Immunisation does not eliminate the need for commonsense precautions for avoiding the risk of infection from known carriers by the routes of infection which have been clearly established, consult Guidance for Clinical Health Care Workers: Protection against Infection with Blood-borne Viruses (available at www.dh.gov.uk). Accidental inoculation of hepatitis B virus-infected blood into a wound, incision, needle-prick, or abrasion may lead to infection, whereas it is unlikely that indirect exposure to a carrier will do so.

Following significant exposure to hepatitis B, an accelerated schedule, with the second dose given 1 month, and the third dose 2 months after the first dose, is recommended. For those at continued risk, a fourth dose should be given 12 months after the first dose. More detailed guidance is given in the handbook Immunisation against Infectious Disease. Specific hepatitis B immunoglobulin p. 1062 (‘HBIG’) is available for use with the vaccine in those accidentally inoculated and in neonates at special risk of infection.

A combined hepatitis A and B vaccine p. 1082 is also available.

Human papillomavirus vaccine

Human papillomavirus vaccines p. 1085 is available as a bivalent vaccine (Cervarix®) or a quadrivalent vaccine (Gardasil®). Cervarix® is licensed for use in females for the prevention of cervical cancer and other pre-cancerous lesions caused by human papillomavirus types 16 and 18. Gardasil® is licensed for use in females for the prevention of cervical and anal cancers, genital warts and pre-cancerous genital (cervical, vulvar, and vaginal) and anal lesions caused by the vaccine papillomavirus types 6, 11, 16, and 18. The vaccines may also provide limited protection against disease caused by other types of human papillomavirus. The two vaccines are not interchangeable and one vaccine product should be used for an entire course.
Human papillomavirus vaccines will be most effective if given before sexual activity starts. From September 2014, a 2-dose schedule is recommended, as long as the first dose is received before the age of 15 years. The first dose is given to females aged 11 to 14 years, and the second dose is given 6–24 months after the first dose (for the purposes of planning the national immunisation programme, it is appropriate to give the second dose 12 months after the first (see Immunisation schedule). If the course is interrupted, it should be resumed (using the same vaccine) but not repeated, even if more than 24 months have elapsed since the first dose or if the girl is then aged 15 years or more. Females receiving their first dose aged 15 years or older require a 3-dose schedule (see Cervarix® and Gardasil®), with the second and third doses given 1 and 4–6 months after the first dose; all 3 doses should be given within a 12-month period. If the course is interrupted, it should be resumed (using the same vaccine) but not repeated, allowing the appropriate interval between the remaining doses. If a 3-dose course of vaccination has been started before September 2014, then where possible this should be completed; if the course is interrupted, it should be resumed (using the same vaccine) but not repeated, allowing the appropriate interval between the remaining doses. Under the national programme in England, females remain eligible to receive the human papillomavirus vaccines p. 1085 up to the age of 18 years if they did not receive the vaccine when scheduled. Where appropriate, immunisation with human papillomavirus vaccines should be offered to females coming into the UK as they may not have been offered protection in their country of origin. The duration of protection has not been established, but current studies suggest that protection is maintained for at least 6 years after completion of the primary course. As the vaccines do not protect against all strains of human papillomavirus, routine cervical screening should continue.

Influenza vaccine

While most viruses are antigenically stable, the influenza viruses A and B (especially A) are constantly altering their antigenic structure as indicated by changes in the haemagglutinins (H) and neuraminidases (N) on the surface of the viruses. It is essential that influenza vaccine p. 1085 in use contain the H and N components of the prevalent strain or strains as recommended each year by the World Health Organization. Immunisation is recommended for persons at high risk, and to reduce transmission of infection. Annual immunisation is strongly recommended for individuals aged over 6 months with the following conditions:

- chronic respiratory disease (includes asthma treated with continuous or repeated use of inhaled or systemic corticosteroids or asthma with previous exacerbations requiring hospital admission);
- chronic heart disease;
- chronic liver disease;
- chronic renal disease;
- chronic neurological disease;
- diabetes mellitus;
- immunosuppression because of disease (including asplenia or splenic dysfunction) or treatment (including prolonged systemic corticosteroid treatment [for over 1 month at dose equivalents of prednisolone: adult and child over 20 kg, 20 mg or more daily; child under 20 kg, 1 mg/kg or more daily] and chemotherapy);
- HIV infection (regardless of immune status).

Seasonal influenza vaccine p. 1085 is also recommended for all pregnant women, for all persons aged over 65 years, for residents of nursing or residential homes for the elderly and other long-stay facilities, and for carers of persons whose welfare may be at risk if the carer falls ill. Influenza immunisation should also be considered for household contacts of immunocompromised individuals.

As part of winter planning, NHS employers should offer vaccination to healthcare workers who are directly involved in patient care. Employers of social care workers should consider similar action. Unless contra-indicated, the live influenza vaccine p. 1085, Fluzeq Tetra®, is preferred in children aged 2–18 years because it provides a higher level of protection than inactivated influenza vaccine p. 1085. From 1 September 2014, seasonal influenza vaccine will also be offered to all children aged 2–4 years (i.e. those born between 2 September 2009 and 1 September 2012).

Information on pandemic influenza, avian influenza and swine influenza may be found at www.dh.gov.uk/pandemicflu and at www.gov.uk/phe.

Japanese encephalitis vaccine

Japanese encephalitis vaccine p. 1086 is indicated for travellers to areas in Asia and the Far East where infection is endemic and for laboratory staff at risk of exposure to the virus. The primary immunisation course of 2 doses should be completed at least one week before potential exposure to Japanese encephalitis virus.

Up-to-date information on the risk of Japanese encephalitis in specific countries can be obtained from the National Travel Health Network and Centre (www.nathnac.org).

Measles, Mumps and Rubella vaccine

Measles vaccine has been replaced by a combined live measles, mumps and rubella vaccine, live p. 1087 (MMR vaccine).

Measles, mumps and rubella vaccine, live aims to eliminate measles, mumps, and rubella (German measles) and congenital rubella syndrome. Every child should receive two doses of measles, mumps and rubella vaccine, live by entry to primary school, unless there is a valid contra-indication. Measles, mumps and rubella vaccine, live should be given irrespective of previous measles, mumps, or rubella infection or vaccination.

The first dose of measles, mumps and rubella vaccine, live is given to children aged 12–13 months. A second dose is given before starting school at 3 years and 4 months–5 years of age (see Immunisation Schedule).

Children presenting for pre-school booster who have not received the first dose of measles, mumps and rubella vaccine, live should be given a dose of measles, mumps and rubella vaccine, live followed 2 months later by a second dose.

At school-leaving age or at entry into further education, measles, mumps and rubella vaccine, live immunisation should be offered to individuals of both sexes who have not received 2 doses during childhood. In those who have received only a single dose of measles, mumps and rubella vaccine, live in childhood, a second dose is recommended to achieve full protection. If 2 doses of measles, mumps and rubella vaccine, live are required, the second dose should be given one month after the initial dose. The decision on whether to vaccinate adults should take into consideration their vaccination history, the likelihood of the individual remaining susceptible, and the future risk of exposure and disease.

Measles, mumps and rubella vaccine, live should be used to protect against rubella in seronegative women of child-bearing age (see Immunisation Schedule); unimmunised healthcare workers who might put pregnant women and other vulnerable groups at risk of rubella or measles should be vaccinated. Measles, mumps and rubella vaccine, live—vaccination a few days after delivery...
is important because about 60% of congenital abnormalities from rubella infection occur in babies of women who have borne more than one child. Immigrants arriving after the age of school immunisation are particularly likely to require immunisation.

Contacts

Measles, mumps and rubella vaccine, live may also be used in the control of outbreaks of measles and should be offered to susceptible children aged under 13 months who are contacts of a case, within 3 days of exposure to infection. Children immunised before 12 months of age should still receive two doses of measles, mumps and rubella vaccine, live at the recommended ages. If one dose of measeles, mumps and rubella vaccine, live has already been given to a child, then the second dose may be brought forward to at least one month after the first, to ensure complete protection. If the child is under 18 months of age and the second dose is given within 3 months of the first, then the routine dose before starting school at 3 years and 4 months–5 years should still be given. Children aged under 9 months for whom avoidance of measles infection is particularly important (such as those with history of recent severe illness) can be given normal immunoglobulin after exposure to measles; routine measles, mumps and rubella vaccine, live p. 1087 immunisation should then be given after at least 3 months at the appropriate age.

Measles, mumps and rubella vaccine, live is not suitable for prophylaxis following exposure to mumps or rubella since the antibody response to the mumps and rubella components is too slow for effective prophylaxis.

Children and adults with impaired immune response should not receive live vaccines (see advice on HIV). If they have been exposed to measles infection they should be given normal immunoglobulin.

Travel

Unimmunised travellers, including children over 6 months, to areas where measles is endemic or epidemic should receive measles, mumps and rubella vaccine, live. Children immunised before 12 months of age should still receive two doses of measles, mumps and rubella vaccine, live at the recommended ages. If one dose of measles, mumps and rubella vaccine, live has already been given to a child, then the second dose should be brought forward to at least one month after the first, to ensure complete protection. If the child is under 18 months of age and the second dose is given within 3 months of the first, then the routine dose before starting school at 3 years and 4 months–5 years should still be given.

Meningococcal vaccine

Almost all childhood meningococcal disease in the UK is caused by Neisseria meningitidis serogroups B and C. Meningococcal group C conjugate vaccine protects only against infection by serogroup C. The risk of meningococcal disease declines with age—immunisation is not generally recommended after the age of 25 years.

Tetravalent meningococcal vaccines that cover serogroups A, C, W135, and Y are available. Although the duration of protection has not been established, the meningococcal groups A, C, W135, and Y conjugate vaccine is likely to provide longer-lasting protection than the unconjugated meningococcal polysaccharide vaccine. The antibody response to serogroup C in unconjugated meningococcal polysaccharide vaccines in young children may be suboptimal (not currently available in the UK).

A meningococcal group B vaccine, Bexsero®, is licensed in the UK against infection caused by Neisseria meningitidis serogroup B. Bexsero® contains 3 recombinant Neisseria meningitidis serogroup B proteins and the outer membrane vesicles from the NZ 98/254 strain, in order to achieve broad protection against Neisseria meningitidis serogroup B; the proteins are adsorbed onto an aluminium compound to stimulate an enhanced immune response.

Childhood immunisation

Meningococcal group C conjugate vaccine provides long-term protection against infection by serogroup C of Neisseria meningitidis. Immunisation consists of 1 dose given at 3 months of age; 2 booster doses are recommended, the first is given at 12–13 months of age (combined with haemophilus influenzae type b vaccine), and the second at 13–15 years of age (see Immunisation Schedule).

Unimmunised children aged 4–12 months should be given 1 dose of meningococcal group C conjugate vaccine and then they should be vaccinated according to the Immunisation Schedule. Unimmunised children aged 1–10 years should be given 1 dose of meningococcal group C conjugate vaccine, followed by a booster dose at 13–15 years of age. Unimmunised individuals aged 10–25 years should be given 1 dose of meningococcal group C conjugate vaccine, but a booster dose is not required.

From August 2014 there will be a catch-up programme for individuals aged under 25 years who are attending university for the first time and who did not receive a dose of meningococcal group C conjugate vaccine at 13–15 years of age.

Patients under 25 years of age with confirmed serogroup C disease, who have previously been immunised with meningococcal group C vaccine, should be offered meningococcal group C conjugate vaccine before discharge from hospital.

Travel

Individuals travelling to countries of risk should be immunised with meningococcal groups A, C, W135, and Y conjugate vaccine, even if they have previously received meningococcal group C conjugate vaccine. If an individual has recently received meningococcal group C conjugate vaccine, an interval of at least 4 weeks should be allowed before administration of the tetravalent (meningococcal groups A, C, W135, and Y) vaccine.

Vaccination is particularly important for those living or working with local people or visiting an area of risk during outbreaks.

Immunisation recommendations and requirements for visa entry for individual countries should be checked before travelling, particularly to countries in Sub-Saharan Africa, Asia, and the Indian sub-continent where epidemics of meningococcal school outbreaks and infection are reported.

Country-by-country information is available from the National Travel Health Network and Centre (www.nathnac.org)

Proof of vaccination with the tetravalent meningococcal groups A with C and W135 and Y vaccine p. 1089 is required for those travelling to Saudi Arabia during the Hajj and Umrah pilgrimages (where outbreaks of the W135 strain have occurred).

Contacts

For advice on the immunisation of laboratory workers and close contacts of cases of meningococcal disease in the UK and on the role of the vaccine in the control of local outbreaks, consult Guidance for Public Health Management of Meningococcal Disease in the UK at www.gov.uk/phe. Also see for antibacterial prophylaxis for prevention of secondary cases of meningococcal meningitis.

The need for immunisation of laboratory staff who work directly with Neisseria meningitidis should be considered.

Pertussis vaccine

Pertussis vaccine is given as a combination preparation containing other vaccines. Acellular vaccines are derived from highly purified components of Bordetella pertussis. Primary immunisation against pertussis (whooping cough)
requires 3 doses of an acellular pertussis-containing vaccine (see Immunisation schedule), given at intervals of 1 month from the age of 2 months.

All children up to the age of 10 years should receive primary immunisation with diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed).

A booster dose of an acellular pertussis-containing vaccine should ideally be given 3 years after the primary course, although, the interval can be reduced to 1 year if the primary course was delayed. Children aged 1–10 years who have not received a pertussis-containing vaccine as part of their primary immunisation should be offered 1 dose of a suitable pertussis-containing vaccine; after an interval of at least 1 year, a booster dose of a suitable pertussis-containing vaccine should be given. Immunisation against pertussis is not routinely recommended in individuals over 10 years of age.

**Vaccination of pregnant women against pertussis**

In response to the pertussis outbreak, the UK health departments introduced a temporary programme (October 2012) to vaccinate pregnant women against pertussis, and this programme will continue until further notice. The aim of the programme is to boost the levels of pertussis-specific antibodies that are transferred through the placenta, from the mother to the fetus, so that the newborn is protected before routine immunisation begins at 2 months of age.

Pregnant women should be offered a single dose of acellular pertussis-containing vaccine (as adsorbed diphtheria [low dose], tetanus, pertussis [acellular, component] and poliomyelitis [inactivated] vaccine; *Boostrix*-IPV®) between 28 to 38 weeks of pregnancy; the optimal time for vaccination is between 28–32 weeks of pregnancy. Pregnant women should be offered a single dose of acellular pertussis-containing vaccine up to the onset of labour if they missed the opportunity for vaccination at 28–38 weeks of pregnancy. A single dose of acellular pertussis-containing vaccine may also be offered to new mothers, who have never previously been vaccinated against pertussis, until the child receives the first vaccination.

While this programme is in place, women who become pregnant again should be offered vaccination during each pregnancy to maximise transplacental transfer of antibody.

**Contacts**

Vaccination against pertussis should be considered for close contacts of cases with pertussis who have been offered antibacterial prophylaxis. Unimmunised or partially immunised contacts under 10 years of age should complete their vaccination against pertussis. A booster dose of an acellular pertussis-containing vaccine is recommended for contacts aged over 10 years who have not received a pertussis-containing vaccine in the last 5 years and who have not received adsorbed diphtheria [low dose], tetanus, and poliomyelitis (inactivated) vaccine in the last month.

**Side-effects**

Local reactions do not contra-indicate further doses.

The vaccine should not be withheld from children with a history to a preceding dose of:
- fever, irrespective of severity;
- persistent crying or screaming for more than 3 hours;
- severe local reaction, irrespective of extent.

**Pneumococcal vaccine**

Pneumococcal vaccine p. 1089 protects against infection with *Streptococcus pneumoniae* (pneumococcus); the vaccines contain polysaccharide from capsular pneumococci. Pneumococcal polysaccharide vaccine contains purified polysaccharide from 23 capsular types of pneumococci, whereas pneumococcal polysaccharide conjugate vaccine (adsorbed) contains polysaccharide from either 10 capsular types (*Synflorix®*) or 13 capsular types (*Prevenar 13®*) and the polysaccharide is conjugated to protein.

The 13-valent conjugate vaccine (*Prevenar 13®*) is used in the childhood immunisation schedule. The recommended schedule consists of 3 doses, the first at 2 months of age, the second at 4 months, and the third at 12–18 months (see Immunisation Schedule).

Pneumococcal vaccine is recommended for individuals at increased risk of pneumococcal infection as follows:
- age over 65 years;
- asplenia or splenic dysfunction (including homozygous sickle cell disease and coeliac disease which could lead to splenic dysfunction);
- chronic respiratory disease (includes asthma treated with continuous or frequent use of a systemic corticosteroid);
- chronic heart disease;
- chronic renal disease;
- chronic liver disease;
- diabetes mellitus requiring insulin or oral hypoglycaemic drugs;
- immune deficiency because of disease (e.g. HIV infection) or treatment (including prolonged systemic corticosteroid treatment for over 1 month at dose equivalents of prednisolone: adult and child over 20 kg, 20 mg or more daily; child under 20 kg, 1 mg/kg or more daily);
- presence of cochlear implant;
- conditions where leakage of cerebrospinal fluid may occur;
- child under 5 years with a history of invasive pneumococcal disease;
- at risk of occupational exposure to metal fume (e.g. welders).

Where possible, the vaccine should be given at least 2 weeks before splenectomy, cochlear implant surgery, chemotherapy, or radiotherapy; patients should be given advice about increased risk of pneumococcal infection. If it is not practical to vaccinate at least 2 weeks before splenectomy, chemotherapy, or radiotherapy, the vaccine should be given at least 2 weeks after the splenectomy or, where possible, at least 3 months after completion of chemotherapy or radiotherapy. Prophylactic antibacterial therapy against pneumococcal infection should not be stopped after immunisation. A patient card and information leaflet for patients with asplenia are available from the Department of Health or in Scotland from the Scottish Executive, Public Health Division 1 (Tel (0131) 244 2501).

**Choice of vaccine**

Children under 2 years at increased risk of pneumococcal infection (see list) should receive the 13-valent pneumococcal polysaccharide conjugate vaccine (adsorbed) at the recommended ages, followed by a single dose of the 23-valent pneumococcal polysaccharide vaccine after their second birthday. Children at increased risk of pneumococcal infection presenting late for vaccination should receive 2 doses (separated by at least 1 month) of the 13-valent pneumococcal polysaccharide conjugate vaccine (adsorbed) before the age of 12 months, and a third dose at 12–13 months. Children over 12 months and under 5 years (who have not been vaccinated or not completed the primary course) should receive a single dose of the 13-valent pneumococcal polysaccharide conjugate vaccine (adsorbed) (2 doses separated by an interval of 2 months in the immunocompromised or those with asplenia or splenic dysfunction). All children under 5 years at increased risk of pneumococcal infection should receive a single dose of the 23-valent pneumococcal polysaccharide vaccine after their second birthday and at least 2 months after the final dose of the 13-valent pneumococcal polysaccharide conjugate vaccine (adsorbed).
Children over 5 years and adults who are at increased risk of pneumococcal disease should receive a single dose of the 23-valent unconjugated pneumococcal polysaccharide vaccine.

Revaccination
In individuals with higher concentrations of antibodies to pneumococcal polysaccharides, revaccination with the 23-valent pneumococcal polysaccharide vaccine more commonly produces adverse reactions. Revaccination is therefore not recommended, except every 5 years in individuals in whom the antibody concentration is likely to decline rapidly (e.g. asplenia, splenic dysfunction and nephrotic syndrome). If there is doubt, the need for revaccination should be discussed with a haematologist, immunologist, or microbiologist.

Poliomyelitis vaccine
Two types of poliomyelitis vaccines (containing strains of poliovirus types 1, 2, and 3) are available, inactivated poliomyelitis vaccine (for injection) and live (oral) poliomyelitis vaccine. Inactivated poliomyelitis vaccines, only available in combined preparation, is recommended for routine immunisation.

A course of primary immunisation consists of 3 doses of a combined preparation containing inactivated poliomyelitis vaccines, starting at 2 months of age with intervals of 1 month between doses (see Immunisation schedule). A course of 3 doses should also be given to all unimmunised adults; no adult should remain unimmunised against poliomyelitis.

Two booster doses of a preparation containing inactivated poliomyelitis vaccines are recommended, the first before school entry and the second before leaving school (see Immunisation schedule). Further booster doses are only necessary for adults at special risk, such as travellers to endemic areas, or laboratory staff likely to be exposed to the viruses, or healthcare workers in possible contact with cases; booster doses should be given to such individuals every 10 years.

Live (oral) poliomyelitis vaccine is no longer available for routine use; its use may be considered during large outbreaks, but advice should be sought from Public Health England. The live (oral) vaccine poses a very rare risk of vaccine-associated paralytic polio because the attenuated strain of the virus can revert to a virulent form. For this reason the live (oral) vaccine must not be used for immunosuppressed individuals or their household contacts. The use of inactivated poliomyelitis vaccines removes the risk of vaccine-associated paralytic polio altogether.

Travel
Unimmunised travellers to areas with a high incidence of poliomyelitis should receive a full 3-dose course of a preparation containing inactivated poliomyelitis vaccines. Those who have not been vaccinated in the last 10 years should receive a booster dose of adsorbed diphtheria [low dose], tetanus and poliomyelitis (inactivated) vaccine.

Information about countries with a high incidence of poliomyelitis can be obtained from www.gov.uk or from the National Travel Health Network and Centre (www.nathnac.org).

Rabies vaccine
Rabies vaccine p. 1090 contains inactivated rabies virus cultivated in either human diploid cells or purified chick embryo cells; vaccines are used for pre- and post-exposure prophylaxis.

Pre-exposure prophylaxis
Immunisation should be offered to those at high risk of exposure to rabies—laboratory staff who handle the rabies virus, those working in quarantine stations, animal handlers, veterinary surgeons and field workers who are likely to be bitten by infected wild animals, certain port officials, and bat handlers. Transmission of rabies by humans has not been recorded but it is advised that those caring for patients with the disease should be vaccinated.

Immunisation against rabies is also recommended where there is limited access to prompt medical care for those living in areas where rabies is enzootic, for those travelling to such areas for longer than 1 month, and for those on shorter visits who may be exposed to unusual risk.

Immunisation against rabies is indicated during pregnancy if there is substantial risk of exposure to rabies and rapid access to post-exposure prophylaxis is likely to be limited.

Up-to-date country-by-country information on the incidence of rabies can be obtained from the National Travel Health Network and Centre (www.nathnac.org) and, in Scotland, from Health Protection Scotland (www.hps.scot.nhs.uk).

Immunisation against rabies requires 3 doses of rabies vaccine p. 1090, with further booster doses for those who remain at frequent risk. To ensure continued protection in persons at high risk (e.g. laboratory workers), the concentration of antirabies antibodies in plasma is used to determine the intervals between doses.

Post-exposure management
Following potential exposure to rabies, the wound or site of exposure (e.g. mucous membrane) should be cleansed under running water and washed for several minutes with soapy water as soon as possible after exposure. Disinfectant and a simple dressing can be applied, but suturing should be delayed because it may increase the risk of introducing rabies virus into the nerves.

Post-exposure prophylaxis against rabies depends on the level of risk in the country, the nature of exposure, and the individual’s immunity. In each case, expert risk assessment and advice on appropriate management should be obtained from the local Public Health England Centre or Public Health England’s Virus Reference Department, Colindale (tel. (020) 8200 4400) or the PHE Colindale Duty Doctor (tel. (020) 8200 6686), in Wales from the Public Health Wales local Health Protection Team or Public Health Wales Virus Reference Laboratory (tel. (029) 2074 7747), in Scotland from the local on-call infectious diseases consultant, and in Northern Ireland from the Public Health Agency Duty Room (tel (028) 9055 3997 / (028) 9063 2662) or the Regional Virology Service (tel. (028) 9024 0503).

There are no specific contra-indications to the use of rabies vaccine for post-exposure prophylaxis and its use should be considered whenever a patient has been attacked by an animal in a country where rabies is enzootic, even if there is no direct evidence of rabies in the attacking animal. Because of the potential consequences of untreated rabies exposure and because rabies vaccination has not been associated with fetal abnormalities, pregnancy is not considered a contra-indication to post-exposure prophylaxis.

For post-exposure prophylaxis of fully immunised individuals (who have previously received pre-exposure or post-exposure prophylaxis with cell-derived rabies vaccine), 2 doses of cell-derived vaccine are likely to be sufficient; the first dose is given on day 0 and the second dose is given between day 3–7. Rabies immunoglobulin is not necessary in such cases.

Post-exposure treatment for unimmunised individuals (or those whose prophylaxis is possibly incomplete) comprises 5 doses of rabies vaccine given over 1 month (on days 0, 3, 7, 14, and the fifth dose is given between day 28–30); also, depending on the level of risk (determined by factors such as the nature of the bite and the country where it was sustained), rabies immunoglobulin p. 1064 is given to unimmunised individuals on day 0 or within 7 days of starting the course of rabies vaccine. The immunisation
course can be discontinued if it is proved that the individual was not at risk.

**Rotavirus vaccine**

Rotavirus vaccine p. 1090 is a live, oral vaccine that protects young children against gastro-enteritis caused by rotavirus infection. The recommended schedule consists of 2 doses, the first at 2 months of age, and the second at 3 months of age (see Immunisation schedule). The first dose of rotavirus vaccine must be given between 6–15 weeks of age and the second dose should be given after an interval of at least 4 weeks; the vaccine should not be started in children 15 weeks of age or older. Ideally, the full course should be completed before 16 weeks of age to provide protection before the main burden of disease, and to avoid a temporal association between vaccination and intussusception; the course must be completed before 24 weeks of age.

The rotavirus vaccine p. 1090 virus is excreted in the stool and may be transmitted to close contacts; however, vaccination of those with immunosuppressed close contacts may protect the contacts from wild-type rotavirus disease and outweigh any risk from transmission of vaccine virus. Carers of a recently vaccinated baby should be advised of the need to wash their hands after changing the baby’s nappies.

**Smallpox vaccine**

Limited supplies of smallpox vaccine are held at the Specialist and Reference Microbiology Division, Public Health England Colindale (Tel. (020) 8280 4400) for the exclusive use of workers in laboratories where pox viruses (such as vaccinia) are handled.

If a wider use of the vaccine is being considered, Guidelines for smallpox response and management in the post-eradication era should be consulted at www.gov.uk/jphe.

**Tetanus vaccine**

Tetanus vaccine contains a cell-free purified toxin of Clostridium tetani adsorbed on aluminium hydroxide or aluminium phosphate to improve antigenicity.

Primary immunisation for children under 10 years consists of 3 doses of a combined preparation containing adsorbed tetanus vaccine, with an interval of 1 month between doses. Following routine childhood vaccination, 2 booster doses of a preparation containing adsorbed tetanus vaccine are recommended, the first before school entry and the second before leaving school (see Immunisation schedule).

The recommended schedule of tetanus vaccination not only gives protection against tetanus in childhood but also gives the basic immunity for subsequent booster doses. In most circumstances, a total of 5 doses of tetanus vaccine is considered sufficient for long term protection.

For primary immunisation of adults and children over 10 years previously unimmunised against tetanus, 3 doses of adsorbed diphtheria [low dose], tetanus and poliomyelitis (inactivated) vaccine are given with an interval of 1 month between doses (see Diphtheria-containing Vaccines). When an individual presents for a booster dose but has been vaccinated following a tetanus-prone wound, the vaccine preparation administered at the time of injury should be determined. If this is not possible, the booster should still be given to ensure adequate protection against all antigens in the booster vaccine.

Very rarely, tetanus has developed after abdominal surgery; patients awaiting elective surgery should be asked about tetanus immunisation and immunised if necessary. Parenteral drug abuse is also associated with tetanus; those abusing drugs by injection should be vaccinated if unimmunised—booster doses should be given if there is any doubt about their immunisation status.

All laboratory staff should be offered a primary course if unimmunised.

**Wounds**

Wounds are considered to be tetanus-prone if they are sustained more than 6 hours before surgical treatment or at any interval after injury and are puncture-type (particularly if contaminated with soil or manure) or show much devitalised tissue or are septic or are compound fractures or contain foreign bodies. All wounds should receive thorough cleansing.

- For clean wounds: fully immunised individuals (those who have received a total of 5 doses of a tetanus-containing vaccine at appropriate intervals) and those whose primary immunisation is complete (with boosters up to date), do not require tetanus vaccine; individuals whose primary immunisation is incomplete or whose boosters are not up to date require a reinforcing dose of a tetanus-containing vaccine (followed by further doses as required to complete the schedule); non-immunised individuals (or those whose immunisation status is not known or who have been fully immunised but are now immunocompromised) should be given a dose of the appropriate tetanus-containing vaccine immediately (followed by completion of the full course of the vaccine if records confirm the need).

- For tetanus-prone wounds: management is as for clean wounds with the addition of a dose of tetanus immunoglobulin given at a different site; in fully immunised individuals and those whose primary immunisation is complete (with boosters up to date) the immunoglobulin is needed only if the risk of infection is especially high (e.g. contamination with manure). Antibacterial prophylaxis (with benzylpenicillin, co-amoxiclav, or metronidazole) may also be required for tetanus-prone wounds.

**Tick-borne encephalitis vaccine**

Tick-borne encephalitis vaccine, inactivated p. 1091 contains inactivated tick-borne encephalitis virus cultivated in chick embryo cells. It is recommended for immunisation of those working in, or visiting, high-risk areas (see International Travel). Those working, walking or camping in warm forested areas of Central and Eastern Europe, Scandinavia, Northern and Eastern China, and some parts of Japan, particularly from April to November when ticks are most prevalent, are at greatest risk of tick-borne encephalitis. For full protection, 3 doses of the vaccine are required; booster doses are required every 3–5 years for those still at risk. Ideally, immunisation should be completed at least one month before travel.

**Typhoid vaccine**

Typhoid vaccine p. 1091 is available as Vi capsular polysaccharide (from Salmonella typhi) vaccine for injection and as live attenuated Salmonella typhi for oral use.

Typhoid immunisation is advised for:

- travellers to areas where typhoid is endemic, especially if staying with or visiting local people;
- travellers to endemic areas where frequent or prolonged exposure to poor sanitation and poor food hygiene is likely;
- laboratory personnel who, in the course of their work, may be exposed to Salmonella typhi.

Typhoid vaccination is not a substitute for scrupulous personal hygiene.

Capsular polysaccharide typhoid vaccine p. 1091 is usually given by intramuscular injection. Children under 2 years may respond suboptimally to the vaccine, but children aged between 1–2 years should be immunised if the risk of typhoid fever is considered high (immunisation is not recommended for infants under 12 months). Revaccination is needed every 3 years on continued exposure.
Vaccines

Oral typhoid vaccine p. 1091 is a live attenuated vaccine contained in an enteric-coated capsule. One capsule taken on alternate days for a total of 3 doses, provides protection 7–10 days after the last dose. Protection may persist for up to 3 years in those constantly (or repeatedly) exposed to Salmonella typhi, but those who only occasionally travel to endemic areas require further courses at intervals of 1 year.

Varicella-zoster vaccine

The live varicella-zoster vaccine p. 1092, Varilrix® and Varivax®, are licensed for immunisation against varicella (chickenpox) in seronegative individuals. They are not recommended for routine use in children, but can be given to seronegative healthy children over 1 year who come into close contact with individuals at high risk of severe varicella infections. The Department of Health recommends these vaccines for seronegative healthcare workers who come into direct contact with patients. Those with a history of chickenpox or shingles can be considered immune, but healthcare workers with a negative or uncertain history should be tested.

Rarely, the varicella-zoster vaccine p. 1092 virus has been transmitted from the vaccinated individual to close contacts. Therefore, contact with the following should be avoided if a vaccine-related cutaneous rash develops within 4–6 weeks of the first or second dose:
- varicella-susceptible pregnant women;
- individuals at high risk of severe varicella, including those with immunodeficiency or those receiving immunosuppressive therapy;
- Healthcare workers who develop a generalised papular or vesicular rash on vaccination should avoid contact with patients until the lesions have crusted. Those who develop a localised rash after vaccination should cover the lesions and patients until the lesions have crusted. Those who develop a varicella-zoster vaccine p. 1092, Zostavax®, is recommended for the prevention of herpes zoster (shingles) in adults who are, or were, 70 years of age on 1 September 2014. The 2014-15, catch-up programme with Zostavax® will be offered to all who are, or were, 78 or 79 years of age on 1 September 2014. A single dose of Zostavax® is likely to give protection for at least 7 years, but the need for, or timing of, a booster dose has not been established. Although Zostavax® is not recommended for the treatment of shingles or post-herpetic neuralgia, it can be given to those with a previous history of shingles; ideally the vaccine should be delayed until systemic antiviral therapy has been completed.

Varicella-zoster immunoglobulin p. 1065 is used to protect susceptible individuals at increased risk of varicella infection.

Yellow fever vaccine

Yellow fever vaccine, live p. 1092, is indicated for those travelling or living in areas where infection is endemic and for laboratory staff who handle the virus or who handle clinical material from suspected cases. Infants under 6 months of age should not be vaccinated because there is a small risk of encephalitis; infants aged 6–9 months should be vaccinated only if the risk of yellow fever is high and unavoidable (seek expert advice). The immunity which probably lasts for life is officially accepted for 10 years starting from 10 days after primary immunisation and for a further 10 years immediately after revaccination.

Travel vaccinations

See advice on Malaria, treatment p. 529.

No special immunisation is required for travellers to the United States, Europe, Australia, or New Zealand, although all travellers should have immunity to tetanus and poliomyelitis (and childhood immunisations should be up to date); Tick-borne encephalitis vaccine is recommended for immunisation of those working in, or visiting, high-risk areas. Certain special precautions are required in non-European areas surrounding the Mediterranean, in Africa, the Middle East, Asia, and South America.

Travellers to areas that have a high incidence of poliomyelitis or tuberculosis should be immunised with the appropriate vaccine; in the case of poliomyelitis previously immunised travellers may be given a booster dose of a preparation containing inactivated poliomyelitis vaccine. BCG immunisation is recommended for travellers aged under 16 years proposing to stay for longer than 3 months (or in close contact with the local population) in countries with an incidence of tuberculosis greater than 40 per 100 000 (list of countries where the incidence of tuberculosis is greater than 40 cases per 100 000 is available from www.gov.uk/phe); it should preferably be given 3 months or more before departure.

Yellow fever immunisation is recommended for travel to the endemic zones of Africa and South America. Many countries require an International Certificate of Vaccination from individuals arriving from, or who have been travelling through, endemic areas; other countries require a certificate from all entering travellers (consult the Department of Health handbook, Health Information for Overseas Travel, www.dh.gov.uk).

Immunisation against meningococcal meningitis is recommended for a number of areas of the world.

Protection against hepatitis A is recommended for travellers to high-risk areas outside Northern and Western Europe, North America, Japan, Australia and New Zealand. Hepatitis A vaccine is preferred and it is likely to be effective even if given shortly before departure; normal immunological response is more likely if no longer given routinely but may be indicated in the immunocompromised. Special care must also be taken with food hygiene.

Hepatitis B vaccine is recommended for those travelling to areas of high or intermediate prevalence who intend to seek employment as healthcare workers or who plan to remain there for lengthy periods and who may therefore be at increased risk of acquiring infection as the result of medical or dental procedures carried out in those countries. Short-term tourists or business travellers are not generally at increased risk of infection but may put themselves at risk by their sexual behaviour when abroad.

Prophylactic immunisation against typhoid is recommended for travellers to enzootic areas on long journeys or to areas out of reach of immediate medical attention.

Travellers who have not had a tetanus booster in the last 10 years and are visiting areas where medical attention may not be accessible should receive a booster dose of adsorbed diphtheria [low dose], tetanus and poliomyelitis (inactivated) vaccine, even if they have received 5 doses of a tetanus-containing vaccine previously.

Typhoid vaccine is indicated for travellers to countries where typhoid is endemic, but the vaccine is no substitute for personal precautions.

There is no requirement for cholera vaccination as a condition for entry into any country, but oral cholera vaccine should be considered for backpackers and those travelling to situations where the risk is greatest (e.g. refugee camps). Regardless of vaccination, travellers to areas where cholera is endemic should take special care with food hygiene.

Advice on diphtheria, on Japanese encephalitis, and on tick-borne encephalitis is included in Health Information for Overseas Travel.
Food hygiene
In areas where sanitation is poor, good food hygiene is important to help prevent hepatitis A, typhoid, cholera, and other diarrhoeal diseases (including travellers’ diarrhoea). Food should be freshly prepared and hot, and uncooked vegetables (including green salads) should be avoided; only fruits which can be peeled should be eaten. Only suitable bottled water, or tap water that has been boiled or treated with sterilising tablets, should be used for drinking.

Information on health advice for travellers
Health professionals and travellers can find the latest information on immunisation requirements and precautions for avoiding disease while travelling from: www.nathnac.org. The handbook, Health Information for Overseas Travel (2010), which draws together essential information for healthcare professionals regarding health advice for travellers, can also be obtained from this website.

Immunisation requirements change from time to time, and information on the current requirements for any particular country may be obtained from the embassy or the Department of Health, Social Services and Public Safety, National Travel Health Network and Centre, Castle Buildings, 2nd Floor Central, 250 Euston Road, London NW1 2PG (for healthcare professionals only)

www.nathnac.org

Travel Medicine Team
Health Protection Scotland
Meridian Court
5 Cadogan Street
Glasgow G2 6QE
Tel: (0141) 300 1130 (2–4 p.m. Monday to Wednesday, 9:30–11:30 a.m. Friday; for registered TRAVAX users only)

www.travax.nhs.uk (free for NHS Scotland users, registration required; subscription fee may be payable for users outside NHS Scotland)

Welsh Assembly Government
Tel (029) 2082 5397 (9 a.m.–5:30 p.m. weekdays)

VACCINES

Vaccines

- Contra-indications
  - Impaired immune response Severely immunosuppressed patients should not be given live vaccines (including those with severe primary immunodeficiency).

- Caution
  - Acute illness • minor illnesses

Caution, Further Information
Vaccination may be postponed if the individual is suffering from an acute illness; however, it is not necessary to postpone immunisation in patients with minor illnesses without fever or systemic upset.

Immunosuppressed patients and there is also a risk of generalised infection with live vaccines. Specialist advice should be sought for those being treated with high doses of corticosteroids (dose equivalents of prednisolone: adults, at least 40 mg daily for more than 1 week; children, 2 mg/kg (or more than 40 mg) daily for at least 1 week or 1 mg/kg daily for 1 month), or other immunosuppressive drugs, and those being treated for malignant conditions with chemotherapy or generalised radiotherapy. Live vaccines should be postponed until at least 2 months after stopping high-dose systemic corticosteroids and at least 6 months after stopping other immunosuppressive drugs or generalised radiotherapy (at least 12 months after discontinuing immunosuppressants following bone-marrow transplantation).


Predisposition to neurological problems
When there is a personal or family history of febrile convulsions, there is an increased risk of these occurring during fever from any cause including immunisation, but this is not a contra-indication to immunisation. In children who have had a seizure associated with fever without neurological deterioration, immunisation is recommended; advice on the management of fever (see Post-immunisation Pyrexia in Infants) should be given before immunisation. When a child has had a convulsion not associated with fever, and the neurological condition is not deteriorating, immunisation is recommended.

Children with stable neurological disorders (e.g. spina bifida, congenital brain abnormality, and peri-natal hypoxic-ischaemic encephalopathy) should be immunised according to the recommended schedule. When there is a still evolving neurological problem, including poorly controlled epilepsy, immunisation should be deferred and the child referred to a specialist. Immunisation is recommended if a cause for the neurological disorder is identified. If a cause is not identified, immunisation should be deferred until the condition is stable.

- Interactions → Appendix 1 (vaccines).

- Side-effects

General Side-effects
- Common or very common
  - Fatigue • fever • gastro-intestinal disturbances • headache • irritability • loss of appetite • lymphangitis • malaise • myalgia
  - Very rare
    - Anaphylaxis (can be fatal) • angioedema (can be fatal) • bronchospasm (can be fatal) • hypersensitivity reactions (can be fatal) • urticaria (can be fatal)
  - Frequency not known
    - Arthralgia • asthenia • dizziness • drowsiness • influenza-like symptoms • lymphadenopathy • paraesthesia • rash

Specific Side-effects
- Common or very common
  - With intradermal use or intramuscular use or subcutaneous use
    - Induration may develop at the injection site
    - Pain • redness • sterile abscess may develop at the injection site

Side-effects, Further Information
Occasionally serious adverse reactions can occur—these should always be reported to the CHM.

Post-immunisation pyrexia in infants
The parent should be advised that if pyrexia develops after childhood immunisation, and the infant seems distressed, paracetamol can be given. Ibuprofen can be used if paracetamol is unsuitable. The parent should be warned to seek medical advice if the pyrexia persists.

Allergy and Cross-sensitivity
Contra-indicated in patients with a confirmed anaphylactic reaction to a preceding dose of a vaccine containing the same antigens or vaccine component (such as antibacterials in viral vaccines).
PREGNANCY Live vaccines should not be administered routinely to pregnant women because of the theoretical risk of fetal infection but where there is a significant risk of exposure to disease, the need for vaccination usually outweighs any possible risk to the fetus. Termination of pregnancy following inadvertent immunisation is not recommended. There is no evidence of risk from vaccinating pregnant women with inactivated viral or bacterial vaccines or toxoids.

BREAST FEEDING Although there is a theoretical risk of live vaccine being present in breast milk, vaccination is not contra-indicated for women who are breast-feeding when there is significant risk of exposure to disease. There is no evidence of risk from vaccinating women who are breast-feeding, with inactivated viral or bacterial vaccines or toxoids.

DIRECTIONS FOR ADMINISTRATION If alcohol or disinfectant is used for cleansing the skin it should be allowed to evaporate before vaccination to prevent possible inactivation of live vaccines. When 2 or more live vaccines are required (and are not available as a combined preparation), they can be administered at any time before or after each other at different sites, preferably in a different limb; if more than one injection is to be given in the same limb, they should be administered at least 2.5 cm apart.

HANDLING AND STORAGE Vaccines should not be given intravenously. Most vaccines are given by the intramuscular route, although some are given by either the intradermal, deep subcutaneous, or oral route. The intramuscular route should not be used in patients with bleeding disorders such as haemophilia or thrombocytopathy, vaccines usually given by the intramuscular route should be given by deep subcutaneous injection instead.

Refrigerated storage is usually necessary; many vaccines need to be stored at 2–8°C and not allowed to freeze. Vaccines should be protected from light.

CONTRA-INDICATIONS Generalised septic skin conditions neonate in household contact with known or suspected case of active tuberculosis
CONTRA-INDICATIONS, FURTHER INFORMATION A lesion-free site should be used to administer BCG vaccine to patients with eczema.

Indications and dose

- anthrax vaccine
- BCG vaccine

Pre-exposure immunisation against anthrax | Post-exposure immunisation

**BY INTRAMUSCULAR INJECTION**
- Adult: Initially 1 dose every 3 weeks for 3 doses, followed by 1 dose after 6 months, to be administered in the deltoid region, 1 dose is equivalent to 0.5 mL
- Booster
- Adult: 1 dose every 12 months, to be administered in deltoid region, 1 dose is equivalent to 0.5 mL

PRESCRIBING AND DISPENSING INFORMATION

- There can be variation in the licensing of different medicines containing the same drug.
- Suspension for injection

EXCIPIENTS: May contain Thiomersal
- ANTHRAX VACCINE (Non-proprietary)
  Anthrax vaccine (alum precipitated sterile filtrate) suspension for injection 0.5ml ampoules | 5 ampoule (Pack) no price available

**INDICATIONS AND DOSE**

Immunisation against tuberculosis

**BY INTRADERMAL INJECTION**
- Child 1-11 months: 0.05 mL, to be injected at insertion of deltoid muscle onto humerus (keloid formation more likely with sites higher on arm); tip of shoulder should be avoided
- Child 1-7 years: 0.1 mL, to be injected at insertion of deltoid muscle onto humerus (keloid formation more likely with sites higher on arm); tip of shoulder should be avoided
- Adult: 0.1 mL, to be injected at insertion of deltoid muscle onto humerus (keloid formation more likely with sites higher on arm); tip of shoulder should be avoided

**SIDE-EFFECTS**
- Rare: Disseminated complications - osteitis - osteomyelitis
- Frequency not known: Prolonged ulceration at the injection site - subcutaneous abscess at the injection site

**PRE-TREATMENT SCREENING**
Apart from children under 6 years, any person being considered for BCG immunisation must first be given a skin test for hypersensitivity to tuberculinprotein (see tuberculin purified protein derivative p. 1066). A skin test is not necessary for a child under 6 years provided that the child has not stayed for longer than 3 months in a country with an incidence of tuberculosis greater than 40 per 100 000, the child has had no contact with a person with tuberculosis, and there is no family history of tuberculosis within the last 5 years.

**DIRECTIONS FOR ADMINISTRATION**

Intradermal injection technique Skin is stretched between thumb and forefinger and needle (size 25G or 26G) inserted (bevel upwards) for about 3 mm into superficial layers of dermis (almost parallel with surface). Needle should be short with short bevel (can usually be seen through epidermis during insertion). Tense raised blanched bleb showing tips of hair follicles is sign of correct injection; 7 mm bleb ≡ 0.1 mL injection, 3 mm bleb ≡ 0.05 mL injection; if considerable
resistance not felt, needle too deep and should be removed and reinserted before giving more vaccine.

**PRESCRIBING AND DISPENSING INFORMATION** Available from health organisations or direct from ImmForm www.immform.dh.gov.uk (SSI brand, multidose vial with diluent).

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for suspension for injection**
- **Bacillus Calmette-Guerin Vaccine (Non-proprietary)**
  
  Bacillus Calmette-Guerin vaccine powder and solvent for suspension for injection vials | 10 vial [P] no price available

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### Cholera vaccine

**INDICATIONS AND DOSE**

Immunisation against cholera (for travellers to endemic or epidemic areas on the basis of current recommendations)

**BY MOUTH**

- Child 2-5 years: 1 dose every 1–6 weeks for 3 doses, if more than 6 weeks have elapsed between doses, the primary course should be restarted, immunisation should be completed at least one week before potential exposure
- Child 6-17 years: 1 dose every 1–6 weeks for 2 doses, if more than 6 weeks have elapsed between doses, the primary course should be restarted, immunisation should be completed at least one week before potential exposure
- Adult: 1 dose every 1–6 weeks for 2 doses, if more than 6 weeks have elapsed between doses, the primary course should be restarted, immunisation should be completed at least one week before potential exposure

**Booster**

**BY MOUTH**

- Child 2-5 years: A single booster dose can be given within 6 months after primary course, if more than 6 months have elapsed since the last vaccination, the primary course should be repeated
- Child 6-17 years: A single booster dose can be given within 2 years after primary course, if more than 2 years have elapsed since the last vaccination, the primary course should be repeated
- Adult: A single booster dose can be given within 2 years after primary course, if more than 2 years have elapsed since the last vaccination, the primary course should be repeated

**CONTRA-INDICATIONS** Acute gastro-intestinal illness

**SIDE-EFFECTS**

- Rare Cough - respiratory symptoms - rhinitis
- Very rare Insomnia - sore throat
- Frequency not known Abdominal pain and cramps - diarrhoea - nausea - vomiting

**DIRECTIONS FOR ADMINISTRATION**

- In children: Dissolve effervescent sodium bicarbonate granules in a glassful of water or chlorinated water (approximately 150 mL). For children over 6 years, add vaccine suspension to make one dose. For child 2–6 years, discard half (approximately 75 mL) of the solution, then add vaccine suspension to make one dose. Drink within 2 hours. Food, drink, and other oral medicines should be avoided for 1 hour before and after vaccination.
- In adults: Dissolve effervescent sodium bicarbonate granules in a glassful of water or chlorinated water (approximately 150 mL). Add vaccine suspension to make one dose. Drink within 2 hours. Food, drink, and other oral medicines should be avoided for 1 hour before and after vaccination.

**SIDE-EFFECTS, FURTHER INFORMATION**

- Local reactions do not usually occur.
- The incidence of local and systemic effects is generally lower with vaccines containing acellular pertussis components than with the whole-cell pertussis vaccine used previously. However, compared with primary vaccination, booster doses with vaccines containing acellular pertussis are reported to increase the risk of injection-site reactions (some of which affect the entire limb); local reactions do not contra-indicate further doses.
- The vaccine should not be withheld from children with a history to a preceding dose of:
  - Fever, irrespective of severity;
  - Persistent crying or screaming for more than 3 hours;
  - Severe local reaction, irrespective of extent.

**UNLICENSED USE** Infanrix-IPV + Hib™ not licensed for use in children over 36 months; Pediacel® not licensed in children over 4 years. However, the Department of Health recommends that these be used for children up to 10 years.

**SIDE-EFFECTS** Atopic dermatitis - hypotonia - restlessness - sleep disturbances - unusual crying in infants

**SPECIAL CONDITIONS**

- Local reactions do not usually occur.

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### Diphtheria with haemophilus influenzae type b vaccine, pertussis, poliomyelitis and tetanus

**INDICATIONS AND DOSE**

Primary immunisation

**BY INTRAMUSCULAR INJECTION**

- Child 2 months-4 years: 0.5 mL every month for 3 doses
- Child 4-10 years: 0.5 mL every 6 months for 3 doses
- Child 11 years-17 years: A single booster dose can be given 6 weeks for 1 dose
- Adult: A single booster dose can be given within 6 months after primary course, if more than 6 months have elapsed since the last vaccination, the primary course should be repeated

**UNLICENSED USE** Infanrix-IPV + Hib™ not licensed for use in children over 36 months; Pediacel® not licensed in children over 4 years. However, the Department of Health recommends that these be used for children up to 10 years.

**SIDE-EFFECTS** Atopic dermatitis - hypotonia - restlessness - sleep disturbances - unusual crying in infants

**SPECIAL CONDITIONS**

- Local reactions do not usually occur.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**

- **Infanrix-IPV + Hib** (GlaxoSmithKline UK Ltd)
  
  Infanrix-IPV + Hib vaccine powder and solvent for suspension for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection [P] no price available

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**PATIENT AND CARER ADVICE**

Counselling on administration advised. Immunisation with cholera vaccine does not provide complete protection and all travellers to a country where cholera exists should be warned that scrupulous attention to food, water, and personal hygiene is essential.

**PRESCRIBING AND DISPENSING INFORMATION** Available as part of childhood schedule from health organisations or ImmForm.
Diphtheria with pertussis, poliomyelitis vaccine and tetanus

**INDICATIONS AND DOSE**

**Primary immunisation**
- **BY INTRAMUSCULAR INJECTION**
  - Child 10-17 years: 0.5 mL every month for 3 doses
  - Adult: 0.5 mL every month for 3 doses

**Booster doses**
- **BY INTRAMUSCULAR INJECTION**
  - Child 10-17 years: 0.5 mL for 1 dose, first booster dose—should be given 3 years after primary course (this interval can be reduced to a minimum of 1 year if the primary course was delayed), then 0.5 mL for 1 dose, second booster dose—should be given 10 years after first booster dose (this interval can be reduced to a minimum of 5 years if previous doses were delayed), second booster dose may also be used as first booster dose in those over 10 years who have received only 3 previous doses of a diphtheria-containing vaccine
  - Adult: 0.5 mL for 1 dose, first booster dose—should be given 3 years after primary course (this interval can be reduced to a minimum of 1 year if the primary course was delayed), then 0.5 mL for 1 dose, second booster dose—should be given 10 years after first booster dose (this interval can be reduced to a minimum of 5 years if previous doses were delayed), second booster dose may also be used as first booster dose in those over 10 years who have received only 3 previous doses of a diphtheria-containing vaccine

**SIDE-EFFECTS** Restlessness • sleep disturbances • unusual crying in infants

**SIDE-EFFECTS, FURTHER INFORMATION**

**Side effects of vaccines containing pertussis** The incidence of local and systemic effects is generally lower with vaccines containing acellular pertussis components than with the whole-cell pertussis vaccine used previously. However, compared with primary vaccination, booster doses with vaccines containing acellular pertussis are reported to increase the risk of injection-site reactions (some of which affect the entire limb); local reactions do not contra-indicate further doses.

The vaccine should not be withheld from children with a history to a preceding dose of:
- • fever, irrespective of severity;
- • persistent crying or screaming for more than 3 hours;
- • severe local reaction, irrespective of extent.

**PREGNANCY** Contra-indicated in pregnant women with a history of encephalopathy of unknown origin within 7 days of previous immunisation with a pertussis-containing vaccine. Contra-indicated in pregnant women with a history of transient thrombocytopenia or neurological complications following previous immunisation against diphtheria or tetanus.

**PRESCRIBING AND DISPENSING INFORMATION** Available as part of childhood immunisation schedule from health organisations or ImmunForm. Available for vaccination of pregnant women from ImmunForm.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**

EXCIPIENTS: May contain Neomycin, polymyxin b, streptomycin

- **Revaxis (sanofi pasteur MSD Ltd)**
  - Revaxis vaccine suspension for injection 0.5ml pre-filled disposable injection | 1 pre-filled disposable injection (POD) £17.56

Haemophilus influenzae type b with meningococcal group C vaccine

**INDICATIONS AND DOSE**

Booster dose (for infants who have received primary immunisation with a vaccine containing *Haemophilus influenzae* type b component)

**BY INTRAMUSCULAR INJECTION**
- **Child 12-13 months:** 0.5 mL for 1 dose

Booster dose (for children who have not been immunised against *Haemophilus influenzae* type b) | Booster dose after recovery from *Haemophilus influenzae* type b disease (for index cases previously vaccinated, with low Hib antibody concentration or if it is not possible to measure antibody concentration)

**BY INTRAMUSCULAR INJECTION**
- **Child 1-9 years:** 0.5 mL for 1 dose
- **Booster dose after recovery from *Haemophilus influenzae* type b disease (for fully vaccinated index cases with asplenia or splenic dysfunction, if previous dose received over 1 year ago)**
- **BY INTRAMUSCULAR INJECTION**
  - **Child 1-7 years:** 0.5 mL for 1 dose
  - **Adult:** 0.5 mL for 1 dose

Booster dose (for patients diagnosed with asplenia, splenic dysfunction or complement deficiency at under 2 years of age)

**BY INTRAMUSCULAR INJECTION**
- **Child 12-13 months:** 0.5 mL for 1 dose, this booster dose should be followed 1 month later by one dose of meningococcal A, C, W135, and Y conjugate vaccine, followed by 0.5 mL for 1 dose, the second dose should be given after the second birthday

Diphtheria with poliomyelitis and tetanus vaccine

**INDICATIONS AND DOSE**

**Primary immunisation**
- **BY INTRAMUSCULAR INJECTION**
  - Child 10-17 years: 0.5 mL every month for 3 doses
  - Adult: 0.5 mL every month for 3 doses

**Booster doses**
- **BY INTRAMUSCULAR INJECTION**
  - Child 10-17 years: 0.5 mL for 1 dose, first booster dose—should be given 3 years after primary course (this interval can be reduced to a minimum of 1 year if the
Hepatitis A vaccine

INDICATIONS AND DOSE

AVAXIM®

Immunisation against hepatitis A infection

BY INTRAMUSCULAR INJECTION

- Child 2-17 years: 0.5 mL for 1 dose, this booster dose should be followed 1 month later by one dose of meningococcal A, C, W135, and Y conjugate vaccine
- Adult: 0.5 mL for 1 dose, this booster dose should be followed 1 month later by one dose of meningococcal A, C, W135, and Y conjugate vaccine

VAQTA®

Immunisation against hepatitis A infection

BY INTRAMUSCULAR INJECTION

- Child 2-17 years: 0.5 mL for 1 dose, then 0.5 mL after 6–12 months, dose given as booster; booster dose may be delayed by up to 3 years if not given after recommended interval following primary dose, the deltoid region is the preferred site of injection. The subcutaneous route may be used for patients with bleeding disorders
- Adult: 0.5 mL for 1 dose, then 0.5 mL after 6–12 months, dose given as booster; booster dose may be delayed by up to 3 years if not given after recommended interval following primary dose, the deltoid region is the preferred site of injection. The subcutaneous route may be used for patients with bleeding disorders

VAQTA® ADULT

Immunisation against hepatitis A infection

BY INTRAMUSCULAR INJECTION

- Adult: Initially 1 mL for 1 dose, then 1 mL after 6–18 months, dose given as booster, the deltoid region is the preferred site of injection. The subcutaneous route may be used for patients with bleeding disorders (but immune response may be delayed)

EPAXAL®

Immunisation against hepatitis A infection

BY INTRAMUSCULAR INJECTION

- Child 1-17 years: Initially 0.5 mL for 1 dose, then 0.5 mL after 6–12 months, dose given as booster; booster dose may be delayed by up to 4 years if not given after recommended interval following primary dose. The deltoid region is the preferred site of injection. The subcutaneous route may be used for patients with bleeding disorders
- Adult: Initially 0.5 mL for 1 dose, then 0.5 mL after 6–12 months, dose given as booster; booster dose may be delayed by up to 4 years if not given after recommended interval following primary dose. The deltoid region is the preferred site of injection. The subcutaneous route may be used for patients with bleeding disorders

Immunisation against hepatitis A infection (splenectomised patients)

BY INTRAMUSCULAR INJECTION

- Child 1-17 years: Initially 0.5 mL for 1 dose, then 0.5 mL after 1–6 months, dose given as booster; booster dose may be delayed by up to 4 years in adults if not given after recommended interval following primary dose. The deltoid region is the preferred site of injection. The subcutaneous route may be used for patients with bleeding disorders
- Adult: Initially 0.5 mL for 1 dose, then 0.5 mL after 1–6 months, dose given as booster; booster dose may be delayed by up to 4 years in adults if not given after recommended interval following primary dose. The deltoid region is the preferred site of injection. The subcutaneous route may be used for patients with bleeding disorders

- ALLERGY AND CROSS-SENSITIVITY

Epaxal® contains influenza virus haemagglutinin grown in the allantoic cavity of chick embryos, therefore contraindicated in those hypersensitive to eggs or chicken proteins.

- MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.
Hepatitis A and B vaccine

The properties listed below are those particular to the combination only. For the properties of the components please consider, hepatitis A vaccine p. 1081, hepatitis B vaccine p. 1083.

**INDICATIONS AND DOSE**

**TWINRIX® PAEDIATRIC**

Immunisation against hepatitis A and hepatitis B infection

BY INTRAMUSCULAR INJECTION

- Child 1-15 years: Initially 0.5 mL every month for 2 doses, then 0.5 mL after 5 months for 1 dose, the deltoid region is the preferred site of injection in older children; anterolateral thigh is the preferred site in infants; not to be injected into the buttock (vaccine efficacy reduced), subcutaneous route used for patients with bleeding disorders (but immune response may be reduced)

**TWINRIX® ADULT**

Immunisation against hepatitis A and hepatitis B infection

BY INTRAMUSCULAR INJECTION

- Child 16-17 years: Initially 1 mL every month for 2 doses, then 1 mL after 5 months for 1 dose, the deltoid region is the preferred site of injection in adults and older children; not to be injected into the buttock (vaccine efficacy reduced), subcutaneous route used for patients with bleeding disorders (but immune response may be reduced)

- Adult: Initially 1 mL for 1 dose, then 1 mL after 7 days for 1 dose, then 1 mL after 14 days for 1 dose, then 1 mL for 1 dose given 12 months after the first dose, the deltoid region is the preferred site of injection in adults and older children; not to be injected into the buttock (vaccine efficacy reduced), subcutaneous route used for patients with bleeding disorders but (immune response may be reduced)

Immunisation against hepatitis A and hepatitis B infection (accelerated schedule for travellers departing within 1 month)

BY INTRAMUSCULAR INJECTION

- Child 16-17 years: Initially 1 mL for 1 dose, then 1 mL after 7 days for 1 dose, then 1 mL after 14 days for 1 dose, then 1 mL for 1 dose given 12 months after the first dose, the deltoid region is the preferred site of injection in adults and older children; not to be injected into the buttock (vaccine efficacy reduced), subcutaneous route used for patients with bleeding disorders (but immune response may be reduced)

**VACCINES**

Hepatitis A and B vaccine

**PRESCRIBING AND DISPENSING INFORMATION**

**AMBIRIX®**

Primary course should be completed with Ambirix® (single component vaccines given at appropriate intervals may be used for booster dose).

**TWINRIX® PREPARATIONS**

Primary course should be completed with Twinrix® (single component vaccines given at appropriate intervals may be used for booster dose).

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**

- **Ambirix®** (GlaxoSmithKline UK Ltd)
- **Twinrix®** (Janssen-Cilag Ltd)

**Hepatitis A with typhoid vaccine**

The properties listed below are those particular to the combination only. For the properties of the components please consider, hepatitis A vaccine p. 1081, typhoid vaccine p. 1091.

**INDICATIONS AND DOSE**

**VIATIM®**

Immunisation against hepatitis A and typhoid infection (primary course)

BY INTRAMUSCULAR INJECTION

- Child 16-17 years: 1 mL for 1 dose, the deltoid region is the preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced). The subcutaneous route may be used for patients with bleeding disorders, booster dose given using single component vaccines
- Adult: 1 mL for 1 dose, the deltoid region is the preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced). The subcutaneous route may be used for patients with bleeding disorders, booster dose given using single component vaccines

Important safety information

Ambirix® and Twinrix® are not recommended for post-exposure prophylaxis following percutaneous (needle-stick), ocular, or mucous membrane exposure to hepatitis B virus.
route may be used for patients with bleeding disorders, booster dose given using single component vaccines

**Hepatix**

Immunisation against hepatitis A and typhoid infection (primary course)

**By intramuscular injection**

- Child 15-17 years: 1 mL for 1 dose, the deltoid region is the preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced). The subcutaneous route may be used for patients with bleeding disorders, booster dose given using single component vaccines
- Adult: 1 mL for 1 dose, the deltoid region is the preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced). The subcutaneous route may be used for patients with bleeding disorders, booster dose given using single component vaccines

**Indications and dose**

**Engerix B**

Immunisation against hepatitis B infection

**By intramuscular injection**

- Neonate: 10 micrograms for 1 dose, then 10 micrograms after 1 month for 1 dose, followed by 10 micrograms after 5 months for 1 dose, anterolateral thigh is preferred site in neonates, infants and young children; not to be injected into the buttock (vaccine efficacy reduced), this dose should not be given to neonates born to hepatitis B surface antigen positive mother.
- Child 1 month-15 years: 10 micrograms for 1 dose, then 10 micrograms after 5 months for 1 dose, deltoid muscle is preferred site of injection in adults and older children; anterolateral thigh is preferred site in infants and young children; not to be injected into the buttock (vaccine efficacy reduced)
- Child 16-17 years: 20 micrograms every month for 3 months, followed by 20 micrograms after 9 months for 1 dose, deltoid muscle is preferred site of injection in adults and older children; anterolateral thigh is preferred site in infants and young children; not to be injected into the buttock (vaccine efficacy reduced)
- Adult: 20 micrograms every month for 3 months, followed by 20 micrograms after 9 months for 1 dose, deltoid muscle is preferred site of injection in adults and older children; not to be injected into the buttock (vaccine efficacy reduced)

Immunisation against hepatitis B infection (accelerated schedule in exceptional cases, e.g. for travellers departing within 1 month)

**By intramuscular injection**

- Adult: 20 micrograms for 1 dose, then 20 micrograms after 7 days for 1 dose, followed by 20 micrograms after 14 days for 1 dose, followed by 20 micrograms after 11 months for 1 dose, deltoid muscle is preferred site of injection in adults and older children; not to be injected into the buttock (vaccine efficacy reduced)

Immunisation against hepatitis B infection (for neonates born to hepatitis B surface antigen positive mother)

**By intramuscular injection**

- Neonate: 10 micrograms once a month for 3 months, first dose to be given at birth with hepatitis B immunoglobulin injection (separate site), followed by 10 micrograms after 10 months for 1 dose, anterolateral thigh is preferred site in neonates; not to be injected into the buttock (vaccine efficacy reduced)

Immunisation against hepatitis B infection (in renal insufficiency, including haemodialysis patients)

**By intramuscular injection**

- Neonate: 10 micrograms every month for 2 months, first dose to be given at birth with hepatitis B immunoglobulin injection (separate site), followed by 10 micrograms after 5 months for 1 dose, anterolateral thigh is preferred site in neonates; not to be injected into the buttock (vaccine efficacy reduced)

Immunisation against hepatitis B infection (accelerated schedule)

**By intramuscular injection**

- Neonate: 10 micrograms every month for 3 months, followed by 10 micrograms after 9 months for 1 dose, anterolateral thigh is preferred site in neonates; not to be injected into the buttock (vaccine efficacy reduced), this dose should not be given to neonates born to hepatitis B surface antigen positive mother.
- Child 1 month-15 years: 10 micrograms every month for 3 months, followed by 10 micrograms after 9 months for 1 dose, anterolateral thigh is preferred site in neonates; not to be injected into the buttock (vaccine efficacy reduced)
- Child 16-17 years: 20 micrograms every month for 3 months, followed by 20 micrograms after 9 months for 1 dose, deltoid muscle is preferred site of injection in adults and older children; anterolateral thigh is preferred site in infants and young children; not to be injected into the buttock (vaccine efficacy reduced)
Vaccination

**Immunisation against hepatitis B infection (accelerated schedule)**

**BY INTRAMUSCULAR INJECTION**

- **Neonate**: 5 micrograms every month for 3 months, followed by 5 micrograms after 9 months for 1 dose, booster doses may be required in immunocompromised patients with low antibody concentration, anterolateral thigh is preferred site in neonates; not to be injected into the buttock (vaccine efficacy reduced).
- **Child 16-17 years**: 10 micrograms every month for 3 months, followed by 10 micrograms after 9 months for 1 dose, booster doses may be required in immunocompromised patients with low antibody concentration, deltoid muscle is preferred site of injection in adults and older children; not to be injected into the buttock (vaccine efficacy reduced).
- **Adult**: 10 micrograms every month for 3 months, followed by 10 micrograms after 9 months for 1 dose, booster doses may be required in immunocompromised patients with low antibody concentration, deltoid muscle is preferred site of injection in adults and older children; not to be injected into the buttock (vaccine efficacy reduced).

**HBVAXPRO**

**Immunisation against hepatitis B infection**

**BY INTRAMUSCULAR INJECTION**

- **Neonate**: 10 micrograms for 1 dose, followed by 5 micrograms after 1 month for 1 dose, then 5 micrograms after 5 months for 1 dose, booster doses may be required in immunocompromised patients with low antibody concentration, anterolateral thigh is preferred site in neonates; not to be injected into the buttock (vaccine efficacy reduced), dose not to be used for neonate born to hepatitis B surface antigen positive mother.
- **Child 15-17 years**: 20 micrograms every month for 3 months, followed by 20 micrograms after 4 months for 1 dose, booster doses may be required in those with low antibody concentration, deltoid muscle is preferred site of injection in adults and older children; not to be injected into the buttock (vaccine efficacy reduced).

**HBVAXPRO**

**Immunisation against hepatitis B infection**

**BY INTRAMUSCULAR INJECTION**

- **Neonate**: 10 micrograms every month for 3 months, followed by 10 micrograms after 9 months for 1 dose, booster doses may be required in immunocompromised patients with low antibody concentration, anterolateral thigh is preferred site in neonates; not to be injected into the buttock (vaccine efficacy reduced), dose not to be used for neonate born to hepatitis B surface antigen positive mother.
- **Child 1 month-15 years**: 5 micrograms every month for 3 months, followed by 5 micrograms after 9 months for 1 dose, booster doses may be required in immunocompromised patients with low antibody concentration, anterolateral thigh is preferred site in infants and young children; not to be injected into the buttock (vaccine efficacy reduced).
- **Adult**: 10 micrograms every month for 3 months, followed by 10 micrograms after 9 months for 1 dose, booster doses may be required in immunocompromised patients with low antibody concentration, deltoid muscle is preferred site of injection in adults and older children; not to be injected into the buttock (vaccine efficacy reduced).
- **Child 16-17 years**: 10 micrograms every month for 3 months, followed by 10 micrograms after 9 months for 1 dose, booster doses may be required in immunocompromised patients with low antibody concentration, deltoid muscle is preferred site of injection in adults and older children; not to be injected into the buttock (vaccine efficacy reduced).
- **Adult**: 10 micrograms every month for 3 months, followed by 10 micrograms after 9 months for 1 dose, booster doses may be required in immunocompromised patients with low antibody concentration, deltoid muscle is preferred site of injection in adults and older children; not to be injected into the buttock (vaccine efficacy reduced).

**FENDRIX**

**Immunisation against hepatitis B infection in renal insufficiency (including pre-haemodialysis and haemodialysis patients)**

**BY INTRAMUSCULAR INJECTION**

- **Child 15-17 years**: 20 micrograms every month for 3 months, followed by 20 micrograms after 4 months for 1 dose, immunisation schedule and booster doses may need to be adjusted in those with low antibody concentration, deltoid muscle is preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced).
Human papillomavirus vaccines

**INDICATIONS AND DOSE**

**GARDASIL**

Prevention of premalignant genital (cervical, vulvar and vaginal) and anal lesions, cervical and anal cancers, and genital warts

**BY INTRAMUSCULAR INJECTION**

- **Child 9-17 years (female):** 0.5 mL for 1 dose, followed by 0.5 mL after 1 month for 1 dose, second dose to be given at least 1 month after the first dose, then 0.5 mL after 3 months, third dose to be given at least 3 months after the second dose, schedule should be completed within 12 months of the first dose, dose to be administered preferably into deltoid region or higher anterolateral thigh, if the course is interrupted, it should be resumed (using the same vaccine) but not repeated, allowing the appropriate interval between the remaining doses.

- **Adult (female):** 0.5 mL for 1 dose, followed by 0.5 mL after 1 month for 1 dose, second dose to be given at least 1 month after the first dose, then 0.5 mL after 3 months, third dose to be given at least 3 months after the second dose, schedule should be completed within 12 months of the first dose, dose to be administered preferably into deltoid region or higher anterolateral thigh, if the course is interrupted, it should be resumed (using the same vaccine) but not repeated, allowing the appropriate interval between the remaining doses.

- **Prevention of premalignant genital (cervical, vulvar, and vaginal) and anal lesions, cervical and anal cancers, and genital warts (alternative schedule)**

**BY INTRAMUSCULAR INJECTION**

- **Child 9-13 years (female):** 0.5 mL for 1 dose, followed by 0.5 mL after 6 months for 1 dose, if the second dose is administered earlier than 6 months after the first dose, a third dose should be administered, dose to be administered preferably into deltoid region or higher anterolateral thigh, if the course is interrupted, it should be resumed (using the same vaccine) but not repeated, even if more than 24 months have elapsed since the first dose or if the girl is then aged 15 years or more.

**CERVARIX**

Prevention of premalignant genital lesions and cervical cancer

**BY INTRAMUSCULAR INJECTION**

- **Child 9-14 years (female):** 0.5 mL for 1 dose, followed by 0.5 mL after 5–7 months for 1 dose, if second dose administered earlier than 5 months after the first, a third dose should be administered, dose to be administered into deltoid region, if the course is interrupted, it should be resumed (using the same vaccine) but not repeated, even if more than 24 months have elapsed since the first dose or if the girl is then aged 15 years or more.

- **Child 15–17 years (female):** 0.5 mL for 1 dose, followed by 0.5 mL after 1–2.5 months for 1 dose, then 0.5 mL after 5–12 months for 1 dose, dose to be administered into deltoid region, if the course is interrupted, it should be resumed (using the same vaccine) but not repeated, allowing the appropriate interval between the remaining doses.

- **Adult (female):** 0.5 mL for 1 dose, followed by 0.5 mL after 1–2.5 months for 1 dose, then 0.5 mL after 5–12 months for 1 dose, dose to be administered into deltoid region, if the course is interrupted, it should be resumed (using the same vaccine) but not repeated, allowing the appropriate interval between the remaining doses.

**PRESCRIPTION AND DISPENSING INFORMATION**

To avoid confusion, prescribers should specify the brand to be dispensed.

**PREGNANCY**

Not known to be harmful, but vaccination should be postponed until completion of pregnancy.

**Vaccines**

**INFLUENZA VACCINE**

Annual immunisation against seasonal influenza (for children who have not received seasonal influenza vaccine previously)

**BY INTRAMUSCULAR INJECTION**

- **Child 6 months–9 years:** 0.5 mL for 1 dose, followed by 0.5 mL after at least 4 weeks for 1 dose

**BY INTRanasal ADMINISTRATION**

- **Child 2–9 years:** 0.1 mL for 1 dose, followed by 0.1 mL after at least 4 weeks for 1 dose, 0.1 mL dose to be administered into each nostril

**Annual immunisation against seasonal influenza**

**BY INTRAMUSCULAR INJECTION**

- **Child 6 months–17 years:** 0.5 mL for 1 dose

- **Adult:** 0.5 mL for 1 dose
BY INTRADERMAL INJECTION
- Adult 18–59 years: 9 micrograms for 1 dose, dose to be injected into deltoid region
- Adult 60 years and over: 15 micrograms for 1 dose, dose to be injected into deltoid region

BY INTRanasal ADMINISTRATION
- Child 2–17 years: 0.1 mL for 1 dose, dose to be administered into each nostril

UNLICENSED USE
Some products containing inactivated influenza vaccine (surface antigen) are not licensed for use in children under 4 years—check product literature.

FLUENZ TETRA® SUSPENSION FOR INJECTION
Not licensed for use in children under 3 years of age.

OPTAFLU® SUSPENSION FOR INJECTION
Not licensed for use in children and adolescents under 18 years.

FLUvin® SUSPENSION FOR INJECTION
Not licensed for use in children under 4 years.

CONTRA-INDICATIONS
Preparations marketed by Pfizer, or CSL Biotherapies in child under 5 years—increased risk of febrile convulsions.

FLUENZ TETRA® SPRAY
Severe asthma, active wheezing, concomitant use with antiviral therapy for influenza

CONTRA-INDICATIONS, FURTHER INFORMATION

FLUENZ TETRA® SPRAY
Concomitant use with antivirals. Avoid antivirals for at least 2 weeks after immunisation; avoid immunisation for at least 48 hours after stopping the antiviral.

CAUTIONS
Increased risk of fever in child 5–9 with preparations marketed by Pfizer or CSL Biotherapies

ENZIRA® SUSPENSION FOR INJECTION
Child 5–9 years (increased risk of fever)—use alternative influenza vaccine if available

SIDE-EFFECTS
GENERAL SIDE-EFFECTS
- Uncommon Epistaxis
- Frequency not known Febrile convulsions - transient thrombocytopenia - vasculitis (in adults)

SPECIFIC SIDE-EFFECTS
- With intranasal use Rhinitis

ALLERGY AND CROSS-SENSITIVITY
Individuals with a history of egg allergy can be immunised with either an egg free influenza vaccine, if available, or an influenza vaccine with an ovalbumin content less than 120 nanograms/mL, facilities should be available to treat anaphylaxis. Vaccines with an ovalbumin content more than 120 nanograms/mL or where content is not stated should not be used in individuals with egg allergy. If an influenza vaccine containing ovalbumin is being considered in those with a history of anaphylaxis to egg or egg allergy with uncontrolled asthma, these individuals should be referred to a specialist in hospital.

PREGNANCY
Inactivated vaccines not known to be harmful.

FLUENZ TETRA® SPRAY
Avoid in pregnancy.

BREAST FEEDING
Inactivated vaccines not known to be harmful.

FLUENZ TETRA® SPRAY
Avoid in breast-feeding.

PRESCRIBING AND DISPENSING INFORMATION

FLUARIX TETRA® SUSPENSION FOR INJECTION
Ovalbumin content less than 100 nanograms/mL.

PATIENT AND CARER ADVICE
Driving and skilled tasks May affect performance of skilled tasks (e.g. driving); effects of alcohol may be enhanced.

FLUENZ TETRA® SPRAY
Avoid close contact with severely immunocompromised patients for 1–2 weeks after vaccination.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Suspension for injection
EXCIPIENTS: May contain Gentamicin, kanamycin, neomycin penicillins, polymyxin b, thiomersal

INFLUENZA VACCINE (Non-proprietary)
Influenza vaccine (split virion, inactivated) suspension for injection 0.5m1 pre-filled syringes | 1 pre-filled disposable injection £5.55–6.59 | 10 pre-filled disposable injection £65.90
Influenza vaccine (surface antigen, inactivated) suspension for injection 0.5ml pre-filled syringes | 10 pre-filled disposable injection £61.50

Agrippal (Novartis Vaccines and Diagnostics Ltd)
Agrippal vaccine suspension for injection 0.5m1 pre-filled syringes | 10 pre-filled disposable injection £58.50

Enzira (Pfizer Ltd)
Enzira vaccine suspension for injection 0.5m1 pre-filled syringes | 1 pre-filled disposable injection £5.25 | 10 pre-filled disposable injection £52.50

Fluarix Tetra (GlaxoSmithKline UK Ltd)
Fluarix Tetra suspension for injection 0.5m1 pre-filled syringes | 1 pre-filled disposable injection £99.40

Fluvirin (Novartis Vaccines and Diagnostics Ltd)
Fluvirin vaccine suspension for injection 0.5m1 pre-filled syringes | 10 pre-filled disposable injection £55.50

Imvac (BGP Products Ltd)
Imvac vaccine suspension for injection 0.5m1 pre-filled syringes | 1 pre-filled disposable injection £65.90 | 10 pre-filled disposable injection £659.00

Influvac Sub-unit (BGP Products Ltd)
Influvac Sub-unit vaccine suspension for injection 0.5m1 pre-filled syringes | 1 pre-filled disposable injection £65.90 | 10 pre-filled disposable injection £659.00

Intanza (sanofi pasteur MSD Ltd)
Intanza 15microgram strain vaccine suspension for injection 0.1ml pre-filled syringes | 1 pre-filled disposable injection £3.05 | 10 pre-filled disposable injection £30.50
Intanza 9microgram strain vaccine suspension for injection 0.1ml pre-filled syringes | 1 pre-filled disposable injection £3.05

Optaflu (Novartis Vaccines and Diagnostics Ltd)
Optaflu vaccine suspension for injection 0.5m1 pre-filled syringes | 1 pre-filled disposable injection £6.59

Emulsion and suspension for emulsion for injection

Pandemrix H1N1 (GlaxoSmithKline UK Ltd)
Pandemrix vaccine emulsion and suspension for emulsion for injection | 500 dose £50 no price available

Spray
EXCIPIENTS: May contain Gelatin, gentamicin

Fluenz Tetra (AstraZeneca UK Ltd)
Fluenz Tetra nasal suspension 0.2ml unit dose | 10 unit dose £180.00

Japanese encephalitis vaccine

INDICATIONS AND DOSE
Immunisation against Japanese encephalitis

BY INTRamuscular INJECTION
- Child 2 months-2 years: 0.25 mL every 28 days for 2 doses, anterolateral thigh is preferred site of injection in infants, the subcutaneous route may be used for patients with bleeding disorders.
- Child 3-17 years: 0.5 mL every 28 days for 2 doses, deltoid muscle is preferred site in older children; anterolateral thigh is preferred in infants, the subcutaneous route may be used for patients with bleeding disorders.
- Adults: 0.5 mL every 28 days for 2 doses, deltoid muscle is preferred site of injection, the subcutaneous route may be used for patients with bleeding disorders.
Measles, mumps and rubella vaccine, live

**INDICATIONS AND DOSE**

Primary immunisation against measles, mumps, and rubella (first dose)
- **BY INTRAMUSCULAR INJECTION OR BY DEEP SUBCUTANEOUS INJECTION**
  - Child 12-13 months: 0.5 mL for 1 dose

Primary immunisation against measles, mumps, and rubella (second dose)
- **BY INTRAMUSCULAR INJECTION OR BY DEEP SUBCUTANEOUS INJECTION**
  - Child 40 months-5 years: 0.5 mL for 1 dose

Rubella immunisation (in seronegative women, susceptible to rubella and in unimmunised, seronegative women, post-partum)
- **BY INTRAMUSCULAR INJECTION OR BY DEEP SUBCUTANEOUS INJECTION**
  - Females of childbearing potential: (consult product literature or local protocols)

Children presenting for pre-school booster, who have not received the primary immunisation (first dose)
- **Immunisation for patients at school-leaving age or at entry into further education, who have not completed the primary immunisation course** | Control of measles outbreak | Immunisation for patients travelling to areas where measles is endemic or epidemic, who have not completed the primary immunisation

**BY INTRAMUSCULAR INJECTION OR BY DEEP SUBCUTANEOUS INJECTION**
- Child 6 months-17 years: (consult product literature or local protocols)
- Adult: (consult product literature or local protocols)

**SIDE-EFFECTS**

- **Uncommon**
  - Cough (in children), migraine (in adults), vertigo (in adults)

- **Rare**
  - Dyspnoea (in adults), neuritis (in adults), palpititation (in adults), tachycardia (in adults), thrombocytopenia (in adults)

**PREGNANCY**

Although manufacturer advises avoid because of limited information, miscarriage has been associated with Japanese encephalitis virus infection acquired during the first 2 trimesters of pregnancy.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Suspension for injection**
- Ixiaro (Novartis Vaccines and Diagnostics Ltd)
- Ixiaro vaccine suspension for injection 0.5ml pre-filled syringes | 1 pre-filled disposable injection (PDM) £59.50

**VACCINATION AND BOWEL DISEASE OR AUTISM**

Reviews undertaken on behalf of the CSM, the Medical Research Council, and the Cochrane Collaboration, have not found any evidence of a link between MMR vaccination and bowel disease or autism. The Chief Medical Officers have advised that the MMR vaccine is the safest and best way to protect children against measles, mumps, and rubella. Information (including fact sheets and a list of references) may be obtained from www.dh.gov.uk/immunisation.

**CAUTIONS**

Antibody response to measles component may be reduced after immunoglobulin administration or blood transfusion—leave an interval of at least 3 months before MMR immunisation

**CAUTIONS, FURTHER INFORMATION**

Administration with other vaccines

MMR vaccine should not be administered on the same day as yellow fever vaccine; there should be a 4-week minimum interval between the vaccines. When protection is rapidly required, the vaccines can be given at any interval and an additional dose of MMR may be considered.

MMR and varicella-zoster vaccine can be given on the same day or separated by a 4-week minimum interval. When protection is rapidly required, the vaccines can be given at any interval and an additional dose of the vaccine given second may be considered.

**SIDE-EFFECTS**

- **Uncommon**
  - Parotid swelling (usually in the third week) • sleep disturbances • unusual crying in infants

- **Rare**
  - Arthropathy (2 to 3 weeks after immunisation) • idiopathic thrombocytopenic purpura

- **Frequency not known**
  - Optic neuritis • peripheral neuritis

**SIDE-EFFECTS, FURTHER INFORMATION**

Malaise, fever, or a rash can occur after the first dose of MMR vaccine—most commonly about a week after vaccination and lasting about 2 to 3 days. Leaflets are available for parents on advice for reducing fever (including the use of paracetamol). Feverile seizures—occur rarely 6 to 11 days after MMR vaccination (the incidence is lower than that following measles infection)

**Idiopathic thrombocytopenic purpura**

Idiopathic thrombocytopenic purpura has occurred rarely following MMR vaccination, usually within 6 weeks of the first dose. The risk of idiopathic thrombocytopenic purpura after MMR vaccine is much less than the risk after infection with wild measles or rubella virus. Children who develop idiopathic thrombocytopenic purpura within 6 weeks of the first dose of MMR should undergo serological testing before the second dose is due; if the results suggest incomplete immunity against measles, mumps or rubella then a second dose of MMR is recommended. The Specialist and Reference Microbiology Division, Health Protection Agency offers free serological testing for children who develop idiopathic thrombocytopenic purpura within 6 weeks of the first dose of MMR.

**Aseptic meningitis**

Post-vaccination aseptic meningitis was reported (rarely and with complete recovery) following vaccination with MMR vaccine containing Urabe mumps vaccine, which has now been discontinued; no cases have been confirmed in association with the currently used Jeryl Lynn mumps vaccine. Children with post-vaccination symptoms are not infectious.

**Frequency of side effects**

Adverse reactions are considerably less frequent after the second dose of MMR vaccine than after the first.

**ALLERGY AND CROSS-SENSITIVITY**

MMR vaccine can be given safely even when the child has had an anaphylactic reaction to food containing egg. Dislike of eggs, refusal to eat eggs, or confirmed anaphylactic reactions to egg-containing food is not a contra-indication to MMR vaccination. Children with a confirmed anaphylactic reaction to the MMR vaccine should be assessed by a specialist.

**UNLICENSED USE**

Not licensed for use in children under 9 months.
Meningococcal group C vaccine

INDICATIONS AND DOSE
Primary immunisation against Neisseria meningitidis
BY INTRAMUSCULAR INJECTION
- Child 3 months: 0.5 mL for 1 dose, the primary immunisation dose is followed by a booster dose of meningococcal group C conjugate vaccine combined with haemophilus influenzae type b vaccine at 12–15 months of age
Second booster dose for immunisation against Neisseria meningitidis
BY INTRAMUSCULAR INJECTION
- Child 13–15 years: 0.5 mL for 1 dose
Immunisation against Neisseria meningitidis in an unimmunised patient
BY INTRAMUSCULAR INJECTION
- Child 4–11 months: 0.5 mL for 1 dose, the primary immunisation dose is followed by a booster dose of meningococcal group C conjugate vaccine combined with haemophilus influenzae type b vaccine at 12–15 months of age, then 0.5 mL for 1 dose, this second booster dose to be given at 13–15 years of age
- Child 1–9 years: 0.5 mL for 1 dose, then 0.5 mL for 1 dose, this booster dose to be given at 13–15 years of age
- Child 10–17 years: 0.5 mL for 1 dose, booster dose is not required
- Adult 18–24 years: 0.5 mL for 1 dose
Patients attending university for the first time (who did not receive second booster dose at 13–15 years)
BY INTRAMUSCULAR INJECTION
- Adult 18–24 years: 0.5 mL for 1 dose
Patients with confirmed serogroup C disease (who have previously been immunised)
BY INTRAMUSCULAR INJECTION
- Child 1–7 years: 0.5 mL for 1 dose, dose to be given before discharge from hospital
- Adult 18–24 years: 0.5 mL for 1 dose, dose to be given before discharge from hospital

SIDE-EFFECTS
- Rare Symptoms of meningitis (but no evidence that vaccine causes meningococcal C meningitis)
- DIRECTIONS FOR ADMINISTRATION Menjugate Kit® may be used via subcutaneous route in children with bleeding disorders.
- PRESCRIBING AND DISPENSING INFORMATION Available as part of childhood immunisation schedule from www.immform.dh.gov.uk.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Powder and solvent for suspension for injection
- Menjugate (Novartis Vaccines and Diagnostics Ltd)
Menjugate vaccine powder and solvent for suspension for injection 0.5mL vials | 1 vial £4.33 | 10 vial no price available

Suppression for injection
- Meningitec (Nuron Biotech B.V.)
Meningitec vaccine suspension for injection 0.5mL pre-filled syringes | 1 pre-filled disposable injection £4.33 | 10 pre-filled disposable injection £43.30
- NeisVac-C (Pfizer Ltd)
NeisVac-C vaccine suspension for injection 0.5mL pre-filled syringes | 10 disposable pre-filled injection £187.50

Meningococcal group B vaccine (rDNA, component, adsorbed)

INDICATIONS AND DOSE
Immunisation against Neisseria meningitidis, primary immunisation
BY DEEP INTRAMUSCULAR INJECTION
- Child 2–5 months: 0.5 mL at least every month for 3 doses, injected preferably into deltoid region (or anterolateral thigh in infants)
Immunisation against Neisseria meningitidis, primary immunisation booster dose
BY DEEP INTRAMUSCULAR INJECTION
- Child 1–2 years: 0.5 mL for 1 dose, injected preferably into deltoid region (or anterolateral thigh in infants)
Immunisation against Neisseria meningitidis, primary immunisation (in unimmunised patients)
BY DEEP INTRAMUSCULAR INJECTION
- Child 6–11 months: 0.5 mL at least every 2 months for 2 doses, booster dose of 0.5 mL given between 1–2 years of age and at least 2 months after completion of primary immunisation, injected preferably into deltoid region (or anterolateral thigh in infants)
- Child 12–23 months: 0.5 mL at least every 2 months for 2 doses, booster dose of 0.5 mL given 12–24 months after completion of primary immunisation, injected preferably into deltoid region (or anterolateral thigh in infants)
- Child 2–10 years: 0.5 mL at least every 2 months for 2 doses, injected preferably into deltoid region (or anterolateral thigh in infants)
- Child 11–17 years: 0.5 mL at least every month for 2 doses, injected preferably into deltoid region
- Adult: 0.5 mL at least every month for 2 doses, injected preferably into deltoid region

SIDE-EFFECTS
- Rare Kawasaki disease (in children) - symptoms of meningitis reported (but no evidence that the vaccine causes meningococcal C meningitis)
- Frequency not known Unusual crying (in children)

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Suspension for injection
EXCIPIENTS: May contain Gelatin, neomycin
- M-M-RVAXPRO (sanofi pasteur MSD Ltd)
 M-M-RVAXPRO vaccine powder and solvent for suspension for injection 0.5mL pre-filled syringes | 1 pre-filled disposable injection £11.00

CONCEPTION AND CONTRACEPTION
Exclude pregnancy before immunisation. Avoid pregnancy for at least 1 month after vaccination.

PRESCRIBING AND DISPENSING INFORMATION Available as part of childhood immunisation schedule from health organisations or ImmForm www.immform.dh.gov.uk.
Meningococcal groups A with C and W135 and Y vaccine

**INDICATIONS AND DOSE**

**MENVEO**
Immunisation against *Neisseria meningitidis*

**BY INTRAMUSCULAR INJECTION**
- Child 3–11 months: 0.5 mL for 1 dose
- Child 1–7 years: 0.5 mL for 1 dose
- Adult: 0.5 mL for 1 dose

**SIDE-EFFECTS**

- **UNLICENSED USE**
  - **MENVEO**: Menveo® is not licensed for use in children under 2 years.

- **SIDE-EFFECTS**
  - **Rare**: Symptoms of meningitis reported (but no evidence under 2 years that the vaccine causes meningococcal C meningitis)

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

- **Powder and solvent for solution for injection**
  - **Menveo** (Novartis Vaccines and Diagnostics Ltd)
    - Menveo vaccine powder and solvent for solution for injection 0.5mL vials | 1 vial [POM] £30.00
  - **Nimenrix** (GliaSanoSmithKline UK Ltd)
    - Nimenrix vaccine powder and solvent for solution for injection 0.5mL pre-filled syringes | 1 pre-filled disposable injection [POM] £30.00

Pneumococcal vaccine

**INDICATIONS AND DOSE**

Immunisation against pneumococcal infection

**BY INTRAMUSCULAR INJECTION OR BY SUBCUTANEOUS INJECTION**
- Child 2–17 years: 0.5 mL for 1 dose
- Adult: 0.5 mL for 1 dose

Immunisation in patients at increased risk of pneumococcal disease

**BY INTRAMUSCULAR INJECTION OR BY SUBCUTANEOUS INJECTION**
- Child 2–4 years: 0.5 mL for 1 dose
- Child 5–17 years: 0.5 mL for 1 dose
- Adult: 0.5 mL for 1 dose

**PREVENAR 13®**

Primary immunisation against pneumococcal infection (first dose)

**BY INTRAMUSCULAR INJECTION**
- Child 2 months: 0.5 mL for 1 dose, anterolateral thigh is preferred site of injection in infants

Primary immunisation against pneumococcal infection (second dose)

**BY INTRAMUSCULAR INJECTION**
- Child 4 months: 0.5 mL for 1 dose, anterolateral thigh is preferred site of injection in infants

Primary immunisation against pneumococcal infection (third dose)

**BY INTRAMUSCULAR INJECTION**
- Child 12-13 months: 0.5 mL for 1 dose, anterolateral thigh is preferred site of injection in infants

Immunisation against pneumococcal infection (in patients who have not been vaccinated or not completed the primary course)

**BY INTRAMUSCULAR INJECTION**
- Child 12 months-4 years: 0.5 mL for 1 dose, Deltoide muscle is preferred site of injection in young children; anterolateral thigh is preferred site in infants

Immunisation against pneumococcal infection, in immunocompromised or asplenic patients or patients with splenic dysfunction (who have not been vaccinated or not completed the primary course)

**BY INTRAMUSCULAR INJECTION**
- Child 12 months-4 years: 0.5 mL every 2 months for 2 doses

**SYNFLORIX®**

Immunisation against pneumococcal infection

**BY INTRAMUSCULAR INJECTION**
- Child 6 weeks-5 years: Deltoide muscle is preferred site of injection in young children; anterolateral thigh is preferred site in infants (consult product literature)

**UNLICENSED USE**

**PREVENAR 13®**

The dose in BNF publications may differ from that in product literature.

**CONTRA-INDICATIONS**
Concomitant use of high potency varicella-zoster vaccine (Zostavax®) with pneumococcal polysaccharide vaccine (in adults)

**PRESCRIBING AND DISPENSING INFORMATION**

**PREVENAR 13®**
Available as part of childhood immunisation schedule from Immform www.immform.dh.gov.uk

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **PNEUMOCOCCAL VACCINE (Non-proprietary)**
  - Pneumococcal polysaccharide vaccine solution for injection 0.5mL vials | 1 vial [POM] £8.32

**Suspension for injection**

- **Prevenar** (Pfizer Ltd)
  - Prevenar 13 vaccine suspension for injection 0.5mL pre-filled syringes | 1 pre-filled disposable injection [POM] £49.10 | 10 pre-filled disposable injection [POM] £491.00
- **Synflorix** (GliaSanoSmithKline UK Ltd)
  - Synflorix vaccine suspension for injection 0.5mL pre-filled syringes | 1 pre-filled disposable injection [POM] £27.60
Rabies vaccine

INDICATIONS AND DOSE
Pre-exposure prophylaxis
BY INTRAMUSCULAR INJECTION
- Child: 1 mL every week for 2 doses (on days 0 and 7), followed by 1 mL after 21 days for 1 dose (on day 28), to be administered in deltoid region or anterolateral thigh in infants, for those at continuous risk, measure plasma-concentration of antibodies every 6 months and give a booster dose if the titre is less than 0.5 units/mL; final dose may be given from day 21, if insufficient time before travel
- Adult: 1 mL every week for 2 doses (on days 0 and 7), followed by 1 mL after 21 days for 1 dose (on day 28), to be administered in deltoid region, for those at continuous risk, measure plasma-concentration of antibodies every 6 months and give a booster dose if the titre is less than 0.5 units/mL; final dose may be given from day 21, if insufficient time before travel
Pre-exposure prophylaxis booster dose (for patients at frequent risk of exposure)
BY INTRAMUSCULAR INJECTION
- Child: 1 mL after 1 year for 1 dose, then 1 mL every 3–5 years for 1 dose, to be administered in deltoid region or anterolateral thigh in infants, the frequency of booster doses may alternatively be determined according to plasma-concentration of antibodies
- Adult: 1 mL after 1 year for 1 dose, then 1 mL every 3–5 years for 1 dose, to be administered in deltoid region, the frequency of booster doses may alternatively be determined according to plasma-concentration of antibodies
Pre-exposure prophylaxis booster dose (for patients at infrequent risk of exposure)
BY INTRAMUSCULAR INJECTION
- Child: 1 mL after 10 years for 1 dose, to be administered in deltoid region or anterolateral thigh in infants
- Adult: 1 mL after 10 years for 1 dose, to be administered in deltoid region
Post-exposure prophylaxis of fully immunised individuals (who have previously received pre-exposure or post-exposure prophylaxis with cell-derived rabies vaccine)
BY INTRAMUSCULAR INJECTION
- Child (administered on expert advice): 1 mL for 1 dose, followed by 1 mL after 3–7 days for 1 dose, to be administered in deltoid region or anterolateral thigh in infants, rabies immunoglobulin is not necessary
- Adult (administered on expert advice): 1 mL for 1 dose, followed by 1 mL after 3–7 days for 1 dose, to be administered in deltoid region, rabies immunoglobulin is not necessary
Post-exposure treatment for unimmunised individuals (or those whose prophylaxis is possibly incomplete)
BY INTRAMUSCULAR INJECTION
- Child (administered on expert advice): 1 mL 5 times a month for 1 month, doses should be given on days 0, 3, 7, 14, and the fifth dose is given between day 28–30, to be administered in deltoid region or anterolateral thigh in infants, depending on the level of risk (determined by factors such as the nature of the bite and the country where it was sustained), rabies immunoglobulin is given to unimmunised individuals on day 0 or within 7 days of starting the course of rabies vaccine, the immunisation course can be discontinued if it is proved that the individual was not at risk

- Adult (administered on expert advice): 1 mL 5 times a month for 1 month, doses should be given on days 0, 3, 7, 14, and the fifth dose is given between day 28–30, to be administered in deltoid region, depending on the level of risk (determined by factors such as the nature of the bite and the country where it was sustained), rabies immunoglobulin is given to unimmunised individuals on day 0 or within 7 days of starting the course of rabies vaccine, the immunisation course can be discontinued if it is proved that the individual was not at risk

SIDE-EFFECTS
- Paresis
- PREGNANCY Because of the potential consequences of untreated rabies exposure and because rabies vaccination has not been associated with fetal abnormalities, pregnancy is not considered a contra-indication to post-exposure prophylaxis. Immunisation against rabies is indicated during pregnancy if there is substantial risk of exposure to rabies and rapid access to post-exposure prophylaxis is likely to be limited.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Powder and solvent for solution for injection
EXCIPIENTS: May contain Neomycin
Rabipur vaccine powder and solvent for solution for injection 1mL vials | 1 vial (BNF) £28.80

Powder and solvent for suspension for injection
EXCIPIENTS: May contain Neomycin
RABIES VACCINE (Non-proprietary)
Rabies vaccine powder and solvent for suspension for injection 1mL vials | 1 vial (BNF) £33.90

Rotavirus vaccine

DRUG ACTION
Rotavirus vaccine is a live, oral vaccine that protects young children against gastro-enteritis caused by rotavirus infection.

INDICATIONS AND DOSE
Immunisation against gastro-enteritis caused by rotavirus
BY MOUTH
- 6–24 weeks: 1.5 mL at least every 4 weeks for 2 doses, first dose must be given between 6–15 weeks of age; course should be completed before 24 weeks of age (preferably before 16 weeks)

CONTRA-INDICATIONS
- History of intussusception • predisposition to intussusception • severe combined immunodeficiency
CONTRA-INDICATIONS, FURTHER INFORMATION
Immunosuppression With the exception of severe combined immunodeficiency, rotavirus vaccine is not contra-indicated in immunosuppressed patients—benefit from vaccination is likely to outweigh the risk, if there is any doubt, seek specialist advice.

CAUTIONS
- Diarrhoea (postpone vaccination) • immunosuppressed close contacts • vomiting (postpone vaccination)

CAUTIONS, FURTHER INFORMATION
The rotavirus vaccine virus is excreted in the stool and may be transmitted to close contacts; however, vaccination of those with immunosuppressed close contacts may protect the contacts from wild-type rotavirus disease and outweigh any risk from transmission of vaccine virus.

SIDE-EFFECTS
- Abdominal cramps • abdominal pain • diarrhoea • nausea • vomiting

PATIENT AND CARER ADVICE
The rotavirus vaccine virus is excreted in the stool and may be transmitted to close contacts; thus, people who become unwell while taking the vaccine should be advised to avoid close contact with young children, according to the rotavirus vaccine manufacturers’ leaflet.
contacts; carers of a recently vaccinated baby should be advised of the need to wash their hands after changing the baby's nappies.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
- **Oral suspension**
  - **Rotarix** (GlaxoSmithKline UK Ltd)
  - Rotarix vaccine live oral suspension 1.5ml pre-filled syringes | 1 unit dose (£34.76)

### Tick-borne encephalitis vaccine, inactivated

#### INDICATIONS AND DOSE

**Initial immunisation against tick-borne encephalitis**

- **BY INTRAMUSCULAR INJECTION**
  - Child 1–5 years: 0.25 mL for 1 dose, followed by 0.25 mL after 1–3 months for 1 dose, then 0.25 mL after 5–12 months for 1 dose, to achieve more rapid protection, second dose may be given 14 days after first dose, to be administered in deltoid region or anterolateral thigh in infants, in immunocompromised patients (including those receiving immunosuppressants), antibody concentration may be measured 4 weeks after second dose and dose repeated if protective levels not achieved
  - Child 6–17 years: 0.5 mL for 1 dose, followed by 0.5 mL after 1–3 months for 1 dose, then 0.5 mL after 5–12 months for 1 dose, to achieve more rapid protection, second dose may be given 14 days after first dose, to be administered in deltoid region, in immunocompromised patients (including those receiving immunosuppressants), antibody concentration may be measured 4 weeks after second dose and dose repeated if protective levels not achieved
  - Adult: 0.5 mL for 1 dose, followed by 0.5 mL after 1–3 months for 1 dose, then 0.5 mL after 5–12 months for 1 dose, to achieve more rapid protection, second dose may be given 14 days after first dose, to be administered in deltoid region, in immunocompromised patients (including those receiving immunosuppressants), antibody concentration may be measured 4 weeks after second dose and dose repeated if protective levels not achieved
- **BY MOUTH**
  - Elderly: 0.5 mL for 1 dose, followed by 0.5 mL after 1–3 months for 1 dose, then 0.5 mL after 5–12 months for 1 dose, to achieve more rapid protection, second dose may be given 14 days after first dose, to be administered in deltoid region, antibody concentration may be measured 4 weeks after second dose and dose repeated if protective levels not achieved

**Immunisation against tick-borne encephalitis, booster doses**

- **BY INTRAMUSCULAR INJECTION**
  - Child 1–7 years: First dose to be given within 3 years after initial course completed and then every 3–5 years (consult product literature)
  - Adult: First dose to be given within 3 years after initial course completed and then every 3–5 years (consult product literature)

- **ALLERGY AND CROSS-SENSITIVITY**
  - Individuals with evidence of previous anaphylactic reaction to egg should not be given tick-borne encephalitis vaccine.

### Typhoid vaccine

#### INDICATIONS AND DOSE

**Immunisation against typhoid fever**

- **BY INTRAMUSCULAR INJECTION**
  - Adult: 0.5 mL for 1 dose, should be given at least 2 weeks before potential exposure to typhoid infection

- **BY MOUTH**
  - Adult: 1 capsule every 2 days for 3 doses

- **CONTRA-INDICATIONS**
  - With oral use acute gastro-intestinal illness

- **INTERACTIONS**
  - Appendix 1 (vaccines)
  - Oral typhoid vaccine is inactivated by concomitant administration of antibacterials or antimalarials:
    - antibacterials should be avoided for 3 days before and after oral typhoid vaccination;
    - **Mefloquine** should be avoided for at least 12 hours before or after oral typhoid;
    - For other antimalarials vaccination with oral typhoid vaccine should be completed at least 3 days before the first dose of the antimalarial (except proguanil hydrochloride with atovaquone, which may be given concomitantly).

- **SIDE-EFFECTS**
  - With oral use abdominal cramps • abdominal pain • diarrhoea • nausea • vomiting

- **DIRECTIONS FOR ADMINISTRATION**
  - Capsule should be taken one hour before a meal. Swallow as soon as possible after placing in mouth with a cold or lukewarm drink.

- **HANDLING AND STORAGE**
  - With oral use It is important to store capsules in a refrigerator.

- **PATIENT AND CARER ADVICE**
  - With oral use Patients or carers should be given advice on how to administer and store typhoid vaccine capsules.

#### MEDICINAL FORMS

- There can be variation in the licensing of different medicines containing the same drug.

**Gastro-resistant capsule**

- **CAUTIONARY AND ADVISORY LABELS**
  - 25
- **Vivotif** (Pasteur MSD Ltd)
  - Vivotif® gastro-resistant capsules | 3 capsule (£14.77)

#### Solution for injection

- **Typhim Vi** (GlaxoSmithKline UK Ltd)
  - Salmonella typhi Vi capsular polysaccharide 50 microgram per 1 mL Typhim Vi 25micrograms/0.5mL vaccine solution for injection pre-filled syringes | 1 pre-filled disposable injection (£9.93) | 10 pre-filled disposable injection (£93.32)

- **Typhim Vi** (SanofiPasteur MSD Ltd)
  - Salmonella typhi Vi capsular polysaccharide 50 microgram per 1 mL Typhim Vi 25micrograms/0.5mL vaccine solution for injection pre-filled syringes | 1 pre-filled disposable injection (£9.30) | 10 pre-filled disposable injection (£93.00)
Varicella-zoster vaccine

**INDICATIONS AND DOSE**

**VARILRIX®**

Prevention of varicella infection (chickenpox)

*BY SUBCUTANEOUS INJECTION*
- Child 1-17 years: 0.5 mL every 4–6 weeks for 2 doses, to be administered preferably into the deltoid region
- Adult: 0.5 mL every 4–6 weeks for 2 doses, to be administered preferably into the deltoid region

**VARIVAX®**

Prevention of varicella infection (chickenpox)

*BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION*
- Child 1-12 years: 0.5 mL for 2 doses, interval of at least 4 weeks between each dose, to be administered into the deltoid region (or higher anterolateral thigh)
- Child 13-17 years: 0.5 mL every 4–8 weeks for 2 doses, to be administered preferably into the deltoid region (or higher anterolateral thigh)
- Adult: 0.5 mL every 4–8 weeks for 2 doses, to be administered preferably into the deltoid region

Prevention of varicella infection (chickenpox) in children with asymptomatic HIV infection

*BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION*
- Child 1-12 years: 0.5 mL every 12 weeks for 2 doses, to be administered into the deltoid region (or higher anterolateral thigh)

**ZOSTAVAX®**

Prevention of herpes zoster (shingles)

*BY SUBCUTANEOUS INJECTION*
- Adult 70-79 years: 0.65 mL for 1 dose, to be administered preferably into the deltoid region

**CAUTIONS**

Post-vaccination close contact with susceptible individuals

**CAUTIONS, FURTHER INFORMATION**

Rarely, the varicella-zoster vaccine virus has been transmitted from the vaccinated individual to close contacts. Therefore, contact with the following should be avoided if a vaccine-related cutaneous rash develops within 4–6 weeks of the first or second dose:

- varicella-susceptible pregnant women;
- individuals at high risk of severe varicella, including those with immunodeficiency or those receiving immunosuppressive therapy.

Healthcare workers who develop a generalised papular or vesicular rash on vaccination should avoid contact with patients until the lesions have crusted. Those who develop a localised rash after vaccination should cover the patients until the lesions have crusted. Those who develop a varicella-like rash on vaccination should avoid contact with varicella-susceptible patients until the lesions have crusted. Those who develop a varicella-like rash on vaccination should avoid contact with patients at high risk of severe varicella.

**Administration with MMR vaccine**

Varicella–zoster and MMR vaccines can be given on the same day or separated by a 4-week minimum interval. When protection is rapidly required, the vaccines can be given at any interval and an additional dose of the vaccine given second may be considered.

**SIDE-EFFECTS**

- Thrombocytopenia
- Frequency not known: Conjunctivitis, varicella-like rash
- CONCEPTION AND CONTRACEPTION: Avoid pregnancy for 3 months after vaccination.

**PRESCRIBING AND DISPENSING INFORMATION**

**ZOSTAVAX®**

Advice in the BNF may differ from that in product literature.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Yellow fever vaccine, live**

**INDICATIONS AND DOSE**

Immunisation against yellow fever

*BY DEEP SUBCUTANEOUS INJECTION*
- Child 6–8 months (administered on expert advice): Infants under 9 months should be vaccinated only if the risk of yellow fever is high and unavoidable (consult product literature or local protocols)
- Child 9 months–17 years: 0.5 mL for 1 dose
- Adult: 0.5 mL for 1 dose

**CONTRA-INDICATIONS**

Children under 6 months—history of thymus dysfunction

**CAUTIONS**

Individuals over 60 years—greater risk of vaccine-associated adverse effects (in adults)

**CAUTIONS, FURTHER INFORMATION**

Administration with MMR vaccine

Yellow fever and MMR vaccines should not be administered on the same day; there should be a 4-week minimum interval between the vaccines. When protection is rapidly required, the vaccines can be given at any interval and an additional dose of MMR may be considered.

**SIDE-EFFECTS**

Neurotropic disease, viscerotropic disease

**SIDE-EFFECTS, FURTHER INFORMATION**

Vaccine-associated adverse effects

Very rare adverse effects, such as viscerotropic disease (yellow-fever vaccine-associated viscerotropic disease, YEL-AVD), a syndrome which may include metabolic acidosis, muscle and liver cirrhosis, and multi-organ failure. Neurological disorders (yellow fever vaccine-associated neurotropic disease, YEL-AND) such as encephalitis have also been reported. These very rare adverse effects usually occur after the first dose of yellow fever vaccine in those with no previous immunity.

**ALLERGY AND CROSS-SENSITIVITY**

Yellow fever vaccine should only be considered under the guidance of a specialist in individuals with evidence of previous anaphylactic reaction to egg.

**PREGNANCY**

Live yellow fever vaccine should not be given during pregnancy because there is a theoretical risk of fetal infection. Pregnant women should be advised not to travel to areas at high risk of yellow fever. If exposure cannot be avoided during pregnancy, then the vaccine should be given if the risk from disease in the mother outweighs the risk to the fetus from vaccination.

**BREAST FEEDING**

Avoid; seek specialist advice if exposure to virus cannot be avoided.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Powder and solvent for solution for injection**

EXCIPIENTS: May contain Neomycin
- Varilrix (GlaxoSmithKline UK Ltd) Varilrix vaccine powder and solvent for solution for injection 0.5mL vials | 1 vial £27.31

**Powder and solvent for suspension for injection**

EXCIPIENTS: May contain Gelatin, Neomycin
- Varivax (sanofi pasteur MSD Ltd) Varivax vaccine powder and solvent for suspension for injection 0.5mL vials | 1 vial £30.28
- Zostavax (sanofi pasteur MSD Ltd) Zostavax powder and solvent for suspension for injection 0.65mL pre-filled syringes | 1 pre-filled disposable injection £99.96
Chapter 15
Anaesthesia

CONTENTS

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2 Local anaesthesia

1 General anaesthesia

General anaesthesia
Several different types of drug are given together during general anaesthesia. Anaesthesia is induced with either a volatile drug given by inhalation or with an intravenously administered drug; anaesthesia is maintained with an intravenous or inhalational anaesthetic. Analgesics, usually short-acting opioids, are also used. The use of neuromuscular blocking drugs necessitates intermittent positive-pressure ventilation. Following surgery, anticholinesterases can be given to reverse the effects of neuromuscular blocking drugs; specific antagonists can be used to reverse central and respiratory depression caused by some drugs used in surgery. A local topical anaesthetic can be used to reduce pain at the injection site.

Individual requirements vary considerably and the recommended doses are only a guide. Smaller doses are indicated in ill, shocked, or debilitated patients and in significant hepatic impairment, while robust individuals may require larger doses. The required dose of induction agent may be less if the patient has been premedicated with a sedative agent or if an opioid analgesic has been used.

Intravenous anaesthetics
Intravenous anaesthetics may be used either to induce anaesthesia or for maintenance of anaesthesia throughout surgery. Intravenous anaesthetics nearly all produce their effect in one arm-brain circulation time. Extreme care is required in surgery of the mouth, pharynx, or larynx where the airway may be difficult to maintain (e.g. in the presence of a tumour in the pharynx or larynx).

To facilitate tracheal intubation, induction is usually followed by a neuromuscular blocking drug or a short-acting opioid.

The doses of all intravenous anaesthetic drugs should be titrated to effect (except when using ‘rapid sequence induction’); lower doses may be required in premedicated patients.

Total intravenous anaesthesia
This is a technique in which major surgery is carried out with all drugs given intravenously. Respiration can be spontaneous, or controlled with oxygen-enriched air. Neuromuscular blocking drugs can be used to provide relaxation and prevent reflex muscle movements. The main problem to be overcome is the assessment of depth of anaesthesia. Target Controlled Infusion (TCI) systems can be used to titrate intravenous anaesthetic infusions to predicted plasma-drug concentrations in ventilated adult patients.

Drugs used for intravenous anaesthesia
Propofol p. 1095, the most widely used intravenous anaesthetic, can be used for induction or maintenance of anaesthesia in adults and children, but it is not commonly used in neonates. Propofol is associated with rapid recovery and less hangover effect than other intravenous anaesthetics. Propofol can also be used for sedation during diagnostic procedures and sedation in adults in intensive care.

Thiopental sodium p. 412 is a barbiturate that is used for induction of anaesthesia, but has no analgesic properties. Induction is generally smooth and rapid, but dose-related cardiovascular and respiratory depression can occur. Awakening from a moderate dose of thiopental sodium is rapid because the drug redistributes into other tissues, particularly fat. However, metabolism is slow and sedative effects can persist for 24 hours. Repeated doses have a cumulative effect and recovery is much slower.

Etomidate p. 1095 is an intravenous agent associated with rapid recovery without a hangover effect. Etomidate causes less hypotension than thiopental sodium and propofol during induction. It produces a high incidence of extraneous muscle movements, which can be minimised by an opioid analgesic or a short-acting benzodiazepine given just before induction.

Ketamine p. 1110 is used rarely. Ketamine causes less hypotension than thiopental sodium and propofol during induction. It is used mainly for paediatric anaesthesia, particularly when repeated administration is required (such as for serial burns dressings); recovery is relatively slow and there is a high incidence of extraneous muscle movements. The main disadvantage of ketamine is the high incidence of hallucinations, nightmares, and other transient psychotic effects; these can be reduced by a benzodiazepine such as diazepam p. 267 or midazolam p. 414.

Inhalational anaesthetics
Inhalational anaesthetics include gases and volatile liquids. Gaseous anaesthetics require suitable equipment for storage and administration. Volatile liquid anaesthetics are administered using calibrated vaporisers, using air, oxygen, or nitrous oxide-oxygen mixtures as the carrier gas. To prevent hypoxia, the inspired gas mixture should contain a minimum of 25% oxygen at all times. Higher concentrations of oxygen (greater than 30%) are usually required during inhalational anaesthesia when nitrous oxide p. 1096 is being administered.

Volatile liquid anaesthetics
Volatile liquid anaesthetics can be used for induction and maintenance of anaesthesia, and following induction with an intravenous anaesthetic.

Isoflurane p. 1098 is a volatile liquid anaesthetic. Heart rhythm is generally stable during isoflurane anaesthesia, but heart-rate can rise, particularly in younger patients.
Systemic arterial pressure and cardiac output can fall, owing to a decrease in systemic vascular resistance. Muscle relaxation occurs and the effects of muscle relaxant drugs are potentiated. Isoflurane is the preferred inhalational anaesthetic for use in obstetrics. Desflurane p. 1097 is a rapid acting volatile liquid anaesthetic; it is reported to have about one-fifth the potency of isoflurane. Emergence and recovery from anaesthesia are particularly rapid because of its low solubility. Desflurane is not recommended for induction of anaesthesia as it is irritating to the upper respiratory tract. Sevoflurane p. 1098 is a rapid acting volatile liquid anaesthetic and is more potent than desflurane. Emergence and recovery are particularly rapid, but slower than desflurane. Sevoflurane is non-irritant and is therefore often used for inhalational induction of anaesthesia; it has little effect on heart rhythm compared with other volatile liquid anaesthetics.

Nitrous oxide
Nitrous oxide p. 1096 is used for maintenance of anaesthesia and, in sub-anaesthetic concentrations, for analgesia. For anaesthesia, nitrous oxide is commonly used in a concentration of 50 to 66% in oxygen as part of a balanced technique in association with other inhalational or intravenous agents. Nitrous oxide is unsatisfactory as a sole anaesthetic owing to lack of potency, but is useful as part of a combination of drugs since it allows a significant reduction in dosage.

For analgesia (without loss of consciousness), a mixture of nitrous oxide and oxygen containing 50% of each gas (Entonox®, Equanox®) is used. Self-administration using a demand valve is popular in obstetric practice, for changing painful dressings, as an aid to postoperative physiotherapy, and in emergency ambulances.

Nitrous oxide may have a deleterious effect if used in patients with an air-containing closed space since nitrous oxide diffuses into such a space with a resulting increase in pressure. This effect may be dangerous in conditions such as pneumothorax, which may enlarge to compromise respiration, or in the presence of intracranial air after head injury, entrapped air following recent underwater dive, or recent intra-ocular gas injection.

Malignant hyperthermia
Malignant hyperthermia is a rare but potentially lethal complication of anaesthesia. It is characterised by a rapid rise in temperature, increased muscle rigidity, tachycardia, and acidosis. The most common triggers of malignant hyperthermia are the volatile anaesthetics. Suxamethonium chloride p. 1102 has also been implicated, but malignant hyperthermia is more likely if it is given following a volatile anaesthetic. Volatile anaesthetics and suxamethonium chloride should be avoided during anaesthesia in patients at high risk of malignant hyperthermia.

Dantrolene sodium p. 1101 is used in the treatment of malignant hyperthermia.

Surgery and long-term medication
The risk of losing disease control on stopping long-term medication before surgery is often greater than the risk posed by continuing it during surgery. It is vital that the anaesthetist knows about all drugs that a patient is (or has been) taking.

Patients with adrenal atrophy resulting from long-term corticosteroid use may suffer a precipitous fall in blood pressure unless corticosteroid cover is provided during anaesthesia and in the immediate postoperative period. Anaesthetists must therefore know whether a patient is, or has been, receiving corticosteroids (including high-dose inhaled corticosteroids).

Other drugs that should normally not be stopped before surgery include antiepileptics, antiparkinsonian drugs, antipsychotics, anxiolytics, bronchodilators, cardiovascular drugs (but see potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, and angiotensin-II receptor antagonists), glaucoma drugs, immunosuppressants, drugs of dependence, and thyroid or antithyroid drugs. Expert advice is required for patients receiving antivirals for HIV infection. See general advice on surgery in diabetic patients.

Patients taking antplatelet medication or an oral anticoagulant present an increased risk for surgery. In these circumstances, the anaesthetist and surgeon should assess the relative risks and decide jointly whether the antplatelet or the anticoagulant drug should be stopped or replaced with heparin (unfractionated) or low molecular weight heparin therapy.

Drugs that should be stopped before surgery include combined oral contraceptives; for advice on hormone replacement therapy. MAOIs can have important interactions with some drugs used during surgery, such as pethidine hydrochloride. Tricyclic antidepressants need not be stopped, but may be an increased risk of arrhythmias and hypotension (and dangerous interactions with vasopressor drugs); therefore, the anaesthetist should be informed if they are not stopped. Lithium should be stopped 24 hours before major surgery but the normal dose can be continued for minor surgery (with careful monitoring of fluids and electrolytes). Potassium-sparing diuretics may need to be withheld on the morning of surgery because hyperkalaemia may develop if renal perfusion is impaired or if there is tissue damage. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor antagonists can be associated with severe hypotension after induction of anaesthesia; these drugs may need to be discontinued 24 hours before surgery. Herbal medicines may be associated with adverse effects when given with anaesthetic drugs and consideration should be given to stopping them before surgery.

Anaesthesia, sedation, and resuscitation in dental practice
Sedation for dental procedures should be limited to conscious sedation. Diazepam p. 267 and temazepam p. 420 are effective anxiolytics for dental treatment in adults.

For details of anaesthesia, sedation, and resuscitation in dental practice see A Conscious Decision: A review of the use of general anaesthesia and conscious sedation in primary dental care; report by a group chaired by the Chief Medical Officer and Chief Dental Officer, July 2000 and associated documents. Further details can also be found in Conscious Sedation in the Provision of Dental Care; report of an Expert Group on Sedation for Dentistry (commissioned by the Department of Health), 2003.

Guidance is also included in Conscious Sedation in Dentistry: Dental Clinical Guidance, Scottish Dental Clinical Effectiveness Programme, June 2012 (www.sdcep.org.uk).
ANAESTHETICS (GENERAL, INTRAVENOUS)

Etomidate

**INDICATIONS AND DOSE**

**Induction of anaesthesia**

- By slow intravenous injection
  - Adult: 150–300 micrograms/kg (max. per dose 60 mg), to be administered over 30–60 seconds (over 60 seconds in patients in whom hypotension might be hazardous)
  - Elderly: 150–200 micrograms/kg (max. per dose 60 mg), to be administered over 30–60 seconds (over 60 seconds in patients in whom hypotension might be hazardous)

**SIDE-EFFECTS**

- Common or very common: Extraneous muscle movement (high incidence) • pain on injection • respiratory depression • seizures • shivering • Stevens-Johnson syndrome

**INTERACTIONS**

- Appendix 1 (anaesthetics, general).

**CAUTIONS AND FURTHER INFORMATION**

- Adrenal insufficiency: Etomidate suppresses adrenocortical function, particularly during continuous administration, and it should not be used for maintenance of anaesthesia. It should be used with caution in patients with underlying adrenal insufficiency, for example, those with sepsis.

**SIDE-EFFECTS, FURTHER INFORMATION**

- Pain on injection: Can be reduced by injecting into a larger vein or by giving an opioid analgesic just before induction.

- Extraneous muscle movement: Extraneous muscle movements can be minimised by an opioid analgesic or a short-acting benzodiazepine given just before induction.

**PREGNANCY**

- May depress neonatal respiration if used during delivery.

**BREAST FEEDING**

- Breast-feeding can be resumed as soon as mother has recovered sufficiently from anaesthesia.

**HEPATIC IMPAIRMENT**

- Reduce dose in liver cirrhosis.

**DIRECTIONS FOR ADMINISTRATION**

- To be administered over 30–60 seconds (over 60 seconds in patients in whom hypotension might be hazardous).

**PATIENT AND CARER ADVICE**

- Patients given sedatives and analgesics during minor outpatient procedures should be very carefully warned about the risk of driving or undertaking skilled tasks afterwards. For a short general anaesthetic the risk extends to at least 24 hours after administration. Responsible persons should be available to take patients home. The dangers of taking alcohol should also be emphasised.

**MEDICINAL FORMS**

- There can be a variation in the licensing of different medicines containing the same drug.

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**Solution for injection**

**EXCIPIENTS:** May contain Propylene glycol

- **Hypnomidate** (Janssen-Cilag Ltd)
  - Etomidate 2 mg per 1 ml Hypnomidate 20mg/10ml solution for injection ampoules | 5 ampoules | £6.90

- **Emulsion for injection**
  - **ETOMIDATE (Non-proprietary)**
    - Etomidate 2 mg per 1 ml Etomidate-Lipuro 20mg/10ml emulsion for injection ampoules | 10 ampoules | £15.62

**Propofol**

**INDICATIONS AND DOSE**

- Induction of anaesthesia using 0.5% or 1% injection
  - By slow intravenous injection or by intravenous infusion
    - Adult 18–54 years: Usual dose 1.5–2.5 mg/kg, to be administered at a rate of 20–40 mg every 10 seconds until response. For debilitated patients use dose for 55 years and over.
    - Adult 55 years and over: Usual dose 1–1.5 mg/kg, to be administered at a rate of 20 mg every 10 seconds until response.

**Maintenance of anaesthesia using 1% injection**

- Initially by intravenous infusion
  - Adult: Usual dose 4–12 mg/kg/hour, alternatively (by slow intravenous injection) 25–50 mg, dose may be repeated according to response, for debilitated patients use dose for elderly.
  - Elderly: Usual dose 3–6 mg/kg/hour, alternatively (by slow intravenous injection) 25–50 mg, dose may be repeated according to response.

**Maintenance of anaesthesia using 2% injection**

- By intravenous infusion
  - Adult 18–54 years: Usual dose 1.5–2.5 mg/kg, to be administered at a rate of 20–40 mg every 10 seconds until response. For debilitated patients use dose for 55 years and over.
  - Adult 55 years and over: Usual dose 1–1.5 mg/kg, to be administered at a rate of 20 mg every 10 seconds until response.

**Induction of anaesthesia using 2% injection**

- By intravenous infusion
  - Adult 18–54 years: Usual dose 1.5–2.5 mg/kg, to be administered at a rate of 20–40 mg every 10 seconds until response. For debilitated patients use dose for 55 years and over.
  - Adult 55 years and over: Usual dose 1–1.5 mg/kg, to be administered at a rate of 20 mg every 10 seconds until response.

**Maintenance of anaesthesia using 1% injection**

- Initially by intravenous infusion
  - Adult: Usual dose 4–12 mg/kg/hour, for debilitated patients use dose for elderly.
  - Elderly: Usual dose 3–6 mg/kg/hour.

**Sedation of ventilated patients in intensive care using 1% or 2% injection**

- By continuous intravenous infusion
  - Adult: Usual dose 0.3–4 mg/kg/hour, adjusted according to response.

**Induction of sedation for surgical and diagnostic procedures using 0.5% or 1% injection**

- By slow intravenous injection
  - Adult: Initially 0.5–1 mg/kg, to be administered over 1–5 minutes, dose and rate of administration adjusted according to desired level of sedation and response.

**Maintenance of sedation for surgical and diagnostic procedures using 0.5% or 1% injection**

- Initially by intravenous infusion
  - Adult: Initially 1.5–4.5 mg/kg/hour, dose and rate of administration adjusted according to desired level of sedation and response, followed by (by slow intravenous injection) 10–20 mg, if rapid increase in sedation required, patients over 55 years or debilitated may require lower initial dose and rate of administration.
Maintenance of sedation for surgical and diagnostic procedures using 2% injection

INITIALLY BY INTRAVENOUS INFUSION

- Adult: Initially 1.5–4.5 mg/kg/hour, dose and rate of administration adjusted according to desired level of sedation and response, followed by (by slow intravenous injection) 10–20 mg using 0.5% or 1% injection (if rapid increase in sedation required), patients over 55 years or debilitated may require lower initial dose and rate of administration.

1096 General anaesthesia

<table>
<thead>
<tr>
<th>INDICATIONS AND DOSE</th>
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<td>Maintenance of anaesthesia in conjunction with other anaesthetic agents</td>
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<tr>
<td>BY INHALATION</td>
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<tr>
<td>Adult: 50–66 %, to be administered using suitable anaesthetic apparatus in oxygen</td>
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<tr>
<td>Analgesia</td>
</tr>
<tr>
<td>Adult: Up to 50 %, to be administered using suitable anaesthetic apparatus in oxygen, adjusted according to the patient’s needs</td>
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</tbody>
</table>

Important safety information

Propofol should only be administered by, or under the direct supervision of, personnel experienced in its use, with adequate training in anaesthesia and airway management, and when resuscitation equipment is available.

- CAUTIONS Acute circulatory failure (shock) · cardiac impairment · cardiovascular disease · elderly · epilepsy · fixed cardiac output · hypotension · hypovolaemia · raised intracranial pressure · respiratory impairment
- INTERACTIONS → Appendix 1 (anaesthetics, general).
- SIDE-EFFECTS
  - Common or very common Headache · hypotension · tachycardia · transient apnoea
  - Uncommon Phlebitis · thrombosis
  - Rare Anaphylaxis · arrhythmia · convulsions (onset can be delayed) · delayed recovery from anaesthesia · euphoria
  - Very rare Discoloration of urine · pancreatitis · pulmonary oedema · sexual disinhibition
- Frequency not known Bradycardia · pain on intravenous injection · propofol infusion syndrome · significant extraneous muscle movements

SIDE-EFFECTS, FURTHER INFORMATION

Bradycardia Bardycardia may be profound and may be treated with intravenous administration of an antimuscarinic drug.

Extrinsic muscle movement

Extraneous muscle movements can be minimised by an opioid analgesic or a short-acting benzodiazepine given just before induction.

Pain on injection Can be reduced by intravenous lidocaine.

Propofol infusion syndrome

Prolonged infusion of propofol doses exceeding 4 mg/kg/hour may result in potentially fatal effects, including metabolic acidosis, arrhythmias, cardiac failure, rhabdomyolysis, hyperlipidaemia, hyperkalaemia, hepatomegaly, and renal failure.

Pregnancy

Max. dose for maintenance of anaesthesia is 6 mg/kg/hour. May depress neonatal respiration if used during delivery.

Breast Feeding

Breast-feeding can be resumed as soon as mother has recovered sufficiently from anaesthesia.

Hepatic impairment

Use with caution.

Renal Impairment

Use with caution.

Monitoring requirements

Monitor blood-lipid concentration if risk of fat overload or if sedation longer than 3 days.

Directions for administration

Shake before use; microbiological filter not recommended; may be administered via a Y-piece close to injection site co-administered with Glucose 5% or Sodium chloride 0.9%. 0.5% emulsion for injection or intermittent infusion; may be administered undiluted, or diluted with Glucose 5% or Sodium chloride 0.9%; dilute to a concentration not less than 1 mg/mL. 1% emulsion for injection or infusion; may be administered undiluted, or diluted with Glucose 5% (Diprivan®) or (Propofol-Lipuro®) or Sodium chloride 0.9% (Propofol-Lipuro® only); dilute to a concentration not less than 2 mg/mL; use within 6 hours of preparation. 2% emulsion for infusion; do not dilute.

Patient and carer advice

Patients given sedatives and analgesics during minor outpatient procedures should be very carefully warned about the risk of driving or undertaking skilled tasks afterwards. For a short general anaesthetic the risk extends to at least 24 hours after administration. Responsible persons should be available to take patients home. The dangers of taking alcohol should also be emphasised.

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

Emulsion for injection

- PROPFOFL (Non-proprietary)
  - Propofol 5 mg per 1 ml Propofol-Lipuro 0.5% emulsion for injection 20ml ampoules | 5 ampoules (P) £14.71
  - Diprivan (AstraZeneca UK Ltd)
  - Propofol 10 mg per 1 ml Diprivan 1% emulsion for injection 20ml ampoules | 5 ampoules (P) £15.36 (Hospital only)

Emulsion for infusion

- Diprivan (AstraZeneca UK Ltd)
  - Propofol 10 mg per 1 ml Diprivan 1% emulsion for infusion 50ml pre-filled syringes | 1 pre-filled disposable injection (P) £10.68
  - Propofol 20 mg per 1 ml Diprivan 2% emulsion for infusion 50ml pre-filled syringes | 1 pre-filled disposable injection (P) £15.16

Anaesthetics (volatile liquid)

Nitrous oxide

INDICATIONS AND DOSE

Maintenance of anaesthesia in conjunction with other anaesthetic agents

By inhalation

- Adult: 50–66 %, to be administered using suitable anaesthetic apparatus in oxygen

Analgesia

By inhalation

- Adult: Up to 50 %, to be administered using suitable anaesthetic apparatus in oxygen, adjusted according to the patient’s needs

Important safety information

Nitrous oxide should only be administered by, or under the direct supervision of, personnel experienced in its use, with adequate training in anaesthesia and airway management, and when resuscitation equipment is available.

- CAUTIONS Entrapped air following recent underwater dive · pneumothorax · presence of intracranial air after head injury · recent intra-ocular gas injection

CAUTIONS, FURTHER INFORMATION

Nitrous oxide may have a deleterious effect if used in patients with an air-containing closed space since nitrous oxide diffuses into such a space with a resulting increase in pressure. This effect may be dangerous in conditions such as pneumothorax, which may enlarge to compromise respiration, or in the presence of intracranial air after head injury, entrapped air following recent underwater dive, or recent intra-ocular gas injection.

INTERACTIONS → Appendix 1 (anaesthetics, general).

SIDE-EFFECTS

Depression of white cell formation · hypoxia · megaloblastic anaemia · neurological toxic effects

SIDE-EFFECTS, FURTHER INFORMATION

Hypoxia

Hypoxia can occur immediately following the administration of nitrous oxide; additional oxygen should always be given for several minutes after stopping the flow of nitrous oxide.

Prolonged exposure

Exposure of patients to nitrous oxide should be avoided whenever possible.

Important safety information

Be aware of the risk of hypoxia in patients with lung disease or at risk of lung injury.

- Monitor arterial oxygen saturation continuously.
  - Do not administer nitrous oxide to patients with an indication of hypoxia.
Volatile halogenated anaesthetics

**Important safety information**
Should only be administered by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management, and when resuscitation equipment is available.

**CONTRA-INDICATIONS** Susceptibility to malignant hyperthermia

**CAUTIONS** Can trigger malignant hyperthermia - raised intracranial pressure (can increase cerebrospinal pressure)

**SIDE-EFFECTS**
- Common or very common Arrhythmias - cardiorespiratory depression - hypotension
- Frequency not known Convulsions - mood changes (that can last several days)

**ALLERGY AND CROSS-SENSITIVITY** Can cause hepatotoxicity in those sensitised to halogenated anaesthetics.

**DIRECTIONS FOR ADMINISTRATION** Volatile liquid anaesthetics are administered using calibrated vapourisers, using air, oxygen, or nitrous oxide-oxygen mixtures as the carrier gas. To prevent hypoxia, the inspired gas mixture should contain a minimum of 25% oxygen at all times.

**PATIENT AND CARER ADVICE** Patients given sedatives and analgesics during minor outpatient procedures should be very carefully warned about the risks of driving or undertaking skilled tasks afterwards. For a short general anaesthetic, the risk extends to at least 24 hours after administration. Responsible persons should be available to take patients home. The dangers of taking alcohol should also be emphasised.

**Desflurane**

**INDICATIONS AND DOSE**
- Induction of anaesthesia (but not recommended)
  - **BY INHALATION**
    - Adult: 4–11%, to be inhaled through specifically calibrated vapouriser

- Maintenance of anaesthesia (in nitrous oxide–oxygen)
  - **BY INHALATION**
    - Adult: 2–6%, to be inhaled through a specifically calibrated vapouriser

- Maintenance of anaesthesia (in oxygen or oxygen-enriched air)
  - **BY INHALATION**
    - Adult: 2.5–8.5%, to be inhaled through a specifically calibrated vapouriser

**Important safety information**
Desflurane should only be administered by, or under the direct supervision of, personnel experienced in its use, with adequate training in anaesthesia and airway management, and when resuscitation equipment is available.

**INTERACTIONS** → Appendix 1 (anaesthetics, general).

**SIDE-EFFECTS** Apnoea - breath-holding - cough - increased secretions - laryngospasm

**PREGNANCY** May depress neonatal respiration if used during delivery.

**BREAST FEEDING** Breast-feeding can be resumed as soon as mother has recovered sufficiently from anaesthesia.

**MEDICINAL FORMS**
- There can be variation in the licensing of different medicines containing the same drug.

**Inhalation gas**
- **NITROUS OXIDE (Non-proprietary)**
  - Nitrous oxide 1 ml per 1 ml
    - Nitrous oxide cylinders size E | 1800 litre [p] no price available
    - Medical Nitrous Oxide cylinders size D | 900 litre [p] no price available
    - Medical Nitrous Oxide cylinders size G | 9000 litre [p] no price available
    - Nitrous oxide cylinders size F | 3600 litre [p] no price available
    - Nitrous oxide cylinders size J | 18000 litre [p] no price available
    - Nitrous oxide cylinders size G | 9000 litre [p] no price available
    - Nitrous oxide cylinders size C | 450 litre [p] no price available
    - Medical Nitrous Oxide cylinders size F | 3600 litre [p] no price available
    - Nitrous oxide cylinders size D | 900 litre [p] no price available
    - Medical Nitrous Oxide cylinders size E | 1800 litre [p] no price available

**Volatile liquid**
- Suprane volatile liquid | 240 ml [p] no price available (Hospital only)
  - **BY INHALATION**
    - Adult: 4–11%, to be inhaled through specifically calibrated vapouriser

**BNF 70**

**General anaesthesia 1097**
Isoflurane

**INDICATIONS AND DOSE**

**Induction of anaesthesia (in oxygen or nitrous oxide-oxygen)**

- BY INHALATION
  - Adult: Initially 0.5–1 %, adjusted according to response, to be administered using specifically calibrated vaporiser

**Maintenance of anaesthesia (in nitrous oxide-oxygen)**

- BY INHALATION
  - Adult: 1–2.5 %, to be administered using specifically calibrated vaporiser; an additional 0.5–1 % may be required when given with oxygen alone

**Maintenance of anaesthesia in caesarean section (in nitrous oxide-oxygen)**

- BY INHALATION
  - Adult: 0.5–0.75 %, to be administered using specifically calibrated vaporiser

**Important safety information**

- Isoflurane should only be administered by, or under the direct supervision of, personnel experienced in its use, with adequate training in anaesthesia and airway management, and when resuscitation equipment is available.

**INTERACTIONS** → Appendix 1 (anaesthetics, general).

**SIDE-EFFECTS**

- Breath-holding
- Cough
- Irritate mucous membrane · laryngospasm

**PREGNANCY**

- May depress neonatal respiration if used during delivery.

**BREAST FEEDING**

- Breast-feeding can be resumed as soon as mother has recovered sufficiently from anaesthesia.

**PATIENT AND CARER ADVICE**

- Patients given sedatives and analgesics during minor outpatient procedures should be carefully warned about the risk of driving or undertaking skilled tasks afterwards. For a short general anaesthetic the risk extends to at least 24 hours after administration. Responsible persons should be available to take patients home. The dangers of taking alcohol should also be emphasised.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Inhalation vapour**

- **ISOFLURANE (Non-proprietary)**
  - Isoflurane 1 ml per 1 ml Isoflurane inhalation vapour
  - 250 ml (£123.00 Hospital only)
  - **AErrane** (Baxter Healthcare Ltd)
  - Isoflurane 1 ml per 1 ml AErrane volatile liquid
  - 250 ml (£123.00 Hospital only)

Sevoflurane

**INDICATIONS AND DOSE**

**Induction of anaesthesia (in oxygen or nitrous oxide-oxygen)**

- BY INHALATION
  - Adult: Initially 0.5–1 %, adjusted according to response, then increased to up to 8 %, to be administered using specifically calibrated vaporiser

**Maintenance of anaesthesia (in oxygen or nitrous oxide-oxygen)**

- BY INHALATION
  - Adult: 0.5–3 %, adjusted according to response, to be administered using specifically calibrated vaporiser

**Important safety information**

- Sevoflurane should only be administered by, or under the direct supervision of, personnel experienced in its use, with adequate training in anaesthesia and airway management, and when resuscitation equipment is available.

**CAUTIONS**

- Susceptibility to QT-interval prolongation

**INTERACTIONS** → Appendix 1 (anaesthetics, general).

- Sevoflurane can interact with carbon dioxide absorbents to form compound A, a potentially nephrotoxic vinyl ether. However, in spite of extensive use, no cases of sevoflurane-induced permanent renal injury have been reported and the carbon dioxide absorbents used in the UK produce very low concentrations of compound A, even in low-flow anaesthetic systems.

**SIDE-EFFECTS**

- Cardiac arrest · dystonia · leucopenia · torsade de pointes · urinary retention

**PREGNANCY**

- May depress neonatal respiration if used during delivery.

**BREAST FEEDING**

- Breast-feeding can be resumed as soon as mother has recovered sufficiently from anaesthesia.

**RENAL IMPAIRMENT**

- Use with caution.

**PATIENT AND CARER ADVICE**

- Patients given sedatives and analgesics during minor outpatient procedures should be carefully warned about the risk of driving or undertaking skilled tasks afterwards. For a short general anaesthetic the risk extends to at least 24 hours after administration. Responsible persons should be available to take patients home. The dangers of taking alcohol should also be emphasised.

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug.

**Inhalation vapour**

- **SEVOFLURANE (Non-proprietary)**
  - Sevoflurane 1 ml per 1 ml Sevoflurane volatile liquid
  - 250 ml (£123.00 Hospital only)

1.1 **Anaesthetic adjuvants**

**Pre-medication and peri-operative drugs**

**Drugs that affect gastric pH**

Regurgitation and aspiration of gastric contents (Mendelson’s syndrome) can be an important complication of general anaesthesia, particularly in obstetrics and during emergency surgery, and requires prophylaxis against acid aspiration. Prophylaxis is also needed in those with gastrointestinal reflux disease and in circumstances where gastric emptying may be delayed.

- An **H₂-receptor antagonist** can be used before surgery to increase the pH and reduce the volume of gastric fluid. It does not affect the pH of fluid already in the stomach and this limits its value in emergency procedures; an oral H₂-receptor antagonist can be given 1–2 hours before the procedure. Antacids are frequently used to neutralise the acidity of the fluid already in the stomach; ‘clear’ (non-particulate) antacids such as sodium citrate are preferred.
Antimuscarinic drugs
Antimuscarinic drugs are used (less commonly nowadays) as premedicants to dry bronchial and salivary secretions which are increased by intubation, upper airway surgery, or some inhalational anaesthetics. They are also used before or with neostigmine p. 912 to prevent bradycardia, excessive salivation, and other muscarinic actions of neostigmine.

They also prevent bradycardia and hypotension associated with drugs such as propofol and suxamethonium chloride.

Atropine sulfate below is now rarely used for premedication but still has an emergency role in the treatment of vagotonic side-effects. Atropine sulfate may have a role in acute arrhythmias after myocardial infarction.

Hyoscine hydrobromide p. 344 reduces secretions and also provides a degree of amnesia, sedation, and anti-emesis. Unlike atropine sulfate it may produce bradycardia rather than tachycardia.

Glycopyrronium bromide p. 1100 reduces salivary secretions. When given intravenously it produces less tachycardia than atropine sulfate. It is widely used with neostigmine for reversal of non-depolarising neuromuscular blocking drugs.

Phenothiazines do not effectively reduce secretions when used alone.

Sedative drugs
Fears and anxiety before a procedure (including the night before) can be minimised by using a sedative drug, usually a benzodiazepine. Premedication may also augment the action of anaesthetics and provide some degree of preoperative amnesia. The choice of drug depends on the individual, the nature of the procedure, the anaesthetic to be used, and other prevailing circumstances such as outpatients, obstetrics, and availability of recovery facilities. The choice also varies between elective and emergency procedures.

Premedics can be given the night before major surgery; a further, smaller dose may be required before surgery. Alternatively, the first dose may be given on the day of the procedure.

Benzodiazepines
Benzodiazepines possess useful properties for premedication including relief of anxiety, sedation, and amnesia; short-acting benzodiazepines taken by mouth are the most common premedicants. Benzodiazepines are also used in intensive care units for sedation, particularly in those receiving assisted ventilation. Flumazenil p. 1132 is used to antagonise the effects of benzodiazepines.

Diazepam p. 267 is used to produce mild sedation with amnesia. It is a long-acting drug with active metabolites and a second period of drowsiness can occur several hours after its administration. Peri-operative use of diazepam in children is not recommended; its effect and timing of response are unreliable and paradoxical effects may occur.

Diazepam is relatively insoluble in water and preparations formulated in organic solvents are painful on intravenous injection and give rise to a high incidence of venous thrombosis (which may not be noticed for several days after the injection). Intramuscular injection of diazepam is painful and absorption is erratic. An emulsion formulated for intravenous injection is less irritant and reduces the risk of venous thrombosis; it is not suitable for intramuscular injection.

Temazepam p. 420 is given by mouth for premedication and has a shorter duration of action and a more rapid onset than oral diazepam; anxiolytic and sedative effects last about 90 minutes although there may be residual drowsiness.

Lorazepam p. 412 produces more prolonged sedation than temazepam and it has marked amnesic effects.

Midazolam p. 414 is a water-soluble benzodiazepine that is often used in preference to intravenous diazepam; recovery is faster than from diazepam, but may be significantly longer in the elderly, in patients with a low cardiac output, or after repeated dosing. Midazolam is associated with profound sedation when high doses are given intravenously or when it is used with certain other drugs.

Other drugs for sedation
Deremodetomodine p. 1110 and clonidine hydrochloride p. 137 are alpha2-adrenergic agonists with sedative properties. Dexmedetomidine p. 1110 is licensed for the sedation of patients receiving intensive care who need to remain responsive to verbal stimulation. Clonidine hydrochloride p. 137 [unlicensed indication] can be used by mouth or by intravenous injection as a sedative agent when adequate sedation cannot be achieved with standard treatment.

Antagonists for central and respiratory depression
Respiratory depression is a major concern with opioid anaesthetics and it may be treated by artificial ventilation or be reversed by naloxone hydrochloride p. 1133. Naloxone hydrochloride will immediately reverse opioid-induced respiratory depression but the dose may have to be repeated because of the short duration of action of naloxone hydrochloride; however, naloxone hydrochloride will also antagonise the analgesic effect.

Flumazenil p. 1132 is a benzodiazepine antagonist for the reversal of the central sedative effects of benzodiazepines after anaesthetic and similar procedures. Flumazenil has a shorter half-life and duration of action than diazepam or midazolam so patients may become resedated.

Doxapram hydrochloride p. 261 is a central and respiratory stimulant but is of limited value in anaesthesia.

Antimuscarinic drugs

Atropine sulfate

The properties listed below are those particular to the drug only. For properties common to the class, see Antimuscarinics Systemic, p. 668.

INDICATIONS AND DOSE
Premedication

**BY INTRAVENOUS INJECTION**
- Child 12–17 years: 300–600 micrograms, to be administered immediately before induction of anaesthesia
- Adult: 300–600 micrograms, to be administered immediately before induction of anaesthesia

**BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION**
- Child 12–17 years: 300–600 micrograms, to be administered 30–60 minutes before induction of anaesthesia
- Adult: 300–600 micrograms, to be administered 30–60 minutes before induction of anaesthesia

Control of muscarinic side-effects of neostigmine in reversal of competitive neuromuscular block

**BY INTRAVENOUS INJECTION**
- Child 12–17 years: 0.6–1.2 mg
- Adult: 0.6–1.2 mg

**Intra-operative bradycardia**

**BY INTRAVENOUS INJECTION**
- Child 12–17 years: 300–600 micrograms, larger doses may be used in emergencies
- Adult: 300–600 micrograms, larger doses may be used in emergencies
Treatment of poisoning by organophosphorus insecticide or nerve agent (in combination with pralidoxime chloride)

**BY INTRAVENOUS INJECTION**
- **Child:** 20 micrograms/kg every 5–10 minutes (max. per dose 2 mg) until the skin becomes flushed and dry, the pupils dilate, and bradycardia is abolished, frequency of administration dependent on the severity of poisoning
- **Adult:** 2 mg every 5–10 minutes until the skin becomes flushed and dry, the pupils dilate, and bradycardia is abolished, frequency of administration dependent on the severity of poisoning

**Bradyardia due to acute massive overdosage of beta-blockers**
- **BY INTRAVENOUS INJECTION**
  - **Child:** 40 micrograms/kg (max. per dose 3 mg)
  - **Adult:** 3 mg

**Excessive bradycardia associated with beta-blocker use**
- **BY INTRAVENOUS INJECTION**
  - **Adult:** 0.6–2.4 mg in divided doses (max. per dose 600 micrograms)

**Symptomatic relief of gastro-intestinal disorders characterised by smooth muscle spasm**
- **BY MOUTH**
  - **Adult:** 0.6–1.2 mg daily, dose to be taken at night

**UNLICENSED USE**
- With use in children Not licensed for use in children under 12 years for intra-operative bradycardia or by intravenous route for premedication. Not licensed for the control of muscarinic side-effects of edrophonium in reversal of competitive neuromuscular block.

**INDICATIONS AND DOSE**
- **Premedication at induction**
  - **BY INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INJECTION**
    - **Adult:** 200–400 micrograms, alternatively 4–5 micrograms/kg (max. per dose 400 micrograms)
- **Intra-operative bradycardia**
  - **BY INTRAVENOUS INJECTION**
    - **Adult:** 200–400 micrograms, alternatively 4–5 micrograms/kg (max. per dose 400 micrograms), repeated if necessary
- **Control of muscarinic side-effects of neostigmine in reversal of non-depolarising neuromuscular block**
  - **BY INTRAVENOUS INJECTION**
    - **Adult:** 10–15 micrograms/kg, alternatively, 200 micrograms per 1 mg of neostigmine to be administered

**Bowel colic in palliative care | Excessive respiratory secretions in palliative care**
- **BY SUBCUTANEOUS INJECTION**
  - **Adult:** 0.6–1.2 mg/24 hours

**GLYCOPYRRONIUM BROMIDE (Non-proprietary)**

**Glycopyrronium bromide**

The properties listed below are those particular to the drug only. For properties common to the class, see Antimuscarinics Systemic, p. 668.

**INDICATIONS AND DOSE**
- **Premedication at induction**
  - **BY INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INJECTION**
    - **Adult:** 200–400 micrograms, alternatively 4–5 micrograms/kg (max. per dose 400 micrograms)
- **Intra-operative bradycardia**
  - **BY INTRAVENOUS INJECTION**
    - **Adult:** 200–400 micrograms, alternatively 4–5 micrograms/kg (max. per dose 400 micrograms), repeated if necessary
- **Control of muscarinic side-effects of neostigmine in reversal of non-depolarising neuromuscular block**
  - **BY INTRAVENOUS INJECTION**
    - **Adult:** 10–15 micrograms/kg, alternatively, 200 micrograms per 1 mg of neostigmine to be administered
- **Bowel colic in palliative care | Excessive respiratory secretions in palliative care**
  - **BY SUBCUTANEOUS INJECTION**
    - **Adult:** 0.6–1.2 mg/24 hours

**MEDICATION FORMS**
- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral suspension, oral solution
1.2 Malignant hyperthermia

MUSCLE RELAXANTS

Dantrolene sodium

- **DRUG ACTION** Acts on skeletal muscle cells by interfering with calcium efflux, thereby stopping the contractile process.

**INDICATIONS AND DOSE**

- **Malignant hyperthermia**
  - **By rapid intravenous injection**
    - Adult: Initially 2–3 mg/kg, then 1 mg/kg, repeated if necessary; maximum 10 mg/kg per course
  - **Chronic severe spasticity of voluntary muscle**
    - **By mouth**
      - Adult: Initially 25 mg daily, then increased to up to 100 mg 4 times a day, dose increased at weekly intervals; usual dose 75 mg 3 times a day

**Important safety information**

Should only be administered by, or under the direct supervision of, personnel experienced in the use of dantrolene when used for malignant hyperthermia.

- **CONTRA-INDICATIONS**
  - With oral use acute muscle spasm - avoid when spasticity is useful, for example, locomotion
  
- **CAUTIONS**
  - With intravenous use avoid extravasation (risk of tissue necrosis)
  - With oral use females (hepatotoxicity) - history of liver disorders (hepatotoxicity) - if doses greater than 400 mg daily (hepatotoxicity) - impaired cardiac function - impaired pulmonary function - patients over 30 years (hepatotoxicity) · therapeutic effect may take a few weeks to develop—discontinue if no response within 6–8 weeks

- **INTERACTIONS**
  - With oral use Caution if concomitant use of hepatotoxic drugs.

- **SIDE-EFFECTS**
  - **Common or very common**
    - With oral use abdominal pain - anorexia - asthenia - chills - diarrhoea (withdraw if severe, discontinue treatment if recurs on re-introduction) - dizziness - drowsiness - fatigue - fever - headache - hepatotoxicity - nausea - pericarditis - pleural effusion - rash - respiratory depression - seizures - speech disturbances - visual disturbances - vomiting
  - **Uncommon**
    - With oral use confusion - constipation - crystalluria - depression - dysphagia - dyspnoea - erratic blood pressure - exacerbation of cardiac insufficiency - haematuria - increased sweating - increased urinary frequency - insomnia - nervousness - tachycardia - urinary incontinence - urinary retention
  - **Frequency not known**
    - With intravenous use dizziness - erythema - hepatotoxicity - injection-site reactions - pulmonary oedema - rash - swelling - thrombophlebitis - weakness

**SIDE-EFFECTS, FURTHER INFORMATION**

- **Hepatotoxicity** Potentially life-threatening hepatotoxicity reported—discontinue if abnormal liver function tests or symptoms of liver disorder; re-introduce only if complete reversal of hepatotoxicity.

- **PREGNANCY**
  - With intravenous use Use only if potential benefit outweighs risk.
  - With oral use Avoid use in chronic spasticity—embryotoxic in animal studies.

- **BREAST FEEDING**
  - With intravenous use Present only if potential benefit outweighs risk.
  - With oral use Present in milk—manufacturer advises avoid use in chronic spasticity.

- **HEPATIC IMPAIRMENT**
  - Avoid—may cause severe liver damage (injection may be used in an emergency for malignant hyperthermia).

- **MONITORING REQUIREMENTS**
  - With oral use Test liver function before and at intervals during therapy.

- **PATIENT AND CARER ADVICE**
  - Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.
  - With oral use Hepatotoxicity Patients should be told how to recognise signs of liver disorder and advised to seek prompt medical attention if symptoms such as anorexia, nausea, vomiting, fatigue, abdominal pain, dark urine, or pruritus develop.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: oral solution, oral suspension

**Capsule**

| **Dantrolium** (Norgine Pharmaceuticals Ltd) |
| Dantrium (25 mg capsules) | 100 capsule [POD] £16.87 DT price = £16.87 |
| Dantrolene sodium 100 mg | Dantrium 100mg capsules | 100 capsule [POD] £43.07 DT price = £43.07 |

**Powder for solution for injection**

- **Dantrium** (Norgine Pharmaceuticals Ltd)
  - Dantrolene sodium 20 mg Dantrium Intravenous 20mg powder for solution for injection vials | 12 vial [POD] £612.00 (Hospital only) | 36 vial [POD] £1,836.00 (Hospital only)

1.3 Neuromuscular blockade

**Neuromuscular blockade**

**Neuromuscular blocking drugs**

Neuromuscular blocking drugs used in anaesthesia are also known as muscle relaxants. By specific blockade of the neuromuscular junction they enable light anaesthesia to be used with adequate relaxation of the muscles of the abdomen and diaphragm. They also relax the vocal cords and allow the passage of a tracheal tube. Their action differs that act on the spinal cord or brain.

Patients who have received a neuromuscular blocking drug should always have their respiration assisted or controlled until the drug has been inactivated or antagonised. They should also receive sufficient concomitant inhalational or intravenous anaesthetic or sedative drugs to prevent awareness.

**Non-depolarising neuromuscular blocking drugs**

Non-depolarising neuromuscular blocking drugs (also known as competitive muscle relaxants) compete with
acetylcholine for receptor sites at the neuromuscular junction and their action can be reversed with anticholinesterases such as neostigmine. Non-depolarising neuromuscular blocking drugs can be divided into the aminosteroid group, comprising pancuronium bromide p. 1104, rocuronium bromide p. 1105, and vecuronium bromide p. 1105; and the benzylisoquinolinium group, comprising atracurium besilate p. 1103, cisatracurium p. 1104, and mivacurium p. 1104.

Non-depolarising neuromuscular blocking drugs have a slower onset of action than suxamethonium chloride. These drugs can be classified by their duration of action as short-acting (15–30 minutes), intermediate-acting (30–40 minutes), and long-acting (60–120 minutes), although duration of action is dose-dependent. Drugs with a shorter or intermediate duration of action, such as atracurium besilate and vecuronium bromide, are more widely used than those with a longer duration of action, such as pancuronium bromide.

Non-depolarising neuromuscular blocking drugs have no sedative or analgesic effects and are not considered to trigger malignant hyperthermia.

For patients receiving intensive care and who require tracheal intubation and mechanical ventilation, a non-depolarising neuromuscular blocking drug is chosen according to its onset of effect, duration of action, and side-effects. Rocuronium bromide, with a rapid onset of effect, may facilitate intubation. Atracurium besilate or cisatracurium may be suitable for long-term neuromuscular blockade since their duration of action is not dependent on elimination by the liver or the kidneys.

Atracurium besilate, a mixture of 10 isomers, is a benzylisoquinolinium neuromuscular blocking drug with an intermediate duration of action. It undergoes non-enzymatic metabolism which is independent of liver and kidney function, thus allowing its use in patients with hepatic or renal impairment. Cardiovascular effects are associated with significant histamine release; histamine release can be minimised by administering slowly or in divided doses over at least 1 minute.

Cisatracurium is a single isomer of atracurium besilate. It is more potent and has a slightly longer duration of action than atracurium besilate and provides greater cardiovascular stability because cisatracurium lacks histamine-releasing effects.

Mivacurium, a benzylisoquinolinium neuromuscular blocking drug, has a short duration of action. It is metabolised by plasma cholinesterase and muscle paralysis is prolonged in individuals deficient in this enzyme. It is not associated with vagolytic activity or ganglionic blockade although histamine release can occur, particularly with rapid injection.

Pancuronium bromide, an aminosteroid neuromuscular blocking drug, has a long duration of action and is often used in patients receiving long-term mechanical ventilation in intensive care units. It lacks a histamine-releasing effect, but vagolytic and sympathomimetic effects can cause tachycardia and hypertension.

Rocuronium bromide exerts an effect within 2 minutes and has the most rapid onset of any of the non-depolarising neuromuscular blocking drugs. It is an aminosteroid neuromuscular blocking drug with an intermediate duration of action. It is reported to have minimal cardiovascular effects; high doses produce mild vagolytic activity.

Vancuronium bromide, an aminosteroid neuromuscular blocking drug, has an intermediate duration of action. It does not generally produce histamine release and lacks cardiovascular effects.

Neutralising neuromuscular blocking drugs
Suxamethonium chloride below has the most rapid onset of action of any of the neuromuscular blocking drugs and is ideal if fast onset and brief duration of action are required, e.g. with tracheal intubation. Unlike the non-depolarising neuromuscular blocking drugs, its action cannot be reversed and recovery is spontaneous; anticholinesterases such as neostigmine potentiate the neuromuscular block.

Suxamethonium chloride (below) should be given after anaesthetic induction because paralysis is usually preceded by painful muscle fasciculations. While tachycardia occurs with single use, bradycardia may occur with repeated doses in adults and with the first dose in children. Premedication with atropine reduces bradycardia as well as the excessive salivation associated with suxamethonium chloride below use.

Prolonged paralysis may occur in dual block, which occurs with high or repeated doses of suxamethonium chloride below and is caused by the development of a non-depolarising block following the initial depolarising block. Individuals with myasthenia gravis are resistant to suxamethonium chloride below but can develop dual block resulting in delayed recovery. Prolonged paralysis may also occur in those with low or atypical plasma cholinesterase. Assisted ventilation should be continued until muscle function is restored.

Drugs for reversal of neuromuscular blockade
Anticholinesterases
Anticholinesterases reverse the effects of the non-depolarising (competitive) neuromuscular blocking drugs such as pancuronium bromide but they prolong the action of the depolarising neuromuscular blocking drug suxamethonium chloride.

Neostigmine is used specifically for reversal of non-depolarising (competitive) blockade. It acts within one minute of intravenous injection and its effects last for 20 to 30 minutes; a second dose may then be necessary. Glycopyronium bromide p. 1100 or alternatively atropine sulfate p. 1099, given before or with neostigmine, prevent bradycardia, excessive salivation, and other muscarinic effects of neostigmine.

Other drugs for reversal of neuromuscular blockade
Sugammadex p. 1106 is a modified gamma cyclodextrin that can be used for rapid reversal of neuromuscular blockade induced by rocuronium bromide or vecuronium bromide. In practice, sugammadex is used mainly for rapid reversal of neuromuscular blockade in an emergency.

NEUROMUSCULAR BLOCKING DRUGS (DEPOLARISING)

Suxamethonium chloride
(Succinylcholine chloride)

**DRUG ACTION**
Suxamethonium acts by mimicking acetylcholine at the neuromuscular junction but hydrolysis is much slower than for acetylcholine; depolarisation is therefore prolonged, resulting in neuromuscular blockade.

**INDICATIONS AND DOSE**
Neuromuscular blockade (short duration) during surgery and intubation

**BY INTRAVENOUS INJECTION**
- **Adult:** 1–1.5 mg/kg

**Important safety information**
Should only be administered by, or under the direct supervision of, personnel experienced in its use.

**CONTRA-INDICATIONS**
Duchenne muscular dystrophy · family history of malignant hyperthermia · hyperkalaemia · low plasma-cholinesterase activity (including severe liver

**SUGammadex PAGES 1105–1106**
Sugammadex is used mainly for rapid reversal of neuromuscular blockade in an emergency.

**HFSA Note**
Sugammadex is a unique intervention for rapid reversal of neuromuscular blockade in cases of emergency. It is not used for maintenance neuromuscular blockade.
Neuromuscular blockade

Non-depolarising neuromuscular blocking drugs

Important safety information
Non-depolarising neuromuscular blocking drugs should only be administered by, or under direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management.

Cautions
Burns (resistance can develop, increased doses may be required) - cardiovascular disease (reduce rate of administration) - electrolyte disturbances (response unpredictable) - fluid disturbances (response unpredictable) - hyperthermia (activity prolonged, lower doses required) - myasthenia gravis (activity prolonged, lower doses required) - neuromuscular disorders (response unpredictable)

Interactions
Appendix 1 (muscle relaxants).

Allergy and cross-sensitivity
Allergic cross-reactivity between neuromuscular blocking drugs has been reported; caution is advised in cases of hypersensitivity to these drugs.

Pregnancy
Mildly prolonged maternal neuromuscular blockade may occur.

Breastfeeding
Unlikely to be present in breast milk in significant amounts (ionised at physiological pH). Breast-feeding may be resumed once the mother has recovered from neuromuscular block.

Hepatic impairment
Prolonged apnoea may occur in severe liver disease because of reduced hepatic synthesis of pseudocholinesterase.

Medicinal forms
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

Solution for injection
- Suxamethonium chloride (Non-proprietary)
  - Suxamethonium chloride 50 mg per 1 ml Suxamethonium chloride 100mg/2ml solution for injection ampoules | 10 ampoule | £5.76–£7.00
  - Anectine (GlaxoSmithKline Ltd)
    - Suxamethonium chloride 50 mg per 1 ml Anectine 100mg/2ml solution for injection ampoules | 5 ampoule | £3.57

NEUROMUSCULAR BLOCKING DRUGS (NON-DEPOLARISING)

Atracurium besilate
(Atracurium besilate)

Indications and dose
Neuromuscular blockade (short to intermediate duration) for surgery and intubation
- Initially by intravenous injection
  - Adult: Initially 300–600 micrograms/kg, then (by intravenous injection) 100–200 micrograms/kg as required, alternatively (by intravenous injection) initially 300–600 micrograms/kg, followed by (by intravenous infusion) 300–600 micrograms/kg/hour

Neuromuscular blockade during intensive care
- Initially by intravenous injection
  - Adult: Initially 300–600 micrograms/kg, initial dose is optional, then (by intravenous infusion) 270–1770 micrograms/kg/hour; (by intravenous infusion) usual dose 650–780 micrograms/kg/hour

Doses at extremes of body-weight
To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.

Side-effects
- Very rare Anaphylactoid reactions
- Frequency not known Acute myopathy (after prolonged use in intensive care) - bronchospasm - hypotension - seizures - skin flushing - tachycardia

Further information
Cardiovascular effects
Cardiovascular effects are associated with significant histamine release; histamine release can be minimised by administering slowly or in divided doses over at least 1 minute.

Directions for administration
For intravenous infusion (Tracrium®; Atracurium besilate injection, Hospira; Atracurium injection/infusion, Genus), give continuously in Glucose 5% or Sodium Chloride 0.9%; stability varies with diluent; dilute requisite dose with infusion fluid to a concentration of 0.5–5 mg/mL.

Medicinal forms
There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
- ATRACURIUM BESILATE (Non-proprietary)
  - Atracurium besilate 10 mg per 1 ml Atracurium besilate 250mg/25ml solution for injection vials | 1 vial | £16.50
    - Atracurium besilate 25mg/2.5ml solution for injection ampoules | 5 ampoule | £8.50–£9.25
    - Atracurium besilate 50mg/5ml solution for injection ampoules | 5 ampoule | £15.00–£17.50
  - Atracurium besilate 250mg/25ml solution for injection ampoules | 2 ampoule | £25.29
Cisatracurium

INDICATIONS AND DOSE
Neuromuscular blockade (intermediate duration) during surgery and intubation

INITIALLY BY INTRAVENOUS INJECTION

- Adult: Initially 150 micrograms/kg, then (by intravenous injection) maintenance 30 micrograms/kg every 20 minutes, alternatively (by intravenous infusion) initially 180 micrograms/kg/hour, then (by intravenous infusion) maintenance 60–120 micrograms/kg/hour, maintenance dose administered after stabilisation

Neuromuscular blockade (intermediate duration) during intensive care

INITIALLY BY INTRAVENOUS INJECTION

- Adult: Initially 150 micrograms/kg, initial dose is optional, then (by intravenous infusion) 180 micrograms/kg/hour, adjusted according to response; (by intravenous infusion) usual dose 30–600 micrograms/kg/hour

Doses at extremes of body-weight

To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.

- SIDE-EFFECTS Acute myopathy (after prolonged use in intensive care) - bradycardia
- DIRECTIONS FOR ADMINISTRATION
  - With intravenous use For intravenous infusion (Nimbex®, Nimbex Forte®), give continuously in Glucose 5% or Sodium Chloride 0.9%; solutions of 2 mg/mL and 5 mg/mL may be infused undiluted; alternatively dilute with infusion fluid to a concentration of 0.1–2 mg/mL.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

- **CISATRACURIAM (Non-proprietary)**
  - Cisatracurium (as Cisatracurium besilate) 2 mg per 1 ml Cisatracurium besilate 20mg/10ml solution for injection vials | 5 vial £37.75 (Hospital only) | 5 vial £37.75
  - Cisatracurium (as Cisatracurium besilate) 5 mg per 1 ml Cisatracurium besilate 150mg/30ml solution for injection vials | 1 vial £45.00 (Hospital only) | 1 vial £18.66
- **Nimbex** (GlaxoSmithKline UK Ltd)
  - Cisatracurium (as Cisatracurium besilate) 2 mg per 1 ml Nimbex 20mg/10ml solution for injection ampoules | 5 ampoule £37.75
  - Cisatracurium (as Cisatracurium besilate) 5 mg per 1 ml Nimbex Forte 150mg/30ml solution for injection vials | 1 vial £31.09

Mivacurium

INDICATIONS AND DOSE
Neuromuscular blockade (short duration) during surgery and intubation

INITIALLY BY INTRAVENOUS INJECTION

- Adult: 70–250 micrograms/kg; (by intravenous injection) maintenance 100 micrograms/kg every 15 minutes, alternatively (by intravenous infusion) maintenance 8–10 micrograms/kg/minute, (by intravenous infusion) adjusted in steps of 1 microgram/kg/minute every 3 minutes if required; (by intravenous infusion) usual dose 6–7 micrograms/kg/minute

Doses at extremes of body-weight

To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.

- **CAUTIONS** Burns (low plasma cholinesterase activity; dose titration required) - elderly
- **SIDE-EFFECTS**
  - Very rare Anaphylactoid reactions
  - Frequency not known Bronchospasm - hypotension - skin flushing - tachycardia
  - **HEPATIC IMPAIRMENT** Reduce dose in severe impairment.
  - **RENAL IMPAIRMENT** Clinical effect prolonged in renal failure—reduce dose according to response.

- **DIRECTIONS FOR ADMINISTRATION**
  - For intravenous infusion, give continuously in Glucose 5% or Sodium chloride 0.9%. Dilute to a concentration of 500 micrograms/mL; may also be given undiluted. Doses up to 150 micrograms/kg may be given over 5–15 seconds, higher doses should be given over 30 seconds. In asthma, cardiovascular disease or in those sensitive to reduced arterial blood pressure, give over 60 seconds.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

- **Mivacurium (GlaxoSmithKline UK Ltd)**
  - Mivacurium (as Mivacurium chloride) 2 mg per 1 ml Mivacurin 10mg/5ml solution for injection ampoules | 5 ampoule £11.95
  - Mivacurin 20mg/10ml solution for injection ampoules | 5 ampoule £22.57

Pancuronium bromide

INDICATIONS AND DOSE
Neuromuscular blockade (long duration) during surgery and intubation

BY INTRAVENOUS INJECTION

- Adult: Initially 100 micrograms/kg, then 20 micrograms/kg as required

Neuromuscular blockade (long duration) during intensive care

BY INTRAVENOUS INJECTION

- Adult: Initially 100 micrograms/kg, initial dose is optional, then 60 micrograms/kg every 60–90 minutes

Doses at extremes of body-weight

To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight.

- **SIDE-EFFECTS** Acute myopathy (after prolonged use in intensive care) - hypertension - tachycardia

SIDE-EFFECTS, FURTHER INFORMATION

Pancuronium lacks histamine-releasing effect, but vagolytic and sympathomimetic effects can cause tachycardia and hypertension.

- **HEPATIC IMPAIRMENT** Possibly slower onset, higher dose requirement, and prolonged recovery time.

- **RENAL IMPAIRMENT** Use with caution; prolonged duration of block.

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.

Solution for injection

- **PANCRONIUM BROMIDE (Non-proprietary)**
  - Pancuronium bromide 2 mg per 1 ml Pancuronium bromide 4mg/2ml solution for injection ampoules | 10 ampoule £50.00
Vecuronium bromide

INDICATIONS AND DOSE
Neuromuscular blockade (intermediate duration) during surgery and intubation

INITIALLY BY INTRAVENOUS INJECTION
- Adult: Initially 600 micrograms/kg; (by intravenous injection) maintenance 150 micrograms/kg, alternatively (by intravenous infusion) maintenance 300–600 micrograms/kg/hour, adjusted according to response
- Elderly: Initially 600 micrograms/kg; (by intravenous injection) maintenance 75–100 micrograms/kg, alternatively (by intravenous infusion) maintenance up to 400 micrograms/kg/hour, adjusted according to response

Neuromuscular blockade (intermediate duration) during intensive care

INITIALLY BY INTRAVENOUS INJECTION
- Adult: Initially 600 micrograms/kg, initial dose is optional; (by intravenous infusion) maintenance 300–600 micrograms/kg/hour for first hour, then (by intravenous infusion), adjusted according to response

Doses at extremes of body-weight
To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal bodyweight.

SIDE-EFFECTS
- Very rare: Anaphylactoid reactions
- Frequency not known: Acute myopathy (after prolonged use in intensive care) • bronchospasm • hypotension • skin flushing • tachycardia

HEPATIC IMPAIRMENT
Use with caution in significant impairment.

RENAL IMPAIRMENT
Use with caution.

DIRECTIONS FOR ADMINISTRATION
Reconstitute each vial with 5 mL. Water for Injections to give 2 mg/mL solution; alternatively reconstitute with up to 10 mL Glucose 5% or Sodium Chloride 0.9% or Water for Injections—unsuitable for further dilution if not reconstituted with Water for Injections. For continuous intravenous infusion, dilute reconstituted solution to a concentration up to 40 micrograms/mL with Glucose 5% or Sodium Chloride 0.9%; reconstituted solution can also be given via drip tubing.

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Powder and solvent for solution for injection
- Norcuron (Merck Sharp & Dohme Ltd)
  Vecuronium bromide 10 mg Norcuron 10mg powder and solvent for solution for injection vials | 10 vial [PSt] £33.73 (Hospital only)

Glycopyrronium bromide with neostigmine

The properties listed below are those particular to the combination only. For the properties of the components please consider, glycopyrronium bromide p. 1100, neostigmine p. 912.

INDICATIONS AND DOSE
Reversal of non-depolarising neuromuscular blockade

BY INTRAVENOUS INJECTION
- Adult: 1–2 mL, repeated if necessary, alternatively 0.02 mL/kg/minute (max. per dose 2 mL), repeated if necessary, dose to be given over 10–30 seconds

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Solution for injection
- GLYCOPHYRRONIUM BROMIDE WITH NEOSTIGMINE (Non-proprietary)
  Glycopyrronium bromide 500 microgram per 1 mL, Neostigmine metilsulfate 2.5 mg per 1 mL
  Glycopyrronium bromide 500 microgram/1mL solution for injection ampoules | 10 ampoule [PSt] £9.11

1.4 Neuromuscular blockade reversal

Drugs used for Neuromuscular blockade reversal not listed below; Neostigmine, p. 912
**CHELATORS AND ANTIDOTES**

**Sugammadex**

**INDICATIONS AND DOSE**

Routine reversal of neuromuscular blockade induced by rocuronium or vecuronium

- **BY INTRAVENOUS INJECTION**
  - Adult: Initially 2–4 mg/kg, then 4 mg/kg if required, administered if recurrence of neuromuscular blockade occurs; consult product literature for further details

Immediate reversal of neuromuscular blockade induced by rocuronium

- **BY INTRAVENOUS INJECTION**
  - Adult: 16 mg/kg (consult product literature)

**Important safety information**

Should only be administered by, or under the direct supervision of, personnel experienced in its use.

- **CAUTIONS**
  - Cardiovascular disease (recovery may be delayed) - elderly (recovery may be delayed) - pre-existing coagulation disorders - recurrence of neuromuscular blockade - monitor respiratory function until fully recovered - use of anticoagulants (unrelated to surgery) - wait 24 hours before re-administering rocuronium - wait 24 hours before re-administering vecuronium

- **INTERACTIONS** → Appendix 1 (sugammadex).

- **SIDE-EFFECTS**
  - Bradycardia - bronchospasm - cardiac arrest - hypersensitivity reactions

- **PREGNANCY**
  - Use with caution — no information available.

- **RENAL IMPAIRMENT**
  - Avoid if eGFR less than 30 mL/minute/1.73 m².

- **NATIONAL FUNDING/ACCESS DECISIONS**

  **Scottish Medicines Consortium (SMC) Decisions**

  The Scottish Medicines Consortium, has advised (February 2013) that sugammadex (Bridion®) is accepted for restricted use within NHS Scotland for the routine reversal of neuromuscular blockade in high-risk patients only, or where prompt reversal of neuromuscular blockade is required.

- **MEDICINAL FORMS**

  There can be variation in the licensing of different medicines containing the same drug.

  **Solution for injection**

  **ELECTROLYTES:** May contain Sodium

  - **Bridion** (Merck Sharp & Dohme Ltd)
    Sugammadex (as Sugammadex sodium) 100 mg per 1 ml Bridion 500 mg/5ml solution for injection vials | 10 vial (POD) £1,491.00 (Hospital only) Bridion 200 mg/2ml solution for injection vials | 10 vial (POD) £596.40 (Hospital only)

**1.5 Peri-operative analgesia**

**Peri-operative analgesia**

**Non-opioid analgesics**

Since non-steroidal anti-inflammatory drugs (NSAIDs) do not depress respiration, do not impair gastro-intestinal motility, and do not cause dependence, they may be useful alternatives or adjuncts to opioids for the relief of postoperative pain. NSAIDs may be inadequate for the relief of severe pain. Acemetacin p. 917, diclofenac sodium p. 921, diclofenac potassium p. 920, flurbiprofen p. 994, ibuprofen p. 927, ketoprofen p. 930, paracetamol p. 354, parecoxib p. 1108, and ketorolac trometamol p. 1107 are licensed for postoperative use. Diclofenac and paracetamol can be given by injection as well as by mouth. Diclofenac sodium, can be given by intravenous infusion for the treatment or prevention of postoperative pain. Intramuscular injections of diclofenac sodium and ketoprofen are rarely used; they are given deep into the gluteral muscle to minimise pain and tissue damage. Ketorolac trometamol is less irritant on intramuscular injection but pain has been reported; it can also be given by intravenous injection.

Suppositories of diclofenac sodium and ketoprofen may be effective alternatives to the parenteral use of these drugs.

**Opioid analgesics**

Opioid analgesics are now rarely used as premedicants; they are more likely to be administered at induction. Pre-operative use of opioid analgesics is generally limited to those patients who require control of existing pain. See general notes on opioid analgesics and their use in postoperative pain. See also the management of opioid-induced respiratory depression.

**Intra-operative analgesia**

Opioid analgesics given in small doses before or with induction reduce the dose requirement of some drugs used during anaesthesia.

Alfentanil p. 357, fentanyl p. 362, and remifentanil p. 1108 are particularly useful because they act within 1–2 minutes and have short durations of action. The initial doses of alfentanil or fentanyl are followed either by successive intravenous injections or by an intravenous infusion; prolonged infusions increase the duration of effect. Repeated intra-operative doses of alfentanil or fentanyl should be given with care since the resulting respiratory depression can persist postoperatively and occasionally it may become apparent for the first time postoperatively when monitoring of the patient might be less intensive. Alfentanil, fentanyl, and remifentanil can cause muscle rigidity, particularly of the chest wall or jaw; this can be managed by the use of neuromuscular blocking drugs. are followed either by successive intravenous injections or by an intravenous infusion; prolonged infusions increase the duration of effect.

In contrast to other opioids which are metabolised in the liver, remifentanil undergoes rapid metabolism by nonspecific blood and tissue esterases; its short duration of action allows prolonged administration at high dosage, without accumulation, and with little risk of residual postoperative respiratory depression. Remifentanil should not be given by intravenous injection intraoperatively, but it is well suited to continuous infusion; a supplementary analgesic is given before stopping the infusion of remifentanil.

**Bupivacaine with fentanyl**

The properties listed below are those particular to the combination only. For the properties of the components please consider, bupivacaine hydrochloride p. 1113, fentanyl p. 362.

**INDICATIONS AND DOSE**

**Postoperative pain (once epidural block established)**

**BY CONTINUOUS EPIDURAL INFUSION**

- **Adult:** 4–18.75 mg/hour of bupivacaine to be administered, maximum 400 mg bupivacaine in 24 hours and 8–30 micrograms/hour of fentanyl to be administered, maximum 720 micrograms fentanyl in 24 hours, to be administered by thoracic, upper abdominal or lower abdominal epidural infusion.
**During labour (once epidural block established)**

**BY CONTINUOUS LUMBAR EPIDURAL INFUSION**

- Adult: 10–18.75 mg/hour of bupivacaine to be administered and 16–30 micrograms/hour of fentanyl to be administered

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for infusion, infusion solution for injection ampoules.

**Solution for infusion**

- Bufyl (AMCO)
  - Bupivacaine hydrochloride 1 mg per 1 ml, Fentanyl 2 microgram per 1 ml
  - Bupivacaine 1mg/ml and 2 microgram/ml 250ml infusion bags | 20 bag £87.00 (Hospital only) Schedule 2 (CD)
  - Bupivacaine 1mg/ml and 2 microgram/ml 500ml infusion bags | 10 bag £92.00 (Hospital only) Schedule 2 (CD)
  - Bupivacaine hydrochloride 1.25 mg per 1 ml, Fentanyl (as Fentanyl citrate) 2 microgram per 1 ml
  - Bupivacaine 1.25mg/ml and 2micrograms/ml 250ml infusion bags | 20 bag £181.00 (Hospital only) Schedule 2 (CD)
  - Bupivacaine 1.25mg/ml and 2micrograms/ml 500ml infusion bags | 10 bag £92.00 (Hospital only) Schedule 2 (CD)

**NON-STEROIDAL ANTI-INFLAMMATORY DRUGS**

**Ketorolac trometamol**

**INDICATIONS AND DOSE**

Short-term management of moderate to severe acute postoperative pain only

**BY INTRAMUSCULAR INJECTION OR BY INTRAVENOUS INJECTION**

- Adult (body-weight up to 50 kg): Initially 10 mg, then 10–30 mg every 4–6 hours as required for maximum duration of treatment 2 days, to be given over at least 15 seconds, frequency may be increased to up to every 2 hours during initial postoperative period; maximum 60 mg per day
- Adult (body-weight 50 kg and above): Initially 10 mg, then 10–30 mg every 4–6 hours as required for maximum duration of treatment 2 days, to be given over at least 15 seconds, frequency may be increased to up to every 2 hours during initial postoperative period; maximum 90 mg per day
- Elderly: Initially 10 mg, then 10–30 mg every 4–6 hours as required for maximum duration of treatment 2 days, to be given over at least 15 seconds, frequency may be increased to up to every 2 hours during initial postoperative period; maximum 60 mg per day

**CONTRA-INDICATIONS**

Active or history of gastrointestinal bleeding - active or history of gastrointestinal ulceration - coagulation disorders - complete or partial syndrome of nasal polyps - confirmed or suspected cerebrovascular bleeding - dehydration - following operations with high risk of haemorrhage or incomplete haemostasis - haemorrhagic diatheses - history of gastrointestinal perforation - hypovolaemia - severe heart failure

**CAUTIONS**

Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - cerebrovascular disease - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - elderly (risk of serious side-effects and fatalities) - heart failure - ischaemic heart disease - peripheral arterial disease - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated) - uncontrolled hypertension

**INTERACTIONS**

- Appendix 1 (NSAIDs).

**SIDE-EFFECTS**

- Rare: Alveolitis - aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) - hepatic damage - interstitial fibrosis associated with NSAIDs can lead to renal failure - pancreatitis - papillary necrosis associated with NSAIDs can lead to renal failure - pulmonary eosinophilia - Stevens-Johnson syndrome - toxic epidermal necrolysis

**SIDE-EFFECTS, FURTHER INFORMATION**

Serious side-effects: For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 915.

**ALLERGY AND CROSS-SENSITIVITY**

Contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID.

**CONCEPTION AND CONTRACEPTION**

Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

**PREGNANCY**

Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

**BREAST FEEDING**

Amount too small to be harmful.

**HEPATIC IMPAIRMENT**

Use with caution; there is an increased risk of gastro-intestinal bleeding and fluid retention. Avoid in severe liver disease.

**RENAL IMPAIRMENT**

- With intramuscular use or intravenous use: The lowest effective dose should be used for the shortest possible duration. Max. 60 mg daily by intramuscular injection or intravenous injection. Avoid if possible or use with caution. Avoid if serum creatinine greater than 160 micromol/litre. Monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **KETOROLAC TROMETAMOL (Non-proprietary)**
  - Ketorolac trometamol 30 mg per 1 ml
  - Ketorolac 30mg/1ml solution for injection ampoules | 6 ampoule £58.56
  - Toradol (Roche Products Ltd)
  - Ketorolac trometamol 30 mg per 1 ml
  - Toradol 30mg/1ml solution for injection ampoules | 5 ampoule £50.36

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**Peri-operative analgesia** **1107**

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**Parecoxib**

- **DRUG ACTION** Parecoxib is a selective inhibitor of cyclo-oxygenase-2.

### INDICATIONS AND DOSE

**Short-term management of acute postoperative pain** by deep intramuscular injection or by intravenous injection
- Adult: Initially 40 mg, then 20–40 mg every 6–12 hours as required for up to 3 days; maximum 80 mg per day
- Elderly (body-weight up to 50 kg): Initially 20 mg; maximum 40 mg per day

- **CONTRA-INDICATIONS** Active gastrointestinal bleeding - active gastrointestinal ulceration - cerebrovascular disease - inflammatory bowel disease - ischaemic heart disease - mild to severe heart failure - peripheral arterial disease
- **CAUTIONS** Allergic disorders - cardiac impairment (NSAIDs may impair renal function) - coagulation defects - connective-tissue disorders - Crohn’s disease (may be exacerbated) - dehystention - elderly (risk of serious side-effects and fatalities) - following coronary artery bypass graft surgery - history of cardiac failure - hypertension - left ventricular dysfunction - oedema - risk factors for cardiovascular events - ulcerative colitis (may be exacerbated)
- **INTERACTIONS** → Appendix 1 (NSAIDs).
- **SIDE-EFFECTS**
  - **Common or very common** Alveolar ostitis - flatulence - hypoaesthesia - hypokalaemia - hypotension - postoperative anaemia - sweating
  - **Uncommon** Anorexia - arthralgia - bradycardia - cardiovascular events - ecchymosis - hyperglycaemia - malaise - pulmonary embolism
  - **Rare** Alveolitis - aseptic meningitis (patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible) - hepatic damage - interstitial fibrosis associated with NSAIDs can lead to renal failure - pancreatitis - papillary necrosis associated with NSAIDs can lead to renal failure - pulmonary eosinophilia - Stevens-Johnson syndrome - toxic epidermal necrolysis - visual disturbances
  - **Frequency not known** Angioedema - blood disorders - blood pressure may be raised - bronchospasms - circulatory collapse - colitis (induction of or exacerbation of) - Crohn’s disease (induction of or exacerbation of) - depression - diarrhoea - dizziness - drowsiness - fluid retention (rarely precipitating congestive heart failure) - gastro-intestinal bleeding - gastro-intestinal discomfort - gastro-intestinal disturbances - gastro-intestinal ulceration - haematuria - headache - hearing disturbances - hypersensitivity reactions - insomnia - nausea - nervousness - photosensitivity - rash - renal failure (especially in patients with pre-existing renal impairment) - tachycardia - tinnitus - vertigo

### SIDE-EFFECTS, FURTHER INFORMATION

**Serious side-effects** For information about cardiovascular and gastro-intestinal side-effects, and a possible exacerbation of symptoms in asthma, see Non-steroidal anti-inflammatory drugs p. 915.

- **ALLERGY AND CROSS-SENSITIVITY** Contraindicated in patients with a history of hypersensitivity to aspirin or any other NSAID— which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID. Contraindicated in patients with a history of allergic drug reactions including sulfonamide hypersensitivity.

- **CONCEPTION AND CONTRACEPTION** Caution—long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

- **PREGNANCY** Avoid unless the potential benefit outweighs the risk. Avoid during the third trimester (risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn); onset of labour may be delayed and duration may be increased.

- **BREAST FEEDING** Avoid—present in milk.

- **HEPATIC IMPAIRMENT** Halve dose in moderate impairment (max. 40 mg daily). Use with caution; there is an increased risk of gastrointestinal bleeding and fluid retention. Avoid in severe liver disease.

- **RENAL IMPAIRMENT** The lowest effective dose should be used for the shortest possible duration. Avoid if possible or use with caution. In renal impairment monitor renal function; sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure.

### NATIONAL FUNDING/ACCESS DECISIONS

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (January 2003) that parecoxib is not recommended for use within NHS Scotland.

- **MEDICINAL FORMS**
  - **Powder for solution for injection**
    - **Dynastat** (Pfizer Ltd)
      - Parecoxib (as Parecoxib sodium) 40 mg Dynastat 40mg powder for solution for injection vials | 10 vial | £9.60
    - **Dynastat** (Pfizer Ltd)
      - Parecoxib (as Parecoxib sodium) 40 mg Dynastat 40mg powder and solvent for solution for injection vials | 5 vial | £7.83

### OPIOIDS

**Remifentanil**

The properties listed below are those particular to the drug only. For properties common to the class, see Opioids, p. 357.

### INDICATIONS AND DOSE

**Analgesia and enhancement of anaesthesia at induction**

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 0.25–1 microgram/kg, dose to be administered over at least 30 seconds, then (by intravenous infusion) 30–60 micrograms/kg/hour, alternatively (by intravenous infusion) initially 30–60 micrograms/kg/hour, if patient to be intubated more than 8 minutes after start of intravenous infusion, initial intravenous injection dose is not necessary

**Assisted ventilation: analgesia and enhancement of anaesthesia during maintenance of anaesthesia**

- **INITIALLY BY INTRAVENOUS INJECTION**
  - Adult: Initially 0.25–1 microgram/kg, dose to be administered over at least 30 seconds, according to anaesthetic technique and adjusted according to response, followed by (by intravenous infusion) 3–120 micrograms/kg/hour, intravenous infusion may be given with or without initial intravenous injection dose; in light anaesthesia supplemental doses by intravenous injection every 2–5 minute
Assisted ventilation: analgesia and sedation in intensive-care patients (for max 3 days)

BY INTRAVENOUS INFUSION
- Adult: Initially 6–9 micrograms/kg/hour, then adjusted in steps of 1.5 micrograms/kg/hour, allow at least 5 minutes between dose adjustments; usual dose 0.36–44.4 micrograms/kg/hour, if an infusion rate of 12 micrograms/kg/hour does not produce adequate sedation add another sedative (consult product literature for details)

Assisted ventilation: additional analgesia during stimulating or painful procedures in intensive-care patients

BY INTRAVENOUS INFUSION
- Adult: Usual dose 15–45 micrograms/kg/hour, maintain infusion rate of at least 6 micrograms/kg/hour for at least 5 minutes before procedure and adjust every 2–5 minutes according to requirements

Spontaneous respiration: analgesia and enhancement of anaesthesia during maintenance of anaesthesia

BY INTRAVENOUS INFUSION
- Adult: Initially 2.4 micrograms/kg/hour, adjusted according to response; usual dose 1.5–6 micrograms/kg/hour

Cardiac surgery
- Adult: (consult product literature)

Doses at extremes of body-weight
To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal bodyweight.

- UNLICENSED USE Remifentanil doses in BNF may differ from those in product literature.
- CONTRA-INDICATIONS Analgesia in conscious patients
- SIDE-EFFECTS
  - Common or very common Hypertension
  - Uncommon Hypoxia
  - Rare Asystole
  - Frequency not known AV block - convulsions

SIDE-EFFECTS, FURTHER INFORMATION

Muscle rigidity Alfentanil can cause muscle rigidity, particularly of the chest wall or jaw; this can be managed by the use of neuromuscular blocking drugs.

Respiratory depression In contrast to other opioids which are metabolised in the liver, remifentanil undergoes rapid metabolism by non-specific blood and tissue esterases; its short duration of action allows prolonged administration at high dosage, without accumulation, and with little risk of residual postoperative respiratory depression.

- PREGNANCY No information available.
- BREAST FEEDING Avoid breast-feeding for 24 hours after administration—present in milk in animal studies.
- RENAL IMPAIRMENT No dose adjustment necessary in renal impairment.
- DIRECTIONS FOR ADMINISTRATION
  - With intravenous use For intravenous infusion (Ultiva®), give continuously in Glucose 5% or Sodium Chloride 0.9% or Water for Injections; reconstitute with infusion fluid to a concentration of 1 mg/mL then dilute further to a concentration of 20–250 micrograms/mL (50 micrograms/mL recommended for general anaesthesia, 20–50 micrograms/mL recommended when used with target controlled infusion (TCI) device).

PRESCRIBING AND DISPENSING INFORMATION
Remifentanil should not be given by intravenous injection intra-operatively, but it is well suited to continuous infusion; a supplementary analgesic is given before stopping the infusion of remifentanil.

- MEDICINAL FORMS
  - There can be variation in the licensing of different medicines containing the same drug.

Powder for solution for injection

- REMIFENTANIL (Non-proprietary)
  - Remifentanil (as Remifentanyl hydrochloride) 1 mg Remifentanil 1mg powder for concentrate for solution for injection vials | 5 vial (PBD) £25.58–£25.60 (Hospital only) Schedule 2 (CD)
  - Remifentanil (as Remifentanyl hydrochloride) 2 mg Remifentanil 2mg powder for concentrate for solution for injection vials | 5 vial (PBD) £29.13–£31.15 (Hospital only) Schedule 2 (CD)
  - Remifentanil (as Remifentanyl hydrochloride) 5 mg Remifentanil 5mg powder for concentrate for solution for injection vials | 5 vial (PBD) £127.00–£127.90 (Hospital only) Schedule 2 (CD)
  - Ultiva (GlaxoSmithKline UK Ltd)
    - Remifentanil (as Remifentanyl hydrochloride) 1 mg Ultiva 1mg powder for solution for injection vials | 5 vial (PBD) no price available (Hospital only) Schedule 2 (CD)
    - Remifentanil (as Remifentanyl hydrochloride) 2 mg Ultiva 2mg powder for solution for injection vials | 5 vial (PBD) no price available (Hospital only) Schedule 2 (CD)
    - Remifentanil (as Remifentanyl hydrochloride) 5 mg Ultiva 5mg powder for solution for injection vials | 5 vial (PBD) no price available (Hospital only) Schedule 2 (CD)

Hyoscine hydrobromide with papaveretum

The properties listed below are those particular to the combination only. For the properties of the components please consider, hyoscine hydrobromide p. 344, papaveretum p. 371.

INDICATIONS AND DOSE
Premedication
BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION
- Adult: 0.5–1 mL

LESS SUITABLE FOR PRESCRIBING Hyoscine hydrobromide with papaveretum is less suitable for prescribing.

- MEDICINAL FORMS
  - Medicines not identified.

1.6 Peri-operative sedation

Conscious sedation for clinical procedures

Sedation of patients during diagnostic and therapeutic procedures is used to reduce fear and anxiety, to control pain, and to minimise excessive movement. The choice of sedative drug will depend upon the intended procedure; some procedures are safer and more successful under anaesthesia. The patient should be monitored carefully; monitoring should begin as soon as the sedative is given or when the patient becomes drowsy, and should be continued until the patient wakes up.
**ALPHA₂-ADRENOCEPTOR AGONISTS**

**Dexmedetomidine**

**INDICATIONS AND DOSE**
Maintenance of sedation during intensive care

**BY INTRAVENOUS INFUSION**
- Adult: 0.7 microgram/kg/hour, adjusted according to response; usual dose 0.2–1.4 micrograms/kg/hour

**Important safety information**
Dexmedetomidine should only be administered by, or under the direct supervision of, personnel experienced in its use, with adequate training in anaesthesia and airway management.

- **CONTRA-INDICATIONS** Acute cerebrovascular disorders - second- or third-degree AV block (unless pacemaker fitted) - uncontrolled hypotension
- **CAUTIONS** Abrupt withdrawal after prolonged use - bradycardia - ischaemic heart disease - malignant hyperthermia - severe cerebrovascular disease (especially at higher doses) - severe neurological disorders - spinal cord injury
- **SIDE-EFFECTS**
  - Common or very common: Agitation - blood pressure changes - bradycardia - changes in blood sugar - dry mouth - hyperthermia - myocardial infarction - myocardial ischaemia - nausea - tachycardia - vomiting
  - Uncommon: Abdominal distension - AV block - decreased cardiac output - dyspnoea - hallucination - hypoalbuminaemia - metabolic acidosis - thirst
- **PREGNANCY** Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies.
- **BREAST FEEDING** Manufacturer advises avoid unless potential benefit outweighs risk—present in milk in animal studies.
- **HEPATIC IMPAIRMENT** Dose reduction may be required. Manufacturer advises caution.
- **MONITORING REQUIREMENTS** Monitor cardiac function. Monitor respiratory function in non-intubated patients.
- **DIRECTIONS FOR ADMINISTRATION** To be diluted before use.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for infusion**
- Dexdor (Orion Pharma (UK) Ltd)
  - Dexmedetomidine (as Dexmedetomidine hydrochloride) 100 microgram per 1 ml
  - Dexdor 1mg/10ml concentrate for solution for infusion vials | 4 vial (Ref) £313.20 (Hospital only)
  - Dexdor 400micrograms/4ml concentrate for solution for infusion vials | 4 vial (Ref) £125.28 (Hospital only)
  - Dexdor 200micrograms/2ml concentrate for solution for infusion ampoules | 5 ampoule (Ref) £78.30 (Hospital only) | 25 ampoule (Ref) £391.50 (Hospital only)

**ANAESTHETICS (GENERAL, INTRAVENOUS, NMDA RECEPTOR ANTAGONISTS)**

**Ketamine**

**INDICATIONS AND DOSE**
Induction and maintenance of anaesthesia for short procedures

**BY INTRAMUSCULAR INJECTION**
- Adult: Initially 6.5–13 mg/kg, adjusted according to response, a dose of 10 mg/kg usually produces 12–25 minutes of surgical anaesthesia

**BY INTRAVENOUS INJECTION**
- Adult: Initially 1–4.5 mg/kg, adjusted according to response, to be administered over at least 60 seconds, a dose of 2 mg/kg usually produces 5–10 minutes of surgical anaesthesia

**Diagnostic manoeuvres and procedures not involving intense pain**
- Adult: Initially 4 mg/kg

**Induction and maintenance of anaesthesia for long procedures**
- Adult: Initially 0.5–2 mg/kg, using an infusion solution containing 1 mg/ml; maintenance 10–45 micrograms/kg/minute, adjusted according to response

**Important safety information**
Ketamine should only be administered by, or under the direct supervision of, personnel experienced in its use, with adequate training in anaesthesia and airway management, and when resuscitation equipment is available.

- **CONTRA-INDICATIONS** Acute porphyrias p. 864 - eclampsia - head trauma - hypertension - pre-eclampsia - raised intracranial pressure - severe cardiac disease - stroke
- **CAUTIONS** Acute circulatory failure (shock) - cardiovascular disease - dehydration - elderly - fixed cardiac output - hallucinations - head injury - hypertension - hypovolaemia - increased cerebrospinal fluid pressure - intracranial mass lesions - nightmares - predisposition to seizures - psychotic disorders - raised intra-ocular pressure - respiratory tract infection - thyroid dysfunction
- **INTERACTIONS** Appendix 1 (anaesthetics, general).
- **SIDE-EFFECTS**
  - Common or very common: Diplopia - hallucinations - hypertension - nausea - nightmares - nystagmus - rash - tachycardia - transient psychotic effects - vomiting
  - Uncommon: Arrhythmias - bradycardia - hypotension - laryngospasm - respiratory depression
  - Rare: Aplacata - cystitis - cystitis - haemorrhagic cystitis - hypersalivation - insomnia
  - Frequency not known: Raised intra-ocular pressure
- **SIDE-EFFECTS, FURTHER INFORMATION** Transient psychotic effects: Incidence of hallucinations, nightmares, and other transient psychotic effects can be reduced by a benzodiazepine such as diazepam or midazolam.
- **PREGNANCY** May depress neonatal respiration if used during delivery.
- **BREAST FEEDING** Avoid for at least 12 hours after last dose.
- **HEPATIC IMPAIRMENT** Consider dose reduction.
- **DIRECTIONS FOR ADMINISTRATION** For continuous intravenous infusion, dilute to a concentration of 1 mg/ml with Glucose 5% or Sodium Chloride 0.9%; use microdrip infusion for maintenance of anaesthesia. For intravenous injection, dilute 100 mg/mL strength to a concentration of not more than 50 mg/ml with Glucose 5% or Sodium Chloride 0.9% or Water for Injections.
- **PATIENT AND CARER ADVICE** Patients given sedatives and analgesics during minor outpatient procedures should be very carefully warned about the risk of driving or undertaking skilled tasks afterwards. For a short general anaesthetic the risk extends to **at least 24 hours** after administration. Responsible persons should be available.
Local anaesthesia

The use of local anaesthetics by injection or by application to mucous membranes to produce local analgesia is covered in this section.

Local anaesthetic drugs act by causing a reversible block to conduction along nerve fibres. They vary widely in their potency, toxicity, duration of action, stability, solubility in water, and ability to penetrate mucous membranes. These factors determine their application, e.g. topical (surface), infiltration, peripheral nerve block, intravenous regional anaesthesia (Bier’s block), plexus, epidural (extradural), or spinal (intrathecal or subarachnoid) block. Local anaesthetics may also be used for postoperative pain relief, thereby reducing the need for analgesics such as opioids.

Bupivacaine hydrochloride p. 1113 has a longer duration of action than other local anaesthetics. It has a slow onset of action, taking up to 30 minutes for full effect. It is often used in lumbar epidural blockade and is particularly suitable for continuous epidural analgesia in labour, or for postoperative pain relief. It is the principal drug used for spinal anaesthesia. Hyperbaric solutions containing glucose may be used for spinal block.

Chloroprocaine hydrochloride p. 1114, a para-aminobenzoic acid ester, is used for spinal anaesthesia in adults where the planned procedure should not exceed 40 minutes.

Levobupivacaine p. 1115, an isomer of bupivacaine, has anaesthetic and analgesic properties similar to bupivacaine hydrochloride, but is thought to have fewer adverse effects.

Lidocaine hydrochloride p. 1116 is effectively absorbed from mucous membranes and is a useful surface anaesthetic in concentrations up to 10%. Except for surface anaesthesia and dental anaesthesia, solutions should not usually exceed 1% in strength. The duration of the block (with adrenaline/epinephrine p. 1196) is about 90 minutes.

Prilocaine hydrochloride p. 1120 is a local anaesthetic of low toxicity which is similar to lidocaine hydrochloride. A hyperbaric solution of prilocaine hydrochloride (containing glucose) may be used for spinal anaesthesia.

Ropivacaine hydrochloride p. 1121 is an amide-type local anaesthetic agent similar to bupivacaine hydrochloride. It is less cardiotoxic than bupivacaine hydrochloride, but also less potent.

Tetracaine p. 1122, a para-aminobenzoic acid ester, is an effective local anaesthetic for topical application; a 4% gel is indicated for anaesthesia before venepuncture or venous cannulation. It is rapidly absorbed from mucous membranes and should never be applied to inflamed, traumatised, or highly vascular surfaces. It should never be used to provide anaesthesia for bronchoscopy or cystoscopy because lidocaine hydrochloride is a safer alternative.

Use of vasoconstrictors

Local anaesthetics cause dilatation of blood vessels. The addition of a vasoconstrictor such as adrenaline/epinephrine to the local anaesthetic preparation diminishes local blood flow, slowing the rate of absorption and thereby prolonging the anaesthetic effect. Great care should be taken to avoid inadvertent intravascular administration of a preparation containing adrenaline/epinephrine, and it is not advisable to give adrenaline/epinephrine with a local anaesthetic injection in digits or appendages because of the risk of ischaemic necrosis.

Adrenaline/epinephrine must be used in a low concentration when administered with a local anaesthetic. Care must also be taken to calculate a safe maximum dose of local anaesthetic when using combination products.

In patients with severe hypertension or unstable cardiac rhythm, the use of adrenaline/epinephrine with a local anaesthetic may be hazardous. For these patients an anaesthetic without adrenaline/epinephrine should be used.

Dental anaesthesia

Lidocaine hydrochloride is widely used in dental procedures; it is most often used in combination with adrenaline/epinephrine. Lidocaine hydrochloride 2% combined with adrenaline/epinephrine 1 in 80 000 (12.5 micrograms/mL) is a safe and effective preparation; there is no justification for using higher concentrations of adrenaline/epinephrine.

The amide-type local anaesthetics articaine and mepivacaine hydrochloride p. 1119 are also used in dentistry; they are available in cartridges suitable for dental use. Mepivacaine hydrochloride is available with or without adrenaline/epinephrine and articaine is available with adrenaline.

In patients with severe hypertension or unstable cardiac rhythm, mepivacaine hydrochloride without adrenaline/epinephrine may be used. Alternatively, prilocaine hydrochloride with or without felypressin can be used but there is no evidence that it is any safer. Felypressin
Severe local anaesthetic-induced cardiovascular toxicity

After injection of a bolus of local anaesthetic, toxicity may develop at any time in the following hour. In the event of signs of toxicity during injection, the administration of the local anaesthetic must be stopped immediately.

Cardiovascular status must be assessed and cardiopulmonary resuscitation procedures must be followed.

In the event of local anaesthetic-induced cardiac arrest, standard cardiopulmonary resuscitation should be initiated immediately. Lidocaine must not be used as anti-arrhythmic therapy. If the patient does not respond rapidly to standard procedures, 20% lipid emulsion such as Intralipid® [unlicensed indication] should be given intravenously at an initial bolus dose of 1.5 mL/kg over 1 minute, followed by an infusion of 15 mL/kg/hour. After 5 minutes, if cardiovascular stability has not been restored or circulation deteriorates, give a maximum of two further bolus doses of 1.5 mL/kg over 1 minute, 5 minutes apart, and increase the infusion rate to 30 mL/kg/hour. Continue infusion until cardiovascular stability and adequate circulation are restored or maximum cumulative dose of 12 mL/kg is given. Standard cardiopulmonary resuscitation must be maintained throughout lipid emulsion treatment.

Propofol is not a suitable alternative to lipid emulsion.

Further advice on ongoing treatment should be obtained from the National Poisons Information Service. Detailed treatment algorithms and accompanying notes are available at www.toxbase.org or can be found in the Association of Anaesthetists of Great Britain and Ireland safety guideline, Management of Severe Local Anaesthetic Toxicity and Management of Severe Local Anaesthetic Toxicity – Accompanying notes.

ANAESTHETICS (LOCAL)

Articaine hydrochloride with adrenaline
(Carticaine hydrochloride with epinephrine)

INDICATIONS AND DOSE

Infiltration anaesthesia in dentistry

- Adult: Consult expert dental sources

Doses at extremes of body-weight

To avoid excessive dosage in obese patients, dose may need to be calculated on the basis of ideal body-weight.

Important safety information

Should only be administered by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management, and should not be administered parenterally unless adequate resuscitation equipment is available.

CONTRA-INDICATIONS Application to damaged skin · application to the middle ear (may cause otoxicity) · complete heart block · injection into infected tissues · injection into inflamed tissues · preparations containing preservatives should not be used for caudal, epidural, or spinal block, or for intravenous regional anaesthesia (Bier’s block)

CONTRA-INDICATIONS, FURTHER INFORMATION

Injection site Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin. Increased absorption into the blood increases the possibility of systemic side-effects, and the local anaesthetic effect may also be reduced by altered local pH.

- CAUTIONS Arrhythmias · arteriosclerosis · cardiovascular disease · cerebrovascular disease · cor pulmonale · debilitated patients (consider dose reduction) · diabetes mellitus · elderly (consider dose reduction) · epilepsy · hypercalcaemia · hyperreflexia · hypertension · hyperthyroidism · hypokalaemia · hypovolaemia · impaired cardiac conduction · impaired respiratory function · ischaemic heart disease · myasthenia gravis · obstructive cardiomyopathy · occlusive vascular disease · organic brain damage · phaeochromocytoma · prostate disorders · psychoneurosis · severe angina · shock · susceptibility to angle-closure glaucoma

CAUTIONS, FURTHER INFORMATION

Use of vasoconstrictors In patients with severe hypertension or unstable cardiac rhythm, the use of adrenaline with a local anaesthetic may be hazardous. For these patients an anaesthetic without adrenaline should be used.

- INTERACTIONS → Appendix 1 (sympathomimetics).

SIDE-EFFECTS Angina · angle-closure glaucoma · anorexia · anxiety · arrhythmias · blurred vision · cardiac arrest · cold extremities · confusion · convulsions · difficulty in micturition · dizziness · drowsiness · dry mouth · dyspnoea · feeling of inebriation · headache · hyperglycaemia · hypersalivation · hypertension (risk of cerebral haemorrhage) · hypokalaemia · insomnia · lightheadedness · metabolic acidosis · methaemoglobinemia · muscle twitching · mydriasis · myocardial depression (resulting in hypotension and bradycardia) · myocardial infarction · nausea · numbness of the tongue and perioral region · pallor · palpitation · paraesthesia (including sensations of hot and cold) · peripheral vasodilatation (resulting in hypotension and bradycardia) · psychosis · pulmonary oedema (on excessive dosage or extreme sensitivity) · restlessness · sweating · tachycardia · tinnitus · tissue necrosis at injection site and of extremities, bowel, liver and kidneys · transient excitation (followed by depression with drowsiness, respiratory failure, unconsciousness, and coma) · tremor · urinary retention · vomiting · weakness

SIDE-EFFECTS, FURTHER INFORMATION

Toxic effects Toxic effects after administration of local anaesthetics are a result of excessively high plasma concentrations; severe toxicity usually results from inadvertent intravascular injection or too rapid injection. Following most regional anaesthetic procedures, maximum arterial plasma concentration of anaesthetic develops within about 10 to 25 minutes, so careful surveillance for toxic effects is necessary during the first 30 minutes after injection. The systemic toxicity of local anaesthetics mainly involves the central nervous and cardiovascular systems.

- ALLERGY AND CROSS-SENSITIVITY Hypersensitivity reactions occur mainly with the ester-type local anaesthetics, such as tetracaine and chloroprocaine; reactions are less frequent with the amide types, such as articaine, bupivacaine, levobupivacaine, lidocaine, mepivacaine, prilocaine, and ropivacaine. Cross-sensitivity reactions may be avoided by using the alternative chemical type.

- PREGNANCY Use only if potential benefit outweighs risk—no information available.

- BREAST FEEDING Avoid breast-feeding for 48 hours after administration.
**Medications**

**Bupivacaine hydrochloride**

**Indications and dose**

**Surgical anaesthesia, lumbar epidural block**

- Adult: 75–150 mg, dose administered using 5 mg/mL (0.5%) solution

**Surgical anaesthesia, field block**

- Adult: Up to 150 mg, dose administered using a 2.5 mg/mL (0.25%) or 5 mg/mL (0.5%) solution

**Surgical anaesthesia, thoracic epidural block**

- Adult: 12.5–50 mg, dose administered using a 2.5 mg/mL (0.25%) or 5 mg/mL (0.5%) solution

**Surgical anaesthesia, caudal epidural block**

- Adult: 50–150 mg, dose administered using a 2.5 mg/mL (0.25%) or 5 mg/mL (0.5%) solution

**Surgical anaesthesia, major nerve block**

- Adult: 50–175 mg, dose administered using 5 mg/mL (0.5%) solution

**Acute pain, intra-articular block**

- Adult: Up to 100 mg, dose administered using a 2.5 mg/mL (0.25%) solution; when co-administered with bupivacaine by another route, total max. 150 mg

**Acute pain, thoracic epidural block**

- Adult: 6.3–18.8 mg/hour, dose administered using a 1.25 mg/mL (0.125%) or 2.5 mg/mL (0.25%) solution; maximum 400 mg per day

**Acute pain, lumbar epidural block**

- Adult: 15–37.5 mg, then (by lumbar epidural) 15–37.5 mg at least every 30 minutes, repeated when required, alternatively (by continuous epidural infusion) 12.5–18.8 mg/hour, dose administered using a 1.25 mg/mL (0.125%) or 2.5 mg/mL (0.25%) solution

**Acute pain, field block**

- Adult: Up to 150 mg, dose administered using a 2.5 mg/mL (0.25%) solution

**Doses at extremes of body-weight**

To avoid excessive dosage in obese patients, dose may need to be calculated on the basis of ideal body-weight.

**Marcaine Heavy**

**Intrathecal anaesthesia for surgery**

- Adult: 10–20 mg

**Important safety information**

The licensed doses stated may not be appropriate in some settings and expert advice should be sought. Should only be administered by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management, and should not be administered parenterally unless adequate resuscitation equipment is available.

**Contra-indications**

Application to the middle ear (can cause ototoxicity). Avoid injection into infected tissues. Avoid injection into inflamed tissues. Complete heart block - preparations containing preservatives should not be used for caudal, epidural, or spinal block, or for intravenous regional anaesthesia (Bier's block) - should not be applied to damaged skin.

**Contra-indications, further information**

**Injection site**

Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin. Increased absorption into the blood increases the possibility of systemic side-effects, and the local anaesthetic effect may also be reduced by altered local pH.

**Cautions**

- Cardiovascular disease - cerebral atheroma - debilitated patients (consider dose reduction) - elderly (consider dose reduction) - epilepsy - hypertension - hypotension - hypovolaemia - impaired cardiac conduction - impaired respiratory function - myasthenia gravis - myocardial depression may be more severe and more resistant to treatment - shock

**Interactions**

- Appendix 1 (bupivacaine).

**Side-effects**

- Arrhythmias - blurred vision - cardiac arrest - convulsions - dizziness - drowsiness - feeling of inebriation - headache - lightheadedness - muscle twitching - myocardial depression (resulting in hypotension and bradycardia) - nausea - numbness of the tongue and perioral region - paraesthesia (including sensations of hot and cold) - peripheral vasodilatation (resulting in hypotension and bradycardia) - restlessless - tinnitus - transient excitation (followed by depression with drowsiness, respiratory failure, unconsciousness, and coma) - tremors - vomiting

**Side-effects, further information**

**Toxic effects**

Toxic effects after administration of local anaesthetics are a result of excessively high plasma concentrations; severe toxicity usually results from inadvertent intravascular injection or too rapid injection. Following most regional anaesthetic procedures, maximum arterial plasma concentration of anaesthetic develops within about 10 to 25 minutes, so careful surveillance for toxic effects is necessary during the first 30 minutes after injection. The systemic toxicity of local anaesthetics mainly involves the central nervous and cardiovascular systems.

**Allergy and cross-sensitivity**

Hypersensitivity reactions occur mainly with the ester-type local anaesthetics, such as tetracaine and chloroprocaine; reactions are less frequent with the amide types, such as articaine, bupivacaine, levobupivacaine, lidocaine, mepivacaine, prilocaine, and ropivacaine. Cross-
sensitivity reactions may be avoided by using the alternative chemical type.

- **PREGNANCY** Use lower doses for intrathecal use during late pregnancy. Large doses during delivery can cause neonatal respiratory depression, hypotonia, and bradycardia after epidural block.

- **BREAST FEEDING** Amount too small to be harmful.

- **HEPATIC IMPAIRMENT** Use with caution in severe impairment.

- **RENAL IMPAIRMENT** Use with caution in severe impairment.

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, infusion, solution for infusion

**Solution for injection**

- **BUPIVACAINE HYDROCHLORIDE (Non-proprietary)**
  - Bupivacaine hydrochloride 2.5 mg per 1 ml Bupivacaine 0.25% solution for injection 10ml Sure-Amp ampoules | 20 ampoule P<sub>FP</sub> £17.50
  - Bupivacaine hydrochloride 5 mg per 1 ml Bupivacaine 0.5% solution for injection 10ml Sure-Amp ampoules | 20 ampoule P<sub>FP</sub> £18.30
  - Bupivacaine 50mg/10ml (0.5%) solution for injection ampoules | 10 ampoule P<sub>FP</sub> no price available
  - **Marcain** (AstraZeneca UK Ltd)
    - Bupivacaine hydrochloride 2.5 mg per 1 ml Marcain 0.25% solution for injection 10ml Polyamp Steripack ampoules | 5 ampoule P<sub>FP</sub> £9.25
    - Bupivacaine hydrochloride 5 mg per 1 ml Marcain 0.5% solution for injection 10ml Polyamp Steripack ampoules | 5 ampoule P<sub>FP</sub> £9.25

**Infusion**

- **BUPIVACAINE HYDROCHLORIDE (Non-proprietary)**
  - Bupivacaine hydrochloride 1 mg per 1 ml Bupivacaine 100mg/100ml (0.1%) infusion bags | 20 bag P<sub>FP</sub> no price available
  - Bupivacaine 250mg/250ml (0.1%) infusion bags | 20 bag P<sub>FP</sub> no price available
  - **Marcain** Bupivacaine hydrochloride 1.25 mg per 1 ml Bupivacaine 312.5mg/250ml (0.125%) infusion bags | 20 bag P<sub>FP</sub> no price available

Bupivacaine with adrenaline

The properties listed below are those particular to the combination only. For the properties of the components please consider, adrenaline/epinephrine p. 196, bupivacaine hydrochloride p. 1113.

**INDICATIONS AND DOSE**

- **Surgical anaesthesia**
  - BY LUMBAR EPIDURAL OR BY LOCAL INFILTRATION OR BY CAUDAL EPIDURAL
    - Adult: (consult product literature)
  - Acute pain management
    - BY LUMBAR EPIDURAL OR BY LOCAL INFILTRATION
    - Adult: (consult product literature)

- **CAUTIONS**

**CAUTIONS, FURTHER INFORMATION**

In patients with severe hypertension or unstable cardiac rhythm, the use of adrenaline with a local anaesthetic may be hazardous. For these patients an anaesthetic without adrenaline should be used.

**MEDICINAL FORMS**

- **Solutions for injection**
  - **ADRENALINE WITH BUPIVACAINE (Non-proprietary)**
    - Adrenaline (as Adrenaline acid tartrate) 5 microgram per 1 ml, Bupivacaine hydrochloride 2.5 mg per 1 ml Bupivacaine

**INDICATIONS AND DOSE**

**Chloroprocaine hydrochloride**

**Indications and dose**

**Intrathecal anaesthesia for surgical procedures lasting up to 40 minutes**

**By slow intrathecal injection**

- **Adult:** 40–50 mg, dose depends on desired length of block

**Doses at extremes of body-weight**

To avoid excessive dosage in obese patients, dose may need to be calculated on the basis of ideal body-weight.

**Important safety information**

The licensed doses stated above may not be appropriate in some settings and expert advice should be sought. Should only be administered by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management, and should not be administered parenterally unless adequate resuscitation equipment is available.

- **CONTRA-INDICATIONS** Application to the middle ear (can cause ototoxicity) • avoid injection into infected tissues • avoid injection into inflamed tissues • complete heart block • preparations containing preservatives should not be used for caudal, epidural, or spinal block, or for intravenous regional anaesthesia (Bier’s block) • severe anaemia • should not be applied to damaged skin

**CONTRA-INDICATIONS, FURTHER INFORMATION**

**Injection site** Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin. Increased absorption into the blood increases the possibility of systemic side-effects, and the local anaesthetic effect may also be reduced by altered local pH.

**CAUTIONS**

- Acute porphyrias p. 864 • cardiovascular disease • debilitated patients (consider dose reduction) • elderly (consider dose reduction) • epilepsy • hypoclovaemia • impaired cardiac conduction • impaired respiratory function • myasthenia gravis • shock

**INTERACTIONS** → Appendix 1 (chloroprocaine).

**SIDE-EFFECTS**

- **Uncommon** Hypertension

**Frequency not known** Arrhythmias • blurred vision • cardiac arrest • convulsions • dizziness • drowsiness • feeling of inebriation • headache • lightheadedness • muscle twitching • myocardial depression (resulting in hypotension and bradycardia) • nausea • numbness of the tongue and perioral region • paraesthesia (including sensations of hot and cold) • peripheral vasodilatation (resulting in hypotension and bradycardia) • restlessness • tinnitus • transient excitation (followed by depression with drowsiness, respiratory failure, unconsciousness, and coma) • tremors • vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

**Toxic effects**

Toxic effects after administration of local anaesthetics are a result of excessively high plasma concentrations; severe toxicity usually results from inadvertent intravascular injection or too rapid injection. Following most regional anaesthetic procedures, maximum arterial plasma concentration of anaesthetic develops within about 10 to 25 minutes, so careful
surveillance for toxic effects is necessary during the first 30 minutes after injection. The systemic toxicity of local anaesthetics mainly involves the central nervous and cardiovascular systems.

- **ALLERGY AND CROSS-SENSITIVITY** Hypersensitivity reactions occur mainly with the ester-type local anaesthetics, such as tetracaine and chloroprocaine; reactions are less frequent with the amide types, such as articaine, bupivacaine, levobupivacaine, lidocaine, mepivacaine, prilocaine, and ropivacaine. Cross-sensitivity reactions may be avoided by using the alternative chemical type.

- **PREGNANCY** Avoid—no information available.

- **BREAST FEEDING** Avoid—no information available.

- **HEPATIC IMPAIRMENT** Use with caution in severe impairment.

- **RENAL IMPAIRMENT** Use with caution in severe impairment.

- **MEDICINAL FORMS**
  There can be variation in the licensing of different medicines containing the same drug.

  **Solution for injection**
  - **Ampres (AMCo)**
    Chloroprocaine hydrochloride 10 mg per 1 ml Ampres 50mg/5ml solution for injection ampoules | 10 ampoule PBO £87.50

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**Levobupivacaine**

### INDICATIONS AND DOSE

**Acute postoperative pain**

- **BY CONTINUOUS EPIDURAL INFUSION**
  - Adult: 12.5–18.75 mg/hour, dose administered using a 1.25 mg/mL (0.125%) or 2.5 mg/mL (0.25%) solution; maximum 400 mg per day

- **Acute labour pain**
  - **INITIALLY BY LUMBAR EPIDURAL**
    - Adult: 15–25 mg every 15 minutes as required, dose administered using a 2.5 mg/mL (0.25%) solution, alternatively (by continuous epidural infusion) 5–12.5 mg/hour, dose administered using a 1.25 mg/mL (0.125%) solution

- **Surgical anaesthesia, peripheral nerve block**
  - **BY REGIONAL ADMINISTRATION**
    - Adult: 2.5–150 mg, dose administered using a 2.5 mg/mL (0.25%) or 5 mg/mL (0.5%) solution

- **Surgical anaesthesia, peribulbar nerve block**
  - **BY REGIONAL ADMINISTRATION**
    - Adult: 7.5–112.5 mg, dose administered using a 7.5 mg/mL (0.75%) solution

- **Surgical anaesthesia for caesarean section**
  - **BY LUMBAR EPIDURAL**
    - Adult: 75–150 mg, to be given over 15–20 minutes, dose administered using a 5 mg/mL (0.5%) solution

- **Surgical anaesthesia**
  - **BY LUMBAR EPIDURAL**
    - Adult: 50–150 mg, to be given over 5 minutes, dose administered using a 5 mg/mL (0.5%) or 7.5 mg/mL (0.75%) solution
  - **BY INTRATHecal INJECTION**
    - Adult: 15 mg, dose administered using a 5 mg/mL (0.5%) solution
  - **BY LOCAL INFILTRATION**
    - Adult: 2.5–150 mg, dose administered using a 2.5 mg/mL (0.25%) solution

### Doses at extremes of body-weight

To avoid excessive dosage in obese patients, dose may need to be calculated on the basis of ideal body-weight.

#### Important safety information

The licensed doses stated may not be appropriate in some settings and expert advice should be sought. Should only be administered by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management, and should not be administered parenterally unless adequate resuscitation equipment is available.

- **CONTRA-INDICATIONS** Application to the middle ear (can cause ototoxicity) - avoid injection into infected tissues - avoid injection into inflamed tissues - complete heart block - preparations containing preservatives should not be used for caudal, epidural, or spinal block, or for intravenous regional anaesthesia (Bier’s block) - should not be applied to damaged skin

- **CONTRA-INDICATIONS, FURTHER INFORMATION**

- **Injection site** Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin. Increased absorption into the blood increases the possibility of systemic side-effects, and the local anaesthetic effect may also be reduced by altered local pH.

- **CAUTIONS** Cardiovascular disease - debilitated patients (consider dose reduction) - elderly (consider dose reduction) - epilepsy - hypovolaemia - impaired cardiac conduction - impaired respiratory function - myasthenia gravis - shock

- **INTERACTIONS** → Appendix 1 (levobupivacaine).

- **SIDE-EFFECTS** Anaemia - arrhythmias - blurred vision - cardiac arrest - convulsions - dizziness - drowsiness - feeling of inebriation - headache - lightheadedness - muscle twitching - myocardial depression (resulting in hypotension and bradycardia) - nausea - numbness of the tongue and perioral region - paraesthesia (including sensations of hot and cold) - peripheral vasodilatation (resulting in hypotension and bradycardia) - pyrexia - restlessness - sweating - tinnitus - transient excitation (followed by depression with drowsiness, respiratory failure, unconsciousness, and coma) - tremors - vomiting

#### SIDE-EFFECTS, FURTHER INFORMATION

**Toxic effects** Toxic effects after administration of local anaesthetics are a result of excessively high plasma concentrations; severe toxicity usually results from inadvertent intravascular injection or too rapid injection. Following most regional anaesthetic procedures, maximum arterial plasma concentration of anaesthetic develops within about 10 to 25 minutes, so careful surveillance for toxic effects is necessary during the first 30 minutes after injection. The systemic toxicity of local anaesthetics mainly involves the central nervous and cardiovascular systems.

- **ALLERGY AND CROSS-SENSITIVITY** Hypersensitivity reactions occur mainly with the ester-type local anaesthetics, such as tetracaine and chloroprocaine; reactions are less frequent with the amide types, such as articaine, bupivacaine, levobupivacaine, lidocaine, mepivacaine, prilocaine, and ropivacaine. Cross-sensitivity reactions may be avoided by using the alternative chemical type.

- **PREGNANCY** Large doses during delivery can cause neonatal respiratory depression, hypotonia, and bradycardia after epidural block. Avoid if possible in the first trimester— toxicity in animal studies. May cause fetal
1116 Local anaesthesia

**Lidocaine hydrochloride**
(Lignocaine hydrochloride)

**INDICATIONS AND DOSE**

Dental practice
- **BY BUCCAL ADMINISTRATION USING OINTMENT**
  - Adult: Rub gently into dry gum

Infiltration anaesthesia
- **BY LOCAL INfiltrATION**
  - Adult: Dose to be given according to patient’s weight and nature of procedure; max. 200 mg, maximum dose 500 mg if given in solutions containing adrenaline

Intravenous regional anaesthesia and nerve block
- Adult: Seek expert advice

Pain relief (in anal fissures, haemorrhoids, pruritis ani, pruritis vulvae, herpes zoster, or herpes labialis)
- Lubricant in cystoscopy | Lubricant in proctoscopy | Lubricant in cystoscopy | Lubricant in proctoscopy

TO THE SKIN USING OINTMENT
- Adult: Apply 1–2 mL as required, avoid long-term use

Sore nipples from breast-feeding
- TO THE SKIN USING OINTMENT
- Adult: Apply using gauze and wash off immediately before next feed

LARYNGOJECT®

Anaesthesia of mucous membranes of oropharynx, trachea, or respiratory tract
- **TO MUCOUS MEMBRANES**
  - Adult: 40–200 mg, to be given as a single dose sprayed, instilled (if a cavity), or applied with a swab (reduce dose according to size, age and condition of patient); usual dose 160 mg

**CONTRA-INDICATIONS**

GENERAL CONTRA-INDICATIONS
All grades of atrioventricular block - severe myocardial depression - sino-atrial disorders

SPECIFIC CONTRA-INDICATIONS
- When used by regional administration Application to the middle ear (can cause ototoxicity) - avoid injection into infected tissues - avoid injection into inflamed tissues -
preparations containing preservatives should not be used for caudal, epidural, or spinal block, or for intravenous regional anaesthesia (Bier’s block). Severe myocardial depression should not be applied to damaged skin.

**CONTRA-INDICATIONS, FURTHER INFORMATION**

- **Injection site** Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin. Increased absorption into the blood increases the possibility of systemic side-effects, and the local anaesthetic effect may also be reduced by altered local pH.

**SIDE-EFFECTS**

- With intravenous use Acute porphyria (consider infusion with glucose for its anti-porphyrinogenic effects) - congestive cardiac failure (consider lower dose) - post cardiac surgery (consider lower dose).
- When used by regional administration Acute porphyria (consider infusion with glucose for its anti-porphyrinogenic effects) - congestive cardiac failure (consider lower dose) - post cardiac surgery (consider lower dose) - debilitated patients (consider dose reduction) - elderly (consider dose reduction) - epilepsy - hypovolaemia - impaired cardiac conduction - impaired respiratory function - myasthenia gravis - shock.
- With oral (topical) use Avoid anaesthesia of the pharynx before meals - risk of choking - can damage plastic cuffs of endotracheal tubes.

**INTERACTIONS** → Appendix 1 (lidocaine). Interactions less likely when lidocaine used topically.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, gel, ointment, spray. There may be variation in licensing of different medicines.

**SIDE-EFFECTS, FURTHER INFORMATION**

**Topical application** A single application of a topical lidocaine preparation does not generally cause systemic side-effects.

**Toxic effects** Toxic effects after administration of local anaesthetics are a result of excessively high plasma concentrations; severe toxicity usually results from inadvertent intravascular injection or too rapid injection. Following most regional anaesthetic procedures, maximum arterial plasma concentration of anaesthetic develops within about 10 to 25 minutes, so careful surveillance for toxic effects is necessary during the first 30 minutes after injection. The systemic toxicity of local anaesthetics mainly involves the central nervous and cardiovascular systems.

**Methaemoglobinemia** Methaemoglobinemia can be treated with an intravenous injection of methylnitroimine chloride; neonates and infants under 6 months are particularly susceptible to methaemoglobinemia.

**Allergy and Cross-Sensitivity** Hypersensitivity reactions occur mainly with the ester-type local anaesthetics, such as tetracaine and chloroprocaine; reactions are less frequent with the amide types, such as articaine, bupivacaine, levobupivacaine, lidocaine, mepivacaine, prilocaine, and ropivacaine. Cross-sensitivity reactions may be avoided by using the alternative chemical type.

**Pregnancy** Crosses the placenta but not known to be harmful in animal studies - use if benefit outweighs risk. When used as a local anaesthetic, large doses can cause fetal bradycardia; if given during delivery can also cause neonatal respiratory depression, hypotonia, or bradycardia after paradigm. May be harmful.

**Breast Feeding** Present in milk but amount too small to be harmful.

**Hepatic Impairment** Caution - increased risk of side-effects.

**Renal Impairment** Possible accumulation of lidocaine and active metabolite; caution in severe impairment.

**Profession Specific Information**

**Dental practitioners’ formulary** Lidocaine ointment 5% may be prescribed. Spray may be prescribed as Lidocaine Spray 10%.

**Scottish Medicines Consortium (SMC) Decisions**

The Scottish Medicines Consortium has advised (July 2008) that Versatis® is accepted for restricted use within NHS Scotland for the treatment of postherpetic neuralgia in patients who are intolerant of first-line systemic therapies or when they have been ineffective.

**Solution for injection**

- **LIDOCAINE HYDROCHLORIDE (Non-proprietary)**
  - Lidocaine hydrochloride 5 mg per 1 ml Lidocaine 50mg/10ml (0.5%) solution for injection ampoules | 10 ampoule (£0.70)
  - Lidocaine hydrochloride 10 mg per 1 ml Lidocaine 100mg/10ml (1%) solution for injection ampoules | 10 ampoule (£1.00) Lidocaine 100mg/10ml (1%) solution for injection ampoules | 10 ampoule (£4.50) DT price = £4.01 Lidocaine 100mg/10ml (1%) solution for injection ampoules | 10 ampoule (£8.80) Lidocaine 200mg/20ml (1%) solution for injection vials | 10 vial (£8.98) Lidocaine 200mg/20ml (1%) solution for injection vials | 10 vial (£18.00–£19.00) Lidocaine 200mg/20ml (1%) solution for injection ampoules | 10 ampoule (£7.00) Lidocaine 200mg/20ml (1%) solution for injection vials | 10 ampoule (£8.80) Lidocaine 200mg/20ml (1%) solution for injection ampoules | 10 ampoule (£10.00) £7.00–£8.50 Lidocaine 50mg/5ml (1%) solution for injection ampoules | 10 ampoule (£2.35–£3.10) DT price = £2.38 Lidocaine 200mg/20ml (1%) solution for injection ampoules | 10 ampoule (£3.50) DT price = £2.00 Lidocaine 50mg/5ml (1%) solution for injection ampoules | 20 ampoule (£6.00) Lidocaine hydrochloride 20 mg per 1 ml Lidocaine 100mg/5ml (2%) solution for injection ampoules | 10 ampoule (£2.43) Lidocaine 400mg/20ml (2%) solution for injection ampoules | 10 ampoule (£4.00–£4.50) Lidocaine 200mg/10ml (2%) solution for injection ampoules | 10 ampoule (£8.00–£9.50) Lidocaine 200mg/10ml (2%) solution for injection ampoules | 20 ampoule (£14.52) £11.00–£12.50 Lidocaine 400mg/20ml (2%) solution for injection ampoules | 10 ampoule (£2.13) Lidocaine 50mg/5ml (2%) solution for injection ampoules | 20 ampoule (£6.00) Lidocaine 400mg/20ml (2%) solution for injection ampoules | 10 ampoule (£8.00–£10.00) DT price = £9.07

**BNF 70**

**Local anaesthesia 1117**

**Anesthesia**

**Versatis®**
Lidocaine with adrenaline

The properties listed below are those particular to the combination only. For the properties of the components please consider, adrenaline hydrochloride p. 1116, lidocaine hydrochloride p. 1116.

INDICATIONS AND DOSE
Anaesthesia before minor skin procedures including venepuncture

TO THE SKIN
- Child 1-2 months: Apply up to 1 g for maximum 1 hour before procedure, to be applied under occlusive dressing, shorter application time of 15–30 minutes is recommended for children with atopic dermatitis (30 minutes before removal of mollusca); maximum 1 dose per day
- Child 3-11 months: Apply up to 2 g for maximum 4 hours before procedure, to be applied under occlusive dressing, shorter application time of 15–30 minutes is recommended for children with atopic dermatitis (30 minutes before removal of mollusca); maximum 2 doses per day
- Child 11-1 years: Apply 1–5 hours before procedure (2–5 hours before procedures on large areas e.g. split skin grafting), a thick layer should be applied under occlusive dressing, shorter application time of 15–30 minutes is recommended for children with atopic dermatitis (30 minutes before removal of mollusca); maximum 2 doses per day
- Child 12-17 years: Apply 1–5 hours before procedure (2–5 hours before procedures on large areas e.g. split skin grafting), a thick layer should be applied under occlusive dressing, shorter application time of 15–30 minutes is recommended for children with atopic dermatitis (30 minutes before removal of mollusca)
- Adult: Apply 1–5 hour before procedure (2–5 hours before procedures on large areas e.g. split skin grafting), a thick layer should be applied under occlusive dressing

Anaesthesia on genital skin before injection of local anaesthetics

TO THE SKIN
- Adult: Apply for 15 minutes (in adult men) and 60 minutes (in adult women), to be applied under occlusive dressing

Lidocaine with phenylephrine

The properties listed below are those particular to the combination only. For the properties of the components please consider, lidocaine hydrochloride p. 1116, phenylephrine hydrochloride p. 166.

INDICATIONS AND DOSE
Anaesthesia before nasal surgery, endoscopy, laryngoscopy, or removal of foreign bodies from the nose

BY INTRanasal ADMINISTRATION
- Adult: Up to 8 sprays

MEDICINAL FORMS
There can be variation in the licensing of different medicines containing the same drug.

Spray
- LIDOCAINE WITH PHENYLEPHRINE (Non-proprietary)
  Lidocaine hydrochloride 50 mg per 1 ml, Phenylephrine hydrochloride 5 mg per 1 ml Lidocaine 5% / Phenylephrine 0.5% nasal spray | 2.5 ml | £11.48

Lidocaine with prilocaine

The properties listed below are those particular to the combination only. For the properties of the components please consider, lidocaine hydrochloride p. 1116, prilocaine hydrochloride p. 1120.

INDICATIONS AND DOSE
Anaesthesia before minor skin procedures including venepuncture
Local anaesthesia

**Anaesthesia before surgical treatment of lesions on genital mucosa**

**TO THE SKIN**
- Adult: Apply up to 10 g, to be applied 5–10 minutes before procedure

**Anaesthesia before cervical curettage**

**TO THE SKIN**
- Adult: Apply 10 g in lateral vaginal fornices for 10 minutes

**Anaesthesia before mechanical cleansing or debridement of leg ulcer**

**TO THE SKIN**
- Adult: Apply up to 10 g for 30–60 minutes, to be applied under occlusive dressing

- **CONTRA-INDICATIONS** Use in child less than 37 weeks corrected gestational age
- **PATIENT AND CARER ADVICE** Medicines for Children leaflet: EMLA cream for local anaesthesia www.medicinesforchildren.org.uk/emla-cream-for-local-anaesthesia

- **MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.
  - **Cream**
    - LIDOCAINE WITH PRIOLOCAINE (Non-proprietary)
      - Lidocaine 25 mg per 1 gram, Prilocaine 25 mg per 1 gram
        - Lidocaine 2.5% / Prilocaine 2.5% cream | 5 gram [P] no price available
        - Emla (AstraZeneca UK Ltd)
      - Lidocaine 25 mg per 1 gram, Prilocaine 25 mg per 1 gram Emla
        - 5% cream | 5 gram [P] £2.25–£2.99 | 25 gram [P] £11.70 |
        - 30 gram [P] £12.30
    - Brands may include Denela

**Lidocaine with tetracaine**

The properties listed below are those particular to the combination only. For the properties of the components please consider, lidocaine hydrochloride p. 1116, tetracaine p. 1122.

- **INDICATIONS AND DOSE**
  - Anaesthesia before dermatological procedures and venepuncture
    - **TO THE SKIN**
      - Adult: Apply 1 mm layer using a spatula 30 minutes before procedure; then peel off immediately before procedure; max. application area 400 cm², application time of 60 minutes indicated for certain procedures, such as laser-assisted tattoo removal and laser leg vein ablation

- **MEDICINAL FORMS**
  - There can be variation in the licensing of different medicines containing the same drug.
  - **Cream**
    - EXCIPIENTS: May contain Hydroxybenzoates (parabens)
      - Plaglis (Galderma (UK) Ltd)
      - Lidocaine 70 mg, Tetracaine 70 mg Plaglis 70mg/g / 70mg/g cream | 15 gram [P] £22.95

**Mepivacaine hydrochloride**

- **INDICATIONS AND DOSE**
  - Infiltration anaesthesia and nerve block in dentistry
    - Child 3-17 years: Consult expert dental sources
    - Adult: Consult expert dental sources

**Doses at extremes of body-weight**

To avoid excessive dosage in obese patients, dose may need to be calculated on the basis of ideal body-weight.

- **CONTRA-INDICATIONS** Application to the middle ear (can cause ototoxicity) - avoid injection into infected tissues - avoid injection into inflamed tissues - complete heart block - preparations containing preservatives should not be used for caudal, epidural, or spinal block, or for intravenous regional anaesthesia (Bier’s block) - should not be applied to damaged skin

**CONTRA-INDICATIONS, FURTHER INFORMATION**

- **Injection site** Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to damaged skin. Increased absorption into the blood increases the possibility of systemic side-effects, and the local anaesthetic effect may also be reduced by altered local pH.

- **CAUTIONS** Cardiovascular disease - children (consider dose reduction) - debilitated patients (consider dose reduction) - elderly (consider dose reduction) - epilepsy - hypovolaemia - impaired cardiac conduction - impaired respiratory function - myasthenia gravis - shock

- **SIDE-EFFECTS** Arrhythmias - blurred vision - cardiac arrest - convulsions - dizziness - drowsiness - feeling of inebriation - headache - lightheadedness - muscle twitching - myocardial depression (resulting in hypotension and bradycardia) - nausea - numbness of the tongue and perioral region - paraesthesia (including sensations of hot and cold) - peripheral vasodilatation (resulting in hypotension and bradycardia) - restlessness - tinnitus - transient excitation (followed by depression with drowsiness, respiratory failure, unconsciousness, and coma) - tremors - vomiting

**SIDE-EFFECTS, FURTHER INFORMATION**

- **Toxic effects** Toxic effects after administration of local anaesthetics are a result of excessively high plasma concentrations; severe toxicity usually results from inadvertent intravascular injection or too rapid injection. Following most regional anaesthetic procedures, maximum arterial plasma concentration of anaesthetic develops within about 10 to 25 minutes, so careful surveillance for toxic effects is necessary during the first 30 minutes after injection. The systemic toxicity of local anaesthetics mainly involves the central nervous and cardiovascular systems.

- **ALLERGY AND CROSS-SENSITIVITY** Hypersensitivity reactions occur mainly with the ester-type local anaesthetics, such as tetracaine and chloroprocaine; reactions are less frequent with the amide types, such as articaine, bupivacaine, levobupivacaine, lidocaine, mepivacaine, prilocaine, and ropivacaine. Cross-sensitivity reactions may be avoided by using the alternative chemical type.

- **PREGNANCY** Use with caution in early pregnancy.

- **BREAST FEEDING** Use with caution.

- **HEPATIC IMPAIRMENT** Use with caution; increased risk of side-effects in severe impairment.

- **RENAI IMPAIRMENT** Use with caution; increased risk of side-effects.
**Mepivacaine with adrenaline**

The properties listed below are those particular to the combination only. For the properties of the components please consider, adrenaline/epinephrine p. 196, mepivacaine hydrochloride p. 1119.

### Indications and dose

**Infiltration anaesthesia and nerve block in dentistry**

**BY LOCAL INFILTRATION**

- **Adult:** consult product literature

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Scandonest plain (Deproco UK Ltd)
  - Mepivacaine hydrochloride 30 mg per 1 ml
- Scandonest special 2% solution for injection 2.2 ml cartridges
- Prioltekal

### CONTRA-INDICATIONS

- Acquired methaemoglobinaemia
- ▶️ By intrathecal injection

### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- Scandonest plain (Deproco UK Ltd)
  - Adrenaline 10 microgram per 1 ml, Mepivacaine hydrochloride 30 mg per 1 ml
- Scandonest special 2% solution for injection 2.2 ml cartridges

### Indications and dose

**Infiltration anaesthesia and nerve block in dentistry**

**BY LOCAL INFILTRATION**

- **Adult:** consult product literature

**SIDE-EFFECTS, FURTHER INFORMATION**

**Toxic effects**

Toxic effects after administration of local anaesthetics are a result of excessively high plasma concentrations; severe toxicity usually results from inadvertent intravascular injection or too rapid injection. Following most regional anaesthetic procedures, maximum arterial plasma concentration of anaesthetic develops within about 10 to 25 minutes, so careful surveillance for toxic effects is necessary during the first 30 minutes after injection. The systemic toxicity of local anaesthetics mainly involves the central nervous and cardiovascular systems.

**Methaemoglobinaemia**

Methaemoglobinaemia can be treated with an intravenous injection of methylthioninium chloride.

**Allergy and cross-sensitivity**

Reactions occur mainly with the ester-type local anaesthetics, such as tetracaine and chloroprocaine; reactions are less frequent with the amide types, such as mepivacaine, prilocaine, and ropivacaine. Cross-sensitivity reactions may be avoided by using the alternative chemical type.

**Pregnancy**

Use lower doses for intrathecal use during late pregnancy. Large doses during delivery can cause neonatal respiratory depression, hypotonia, and bradycardia after epidural block. Avoid paracervical or pudendal block in obstetrics (neonatal methaemoglobinaemia reported).

**Breast feeding**

Present in milk but not known to be harmful.

**Hepatic impairment**

Lower doses may be required for intrathecal anaesthesia. Use with caution.

**Renal impairment**

Lower doses may be required for intrathecal anaesthesia. Use with caution.

**National funding/access decisions**

**Prioltekal**

Scottish Medicines Consortium (SMC) Decisions

With intrathecal use The Scottish Medicines Consortium has advised (December 2010) that prilocaine 2% hyperbaric...
solution for injection (Prilokalc®) is accepted for restricted use within NHS Scotland for use in spinal anaesthesia in ambulatory surgery settings.

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

**Solution for injection**
- Citanest (AstraZeneca UK Ltd)
  Prilocaine hydrochloride 10 mg per 1 ml Citanest 3% solution for injection 50ml vials | 1 vial £5.06
- Prilokalc (AMCo)
  Prilocaine hydrochloride 20 mg per 1 ml Prilokalc 100mg/5ml solution for injection ampoules | 1 ampoule £78.75

**INDICATIONS AND DOSE**
Dental anaesthesia
- Adult: Consult expert dental sources for specific advice

**SIDE-EFFECTS**

**INTERACTIONS**

**CONTRA-INDICATIONS** Application to the middle ear (can cause ototoxicity). Avoid injection into infected tissues - avoid injection into inflamed tissues - complete heart block - preparations containing preservatives should not be used for caudal, epidural, or spinal block, or for intravenous regional anaesthesia (Bier’s block) - should not be applied to damaged skin

**CAUTIONS** Acute porphyrias p. 864 - cardiovascular disease - debilitated patients (consider dose reduction) - elderly (consider dose reduction) - epilepsy - hypovolaemia - impaired cardiac conduction - impaired respiratory function - myasthenia gravis - shock

**SIDE-EFFECTS**
- Common or very common - Hypertension - pyrexia
- Uncommon - Hypothermia - syncope
- Frequency not known - Arrhythmias - blurred vision - cardiac arrest - convulsions - dizziness - drowsiness - feeling of inebriation - headache - lightheadedness - muscle twitching - myocardial depression (resulting in hypotension and bradycardia) - nausea - numbness of the tongue and perioral region - paraesthesia (including sensations of hot and cold) - peripheral vasodilatation (resulting in hypotension and bradycardia) - restlessness - tinnitus - transient excitation (followed by depression with drowsiness, respiratory failure, unconsciousness, and coma) - tremors - vomiting

**Important safety information**
Should only be administered by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management, and should not be administered parenterally unless adequate resuscitation equipment is available.

**Ropivacaine hydrochloride**

**INDICATIONS AND DOSE**

**Acute pain, peripheral nerve block**
- Adult: 10–20 mg/hour, dose administered as a continuous infusion or by intermittent injection using a 2 mg/mL (0.2%) solution

**Acute pain, field block**
- Adult: 2–200 mg, dose administered using a 2 mg/mL (0.2%) solution

**Acute pain, lumbar epidural block**
- Adult: 20–40 mg, followed by 20–30 mg at least every 30 minutes, dose administered using a 2 mg/mL (0.2%) solution

**Acute labour pain**
- Adult: 12–20 mg/hour, dose administered using a 2 mg/mL (0.2%) solution

**Acute postoperative pain**
- Adult: Up to 28 mg/hour, dose administered using a 2 mg/mL (0.2%) solution

**Postoperative pain, thoracic epidural block**
- Adult: 12–28 mg/hour, dose administered using a 2 mg/mL (0.2%) solution

**Surgical anaesthesia, field block**
- Adult: 7.5–225 mg, dose administered using a 7.5 mg/mL (0.75%) solution

**Surgical anaesthesia, major nerve block (brachial plexus block)**
- Adult: 225–300 mg, dose administered using a 7.5 mg/mL (0.75%) solution

**Surgical anaesthesia, thoracic epidural block (to establish block for postoperative pain)**
- Adult: 38–113 mg, dose administered using a 7.5 mg/mL (0.75%) solution

**Surgical anaesthesia for caesarean section**
- Adult: 113–150 mg, to be administered in incremental doses using a 7.5 mg/mL (0.75%) solution

**Doses at extremes of body-weight**
To avoid excessive dosage in obese patients, dose may need to be calculated on the basis of ideal bodyweight.

**Prilocaine with felypressin**

The properties listed below are those particular to the combination only. For the properties of the components please consult, prilocaine hydrochloride p. 1120.

**Indications and dose**
Dental anaesthesia
- Adult: Consult expert dental sources for specific advice

**MEDICINAL FORMS**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- Citanest with Octapressin (Dentsply Ltd)
  Felypressin 0.03 unit per 1 ml, Prilocaine hydrochloride 30 mg per 1 ml Citanest 3% with Octapressin Dental 0.054 units/1.8 ml solution for injection self-aspirating cartridges | 100 cartridge £75.00
- Citanest 3% with Octapressin Dental 0.066 units/2.2 ml solution for injection self-aspirating cartridges | 100 cartridge £75.00

**Important safety information**
Should only be administered by, or under the direct supervision of, personnel experienced in their use, with adequate training in anaesthesia and airway management, and should not be administered parenterally unless adequate resuscitation equipment is available.
### Local anaesthesia

#### SIDE-EFFECTS, FURTHER INFORMATION

**Toxic effects**
Toxic effects after administration of local anaesthetics are a result of excessively high plasma concentrations; severe toxicity usually results from inadvertent intravascular injection or too rapid injection. Following most regional anaesthetic procedures, maximum arterial plasma concentration of anaesthetic develops within about 10 to 25 minutes, so careful surveillance for toxic effects is necessary during the first 30 minutes after injection. The systemic toxicity of local anaesthetics mainly involves the central nervous and cardiovascular systems.

- **ALLERGY AND CROSS-SENSITIVITY**
  Hypersensitivity reactions occur mainly with the ester-type local anaesthetics, such as tetracaine and chloroprocaine; reactions are less frequent with the amide types, such as articaine, bupivacaine, levobupivacaine, lidocaine, mepivacaine, prilocaine, and ropivacaine. Cross-sensitivity reactions may be avoided by using the alternative chemical type.

- **PREGNANCY**
  Not known to be harmful. Do not use for paracervical block in obstetrics.

- **BREAST FEEDING**
  Not known to be harmful.

- **HEPATIC IMPAIRMENT**
  Use with caution in severe impairment.

- **RENAL IMPAIRMENT**
  Caution in severe impairment. Increased risk of systemic toxicity in chronic renal failure.

#### MEDICINAL FORMS

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

<table>
<thead>
<tr>
<th>ELECTROLYTES: May contain Sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROPIVACAINE HYDROCHLORIDE (Non-proprietary)</td>
</tr>
<tr>
<td>Ropivacaine hydrochloride 2 mg per 1 ml Ropivacaine 20mg/10ml solution for injection ampoules</td>
</tr>
<tr>
<td>Ropivacaine hydrochloride 7.5 mg per 1 ml Ropivacaine 75mg/10ml solution for injection ampoules</td>
</tr>
<tr>
<td>Ropivacaine hydrochloride 10 mg per 1 ml Ropivacaine 100mg/10ml solution for injection ampoules</td>
</tr>
<tr>
<td>Naropin (AstraZeneca UK Ltd)</td>
</tr>
<tr>
<td>Ropivacaine hydrochloride 2 mg per 1 ml Naropin 20mg/10ml solution for injection ampoules</td>
</tr>
<tr>
<td>Ropivacaine hydrochloride 7.5 mg per 1 ml Naropin 75mg/10ml solution for injection ampoules</td>
</tr>
<tr>
<td>Ropivacaine hydrochloride 10 mg per 1 ml Naropin 100mg/10ml solution for injection ampoules</td>
</tr>
</tbody>
</table>

**Infusion**

<table>
<thead>
<tr>
<th>ELECTROLYTES: May contain Sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROPIVACAINE HYDROCHLORIDE (Non-proprietary)</td>
</tr>
<tr>
<td>Ropivacaine hydrochloride 2 mg per 1 ml Ropivacaine 400mg/200ml infusion bags</td>
</tr>
<tr>
<td>Naropin (AstraZeneca UK Ltd)</td>
</tr>
<tr>
<td>Ropivacaine hydrochloride 2 mg per 1 ml Naropin 400mg/200ml infusion Polybags</td>
</tr>
</tbody>
</table>

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**Tetracaine**  
*(Amethocaine)*

#### INDICATIONS AND DOSE

**Anaesthesia before venepuncture or venous cannulation**

- **Child 1 month-4 years:** Apply contents of up to 1 tube (applied at separate sites at a single time or appropriate proportion) to site of venepuncture or venous cannulation and cover with occlusive dressing; remove gel and dressing after 30 minutes for venepuncture and after 45 minutes for venous cannulation

#### PATIENT AND CARER ADVICE

**Mediterranean forms**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: cream

**Gel**

<table>
<thead>
<tr>
<th>EXCIPIENTS: May contain Hydroxybenzoates (parabens)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ametop 4% gel</td>
</tr>
</tbody>
</table>

Also available in combination with *lidocaine*, p. 1119

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### Venepuncture and after 45 minutes for venous cannulation

- **Child 5-17 years:** Apply contents of up to 5 tubes (applied at separate sites at a single time or appropriate proportion) to site of venepuncture or venous cannulation and cover with occlusive dressing; remove gel and dressing after 30 minutes for venepuncture and after 45 minutes for venous cannulation

#### CONTRA-INDICATIONS

Should not be applied to damaged skin.

#### SIDE-EFFECTS

Local skin reactions

**SIDE-EFFECTS, FURTHER INFORMATION**

The systemic toxicity of local anaesthetics mainly involves the central nervous and cardiovascular systems; systemic side effects unlikely as minimal absorption following topical application.

- **ALLERGY AND CROSS-SENSITIVITY**
  Hypersensitivity reactions occur mainly with the ester-type local anaesthetics, such as tetracaine and chloroprocaine; reactions are less frequent with the amide types, such as articaine, bupivacaine, levobupivacaine, lidocaine, mepivacaine, prilocaine, and ropivacaine. Cross-sensitivity reactions may be avoided by using the alternative chemical type.

- **BREAST FEEDING**
  Not known to be harmful.

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**Tetracaine**

*Amethocaine*
Chapter 16
Emergency treatment of poisoning

CONTENTS
1 Active elimination from the gastro-intestinal tract page 1130
2 Chemical toxicity 1131
  2.1 Cyanide toxicity 1131
  2.2 Organophosphorous toxicity 1131
3 Drug toxicity 1132
  3.1 Benzodiazepine toxicity 1132
3.2 Digoxin toxicity 1132
3.3 Heparin toxicity 1133
3.4 Opioid toxicity 1133
3.5 Paracetamol toxicity 1134
4 Methaemoglobinemia 1135
5 Snake bites 1136

Emergency treatment of poisoning

These notes provide only an overview of the treatment of poisoning, and it is strongly recommended that either TOXBASE or the UK National Poisons Information Service be consulted when there is doubt about the degree of risk or about management.

Hospital admission
Patients who have features of poisoning should generally be admitted to hospital. Patients who have taken poisons with delayed action should also be admitted, even if they appear well. Delayed-action poisons include aspirin p. 104, iron, paracetamol p. 354, tricyclic antidepressants, and co-phenotrope p. 55 (diphenoxylate with atropine, Lomotil®); the effects of modified-release preparations are also delayed. A note of all relevant information, including what treatment has been given, should accompany the patient to hospital.

Further information
TOXBASE, the primary clinical toxicology database of the National Poisons Information Service, is available on the internet to registered users at www.toxbase.org (a backup site is available at www.toxbasebackup.org if the main site cannot be accessed). It provides information about routine diagnosis, treatment, and management of patients exposed to drugs, household products, and industrial and agricultural chemicals.

Specialist information and advice on the treatment of poisoning is available day and night from the UK National Poisons Information Service on the following number:
Tel: 0844 892 0111.

Advice on laboratory analytical services can be obtained from TOXBASE or from the National Poisons Information Service. Help with identifying capsules or tablets may be available from a regional medicines information centre or from the National Poisons Information Service (out of hours).

General care
It is often impossible to establish with certainty the identity of the poison and the size of the dose. This is not usually important because only a few poisons (such as opioids, paracetamol p. 354, and iron) have specific antidotes; few patients require active removal of the poison. In most patients, treatment is directed at managing symptoms as they arise. Nevertheless, knowledge of the type and timing of poisoning can help in anticipating the course of events. All relevant information should be sought from the poisoned individual and from carers or parents. However, such information should be interpreted with care because it may not be complete or entirely reliable. Sometimes symptoms arise from other illnesses and patients should be assessed carefully. Accidents may involve domestic and industrial products (the contents of which are not generally known). The National Poisons Information Service should be consulted when there is doubt about any aspect of suspected poisoning.

Respiration
Respiration is often impaired in unconscious patients. An obstructed airway requires immediate attention. In the absence of trauma, the airway should be opened with simple measures such as chin lift or jaw thrust. An oropharyngeal or nasopharyngeal airway may be useful in patients with reduced consciousness to prevent obstruction, provided ventilation is adequate. Intubation and ventilation should be considered in patients whose airway cannot be protected or who have respiratory acidosis because of inadequate ventilation; such patients should be monitored in a critical care area.

Most poisons that impair consciousness also depress respiration. Assisted ventilation (either mouth-to-mouth or using a bag-valve-mask device) may be needed. Oxygen is not a substitute for adequate ventilation, although it should be given in the highest concentration possible in poisoning with carbon monoxide and irritant gases.

Blood pressure
Hypotension is common in severe poisoning with central nervous system depressants. A systolic blood pressure of less than 70 mmHg may lead to irreversible brain damage or renal tubular necrosis. Hypotension should be corrected initially by raising the foot of the bed and administration of an infusion of either sodium chloride p. 851 or a colloid. Vasoconstrictor sympathomimetics are rarely required and their use may be discussed with the National Poisons Information Service.

Fluid depletion without hypotension is common after prolonged coma and after aspirin p. 104 poisoning due to vomiting, sweating, and hyperpnoea.

Hypertension, often transient, occurs less frequently than hypotension in poisoning; it may be associated with sympathomimetic drugs such as amphetamines, phencyclidine, and cocaine.

Heart
Cardiac conduction defects and arrhythmias can occur in acute poisoning, notably with tricyclic antidepressants, some antipsychotics, and some antihistamines. Arrhythmias
often respond to correction of underlying hypoxia, acidosis, or other biochemical abnormalities, but ventricular arrhythmias that cause serious hypotension require treatment. If the QT interval is prolonged, specialist advice should be sought because the use of some anti-arrhythmic drugs may be inappropriate. Supraventricular arrhythmias are seldom life-threatening and drug treatment is best withheld until the patient reaches hospital.

**Body temperature**

Hypothermia may develop in patients of any age who have been deeply unconscious for some hours, particularly following overdose with barbiturates or phenothiazines. It may be missed unless core temperature is measured using a low-reading rectal thermometer or by some other means. Hypothermia should be managed by prevention of further heat loss and appropriate re-warming as clinically indicated. Hypothermia can develop in patients taking CNS stimulants; children and the elderly are also at risk when taking therapeutic doses of drugs with antimuscarinic properties. Hyperthermia is initially managed by removing all unnecessary clothing and using a fan. Sponging with tepid water will promote evaporation. Advice should be sought from the National Poisons Information Service on the management of severe hyperthermia resulting from conditions such as the serotonin syndrome. Both hypothermia and hyperthermia require urgent hospitalisation for assessment and supportive treatment.

**Convulsions**

Single short-lived convulsions (lasting less than 5 minutes) do not require treatment. If convulsions are protracted or recur frequently, lorazepam p. 412 or diazepam p. 267 (preferably as emulsion) should be given by slow intravenous injection into a large vein. Benzodiazepines should not be given by the intramuscular route for convulsions. If the intravenous route is not readily available, midazolam oromucosal solution p. 414 [unlicensed use in adults and children under 3 months] can be given by the buccal route or diazepam can be administered as a rectal solution.

**Methaemoglobinemia**

Drug- or chemical-induced methaemoglobinemia should be treated with methylene blue chloride p. 1135 if the methylene blue concentration is 30% or higher, or if symptoms of tissue hypoxia are present despite oxygen therapy. Methylene blue chloride reduces the ferric iron of methaemoglobin back to the ferrous iron of haemoglobin; in high doses, methylene blue chloride can itself cause methaemoglobinemia.

**Removal and elimination**

**Prevention of absorption**

Given by mouth, activated charcoal p. 1130 can bind many poisons in the gastro-intestinal system, thereby reducing their absorption. The sooner it is given the more effective it is, but it may still be effective up to 1 hour after ingestion of the poison—longer in the case of modified-release preparations or of drugs with antimuscarinic (anticholinergic) properties. It is particularly useful for the prevention of absorption of poisons that are toxic in small amounts, such as antidepressants.

**Active elimination techniques**

Repeated doses of activated charcoal by mouth enhance the elimination of some drugs after they have been absorbed; repeated doses are given after overdosage with:

- Carbamazepine
- Dapsone
- Phenobarbital
- Quinine
- Theophylline

If vomiting occurs after dosing it should be treated (e.g. with an antiemetic drug) since it may reduce the efficacy of charcoal treatment. In cases of intolerance, the dose may be reduced and the frequency increased but this may compromise efficacy.

Activated charcoal p. 1130 should not be used for poisoning with petroleum distillates, corrosive substances, alcohols, malathion, cyanides and metal salts including iron and lithium salts.

Other techniques intended to enhance the elimination of poisons after absorption are only practicable in hospital and are only suitable for a small number of severely poisoned patients. Moreover, they only apply to a limited number of poisons. Examples include:

- haemodialysis for ethylene glycol, lithium, methanol, phenobarbital, salicylates, and sodium valproate;
- alkalinisation of the urine for salicylates.

**Removal from the gastro-intestinal tract**

Gastric lavage is rarely required; for substances that cannot be removed effectively by other means (e.g. iron), it should be considered only if a life-threatening amount has been ingested within the previous hour. It should be carried out only if the airway can be protected adequately. Gastric lavage is contra-indicated if a corrosive substance or a petroleum distillate has been ingested, but it may occasionally be considered in patients who have ingested drugs that are not adsorbed by charcoal, such as iron or lithium. Induction of emesis (e.g. with ipecacuanha) is not recommended because there is no evidence that it affects absorption and it may increase the risk of aspiration. Whole bowel irrigation (by means of a bowel cleansing preparation) has been used in poisoning with certain modified-release or enteric-coated formulations, in severe poisoning with iron and lithium salts, and if illicit drugs are carried in the gastro-intestinal tract (‘body-packing’). However, it is not clear that the procedure improves outcome and advice should be sought from the National Poisons Information Service.

**Specific Drugs**

**Alcohol**

Acute intoxication with alcohol (ethanol) is common in adults but also occurs in children. The features include ataxia, dysarthria, nystagmus, and drowsiness, which may progress to coma, with hypotension and acidosis. Aspiration of vomit is a special hazard and hypoglycaemia may occur in children and some adults. Patients are managed supportivey, with particular attention to maintaining a clear airway and measures to reduce the risk of aspiration of gastric contents. The blood glucose is measured and glucose given if indicated.

**Analgesics**

**Aspirin**

The main features of salicylate poisoning are hyperventilation, tinnitus, deafness, vasodilatation, and sweating. Coma is uncommon but indicates very severe poisoning. The associated acid-base disturbances are complex.

Treatment must be in hospital, where plasma salicylate, pH, and electrolytes can be measured; absorption of aspirin may be slow and the plasma-salicylate concentration may continue to rise for several hours, requiring repeated measurement. Plasma-salicylate concentration may not correlate with clinical severity in the young and the elderly, and clinical and biochemical assessment is necessary. Generally, the clinical severity of poisoning is less below a plasma-salicylate concentration of 500 mg/litre (3.6 mmol/litre), unless there is evidence of metabolic acidosis. Activated charcoal can be given within 1 hour of ingesting more than 125 mg/kg of aspirin. Fluid losses...
should be replaced and intravenous sodium bicarbonate may be given (ensuring plasma-potassium concentration is within the reference range) to enhance urinary salicylate excretion (optimum urinary pH 7.5–8.5).

Plasma-potassium concentration should be corrected before giving sodium bicarbonate as hypokalaemia may complicate alkalinisation of the urine.

Haemodialysis is the treatment of choice for severe salicylate poisoning and should be considered when the plasma-salicylate concentration exceeds 700 mg/litre (5.1 mmol/litre) or in the presence of severe metabolic acidosis.

**Opioids**

Opioids (narcotic analgesics) cause coma, respiratory depression, and pinpoint pupils. The specific antidote naloxone hydrochloride p. 1133 is indicated if there is coma or bradypnoea. Since naloxone has a shorter duration of action than many opioids, close monitoring and repeated injections are necessary according to the respiratory rate and depth of coma. When repeated administration of naloxone is required, it can be given by continuous intravenous infusion instead and the rate of infusion adjusted according to vital signs. The effects of some opioids, such as buprenorphine, are only partially reversed by naloxone. Dextropropoxyphene and methadone have very long durations of action; patients may need to be monitored for long periods following large overdoses.

Norpropoxyphene, a metabolite of dextropropoxyphene, also has cardiotoxic effects which may require treatment with sodium bicarbonate p. 848, or magnesium sulfate p. 858, or both; arrhythmias may occur for up to 12 hours.

**Paracetamol**

In cases of intravenous paracetamol poisoning contact the National Poisons Information Service for advice on risk assessment and management.

Toxic doses of paracetamol may cause severe hepatocellular necrosis and, much less frequently, renal tubular necrosis. Nausea and vomiting, the only early features of poisoning, usually settle within 24 hours. Persistence beyond this time, often associated with the onset of right subcostal pain and tenderness, usually indicates development of hepatic necrosis. Liver damage is maximal 3–4 days after paracetamol overdose and may lead to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Therefore, despite a lack of significant early symptoms, patients who have taken an overdose of paracetamol should be transferred to hospital urgently.

To avoid underestimating the potentially toxic paracetamol dose ingested by obese patients who weigh more than 110 kg, use a body-weight of 110 kg (rather than their actual body-weight) when calculating the total dose of paracetamol ingested (in mg/kg).

Acetylcysteine p. 1134 protects the liver if infused up to, and possibly beyond, 24 hours of ingesting paracetamol. It is most effective if given within 8 hours of ingestion, after which effectiveness declines. Very rarely, giving
Emergency treatment of poisoning

Acetylecysteine by mouth [unlicensed route] is an alternative if intravenous access is not possible—contact the National Poisons Information Service for advice.

Neonates less than 45 weeks corrected gestational age may be more susceptible to paracetamol-induced liver toxicity, therefore, treatment with acetylecysteine should be considered in all paracetamol overdoses, and advice should be sought from the National Poisons Information Service.

Acute overdose

Hepatotoxicity may occur after a single ingestion of more than 150 mg/kg paracetamol taken in less than 1 hour. Rarely, hepatotoxicity may develop with single ingestions as low as 75 mg/kg of paracetamol taken in less than 1 hour. Patients who have ingested 75 mg/kg or more of paracetamol in less than 1 hour should be referred to hospital. Administration of charcoal, activated p. 1130 should be considered if paracetamol in excess of 150 mg/kg is thought to have been ingested within the previous hour.

Patients at risk of liver damage and, therefore, requiring acetylecysteine, can be identified from a single measurement of the plasma-paracetamol concentration, related to the time from ingestion, provided this time interval is not less than 4 hours; earlier samples may be misleading. The concentration is plotted on a paracetamol treatment graph, with a reference line (‘treatment line’) joining plots of 100 μmol/litre (0.66 mmol/litre) at 4 hours and 3.13 μmol/litre (0.02 mmol/litre) at 24 hours. Acetylecysteine treatment should commence immediately in patients:

- whose plasma-paracetamol concentration falls on or above the treatment line on the paracetamol treatment graph;
- who present 8–24 hours after taking an acute overdose of more than 150 mg/kg of paracetamol, even if the plasma-paracetamol concentration is not yet available; acetylecysteine can be discontinued if the plasma-paracetamol concentration is later reported to be below the treatment line on the paracetamol treatment graph, provided that the patient is asymptomatic and liver function tests, serum creatinine and INR are normal.

The prognostic accuracy of a plasma-paracetamol concentration taken after 15 hours is uncertain, but a concentration on or above the treatment line on the paracetamol treatment graph should be regarded as carrying a serious risk of liver damage. If more than 15 hours have elapsed since ingestion, or there is doubt about appropriate management, advice should be sought from the National Poisons Information Service.

‘Staggered’ overdose, uncertain time of overdose, or therapeutic excess

A ‘staggered’ overdose involves ingestion of a potentially toxic dose of paracetamol over more than one hour, with the possible intention of causing self-harm. Therapeutic excess is the inadvertent ingestion of a potentially toxic dose of paracetamol during its clinical use. The paracetamol treatment graph is unreliable if a ‘staggered’ overdose is taken, if there is uncertainty about the time of the overdose, or if there is therapeutic excess. In these cases, patients who have taken more than 150 mg/kg of paracetamol in any 24-hour period are at risk of toxicity and should be commenced on acetylecysteine immediately, unless it is more than 24 hours since the last ingestion, the patient is asymptomatic, the plasma-paracetamol concentration is undetectable, and liver function tests, serum creatinine and INR are normal.

Rarely, toxicity can occur with paracetamol doses between 75–150 mg/kg in any 24-hour period; clinical judgement of the individual case is necessary to determine whether to treat those who have ingested this amount of paracetamol. For small adults, this may be within the licensed dose, but ingestion of a licensed dose of paracetamol is not considered an overdose.

Although there is some evidence suggesting that factors such as the use of liver enzyme-inducing drugs (e.g. carbamazepine p. 387, efavirenz p. 558, nevirapine p. 560, phenobarbital p. 409, phenytoin p. 398, primidone p. 401, rifabutin p. 507, rifampicin p. 508, St John’s wort), chronic alcoholism, and starvation may increase the risk of hepatotoxicity, the CHM has advised that these should no longer be used in the assessment of paracetamol toxicity.

Significant toxicity is unlikely if, 24 hours or longer after the last paracetamol ingestion, the patient is asymptomatic, the plasma-paracetamol concentration is undetectable, and liver function tests, serum creatinine and INR are normal. Patients with clinical features of hepatic injury such as jaundice or hepatic tenderness should be treated urgently with acetylecysteine. If there is uncertainty about a patient’s risk of toxicity after paracetamol overdose, treatment with acetylecysteine should be commenced. Advice should be sought from the National Poisons Information Service whenever necessary.

Acetylecysteine dose and administration

For paracetamol overdosage, acetylecysteine p. 1134 is given in a total dose that is divided into 3 consecutive intravenous infusions over a total of 21 hours. The tables below include the dose of acetylecysteine, for adults and children of body-weight 40 kg and over, in terms of the volume of Acetylcysteine Concentrate for Intravenous Infusion required for each of the 3 infusions. The requisite dose of acetylecysteine is added to Glucose Intravenous Infusion 5% p. 852.

**First infusion** (based on an acetylecysteine dose of approx. 150mg/kg) — add requisite volume of Acetylecysteine Concentrate for Intravenous Infusion to 200mL Glucose Intravenous Infusion 5%; infuse over 1 hour.

<table>
<thead>
<tr>
<th>Body-weight</th>
<th>Volume of Acetylcysteine Concentrate for Intravenous infusion 200 mg/mL required to prepare first infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–49 kg</td>
<td>34 mL</td>
</tr>
<tr>
<td>50–59 kg</td>
<td>42 mL</td>
</tr>
<tr>
<td>60–69 kg</td>
<td>49 mL</td>
</tr>
<tr>
<td>70–79 kg</td>
<td>57 mL</td>
</tr>
<tr>
<td>80–89 kg</td>
<td>64 mL</td>
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<tr>
<td>90–99 kg</td>
<td>72 mL</td>
</tr>
<tr>
<td>100–109 kg</td>
<td>79 mL</td>
</tr>
<tr>
<td>≥110 kg</td>
<td>83 mL (max. dose)</td>
</tr>
</tbody>
</table>

**Second infusion** (based on an acetylecysteine dose of approx. 50mg/kg; start immediately after completion of first infusion) — add requisite volume of Acetylecysteine Concentrate for Intravenous Infusion to 500mL Glucose Intravenous Infusion 5%; infuse over 4 hours.

<table>
<thead>
<tr>
<th>Body-weight</th>
<th>Volume of Acetylcysteine Concentrate for Intravenous infusion 200 mg/mL required to prepare second infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–49 kg</td>
<td>12 mL</td>
</tr>
<tr>
<td>50–59 kg</td>
<td>14 mL</td>
</tr>
<tr>
<td>60–69 kg</td>
<td>17 mL</td>
</tr>
<tr>
<td>70–79 kg</td>
<td>19 mL</td>
</tr>
<tr>
<td>80–89 kg</td>
<td>22 mL</td>
</tr>
<tr>
<td>90–99 kg</td>
<td>24 mL</td>
</tr>
<tr>
<td>100–109 kg</td>
<td>27 mL</td>
</tr>
<tr>
<td>≥110 kg</td>
<td>28 mL (max. dose)</td>
</tr>
</tbody>
</table>
Antimalarials
Overdosage with quinine, chloroquine, or hydroxychloroquine is extremely hazardous and difficult to treat. Urgent advice from the National Poisons Information Service is essential. Life-threatening features include arrhythmias (which can have a very rapid onset) and convulsions (which can be intractable).

Antipsychotics
Phenothiazines and related drugs
Phenothiazines cause less depression of consciousness and respiration than other sedatives. Hypotension, hypothermia, sinus tachycardia, and arrhythmias may complicate poisoning. Dystonic reactions can occur with therapeutic doses (particularly with prochlorperazine and trifluoperazine), and convulsions may occur in severe cases. Arrhythmias may respond to correction of hypoxia, acidosis, and other biochemical abnormalities, but specialist advice should be sought if arrhythmias result from a prolonged QT interval; the use of some anti-arrhythmic drugs can worsen such arrhythmias. Dystonic reactions are rapidly abolished by injection of drugs such as procyclidine hydrochloride p. 326 or diazepam p. 267 (emulsion preferred).

Second-generation antipsychotic drugs
Features of poisoning by second-generation antipsychotic drugs include drowsiness, convulsions, extrapyramidal symptoms, hypotension, and ECG abnormalities (including prolongation of the QT interval). Management is supportive. Charcoal, activated p. 1130 can be given within 1 hour of ingesting a significant quantity of a second-generation antipsychotic drug.

Benzodiazepines
Benzodiazepines taken alone cause drowsiness, ataxia, dysarthria, nystagmus, and occasionally respiratory depression, and coma. Charcoal, activated p. 1130 can be given within 1 hour of ingesting a significant quantity of benzodiazepine, provided the patient is awake and the airway is protected. Benzodiazepines potentiate the effects of other central nervous system depressants taken concomitantly. Use of the benzodiazepine antagonist flumazenil p. 1132 [unlicensed indication] can be hazardous, particularly in mixed overdoses involving tricyclic antidepressants or in benzodiazepine-dependent patients. Flumazenil may prevent the need for ventilation, particularly in patients with severe respiratory disorders; it should be used on expert advice only and not as a diagnostic test in patients with a reduced level of consciousness.

Beta blockers
Therapeutic overdosages with beta-blockers may cause lightheadedness, dizziness, and possibly syncope as a result of bradycardia and hypotension; heart failure may be precipitated or exacerbated. These complications are most likely in patients with conduction system disorders or impaired myocardial function. Bradycardia is the most common arrhythmia caused by beta-blockers, but sotalol may induce ventricular tachyarrhythmias (sometimes of the torsade de points type). The effects of massive overdosage can vary from one beta-blocker to another; propranolol overdosage in particular may cause coma and convulsions. Acute massive overdosage must be managed in hospital and expert advice should be obtained. Maintenance of a clear airway and adequate ventilation is mandatory. An intravenous injection of atropine sulfate p. 1099 is required to treat bradycardia. Cardiogenic shock unresponsive to atropine sulfate is probably best treated with an intravenous injection of glucagon p. 618 [unlicensed] in glucose 5% (with precautions to protect the airway in case of vomiting) followed by an intravenous infusion. If glucagon is not effective, a second intravenous injection of glucagon should be given.

Antidepressants
Tricyclic and related antidepressants
Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, and cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. Metabolic acidosis may complicate severe poisoning; delirium with confusion, agitation, and visual and auditory hallucinations are common during recovery. Assessment in hospital is strongly advised in case of poisoning by tricyclic and related antidepressants but symptomatic treatment can be given before transfer. Supportive measures to ensure a clear airway and adequate ventilation during transfer are mandatory. Intravenous lorazepam or intravenous diazepam (preferably in emulsion form) may be required to treat convulsions. Activated charcoal given within 1 hour of the overdose reduces absorption of the drug. Although arrhythmias are worrying, some will respond to correction of hypoxia and acidosis. The use of anti-arrhythmic drugs is best avoided, but intravenous infusion of sodium bicarbonate can arrest arrhythmias or prevent them in those with an extended QRS duration. Diazepam given by mouth is usually adequate to sedate delirious patients but large doses may be required.

The National Poisons Information Service (Tel: 0844 892 0111) will provide specialist advice on all aspects of poisoning day and night.

Selective serotonin re-uptake inhibitors (SSRIs)
Symptoms of poisoning by selective serotonin re-uptake inhibitors include nausea, vomiting, agitation, tremor, nystagmus, drowsiness, and sinus tachycardia; convulsions may occur. Rarely, severe poisoning results in the serotonin syndrome, with marked neuropsychiatric effects, neuromuscular hyperactivity, and autonomic instability; hyperthermia, rhabdomyolysis, renal failure, and coagulopathies may develop.

Management of SSRi poisoning is supportive. Activated charcoal given within 1 hour of the overdose reduces absorption of the drug. Convulsions can be treated with lorazepam, diazepam, or midazolam oromucosal solution [unlicensed use in adults and children under 3 months] (see Convolusions p. 1124. Contact the National Poisons Information Service for the management of hyperthermia or the serotonin syndrome.

Emergency treatment of poisoning

Third infusion (based on an acetylcysteine dose of approx. 100mg/kg; start immediately after completion of second infusion)—add requisite volume of Acetylcysteine Concentrate for Intravenous Infusion to 1 litre Glucose Intravenous Infusion 5%; infuse over 16 hours.

<table>
<thead>
<tr>
<th>Third infusion</th>
<th>Body-weight</th>
<th>Volume of Acetylcysteine Concentrate for Intravenous Infusion 200 mg/mL required to prepare third infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49 kg</td>
<td>23 mL</td>
<td></td>
</tr>
<tr>
<td>50-59 kg</td>
<td>28 mL</td>
<td></td>
</tr>
<tr>
<td>60-69 kg</td>
<td>33 mL</td>
<td></td>
</tr>
<tr>
<td>70-79 kg</td>
<td>38 mL</td>
<td></td>
</tr>
<tr>
<td>80-89 kg</td>
<td>43 mL</td>
<td></td>
</tr>
<tr>
<td>90-99 kg</td>
<td>48 mL</td>
<td></td>
</tr>
<tr>
<td>100-109 kg</td>
<td>53 mL</td>
<td></td>
</tr>
<tr>
<td>&gt;110 kg</td>
<td>55 mL (max. dose)</td>
<td></td>
</tr>
</tbody>
</table>
Emergency treatment of poisoning

available, intravenous isoprenaline (available from 'special-order' manufacturers or specialist importing companies) is an alternative. A cardiac pacemaker can be used to increase the heart rate.

**Calcium-channel blockers**
Features of calcium-channel blocker poisoning include nausea, vomiting, dizziness, agitation, confusion, and coma in severe poisoning. Metabolic acidosis and hyperglycaemia may occur. Verapamil and diltiazem have a profound cardiac depressant effect causing hypotension and arrhythmias, including complete heart block and asystole. The dihydropyridine calcium-channel blockers cause severe hypotension secondary to profound peripheral vasodilatation.

Charcoal, activated p. 1130 should be considered if the patient presents within 1 hour of overdosage with a calcium-channel blocker; repeated doses of activated charcoal are considered if a modified-release preparation is involved. In patients with significant features of poisoning, calcium chloride p. 857 or calcium gluconate p. 857 is given by injection; atropine sulfate p. 1099 is given to correct symptomatic bradycardia. In severe cases, an insulin and glucose infusion may be required in the management of hypoglycaemia and myocardial failure. For the management of hypotension, the choice of inotropic sympathomimetic depends on whether hypotension is secondary to vasodilatation or to myocardial depression—advice should be sought from the National Poisons Information Service.

**Iron salts**
Iron poisoning in childhood is usually accidental. The symptoms are nausea, vomiting, abdominal pain, diarrhoea, haematemesis, and rectal bleeding. Hypotension and hepatocellular necrosis can occur later. Coma, shock, and metabolic acidosis indicate severe poisoning.

Advice should be sought from the National Poisons Information Service if a significant quantity of iron has been ingested within the previous hour. Mortality is reduced by intensive and specific therapy with desferrioxamine mesilate p. 839, which chelates iron. The serum iron concentration is measured as an emergency and intravenous desferrioxamine mesilate given to chelate absorbed iron in excess of the expected iron binding capacity. In severe toxicity intravenous desferrioxamine mesilate should be given immediately without waiting for the result of the serum-iron measurement.

**Lithium**
Most cases of lithium intoxication occur as a complication of long-term therapy and are caused by reduced excretion of the drug because of a variety of factors including dehydration, deterioration of renal function, infections, and co-administration of diuretics or NSAIDs (or other drugs that interact). Acute deliberate overdoses may also occur with delayed onset of symptoms (12 hours or more) owing to slow entry of lithium into the tissues and continuing absorption from modified-release formulations.

The early clinical features are non-specific and may include apathy and restlessness which could be confused with mental changes arising from the patient’s depressive illness. Vomiting, diarrhoea, ataxia, weakness, dysarthria, muscle twitching, and tremor may follow. Severe poisoning is associated with convulsions, coma, renal failure, electrolyte imbalance, dehydration, and hypotension.

Therapeutic serum-lithium concentrations are within the range of 0.4–1 mmol/litre; concentrations in excess of 2 mmol/litre are usually associated with serious toxicity and such cases may need treatment with haemodialysis if neurological symptoms or renal failure are present. In acute overdosage much higher serum-lithium concentrations may be present without features of toxicity and all that is usually necessary is to take measures to increase urine output (e.g. by increasing fluid intake but avoiding diuretics). Otherwise, treatment is supportive with special regard to electrolyte balance, renal function, and control of convulsions. Gastric lavage may be considered if it can be performed within 1 hour of ingesting significant quantities of lithium. Whole-bowel irrigation should be considered for significant ingestion, but advice should be sought from the National Poisons Information Service.

**Stimulants**
Amphetamines cause wakefulness, excessive activity, paranoia, hallucinations, and hypertension followed by exhaustion, convulsions, hyperthermia, and coma. The early stages can be controlled by diazepam p. 267 orlorazepam p. 412; advice should be sought from the National Poisons Information Service on the management of hypertension. Later, rapid sponging, anticonvulsants, and artificial respiration may be needed.

**Cocaine**
Cocaine stimulates the central nervous system, causing agitation, dilated pupils, tachycardia, hypertension, hallucinations, hyperthermia, hyperventilation, and hyperreflexia; cardiac effects include chest pain, myocardial infarction, and arrhythmias.

Initial treatment of cocaine poisoning involves intravenous administration of diazepam p. 267 to control agitation and cooling measures for hyperthermia (see Body temperature); hypertension and cardiac effects require specific treatment and expert advice should be sought.

**Ecstasy**
Ecstasy (methylenedioxymethamphetamine, MDMA) may cause severe reactions, even at doses that were previously tolerated. The most serious effects are delirium, coma, convulsions, ventricular arrhythmias, hyperthermia, rhabdomyolysis, acute renal failure, acute hepatitis, disseminated intravascular coagulation, adult respiratory distress syndrome, hyperreflexia, hypotension and intracerebral haemorrhage; hyponatraemia has also been associated with ecstasy use.

Treatment of methylenedioxymethamphetamine poisoning is supportive, with diazepam p. 267 to control severe agitation or persistent convulsions and close monitoring including ECG. Self-induced water intoxication should be considered in patients with ecstasy poisoning.

‘Liquid ecstasy’ is a term used for sodium oxybate (gamma-hydroxybutyrate, GHB), which is a sedative.

The National Poisons Information Service (Tel: 0844 892 0111) will provide specialist advice on all aspects of poisoning day and night.

**Theophylline**
Theophylline and related drugs are often prescribed as modified-release formulations and toxicity can therefore be delayed. They cause vomiting (which may be severe and intractable), agitation, restlessness, dilated pupils, sinus tachycardia, and hyperglycaemia. More serious effects are haematemesis, convulsions, and supraventricular and ventricular arrhythmias. Severe hypokalaemia may develop rapidly.

Repeated doses of activated charcoal can be used to eliminate theophylline even if more than 1 hour has elapsed after ingestion and especially if a modified-release preparation has been taken (see also under Active Elimination Techniques). Ondansetron p. 349 may be effective for severe vomiting that is resistant to other antiemetics [unlicensed indication]. Hypokalaemia is corrected by intravenous infusion of potassium chloride p. 863 and may be so severe as to require 60 mmol/hour (high doses require ECG monitoring). Convulsions should be
controlled by intravenous administration of lorazepam p. 412 or diazepam p. 267 (see Convulsions). Sedation with diazepam may be necessary in agitated patients.

Provided the patient does not suffer from asthma, a short-acting beta-blocker can be administered intravenously to reverse severe tachycardia, hypokalaemia, and hyperglycaemia.

Other poisons
Consult either the National Poisons Information Service day and night or TOXBASE, see under the National Poisons Information Service.

Cyanides
Oxygen should be administered to patients with cyanide poisoning. The choice of antidote depends on the severity of poisoning, certainty of diagnosis, and the cause. Dicobalt edetate p. 1131 is the antidote of choice when there is a strong clinical suspicion of severe cyanide poisoning, but it should not be used as a precautionary measure. Dicobalt edetate itself is toxic, associated with anaphylactoid reactions, and is potentially fatal if administered in the absence of cyanide poisoning. A regimen of sodium nitrite p. 1131 followed by sodium thiosulfate p. 1131 is an alternative if dicobalt edetate is not available.

Hydroxocobalamin p. 837 (Cyanokit®—no other preparation of hydroxocobalamin is suitable) can be considered for use in victims of smoke inhalation who show signs of significant cyanide poisoning.

Ethylene glycol and methanol
Fomepizole (available from ‘special-order’ manufacturers or specialist importing companies) is the treatment of choice for ethylene glycol and methanol (methyl alcohol) poisoning. If necessary, ethanol (by mouth or by intravenous infusion) can be used, but with caution. Advice on the treatment of ethylene glycol and methanol poisoning should be obtained from the National Poisons Information Service. It is important to start antidote treatment promptly in cases of suspected poisoning with these agents.

Heavy metals
Heavy metal antidotes include succimer (DMSA) [unlicensed], unithiol (DMPS) [unlicensed], sodium calcium edetate [unlicensed], and dimercaprol. Dimercaprol in the management of heavy metal poisoning has been superseded by other chelating agents. In all cases of heavy metal poisoning, the advice of the National Poisons Information Service should be sought.

Noxious gases
Carbon monoxide
Carbon monoxide poisoning is usually due to inhalation of smoke, car exhaust, or fumes caused by blocked flues or incomplete combustion of fuel gases in confined spaces.

Immediate treatment of carbon monoxide poisoning is essential. The person should be moved to fresh air, the airway cleared, and high-flow oxygen 100% administered through a tight-fitting mask with an inflated face seal. Artificial respiration should be given as necessary and continued until adequate spontaneous breathing starts, or stopped only after persistent and efficient treatment of cardiac arrest has failed. The patient should be admitted to hospital because complications may arise after a delay of hours or days. Cerebral oedema may occur in severe poisoning and is treated with an intravenous infusion of mannitol p. 202. Referral for hyperbaric oxygen treatment should be discussed with the National Poisons Information Service if the patient is pregnant or in cases of severe poisoning, such as if the patient is or has been unconscious, or has psychiatric or neurological features other than a headache, or has myocardial ischaemia or an arrhythmia, or has a blood carboxyhaemoglobin concentration of more than 20%.

Sulfur dioxide, chlorine, phosgene, ammonia
All of these gases can cause upper respiratory tract and conjunctival irritation. Pulmonary oedema, with severe breathlessness and cyanosis may develop suddenly up to 36 hours after exposure. Death may occur. Patients are kept under observation and those who develop pulmonary oedema are given oxygen. Assisted ventilation may be necessary in the most serious cases.

CS spray
CS spray, which is used for riot control, irritates the eyes (hence ‘tear gas’) and the respiratory tract; symptoms normally settle spontaneously within 15 minutes. If symptoms persist, the patient should be removed to a well-ventilated area, and the exposed skin washed with soap and water after removal of contaminated clothing. Contact lenses should be removed and rigid ones washed (soft ones should be discarded). Eye symptoms should be treated by irrigating the eyes with physiological saline (or water if saline is not available) and advice sought from an ophthalmologist. Patients with features of severe poisoning, particularly respiratory complications, should be admitted to hospital for symptomatic treatment.

Nerve agents
Treatment of nerve agent poisoning is similar to organophosphorus insecticide poisoning, but advice must be sought from the National Poisons Information Service. The risk of cross-contamination is significant; adequate decontamination and protective clothing for healthcare personnel are essential. In emergencies involving the release of nerve agents, kits (‘NAAS pods’) containing pralidoxime chloride p. 1131 can be obtained through the Ambulance Service from the National Blood Service (or the Welsh Blood Service in South Wales or designated hospital pharmacies in Northern Ireland and Scotland—see TOXBASE for list of designated centres).

Pesticides
Organophosphorus insecticides
Organophosphorus insecticides are usually supplied as powders or dissolved in organic solvents. They are absorbed through the bronchi and intact skin as well as through the gut and inhibit cholinesterase activity, thereby prolonging and intensifying the effects of acetylcholine. Toxicity between different compounds varies considerably, and onset may be delayed after skin exposure. Anxiety, restlessness, dizziness, headache, miosis, nausea, hypersalivation, vomiting, abdominal colic, diarrhoea, bradycardia, and sweating are common features of organophosphorus poisoning. Muscle weakness and fasciculation may develop and progress to generalised flaccid paralysis, including the ocular and respiratory muscles. Convulsions, coma, pulmonary oedema with copious bronchial secretions, hypoxia, and arrhythmias occur in severe cases. Hyperglycaemia and glycosuria without ketonuria may also be present.

Further absorption of the organophosphorus insecticide should be prevented by moving the patient to fresh air, removing soiled clothing, and washing contaminated skin. In severe poisoning it is vital to ensure a clear airway, frequent removal of bronchial secretions, and adequate ventilation and oxygenation; gastric lavage may be considered provided that the airway is protected. Atropine sulfate p. 1099 will reverse the muscarinic effects of acetylcholine and is given by intravenous injection until the skin becomes flushed and dry, the pupils dilate, and bradycardia is abolished.

Pralidoxime chloride p. 1131, a cholinesterase reactivator, is used as an adjunct to atropine sulfate in moderate or severe poisoning. It improves muscle tone within 30 minutes of administration. Pralidoxime chloride is

Emergency treatment of poisoning 1129
Emergency treatment of poisoning

National Poisons Information Service

from designated centres, the names of which are held by the

or foot, swelling extends beyond the wrist or ankle within

marked local envenoming such that after bites on the hand

viper snake venom antiserum treatment p.

and systemic reactions in patients with systemic

wasp venom can be used to reduce the risk of anaphylaxis

relieve itching. A vaccine containing extracts of bee and

anaphylaxis. A short course of an oral antihistamine or a

be used for asthmatic reactions, see also the management of

severe hypersensitivity. An inhaled bronchodilator should

The severe pain of weeverfish (Trachinus draco) and

ports should be removed as quickly as possible.

and spiders, stings by scorpions and fish. For information

Activated charcoal doses in BNF may

SIDE-EFFECTS

UNLICENSED USE

Activated charcoal doses in BNF may
differ from those in product literature.

CAUTIONS

Comatose patient (risk of aspiration—ensure

Airway is protected)

Accelerated elimination of teriflunomide

BY MOUTH USING GRANULES

Adult: 50 g every 12 hours for 11 days

Accelerated elimination of leflunomide (washout procedure)

BY MOUTH USING GRANULES

Adult: 50 g 4 times a day for 11 days

1 Active elimination from the gastro-intestinal tract

CHELATORS AND ANTIDOTES

Charcoal, activated

INDICATIONS AND DOSE

Reduction of absorption of poisons in the gastro-intestinal system

BY MOUTH

Neonate: 1 g/kg.

Child 1 month-11 years: 1 g/kg (max. per dose 50 g)

Child 12-17 years: 50 g

Adult: 50 g

Active elimination of poisons

BY MOUTH

Neonate: 1 g/kg every 4 hours, dose may be reduced and the frequency increased if not tolerated.

Child 1 month-11 years: 1 g/kg every 4 hours (max. per dose 50 g), dose may be reduced and the frequency increased if not tolerated.

Child 12-17 years: Initially 50 g, then 50 g every 4 hours, reduced if not tolerated to 25 g every 2 hours, alternatively 12.5 g every 1 hour, dose may be reduced if higher doses not tolerated but this may compromise efficacy.

Adult: Initially 50 g, then 50 g every 4 hours. reduced if not tolerated to 25 g every 2 hours, alternatively 12.5 g every 1 hour, dose may be reduced if higher doses not tolerated but this may compromise efficacy.

Active elimination of leflunomide

BY MOUTH USING GRANULES

Adult: 50 g every 12 hours for 11 days

Active elimination of leflunomide (washout procedure)

BY MOUTH USING GRANULES

Adult: 50 g 4 times a day for 11 days

Marine stings

The severe pain of weeverfish (Trachinus draco) and

Portuguese man-o’-war stings can be relieved by immersing

the stung area immediately in uncomfortably hot, but not

scalding, water (not more than 45°C). People stung by

jellyfish and Portuguese man-o’-war around the UK coast

should be removed from the sea as soon as possible.

Adherent tentacles should be lifted off carefully (wearing
gloves or using tweezers) or washed off with seawater.

Alcoholic solutions, including suntan lotions, should not be applied because they can cause further discharge of stinging hairs. Ice packs can be used to reduce pain.

Other poisons

Consult either the National Poisons Information Service or

TOXBASE.

The National Poisons Information Service (Tel: 0844 892 0111) will provide specialist advice on all aspects of poisoning day and night.

1130 Active elimination from the gastro-intestinal tract

BNF 70

continued until the patient has not required atropine sulfate for 12 hours. Pralidoxime can be obtained from designated centres, the names of which are held by the National Poisons Information Service.

Snake bites and animal stings

Snake bites

Envenoming from snake bite is uncommon in the UK. Many exotic snakes are kept, some illegally, but the only indigenous venomous snake is the adder (Vipera berus). The bite may cause local and systemic effects. Local effects include pain, swelling, bruising, and tender enlargement of regional lymph nodes. Systemic effects include early anaphylactic symptoms (transient hypotension with syncope, angioedema, urticaria, abdominal colic, diarrhoea, and vomiting), with later persistent or recurrent hypotension, ECG abnormalities, spontaneous systemic bleeding, coagulopathy, adult respiratory distress syndrome, and acute renal failure. Fatal envenoming is rare but the potential for severe envenoming must not be underestimated.

Early anaphylactic symptoms should be treated with adrenaline/epinephrine p. 196. Indications for European viper snake venom antiserum treatment p. 1136 include systemic envenoming, especially hypotension, ECG abnormalities, vomiting, haemostatic abnormalities, and marked local envenoming such that after bites on the hand or foot, swelling extends beyond the wrist or ankle within 4 hours of the bite. For those patients who present with clinical features of severe envenoming (e.g. shock, ECG abnormalities, or local swelling that has advanced from the foot to above the knee or from the hand to above the elbow within 2 hours of the bite), a higher initial dose of the European viper snake venom antiserum is recommended; if symptoms of systemic envenoming persist contact the National Poisons Information Service.

Adrenaline/epinephrine injection must be immediately to hand for treatment of anaphylactic reactions to the European viper snake venom antiserum.

Antivenom is available for bites by certain foreign snakes and spiders, stings by scorpions and fish. For information on identification, management, and for supply in an emergency, telephone the National Poisons Information Service. Whenever possible the TOXBASE entry should be read, and relevant information collected, before telephoning the National Poisons Information Service.

Insect stings

Stings from ants, wasps, hornets, and bees cause local pain and swelling but seldom cause severe direct toxicity unless many stings are inflicted at the same time. If the sting is in the mouth or on the tongue local swelling may threaten the upper airway. The stings from these insects are usually treated by cleaning the area with a topical antiseptic. Bee stings should be removed as quickly as possible.

Anaphylactic reactions require immediate treatment with intramuscular adrenaline/epinephrine p. 196; self-administered intramuscular adrenaline/epinephrine (e.g. EpiPen®) is the best first-aid treatment for patients with severe hypersensitivity. An inhaled bronchodilator should be used for asthmatic reactions, see also the management of anaphylaxis. A short course of an oral antihistamine or a topical corticosteroid may help to reduce inflammation and relieve itching. A vaccine containing extracts of bee and wasp venom can be used to reduce the risk of anaphylaxis and systemic reactions in patients with systemic hypersensitivity to bee or wasp stings.

Marine stings

The severe pain of weeverfish (Trachinus draco) and

Portuguese man-o’-war stings can be relieved by immersing the stung area immediately in uncomfortably hot, but not scalding, water (not more than 45°C). People stung by jellyfish and Portuguese man-o’-war around the UK coast should be removed from the sea as soon as possible. Adherent tentacles should be lifted off carefully (wearing gloves or using tweezers) or washed off with seawater. Alcoholic solutions, including suntan lotions, should not be applied because they can cause further discharge of stinging hairs. Ice packs can be used to reduce pain.

Other poisons

Consult either the National Poisons Information Service or TOXBASE.

The National Poisons Information Service (Tel: 0844 892 0111) will provide specialist advice on all aspects of poisoning day and night.
2 Chemical toxicity

2.1 Cyanide toxicity

CHELATORS AND ANTIDOTES

Dicobalt edetate

**INDICATIONS AND DOSE**

Severe poisoning with cyanides

**BY INTRAVENOUS INJECTION**

- Child: Consult the National Poisons Information Service
- Adult: 300 mg, to be given over 1 minute (or 5 minutes if condition less serious), dose to be followed immediately by 50 mL of glucose intravenous infusion 50%; if response inadequate a second dose of both may be given, but risk of cobalt toxicity

**CAUTIONS** Owing to toxicity to be used only for definite cyanide poisoning when patient tending to lose, or has lost, consciousness

**SIDE-EFFECTS** Anaphylactoid reactions - cardiac abnormalities - facial oedema - hypotension - laryngeal oedema - tachycardia - vomiting

**EXCEPTIONS TO LEGAL CATEGORY** Prescription only medicine restriction does not apply where administration is for saving life in emergency.

**MEDICINAL FORMS** There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **DICOBALT EDETATE (Non-proprietary)**
  Dicobalt edetate 15 mg per 1 mL
  Dicobalt edetate 100 mg/20 mL solution for injection ampoules | 6 ampoule [GBP] £11.20

Sodium nitrite

**INDICATIONS AND DOSE**

Poisoning with cyanides (used in conjunction with sodium thiosulfate)

**BY INTRAVENOUS INJECTION**

- Child: 4–10 mg/kg (max. per dose 300 mg), to be given over 5–20 minutes followed by sodium thiosulphate injection
- Adult: 300 mg, to be given over 5–20 minutes (as sodium nitrite injection 30 mg/mL)

**Dose equivalence and conversion**

4–10 mg/kg equates to 0.13–0.33 mL/kg of a 3% solution.

**SIDE-EFFECTS** Flushing (due to vasodilatation) - headache (due to vasodilatation)

**EXCEPTIONS TO LEGAL CATEGORY** Prescription only medicine restriction does not apply where administration is for saving life in emergency.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection

Sodium thiosulfate

**INDICATIONS AND DOSE**

Poisoning with cyanides (used in conjunction with sodium nitrite)

**BY INTRAVENOUS INJECTION**

- Child: 400 mg/kg (max. per dose 12.5 g), to be given over 10 minutes, dose may be repeated in severe cyanide poisoning if dicobalt edetate not available
- Adult: 12.5 g, to be given over 10 minutes (as sodium thiosulfate injection 500 mg/mL), dose may be repeated in severe cyanide poisoning if dicobalt edetate not available

**Dose equivalence and conversion**

400 mg/kg equates to 0.8 mL/kg of a 50% solution.

**EXCEPTIONS TO LEGAL CATEGORY** Prescription only medicine restriction does not apply where administration is for saving life in emergency.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, solution for infusion, liquid

2.2 Organophosphorous toxicity

Drugs used for Organophosphorous toxicity not listed below: Atropine sulfate, p. 1099

CHELATORS AND ANTIDOTES

Pralidoxime chloride

**INDICATIONS AND DOSE**

Adjuant at atropine in the treatment of poisoning by organophosphorus insecticide or nerve agent

**BY INTRAVENOUS INFUSION**

- Child: Initially 30 mg/kg, to be given over 20 minutes, followed by 8 mg/kg/hour; maximum 12 g per day

continued →
Emergency treatment of poisoning

Flumazenil
Benzodiazepine toxicity

EXCEPTIONS TO LEGAL CATEGORY
PRESCRIBING AND DISPENSING INFORMATION

In children

DIRECTIONS FOR ADMINISTRATION
RENAL IMPAIRMENT
SIDE-EFFECTS
CAUTIONS
CONTRA-INDICATIONS
UNLICENSED USE

poisoning day and night.
National Poisons Information Service

Toxicity or from the National Blood Service (or Welsh

from designated centres for organophosphorus insecticide

Adult:

▶ Reversal of sedative effects of benzodiazepines in intensive
care (if drowsiness recurs after initial dose)
INITIALLY BY INTRAVENOUS INFUSION
Adult: 100–400 micrograms/hour, adjusted according
to response, alternatively (by intravenous injection)
300 micrograms, adjusted according to response

In children

DIRECTIONS FOR ADMINISTRATION
The loading dose may be
administered by intravenous injection (diluted to a
concentration of 50 mg/mL with water for injections) over
at least 5 minutes if pulmonary oedema is present or if it
is not practical to administer an intravenous infusion.

In children For intravenous infusion, reconstitute each vial
with 20 mL Water for Injections, then dilute to a
concentration of 10–20 mg/mL with Sodium Chloride
0.9%.

PRESCRIBING AND DISPENSING INFORMATION
Available from designated centres for organophosphorous insecticide
poisoning or from the National Blood Service (or Welsh
Ambulance Services for Mid West and South East Wales)—see TOXBASE for list of designated centres).

EXCEPTIONS TO LEGAL CATEGORY
Prescription only
Medicine restriction does not apply where administration
is for saving life in emergency.

The National Poisons Information Service (Tel: 0844
892 0111) will provide specialist advice on all aspects of
poisoning day and night.

3 Drug toxicity

3.1 Benzodiazepine toxicity

BENZODIAZEPINE ANTAGONISTS

Flumazenil

INDICATIONS AND DOSE
Reversal of sedative effects of benzodiazepines in
anaesthesia and clinical procedures
BY INTRAVENOUS INJECTION
- Adult: 200 micrograms, dose to be administered over
15 seconds, then 100 micrograms every 1 minute if
required; usual dose 300–600 micrograms; maximum
1 mg per course

Reversal of sedative effects of benzodiazepines in intensive
care
BY INTRAVENOUS INJECTION
- Adult: 300 micrograms, dose to be administered over
15 seconds, then 100 micrograms every 1 minute if
required; maximum 2 mg per course

Reversal of sedative effects of benzodiazepines in intensive
care
INITIALLY BY INTRAVENOUS INFUSION
- Adult: 100–400 micrograms/hour, adjusted according
to response, alternatively (by intravenous injection)
300 micrograms, adjusted according to response

Important safety information
Should only be administered by, or under the direct
supervision of, personnel experienced in their use.

CONTRA-INDICATIONS
Life-threatening condition (e.g.
rised intracranial pressure, status epilepticus) controlled
by benzodiazepines

CAUTIONS
Avoid rapid injection following major surgery
Avoid rapid injection in high-risk or anxious patients
benzodiazepine dependence (may precipitate withdrawal
symptoms) elderly ensure neuromuscular blockade
vented before giving head injury (rapid reversal of
benzodiazepine sedation may cause convulsions) history
of panic disorders (risk of recurrence) prolonged
benzodiazepine therapy for epilepsy (risk of convulsions)
short-acting (repeat doses may be necessary
benzodiazepine effects may persist for at least 24 hours)

SIDE-EFFECTS
- Common or very common Nausea • vomiting
- Uncommon Anxiety • fear • palpitation
- Frequency not known Agitation • chills • convulsions
(particularly in those with epilepsy) • dizziness • flushing
• sensory disturbance • sweating • tachycardia • transient
hypertension
- PREGNANCY Not known to be harmful
- BREAST FEEDING Avoid breast-feeding for 24 hours
- HEPATIC IMPAIRMENT Carefully titrate dose

DIRECTIONS FOR ADMINISTRATION
For continuous
intravenous infusion, dilute with Glucose 5% or Sodium
Chloride 0.9%.

MEDICINAL FORMS
There can be variation in the licensing of different medicines
containing the same drug.

Solution for injection
- FLUMAZENIL (Non-proprietary)
Flumazenil 100 microgram per 1 ml
Flumazenil 500micrograms/5ml solution for injection ampoules
5 ampoule (PZN) E67.50–E72.46

3.2 Digoxin toxicity

CHELATORS AND ANTIDOTES

Digoxin-specific antibody

INDICATIONS AND DOSE
Treatment of known or strongly suspected life-threatening
digoxin toxicity associated with ventricular arrhythmias or
bradyarrhythmias unresponsive to atropine and when
measures beyond the withdrawal of digoxin and
correction of any electrolyte abnormalities are considered
necessary
BY INTRAVENOUS INFUSION
- Child: Serious cases of digoxin toxicity should be
discussed with the National Poisons Information
Service (consult product literature)
- Adult: Serious cases of digoxin toxicity should be
discussed with the National Poisons Information
Service (consult product literature)
### 3.3 Heparin toxicity

**CHELATORS AND ANTIDOTES**

#### Protamine sulfate

**INDICATIONS AND DOSE**

- **Overdosage with intravenous injection of unfractionated heparin**
  - **BY INTRAVENOUS INJECTION**
    - Adult: Dose to be administered at a rate not exceeding 5 mg/minute, 1 mg neutralises 80–100 units heparin when given within 15 minutes; if longer than 15 minute since heparin, less protamine required (consult product literature for details) as heparin rapidly excreted; maximum 50 mg
  - **Overdosage with intravenous infusion of unfractionated heparin**
    - Adult: 25–50 mg, to be administered once heparin infusion stopped at a rate not exceeding 5 mg/minute
  - **Overdosage with subcutaneous injection of unfractionated heparin**
    - Initially by intravenous injection
      - Adult: Initially 25–50 mg, to be administered at a rate not exceeding 5 mg/minute, 1 mg neutralises 100 units heparin, then (by intravenous infusion), any remaining dose to be administered over 8–16 hours; maximum 50 mg per course
    - **Overdosage with subcutaneous injection of low molecular weight heparin**
      - **BY INTRAVENOUS INJECTION OR BY CONTINUOUS INTRAVENOUS INFUSION**
        - Adult: Dose to be administered by intermittent intravenous injection at a rate not exceeding 5 mg/minute, 1 mg neutralises approx. 100 units low molecular weight heparin (consult product literature of low molecular weight heparin for details); maximum 50 mg

**CAUTIONS** Excessive doses can have an anticoagulant effect

**SIDE-EFFECTS** Anaphylaxis · angioedema · back pain · bradycardia · dyspnoea · flushing · hypersensitivity reactions · hypertension · hypotension · lassitude · nausea · pulmonary oedema · rebound bleeding · vomiting

**ALLERGY AND CROSS-SENSITIVITY** Caution if increased risk of allergic reaction to protamine (includes previous treatment with protamine or protamine insulin, allergy to fish, men who are infertile, or who have had a vasectomy and who may have antibodies to protamine).

**MONITORING REQUIREMENTS** Monitor activated partial thromboplastin time or other appropriate blood clotting parameters.

**PRESCRIBING AND DISPENSING INFORMATION**

The long half-life of low molecular weight heparins should be taken into consideration when determining the dose of protamine sulfate; the effects of low molecular weight heparins can persist for up to 24 hours after administration.

**MEDICINAL FORMS**

There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**

- **Protamine sulfate** (non-proprietary)
  - Protamine sulfate 10 mg per 1 ml Protamine sulfate 300mg/10ml solution for injection ampoules | 5 ampoule | no price available Protamine sulfate 50mg/5ml solution for injection ampoules | 10 ampoule | £49.55

### 3.4 Opioid toxicity

**OPIOID RECEPTOR ANTAGONISTS**

#### Naloxone hydrochloride

**INDICATIONS AND DOSE**

- **Overdosage with opioids**
  - **BY INTRAVENOUS INJECTION OR BY SUBCUTANEOUS INJECTION OR BY INTRAMUSCULAR INJECTION**
    - Neonate: Initially 100 micrograms/kg, if no response, repeat at intervals of 1 minute to a total max. 2 mg, then review diagnosis; further doses may be required if respiratory function deteriorates.
    - Child 1 month–11 years: Initially 100 micrograms/kg, if no response, repeat at intervals of 1 minute to a total max. 2 mg, then review diagnosis; further doses may be required if respiratory function deteriorates.
    - Child 12–17 years: Initially 400 micrograms, then 800 micrograms for up to 2 doses at 1 minute intervals if no response to preceding dose, then increased to 2 mg for 1 dose if still no response, then review diagnosis; further doses may be required if respiratory function deteriorates, 4 mg dose may be required in seriously poisoned patients
    - Adult: Initially 400 micrograms, then 800 micrograms for up to 2 doses at 1 minute intervals if no response to preceding dose, then increased to 2 mg for 1 dose if still no response, then review diagnosis; further doses may be required if respiratory function deteriorates, 4 mg dose may be required in seriously poisoned patients
  - **BY CONTINUOUS INTRAVENOUS INFUSION**
    - Neonate: Using an infusion pump, adjust rate according to response (initially, rate may be set at 60% of the initial resuscitative intravenous injection dose per hour). The initial resuscitative intravenous injection dose is that which maintained satisfactory ventilation for at least 15 minutes.
    - Child: Using an infusion pump, adjust rate according to response (initially, rate may be set at 60% of the initial resuscitative intravenous injection dose per hour). The initial resuscitative intravenous injection dose is that which maintained satisfactory ventilation for at least 15 minutes.
    - Adult: Using an infusion pump, adjust rate according to response (initially, rate may be set at 60% of the initial resuscitative intravenous injection dose per hour). The initial resuscitative intravenous injection dose is that which maintained satisfactory ventilation for at least 15 minutes.
**1134 Drug toxicity**

**Overdose with opioids in a non-medical setting**

**BY INTRAMUSCULAR INJECTION**
- Adult: 400 micrograms every 2–3 minutes, to be injected into deltoid region or anterolateral thigh. Each dose given in subsequent resuscitation cycles if patient not breathing normally, continue until consciousness regained, breathing normally, medical assistance available, or contents of syringe used up.

**Reversal of postoperative respiratory depression initially by intravenous injection**
- Neonate: 1 microgram/kg, repeated every 2–3 minutes if required.
- Child 1 month–1 year: 1 microgram/kg, repeated every 2–3 minutes if required.
- Child 12–17 years: Initially 100–200 micrograms, alternatively 1.5–3 micrograms/kg; if response inadequate, give subsequent dose (by intravenous injection) of 100 micrograms every 2 minutes; alternatively, subsequent doses of 100 micrograms can be given by intramuscular injection every 1–2 hours.
- Adult: Initially 100–200 micrograms, alternatively 1.5–3 micrograms/kg; if response inadequate, give subsequent dose (by intravenous injection) of 100 micrograms every 2 minutes; alternatively, subsequent doses of 100 micrograms can be given by intramuscular injection every 1–2 hours.

**Reversal of respiratory and CNS depression resulting from opioid administration to mother during labour**
- Neonate: 1 microgram/kg, repeated every 2–3 minutes if required.
- Child 1–17 years: 1 microgram/kg, repeated every 3–5 minutes if required.

**Pharmacokinetics**
Naloxone has a short duration of action; repeated doses or infusion may be necessary to reverse effects of opioids with longer duration of action.

**Important:** Only give by subcutaneous or intramuscular routes if intravenous route is not feasible; intravenous administration has more rapid onset of action.

**Unlicensed use**
Naloxone doses in BNF may differ from those in product literature.

**Important safety information**

**Safe practice**
Doses used in acute opioid overdose may not be appropriate for the management of opioid-induced respiratory depression and sedation in those receiving palliative care and in chronic opioid use.

**Caution**
Cardiovascular disease or those receiving cardioactive drugs (serious adverse cardiovascular effects reported) - maternal physical dependence on opioids (may precipitate withdrawal in newborn) - pain - physical dependence on opioids (precipitates withdrawal)

**Caution, further information**

**Titration of dose**
In postoperative use, the dose should be titrated for each patient in order to obtain sufficient respiratory response; however, naloxone antagonises analgesia.

**Side-effects**
- **Common or very common** Cardiac arrest (in children) - dizziness - dyspnoea (in children) - headache - hypertension - hyperventilation (in children) - hypotension - nausea - pulmonary oedema (in children) - tachycardia - ventricular fibrillation (in children) - vomiting

**Uncommon** Agitation (in children) - arrhythmia (in adults) - bradycardia (in adults) - diarrhoea - dry mouth - excitement (in children) - hyperventilation (in adults) - paraesthesia (in children) - sweating - tremor

**Rare** Seizures (in adults)

**Very rare** Anaphylaxis (in adults) - cardiac arrest (in adults) - erythema multiforme - hypersensitivity reactions (in adults) - pulmonary oedema (in adults) - seizures (in children) - ventricular fibrillation (in adults)

**Frequency not known**
Agitation (in adults)

**Pregnancy**
Use only if potential benefit outweighs risk.

**Breast feeding**
Not orally bioavailable.

**Directions for administration**
- With intravenous use in children For continuous intravenous infusion, dilute to a concentration of up to 200 micrograms/mL with Glucose 5% or Sodium Chloride 0.9%
- With intravenous use in adults For intravenous infusion (Minijet® Naloxone Hydrochloride), give continuously in Glucose 5% or Sodium Chloride 0.9%. Dilute to a concentration of up to 200 micrograms/mL and administer via an infusion pump.

**Medicinal forms**
There can be variation in the licensing of different medicines containing the same drug.

**Solution for injection**
- **Naloxone Hydrochloride (Non-proprietary)**
  - Naloxone hydrochloride 20 microgram per 1 ml Naloxone 40 micrograms/2 ml solution for injection ampoules | 10 ampoules | £55.00
  - Naloxone hydrochloride 400 microgram per 1 ml Naloxone 400 micrograms/1 ml solution for injection Minijet pre-filled syringes | 1 pre-filled disposable injection | £20.40
  - Naloxone 2 mg/5 ml solution for injection Minijet pre-filled syringes | 1 pre-filled disposable injection | £20.40
  - Naloxone 400 micrograms/1 ml solution for injection Minijet pre-filled syringes | 1 pre-filled disposable injection | £17.70
  - Naloxone 800 micrograms/2 ml solution for injection Minijet pre-filled syringes | 1 pre-filled disposable injection | £53.70
- **Prenoxad** (Martindale Pharmaceuticals Ltd)
  - Naloxone hydrochloride 1 mg per 1 ml Prenoxad 2 mg/2 ml solution for injection pre-filled syringes | 1 pre-filled disposable injection | £18.00

3.5 Paracetamol toxicity

**Chelators and Antidotes**

**Acetylcysteine**

**Indications and dose**

**Paracetamol overdose**

**By intravenous infusion**
- Child (body-weight up to 20 kg): Initially 150 mg/kg over 1 hour, dose to be administered in 3 mL/kg glucose 5%, followed by 50 mg/kg over 4 hours, dose to be administered in 7 mL/kg glucose 5%, then 100 mg/kg over 16 hours, dose to be administered in 14 mL/kg glucose 5%
- Child (body-weight 20–39 kg): Initially 150 mg/kg over 1 hour, dose to be administered in 100 mL glucose 5%, followed by 50 mg/kg over 4 hours, dose to be administered in 250 mL glucose 5%, then 100 mg/kg over 16 hours, dose to be administered in 500 mL glucose 5%
- Child (body-weight 40 kg and above): 150 mg/kg over 1 hour, dose to be administered in 200 mL Glucose
Intravenous Infusion 5%, then 50 mg/kg over 4 hours, to be started immediately after completion of first infusion, dose to be administered in 500 mL Glucose Intravenous Infusion 5%.

- Adult (body-weight 40 kg and above): 150 mg/kg over 1 hour, dose to be administered in 200 mL Glucose Intravenous Infusion 5%, then 50 mg/kg over 4 hours, to be started immediately after completion of first infusion, dose to be administered in 500 mL Glucose Intravenous Infusion 5%, then 100 mg/kg over 16 hours, to be started immediately after completion of second infusion, dose to be administered in 1 litre Glucose Intravenous Infusion 5%.

- Child 3 months: Initially 1–2 mg/kg, then 1–2 mg/kg after 30–60 minutes if required, to be given over 5 minutes, seek advice from National Poisons Information Service if further repeat doses are required; maximum 7 mg/kg per course

**Methaemoglobinaemia 1135**

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: granules, tablet, eye drops, effervescent tablet, oral solution, capsule, liquid

**Solution for infusion**

**ELECTROLYTES:** May contain Sodium

- **ACETYLCYSTEINE (Non-proprietary)**
  - Acetylcysteine 200 mg per 1 ml Acetylcysteine 2g/10ml solution for infusion ampoules | 10 ampoule [POC] £19.58
  - Parvolex (Phoenix Labs Ltd)
    - Acetylcysteine 200 mg per 1 ml Parvolex 2g/10ml concentrate for solution for infusion ampoules | 10 ampoule [POC] £22.50

**INDICATIONS AND DOSE**

**Drug or chemical-induced methaemoglobinaemia**

**BY SLOW INTRAVENOUS INJECTION**

- Child 3 months-17 years: Initially 1–2 mg/kg, then 1–2 mg/kg after 30–60 minutes if required, to be given over 5 minutes, seek advice from National Poisons Information Service if further repeat doses are required; maximum 7 mg/kg per course

**Aniline- or dapsone-induced methaemoglobinaemia**

**BY SLOW INTRAVENOUS INJECTION**

- Child 3 months-17 years: Initially 1–2 mg/kg, then 1–2 mg/kg after 30–60 minutes if required, to be given over 5 minutes, seek advice from National Poisons Information Service if further repeat doses are required; maximum 4 mg/kg per course

**SIDE-EFFECTS**

- Hypersensitivity-like reactions - rash, slight increase in INR, may slightly increase prothrombin time

**INTERACTIONS**

- → Appendix 1 (methylthioninium).

**MEDICINAL FORMS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, irrigation site pain; not compatible with Sodium Chloride 0.9%.

**Solution for injection**

- **METHYLTHIONIUM CHLORIDE (Non-proprietary)**
  - Methylthioninium chloride 5 mg per 1 ml Methylthioninium chloride Proveblue 50mg/10ml solution for injection ampoules | 5 ampoule [POC] £196.89

**CHELATORS AND ANTIDOTES**

**Methylen blue (Methylene blue)**

**INDICATIONS AND DOSE**

**Drug or chemical-induced methaemoglobinaemia**

**BY SLOW INTRAVENOUS INJECTION**

- Adult: Initially 1–2 mg/kg, then 1–2 mg/kg after 30–60 minutes if required, to be given over 5 minutes, seek advice from National Poisons Information Service if further repeat doses are required; maximum 7 mg/kg per course

**CAUTIONS**

- Asthma (see Side-effects for management of asthma but do not delay acetylcysteine treatment) · atopy · may slightly increase INR · may slightly increase prothrombin time

**SIDE-EFFECTS**

- Hypersensitivity-like reactions - rash, slight increase in INR, may slightly increase prothrombin time

**INTERACTIONS**

- → Appendix 1 (methylthioninium).

**SIDE-EFFECTS**

- Abdominal pain · agitation · anxiety · arrhythmia · blue-green discoloration of faeces · blue-green discoloration of skin · blue-green discoloration of urine · chest pain · confusion · dizziness · dyspnoea · fever · haemolytic anaemia · headache · hyperbilirubinaemia (in infants) · hypertension · hypotension · methaemoglobinaemia · mydriasis · nausea · sweating · tachypnoea · tremor · vomiting

**PREGNANCY**

- No information available, but risk to fetus of untreated methaemoglobinaemia likely to be significantly higher than risk of treatment.

**BREAST FEEDING**

- Manufacturer advises avoid breastfeeding for up to 6 days after administration—no information available.

**RENAL IMPAIRMENT**

- Use with caution in severe impairment; dose reduction may be required.

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use in children For intravenous infusion (Parvolex®), give continuously in Glucose 5% or Sodium chloride 0.9%. Glucose Intravenous Infusion 5% is the preferred fluid; Sodium Chloride Intravenous Infusion 0.9% is an alternative if Glucose Intravenous Infusion 5% is unsuitable.

**MEDICATIONS**

- There can be variation in the licensing of different medicines containing the same drug. Forms available from special-order manufacturers include: solution for injection, irrigation site pain; not compatible with Sodium Chloride 0.9%.

**Solution for injection**

- **METHYLTHIONIUM CHLORIDE (Non-proprietary)**
  - Methylthioninium chloride 5 mg per 1 ml Methylthioninium chloride Proveblue 50mg/10ml solution for injection ampoules | 5 ampoule [POC] £196.89

**Methaemoglobinemia 1135**

**CAUTIONS**

- Asthma (see Side-effects for management of asthma but do not delay acetylcysteine treatment) · atopy · may slightly increase INR · may slightly increase prothrombin time

**SIDE-EFFECTS**

- Hypersensitivity-like reactions - rash, slight increase in INR, may slightly increase prothrombin time

**INTERACTIONS**

- → Appendix 1 (methylthioninium).

**SIDE-EFFECTS**

- Abdominal pain · agitation · anxiety · arrhythmia · blue-green discoloration of faeces · blue-green discoloration of skin · blue-green discoloration of urine · chest pain · confusion · dizziness · dyspnoea · fever · haemolytic anaemia · headache · hyperbilirubinaemia (in infants) · hypertension · hypotension · methaemoglobinaemia · mydriasis · nausea · sweating · tachypnoea · tremor · vomiting

**PREGNANCY**

- No information available, but risk to fetus of untreated methaemoglobinaemia likely to be significantly higher than risk of treatment.

**BREAST FEEDING**

- Manufacturer advises avoid breastfeeding for up to 6 days after administration—no information available.

**RENAL IMPAIRMENT**

- Use with caution in severe impairment; dose reduction may be required.

**DIRECTIONS FOR ADMINISTRATION**

- With intravenous use in children For intravenous infusion, dose to be started immediately after completion of first infusion, dose to be administered in 500 mL Glucose Intravenous Infusion 5%.

- Child 3 months: Initially 1–2 mg/kg, then 1–2 mg/kg after 30–60 minutes if required, to be given over 5 minutes, seek advice from National Poisons Information Service if further repeat doses are required; maximum 7 mg/kg per course

- Adult: Initially 1–2 mg/kg, then 1–2 mg/kg after 30–60 minutes if required, to be given over 5 minutes, seek advice from National Poisons Information Service if further repeat doses are required; maximum 4 mg/kg per course
5 Snake bites

ANTISERA

European viper snake venom antiserum

INDICATIONS AND DOSE

Systemic envenoming from snake bites

BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION

▶ Child: Initially 10 mL for 1 dose, then 10 mL after 1–2 hours if required, the second dose should only be given if symptoms of systemic envenoming persist after the first dose, if symptoms of systemic envenoming persist contact the National Poisons Information Service

▶ Adult: Initially 10 mL for 1 dose, then 10 mL after 1–2 hours if required, the second dose should only be given if symptoms of systemic envenoming persist after the first dose, if symptoms of systemic envenoming persist contact the National Poisons Information Service

Severe systemic envenoming from snake bites in patients presenting with clinical features

BY INTRAVENOUS INJECTION OR BY INTRAVENOUS INFUSION

▶ Child: Initially 20 mL for 1 dose, if symptoms of systemic envenoming persist contact the National Poisons Information Service

▶ Adult: Initially 20 mL for 1 dose, if symptoms of systemic envenoming persist contact the National Poisons Information Service

DIRECTIONS FOR ADMINISTRATION

By intravenous injection give over 10–15 minutes or by intravenous infusion over 30 minutes after diluting in sodium chloride 0.9% (use 5 mL diluent/kg body-weight).

PRESCRIBING AND DISPENSING INFORMATION To order, email immform@dh.gsi.gov.uk.

The National Poisons Information Service (Tel: 0844 892 0111) will provide specialist advice on all aspects of poisoning day and night.
Appendix 1

Interactions

Two or more drugs given at the same time may exert their effects independently or may interact. The interaction may be potentiation or antagonism of one drug by another, or occasionally some other effect. Adverse drug interactions should be reported to the Medicines and Healthcare products Regulatory Agency (MHRA), through the Yellow Card Scheme (see Adverse Reactions to Drugs), as for other adverse drug reactions.

Drug interactions may be pharmacodynamic or pharmacokinetic.

Pharmacodynamic interactions
These are interactions between drugs which have similar or antagonistic pharmacological effects or side-effects. They may be due to competition at receptor sites, or occur between drugs acting on the same physiological system. They are usually predictable from a knowledge of the pharmacology of the interacting drugs; in general, those demonstrated with one drug are likely to occur with related drugs. They occur to a greater or lesser extent in most patients who receive the interacting drugs.

Pharmacokinetic interactions
These occur when one drug alters the absorption, distribution, metabolism, or excretion of another, thus increasing or reducing the amount of drug available to produce its pharmacological effects. They are not easily predicted and many of them affect only a small proportion of patients taking the combination of drugs. Pharmacokinetic interactions occurring with one drug cannot be assumed to occur with related drugs unless their pharmacokinetic properties are known to be similar.

Pharmacokinetic interactions are of several types:

Affecting absorption The rate of absorption or the total amount absorbed can both be altered by drug interactions. Delayed absorption is rarely of clinical importance unless high peak plasma concentrations are required (e.g. when giving an analgesic). Reduction in the total amount absorbed, however, may result in ineffective therapy.

Due to changes in protein binding To a variable extent most drugs are loosely bound to plasma proteins. Protein-binding sites are non-specific and one drug can displace another thereby increasing its proportion free to diffuse from plasma to its site of action. This only produces a detectable increase in effect if it is an extensively bound drug (more than 90%) that is not widely distributed throughout the body. Even so displacement rarely produces more than transient potentiation because this increased concentration of free drug results in an increased rate of elimination.

Displacement from protein binding plays a part in the potentiation of warfarin by sulfonamides and tolbutamide but the importance of these interactions is due mainly to the fact that warfarin metabolism is also inhibited.

Affecting metabolism Many drugs are metabolised in the liver. Induction of the hepatic microsomal enzyme system by one drug can gradually increase the rate of metabolism of another, resulting in lower plasma concentrations and a reduced effect. On withdrawal of the inducer plasma concentrations increase and toxicity may occur. Barbiturates, griseofulvin, many antiepileptics, and rifampicin are the most important enzyme inducers. Drugs affected include warfarin and the oral contraceptives.

Conversely when one drug inhibits the metabolism of another higher plasma concentrations are produced, rapidly resulting in an increased effect with risk of toxicity. Some drugs which potentiate warfarin and phenytoin do so by this mechanism.

Isoenzymes of the hepatic cytochrome P450 system interact with a wide range of drugs. Drugs may be substrates, inducers or inhibitors of the different isoenzymes. A great deal of in-vitro information is available on the effect of drugs on the isoenzymes; however, since drugs are eliminated by a number of different metabolic routes as well as renal excretion, the clinical effects of interactions cannot be predicted accurately from laboratory data on the cytochrome P450 isoenzymes. Except where a combination of drugs is specifically contra-indicated, the BNF presents only interactions that have been reported in clinical practice. In all cases the possibility of an interaction must be considered if toxic effects occur or if the activity of a drug diminishes.

Affecting renal excretion Drugs are eliminated through the kidney both by glomerular filtration and by active tubular secretion. Competition occurs between those which share active transport mechanisms in the proximal tubule. For example, salicylates and some other NSAIDs delay the excretion of methotrexate; serious methotrexate toxicity is possible.

Relative importance of interactions
Many drug interactions are harmless and many of those which are potentially harmful only occur in a small proportion of patients; moreover, the severity of an interaction varies from one patient to another. Drugs with a small therapeutic ratio (e.g. phenytoin) and those which require careful control of dosage (e.g. anticoagulants, antihypertensives, and antidiabetics) are most often involved.

Patients at increased risk from drug interactions include the elderly and those with impaired renal or liver function. Serious interactions The symbol ● has been placed against interactions that are potentially serious and where concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring).

Interactions that have no symbol do not usually have serious consequences.
List of drug interactions
The following is an alphabetical list of drugs and their interactions, to avoid excessive cross-referencing, each drug or group is listed twice: in the alphabetical list and also against the drug or group with which it interacts.

**Abacavir**
- Analgesics: abacavir possibly reduces plasma concentration of METHAMFETAMINE
- Antibacterials: plasma concentration of abacavir possibly reduced by RIFAMPICIN
- Antiepileptics: plasma concentration of abacavir possibly reduced by FOSPHENYTOIN, PHENOBARBITAL, PHENYTOIN and DEXTROMETHORPHAN
- Antivirals: abacavir possibly reduces effects of RIBAVIRIN; plasma concentration of abacavir reduced by TIPRANAVIR
- Orlistat: absorption of abacavir possibly reduced by ORLISTAT

**Abiraterone**
- Analgesics: abiraterone increases plasma concentration of DEXTROMETHORPHAN
- Antibacterials: plasma concentration of abiraterone possibly reduced by RIFABUTIN—manufacturer of abiraterone advises avoid concomitant use; plasma concentration of abiraterone reduced by Rifampicin—manufacturer of abiraterone advises avoid concomitant use
- Antidepressants: plasma concentration of abiraterone possibly reduced by ST JOHN'S WORT—manufacturer of abiraterone advises avoid concomitant use
- Antiepileptics: plasma concentration of abiraterone possibly reduced by PHENOBARBITAL, PHENYTOIN and PRIMIDONE—manufacturer of abiraterone advises avoid concomitant use

**Acarbose** see Antidiabetics

**ACE Inhibitors** (continued)
- Antidepressants: hypotensive effect of ACE inhibitors possibly enhanced by MAOIs
- Antidiabetics: ACE inhibitors possibly enhance hypoglycaemic effect of INSULIN, METFORMIN and SULfonylureAS
- Antipsychotics: enhanced hypotensive effect when ACE inhibitors given with ANTIpsYCHOTICS
- Anxiolytics and Hypnotics: enhanced hypotensive effect when ACE inhibitors given with ANXIOLYtics AND HYPnotics
- Avanafil: hypotensive effect of enalapril possibly enhanced by AVANAFIL
- Azathioprine: increased risk of anaemia or leucopenia when captopril given with AZATHIOPRINE especially in renal impairment; increased risk of anaemia when enalapril given with AZATHIOPRINE especially in renal impairment
- Bee Venom Extracts: possible severe anaphylactoid reaction when ACE inhibitors given with BEE VENOM EXTRACTS
- Beta-blockers: enhanced hypotensive effect when ACE inhibitors given with BETA-BLOCKers
- Calcium-Channel Blockers: enhanced hypotensive effect when ACE inhibitors given with CALCIUM-CHANNEL BLOCKERS
- Cardiac Glycosides: captopril possibly increases plasma concentration of DIGOXIN
- Cilostazol: increased risk of hyperkalaemia when ACE inhibitors given with CLOPIDOGREL
- Clonidine: enhanced hypotensive effect when ACE inhibitors given with CLONIDINE; antihypertensive effect of captopril possibly delayed by previous treatment with CLONIDINE
- Corticosteroids: hypotensive effect of ACE inhibitors antagonised by CORTICOSTERoids
- Cytotoxics: increased risk of angioedema when ACE inhibitors given with, EVEROLIMUS
- Diazoxide: enhanced hypotensive effect when ACE inhibitors given with DIAZoxide
- Diuretics: enhanced hypotensive effect when ACE inhibitors given with DIUREtics; increased risk of severe hyperkalaemia when ACE inhibitors given with POTASSium-SPARing DIuretics AND ALDOSTERONE ANTAGOnists
- Dopaminergics: enhanced hypotensive effect when ACE inhibitors given with CO-BENEDOLpa, CO-CARELOpa or LEVODOPpa
- Lithium: ACE inhibitors reduce excretion of LITHIUM (increased plasma concentration)
- Methylprednisolone: enhanced hypotensive effect when ACE inhibitors given with METHYLPREDNISOLONE
- Moxisylyte: enhanced hypotensive effect when ACE inhibitors given with MOXISylyTE
- Moxonidine: enhanced hypotensive effect when ACE inhibitors given with MOXONIDINE
- Muscle Relaxants: enhanced hypotensive effect when ACE inhibitors given with BACLOFEN or TZANIDINE
- Nitrites: enhanced hypotensive effect when ACE inhibitors given with NITRATES
- Oestrogens: hypotensive effect of ACE inhibitors antagonised by OESTROGENs
- Potassium Salts: increased risk of severe hyperkalaemia when ACE inhibitors given with POTASSIUM SALTS
- Prostaglandins: enhanced hypotensive effect when ACE inhibitors given with APROstenol
- Sodium Aurothiomalate: flushing and hypotension reported when ACE inhibitors given with SODIUM AUROTHIOMALATE
- Vasodilator Antihypertensives: enhanced hypotensive effect when ACE inhibitors given with HYDRAZINE, MinoxidIL or SODIUM NITROPRUSSIIDE
- Wasp Venom Extracts: possible severe anaphylactoid reaction when ACE inhibitors given with WASP VENOM EXTRACTS

**Acetebutolol** see Beta-blockers

**Aceleclofenac** see NSAIDs

**Aciometacin** see NSAIDs

**Acenocoumarol** see Coumarins

**Acetazolamide** see Diuretics

**AcidoCin**
- NOTE Interactions do not apply to topical aciclovir preparations
- Aminophylline: aciclovir possibly increases plasma concentration of AMINOPHYLLINE
Appendix 1 Interactions

Adalimumab

- Increased risk of nephrotoxicity when adalimumab given with CYCLOSPORIN
- Mycophenolate: plasma concentration of adalimumab increased by MYCOPHENOLATE, also plasma concentration of inactive metabolite of mycophenolate increased
- Tacrolimus: possible increased risk of nephrotoxicity when adalimumab given with TACROLIMUS
- Theophylline: adalimumab possibly increases plasma concentration of THEOPHYLLINE

Aciclovir (continued)

- Increased risk of nephrotoxicity when adalimumab given with CYCLOSPORIN
- Mycophenolate: plasma concentration of aciclovir increased by MYCOPHENOLATE, also plasma concentration of inactive metabolite of mycophenolate increased
- Theophylline: aciclovir possibly increases plasma concentration of THEOPHYLLINE

Aclidinium see Retinoids

Acrivastine see Antihistamines

Adenine

NOTE Possibility of interaction with drugs having tendency to impair myocardial conduction
- Aminophylline: anti-arrhythmic effect of adenosine antagonised by AMINOPHYLLINE—manufacturer of adenine advises avoid aminophylline for 24 hours before adenine
- Anaesthetics, Local: increased myocardial depression when anti-arrhythmics given with BUPIVACAINE, LEVOBUPIVACAINE, PHENOLCAINE or BOPIVACAINE
- Anti-arrhythmics: increased myocardial depression when anti-arrhythmics given with other ANTI-ARRHYTHMICS
- Anti-arrhythmics that prolong the QT interval given with other ANTI-ARRHYTHMICS that prolong the QT interval
- Beta-blockers: increased myocardial depression when anti-arrhythmics given with other BETA-BLOCKERS
- Caffeine citrate: anti-arrhythmic effect of adenosine antagonised by CAFFEINE CITRATE—manufacturer of adenine advises avoid caffeine citrate for at least 12 hours before adenine
- Dipyradomol: effect of adenine enhanced and extended by DIPYRIMIDOL (important risk of toxicity)—reduce dose of adenine, see p. 87
- Nicotine: effects of adenine possibly enhanced by NICOTINE
- Theophylline: anti-arrhythmic effect of adenine antagonised by THEOPHYLLINE—manufacturer of adenine advises avoid theophylline for 24 hours before adenine

Adrenergic Neurone Blockers

- Alcohol: enhanced hypotensive effect when adrenergic neurone blockers given with ALCOHOL
- Alpha-blockers: enhanced hypotensive effect when adrenergic neurone blockers given with ALPHA-BLOCKERS
- Anaesthetics, General: enhanced hypotensive effect when adrenergic neurone blockers given with GENERAL ANAESTHETICS
- Analgesics: enhanced hypotensive effect when adrenergic neurone blockers given with ANGIOTENSIN-II RECEPTOR ANTAGONISTS
- Antidepressants: enhanced hypotensive effect when adrenergic neurone blockers given with MAOIS; hypotensive effect of adrenergic neurone blockers antagonised by TRICYCLICS
- Antipsychotics: hypotensive effect of adrenergic neurone blockers antagonised by HALOPERIDOL; hypotensive effect of adrenergic neurone blockers antagonised by higher doses of
### Appendix 1 Interactions

#### Afatinib (continued)
- Ciclosporin: plasma concentration of afatinib possibly increased by Ciclosporin — manufacturer of afatinib advises separating administration of ciclosporin by 6 to 12 hours.
- Tacrolimus: plasma concentration of afatinib possibly increased by tacrolimus — manufacturer of afatinib advises separating administration of tacrolimus by 6 to 12 hours.

#### Agalsidase Alfa and Beta
- Antiarhythmic: effects of agalsidase alfa and beta possibly inhibited by AMIODARONE and ALCYLAMINES (manufacturers of agalsidase alfa and beta advise avoid concomitant use).
- Antibacterials: effects of agalsidase alfa and beta possibly inhibited by Gentamicin (manufacturers of agalsidase alfa and beta advise avoid concomitant use).
- Antimalarials: effects of agalsidase alfa and beta possibly inhibited by Chloroquine and Hydroxychloroquine (manufacturers of agalsidase alfa and beta advise avoid concomitant use).

#### Alcohol
- Antidepressants: possible increased hypotensive effect when alcohol given with AVANAFIL.
- Beta-blockers: enhanced hypotensive effect when alcohol given with Beta-blockers.
- Calcium-channel blockers: enhanced hypotensive effect when alcohol given with Calcium-channel blockers.
- Diazoxide: increased sedative effect when alcohol given with Diazoxide.
- Disulfiram: disulfiram-like reaction when alcohol given with Disulfiram.
- Dopaminergic: alcohol reduces tolerance to Bromocriptine.
- Lipid-regulating Drugs: avoidance of alcohol advised by manufacturer of Lomitapide.
- Nitrovasodilators: enhanced hypotensive effect when alcohol given with Nitrovasodilators.
- Nitrates: enhanced hypotensive effect when alcohol given with Nitrates.
- Paraldehyde: increased sedative effect when alcohol given with Paraldehyde.
- Retinoids: enhanced hypotensive effect when alcohol given with Retinoids.
- Sympathomimetics: increased sedative effects of alcohol possibly enhanced by Methylphenidate.
- Vasodilators: enhanced hypotensive effect when alcohol given with Vasodilators.

#### Alcohol (continued)
- Antiepileptics: alcohol possibly increases CNS side-effects of Carbamazepine.
- Chronic heavy consumption of alcohol possibly reduces plasma concentration of fosphenytoin and Phenytoin.
- Increased sedative effect when alcohol given with Phenobarbital or Primidone.
- Increased risk of blurred vision when alcohol given with Retigabine.
- Antifungals: possibility of disulfiram-like reaction when alcohol given with ketoconazole.
- Effects of alcohol possibly enhanced by griseofulvin.
- Antihistamines: increased sedative effect when alcohol given with Antihistamines.
- Antimuscarnics: increased sedative effect when alcohol given with Hyoscine.
- Antipsychotics: increased sedative effect when alcohol given with Antipsychotics.
- Anxiolytics and Hypnotics: increased sedative effect when alcohol given with Anxiolytics and Hypnotics.
- Avanafil: possible enhanced hypotensive effect when alcohol given with Avanafil.
- Beta-blockers: enhanced hypotensive effect when alcohol given with Beta-blockers.
- Calcium-channel blockers: enhanced hypotensive effect when alcohol given with Calcium-channel blockers.
- Diazoxide: increased sedative effect when alcohol given with Diazoxide.
- Dopaminergic: alcohol reduces tolerance to Bromocriptine.
- Lipid-regulating Drugs: avoidance of alcohol advised by manufacturer of Lomitapide.
- Nitrates: enhanced hypotensive effect when alcohol given with Nitrates.
- Paraldehyde: increased sedative effect when alcohol given with Paraldehyde.
- Retinoids: presence of alcohol causes etretinate to be formed from Acitretin (increased risk of teratogenicity in women of child-bearing potential).
- Sympathomimetics: alcohol possibly enhances effects of Methylphenidate.
- Vasodilators: enhanced hypotensive effect when alcohol given with Vasodilators.
Aliskiren
- Beta-blockers: enhanced hypotensive effect when aliskiren given with BETA-BLOCKERS
- Calcium-channel Blockers: enhanced hypotensive effect when aliskiren given with CALCIUM-CHANNEL BLOCKERS
- Clonidine: enhanced hypotensive effect when aliskiren given with CLONIDINE
- Corticosteroids: manufacturer of aliskiren advises avoid concomitant use with CORTICOSTEROIDS
- Cytotoxics: manufacturer of aliskiren advises avoid concomitant use with GLUCOTIDE, DACARBASINE and VINBLASTINE
- Diazoxide: enhanced hypotensive effect when aliskiren given with DIAZOXIDE
- Diuretics: enhanced hypotensive effect when aliskiren given with DIURETICS
- Moxonidine: enhanced hypotensive effect when aliskiren given with METHYLDOPA
- Nitrates: enhanced hypotensive effect when aliskiren given with NITRATES
- Vasodilator Antihypertensives: enhanced hypotensive effect when aliskiren given with HYDRALAZINE, MINOXIDIL OF SODIUM NITROPRUSSIDE

Alentuzumab
- Anti-psychotics: avoid concomitant use of cytoxotytics with CLOzapine (increased risk of agranulocytosis)
- Vaccines: risk of generalised infections when monoclonal antibodies given with live VACCINES—avoid concomitant use

Alendronic Acid see Bisphosphonates

Alfacalcidol see Vitamins

Alfentanil see Opioid Analgesics

Alfuzosin see Alpha-blockers

Alimemazine see Antihistamines

Aliskiren
- ACE inhibitors: increased risk of hyperkalaemia, hypotension, and impaired renal function when aliskiren given with ACE INHIBITORS—avoid concomitant use
- Analgesics: hypotensive effect of aliskiren possibly antagonised by NSAIDS
- Angiotensin-II Receptor Antagonists: increased risk of hyperkalaemia, hypotension, and impaired renal function when aliskiren given with ANGIOTENSIN-II RECEPTOR ANTAGONISTS—avoid concomitant use; plasma concentration of aliskiren possibly reduced by INDORAMIN
- Antibacterials: plasma concentration of aliskiren reduced by RIFAMPICIN
- Anticoagulants: increased risk of hyperkalaemia when aliskiren given with HEPARINS
- Antifungals: plasma concentration of aliskiren increased by KETOCONAZOLE; plasma concentration of aliskiren increased by IRACONAZOLE—avoid concomitant use
- Calcium-channel Blockers: Plasma concentration of aliskiren increased by VERAPAMIL
- Cilostazol: plasma concentration of aliskiren increased by CYCLOSPORIN—avoid concomitant use
- Diuretics: aliskiren reduces plasma concentration of FUROSEMIDE; increased risk of hyperkalaemia when aliskiren given with POTASSIUM-SPARING DIURETICS AND ALDOSTERONE ANTAGONISTS
- Grapefruit Juice: plasma concentration of aliskiren reduced by GRAPEFRUIT JUICE—avoid concomitant use
- Potassium Salts: increased risk of hyperkalaemia when aliskiren given with POTASSIUM SALTS

Altrinetin see Retinoids

Alkylydring Drugs see Bendamustine, Busulfan, Carmustine, Cyclophosphamide, Estraantrum, Ifosfamide, Lomustine, Melphalan, and Thiopeta

Allopurinol
- ACE inhibitors: manufacturers state possible increased risk of leucopenia and hypersensitivity reactions when allopurinol given with ACE INHIBITORS especially in renal impairment
- Aminophylline: allopurinol possibly increases plasma concentration of AMINOPHYLLINE

Allopurinol (continued)
- Antibacterials: increased risk of rash when allopurinol given with AMOXICILLIN, AMPICILLIN OR CO-AMOXICLAV
- Anticoagulants: allopurinol possibly enhances anticoagulant effect of COUMARINS
- Antineoplastic: allopurinol increases plasma concentration of DIDANOSINE (risk of toxicity)—avoid concomitant use
- Azathioprine: allopurinol enhances effects and increases toxicity of AZATHIOPRINE (reduce dose of azathioprine to one quarter of usual dose)
- Ciclosporin: allopurinol possibly increases plasma concentration of CYCLOSPORIN (risk of nephrotoxicity)
- Cytotoxics: avoidance of allopurinol advised by manufacturer of CAPECITABINE; allopurinol enhances effects and increases toxicity of MERCAPTOPURINE (reduce dose of mercaptopurine to one quarter of usual dose)
- Diuretics: increased risk of hypersensitivity when allopurinol given with THIAZIDES AND RELATED DIURETICS especially in renal impairment
- Theophylline: allopurinol possibly increases plasma concentration of THEOPHYLLINE

Almotriptan see 5HT1-receptor Agonists (under HT)

Alogliptin see Antidiabetics

Alpha-adrenoceptor Stimulants see Apraclonidine, Brimonidine, Clonidine, and Methyldopa

Alpha-blockers
- ACE inhibitors: enhanced hypotensive effect when alpha-blockers given with ACE INHIBITORS
- Adrenergic Neurone Blockers: enhanced hypotensive effect when alpha-blockers given with ADRENERGIC NEURONE BLOCKERS
- Alcohol: enhanced hypotensive effect when alpha-blockers given with ALCOHOL; increased sedative effect when indoramin given with ALCOHOL
- Aliskiren: enhanced hypotensive effect when alpha-blockers given with ALDESLEUKIN
- Analgesics: enhanced hypotensive effect when alpha-blockers given with GENERAL ANALGESICS
- Anticoagulants: increased risk of first-dose hypotension with post-synaptic alpha-blockers
- Antihistamines: enhanced hypotensive effect when alpha-blockers given with Alpha-blockers
- Antivirals: enhanced hypotensive effect when alpha-blockers given with ALDESLEUKIN
- Antivirals: enhanced hypotensive effect when alpha-blockers given with ANTIVIRALS
- Beta-blockers: enhanced hypotensive effect when alpha-blockers given with BETA-BLOCKERS
- Calcium-channel Blockers: enhanced hypotensive effect when alpha-blockers given with CALCIUM-CHANNEL BLOCKERS
- Cardiovascular Drugs: enhanced hypotensive effect when alpha-blockers given with CARDIOVASCULAR DRUGS
- Cardiac Glycosides: prazosin increases plasma concentration of DIGOXIN
- Clonidine: enhanced hypotensive effect when alpha-blockers given with CLONIDINE
### Interactions

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Interactions</th>
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</thead>
<tbody>
<tr>
<td><strong>Alpha-blockers</strong> (continued)</td>
<td>- Cobicistat: plasma concentration of alfuzosin possibly increased by Cobicistat - Mannitol: manufacturer of tobramycin advises avoid concomitant use</td>
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<tr>
<td></td>
<td>- Corticosteroids: hypotensive effect of alpha-blockers enhanced by Corticosteroids</td>
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<td>- Cytotoxics: avoidance of alfuzosin advised by manufacturer of <em>IDELALISIB</em></td>
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<td>- Diazoxide: enhanced hypotensive effect when alpha-blockers given with Diazoxide</td>
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<td>- Diuretics: enhanced hypotensive effect when alpha-blockers given with Diuretics, also increased risk of first-dose hypotension with post-synaptic alpha-blockers such as prazosin</td>
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<td>- Dopaminergics: enhanced hypotensive effect when alpha-blockers given with Dopaminergics</td>
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<td>- Mostilysite: possible severe postural hypotension when alpha-blockers given with Mostilysite</td>
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<td>- Moxonidine: enhanced hypotensive effect when alpha-blockers given with Moxonidine</td>
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<td>- Muscle Relaxants: enhanced hypotensive effect when alpha-blockers given with Muscle Relaxants</td>
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<td>- Nitrates: enhanced hypotensive effect when alpha-blockers given with Nitrates</td>
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<td>- Oestrogens: hypotensive effect of alpha-blockers antagonised by Oestrogens</td>
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<td>- Prostaglandins: enhanced hypotensive effect when alpha-blockers given with Prostaglandins</td>
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<td>- Silodosin: enhanced hypotensive effect when alpha-blockers given with Silodosin (avoid alpha-blockers for 4 hours after silodosin) when patient is stable on the alpha blocker initiate silodosin at the lowest possible dose</td>
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<td>- Sympathomimetics: avoid concomitant use of tolazoline with Sympathomimetics (e.g. phenetidine) or Dopamine</td>
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<td></td>
<td>- Tadalafl: enhanced hypotensive effect when alpha-blockers given with Tadalafl when patient is stable on the alpha blocker initiate tadalafl at the lowest possible dose; enhanced hypotensive effect when doxazosin given with Tadalafl - manufacturer of tadalafl advises avoid concomitant use</td>
</tr>
<tr>
<td></td>
<td>- Ulcer-healing Drugs: effects of tolazoline antagonised by Ulcer-healing Drugs and Potassium Salts</td>
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<tr>
<td></td>
<td>- Vardenafil: enhanced hypotensive effect when alpha-blockers given with Vardenafil when patient is stable on the alpha blocker initiate vardenafil at the lowest possible dose — separate doses by 6 hours (except with tamsulosin)</td>
</tr>
<tr>
<td></td>
<td>- Vasodilator Antihypertensives: enhanced hypotensive effect when alpha-blockers given with Hydrazine, Minoxidil or Sodium Nitroprusside</td>
</tr>
</tbody>
</table>

**Alpha-blockers (post-synaptic)** see Alpha-blockers

**Alprazolam** see Anxiolytics and Hypnotics

**Alprostadil** see Prostaglandins

**Aluminium Hydroxide** see Antacids

**Amanitadine**

- Antimalarials: plasma concentration of amantadine possibly increased by Quinine
- Antipsychotics: increased risk of extrapyramidal side-effects when amantadine given with Antipsychotics
- Bupropion: increased risk of side-effects when amantadine given with Buproprion
- Memantine: increased risk of CNS toxicity when amantadine given with Memantine (manufacturer of memantine advises avoid concomitant use); effects of dopaminergics possibly enhanced by Memantine
- Methyldopa: increased risk of extrapyramidal side-effects when amantadine given with Methyldopa; antiparkinsonian effect of dopaminergics antagonised by Methyldopa
- Tetrabenazine: increased risk of extrapyramidal side-effects when amantadine given with Tetrabenazine

**Ambrisantan**

- Antibacterials: plasma concentration of ambrisantan possibly increased by Rifampicin

**Ambrissept (continued)**

- Ciclosporin: plasma concentration of ambrisantan increased by Ciclosporin
- Tiazoxide: increased hypotensive effect when alpha-blockers given with Tiazoxide
- Adenosine: increased hypotensive effect when alpha-blockers given with Adenosine; plasma concentration of aminophylline possibly reduced by Adenosine; increased risk of convulsions when patient is stable on the alpha blocker when adenosine is given with aminophylline |

**Antibacterials**

- *Agalasidae Alpha* and Beta: gentamicin possibly inhibits effects of Agalasidae Alpha and Beta (manufacturers of agalasidae alpha and beta advise avoid concomitant use)
- Analgesics: plasma concentration of amikacin and gentamicin in neonates possibly increased by Indomethacin
- Antibacterials: neomycin reduces absorption of PHENOXYMETHYPENCILLIN; increased risk of nephrotoxicity when aminoglycosides given with COLISTIMETHATE SODIUM or POLYMIXINS; increased risk of nephrotoxicity and ototoxicity when aminoglycosides given with CAPREOMYCIN or VANCOMYCIN; possible increased risk of nephrotoxicity when aminoglycosides given with CEPHALOSPORINS
- Anticoagulants: experience in anticoagulant clinics suggests that INR possibly altered when neomycin (given for local action on gut) is given with Contraceptives or Phenindione
- Antidiabetics: neomycin possibly enhances hypoglycaemic effect of Acarbose, also severity of gastro-intestinal effects increased
- Antifungals: increased risk of nephrotoxicity when aminoglycosides given with Ambrofixcin
- Bisphosphonates: increased risk of hypocalcaemia when aminoglycosides given with Bisphosphonates
- Cardiac Glycosides: gentamicin possibly increases plasma concentration of Digoxin; neomycin reduces absorption of Digoxin
- Ciclosporin: increased risk of nephrotoxicity when aminoglycosides given with Ciclosporin
- Cytotoxics: neomycin possibly reduces absorption of Methotrexate; neomycin reduces bioavailability of Sorafenib; increased risk of nephrotoxicity and possibly of ototoxicity when aminoglycosides given with Platinum Compounds
- Diuretics: increased risk of otoxicity when aminoglycosides given with Loop Diuretics
- Mannitol: manufacturer of tobramycin advises avoid concomitant use with Mannitol
- Muscle Relaxants: aminoglycosides enhance effects of Non-depolarising Muscle Relaxants and Succinylcholine or Pyridostigmine
- Parasympathomimetics: aminoglycosides antagonise effects of Neostigmine and Pyridostigmine
- Tacrolimus: increased risk of nephrotoxicity when aminoglycosides given with Tacrolimus
- Vaccines: antibacterials inactivate ORAL TYPHOID VACCINE — see under Typhoid Vaccine in BNF
- Vitamins: neomycin possibly reduces absorption of Vitamin A

**Aminophylline**

- Allopurinol: plasma concentration of aminophylline possibly increased by Allopurinol
- Anaesthetics, General: increased risk of convulsions when aminophylline given with Ketamine
- Anti-arrhythmics: aminophylline antagonises anti-arrhythmic effect of Adenosine — manufacturer of adenosine advises avoid aminophylline for 24 hours before adenosine; plasma concentration of aminophylline increased by Propafenone
- Antibacterials: plasma concentration of aminophylline possibly increased by Clarithromycin and Isoniazid; plasma concentration of aminophylline increased by Erythromycin (also aminophylline may reduce absorption of oral erythromycin); plasma concentration of aminophylline increased by Ciprofl oxacin and Norfloxac in; metabolism of aminophylline accelerated by Rifampicin (reduced plasma concentration); possible increased risk of convulsions when aminophylline given with Quinolones
- Antidepressants: plasma concentration of aminophylline increased by Fluvoxamine (concomitant use should usually be avoided, but where not possible halve aminophylline dose and monitor plasma-aminophylline concentration); plasma concentration of aminophylline possibly reduced by St John’s Wort
Aminophylline (continued)
- Antiepileptics: metabolism of aminophylline accelerated by CARBAMAZEPINE, PHENOBARBITAL and PRIMIDONE (reduced effect); plasma concentration of both drugs reduced when aminophylline given with FOSPHENYT OIN and PHENYTOIN.
- Antifungals: plasma concentration of aminophylline possibly increased by FLUCONAZOLE and KETOCONAZOLE.
- Antivirals: plasma concentration of aminophylline possibly increased by ACICLOVIR and VALACLOVIR; metabolism of amiodarone is accelerated by RITONAVIR (reduced plasma concentration).
- Anxiolytics and Hypnotics: aminophylline possibly reduces effects of BENZODIAZEPINES.
- Caffeine citrate: avoidance of aminophylline advised by manufacturer of CAFFEINE CITRATE.
- Calcium-channel Blockers: plasma concentration of aminophylline possibly increased by CALCUM-CHANNEL BLOCKERS (enhanced effect); plasma concentration of aminophylline increased by DILTIAZEM; plasma concentration of aminophylline increased by VERAPAMIL (enhanced effect).
- Corticosteroids: increased risk of hypokalaemia when aminophylline given with CORTICOSTEROIDS.
- Cytoxics: plasma concentration of aminophylline possibly increased by METHOTREXATE.
- Deferasirox: plasma concentration of aminophylline increased by DEFERASIRAX (consider reducing dose of aminophylline).
- Disulfiram: metabolism of aminophylline inhibited by DISULFIRAM (increased risk of toxicity).
- Diuretics: increased risk of hypokalaemia when aminophylline given with ACETAZOLAMIDE, LOOP DIURETICS or THIAZIDES and RELATED DIURETICS.
- Dopaminergic agonists: increased CNS stimulation when aminophylline given with DOXAPRAM.
- interferons: metabolism of aminophylline inhibited by INTERFERON ALFA and INTERFERON ALFA 2B (consider reducing dose of aminophylline).
- Leukotriene Receptor Antagonists: plasma concentration of aminophylline possibly increased by ZAFIRLUKAST, also plasma concentration of zafirlukast reduced.
- Lithium: aminophylline increases excretion of LITHIUM (reduced plasma concentration).
- Oestrogens: plasma concentration of aminophylline increased by OESTROGENS (consider reducing dose of aminophylline).
- Pentoxifylline: plasma concentration of aminophylline increased by PENTOXIFYLLINE.
- Roflumilast: avoidance of aminophylline advised by manufacturer of ROFLUMILAST.
- Sulfinpyrazone: plasma concentration of aminophylline reduced by SULFINPYRAZONE.
- Symptomametics: manufacturer of aminophylline advises avoid concomitant use with EPEDRINE in children.
- Symptomametics, Beta-2: increased risk of hypokalaemia when aminophylline given with high doses of BETA-2 SYMPTOMAMETICS.
- Ulcer-healing Drugs: metabolism of aminophylline inhibited by CIMETIDINE (increased plasma concentration); absorption of aminophylline possibly reduced by SUCRALFATE (give at least 2 hours apart).
- Vaccines: plasma concentration of aminophylline possibly increased by INFLUENZA VACCINE.

Aminosaliclylates see individual drugs

Aminophylline

NOTE Aminophylline has a long half-life; there is a potential for drug interactions to occur for several weeks (or even months) after treatment with it has been stopped.
- Agalactasidase Alfa and Beta: aminophylline possibly inhibits effects of AGALACTASIDASE ALFA AND BETA (manufacturers of agalactasidase alfa and beta advise avoid concomitant use).
- Anaesthetics: Local: increased myocardial depression when anti-arrhythmics given with BUPIVACAINE, LEVOBUPIVACAINE, PRILOCaine or ROPIVACAINE.
- Anti-arrhythmics: increased myocardial depression when anti-arrhythmics given with other ANTI-ARRHYTHMICS; increased risk of ventricular arrhythmias when aminophylline given with DISOPYRAMIDE or DROPERIDONE—avoid concomitant use.

Amiodarone

- Anti-arrhythmics (continued)
  - aminophylline increases plasma concentration of FLECAINIDE (halve dose of flecainide).
- Antibacterials: increased risk of ventricular arrhythmias when amiodarone given with piperacillin—ERITHROMYCIN—avoid concomitant use; increased risk of ventricular arrhythmias when amiodarone given with LEVOFLOXACIN or MOXIFLOXACIN—avoid concomitant use; possible increased risk of ventricular arrhythmias when amiodarone given with SULFA-METHOXYAZOLE and TRIMETHOPRIM (as co-trimoxazole)—manufacturer of amiodarone advises avoid concomitant use of co-trimoxazole; increased risk of ventricular arrhythmias when amiodarone given with DELAMAND; avoidance of amiodarone advised by manufacturer of FIDAXOMICIN; possible increased risk of ventricular arrhythmias when amiodarone given with TELITROMYCIN.
- Anticoagulants: amiodarone inhibits metabolism of COUMARINS and PHENINDIONE (enhanced anticoagulant effect); amiodarone increases plasma concentration of DABIGATRAN (see under Dabigatran Eteixilate, p. 117).
- Anti-arrhythmics: increased risk of ventricular arrhythmias when amiodarone given with TRICYCLICS—avoid concomitant use.
- Antiepileptics: amiodarone inhibits metabolism of FOSPHENYT OIN and PHENYTOIN (increased plasma concentration).
- Anti-arrhythmics: increased risk of ventricular arrhythmias when amiodarone given with MIZOLASTINE—avoid concomitant use.
- Antimalarials: avoidance of amiodarone advised by manufacturer of ARTEMETHER with LUMESANTRINE (risk of ventricular arrhythmias); avoidance of amiodarone advised by manufacturer of ARTENIMOL with PIPERAQUINE (possible risk of ventricular arrhythmias); increased risk of ventricular arrhythmias when amiodarone given with CHLOROQUINE, HYDROXYCHLOROQUINE, MELOQUIN or QUININE—avoid concomitant use.
- Antimuscarinics: increased risk of ventricular arrhythmias when amiodarone given with TOLERODINE.
- Antipsychotics: increased risk of ventricular arrhythmias when anti-arrhythmics that prolong the QT interval given with ANTIPSYCHOTICS that prolong the QT interval; increased risk of ventricular arrhythmias when amiodarone given with BENPERIDOL—manufacturer of benperidol advises avoid concomitant use; increased risk of ventricular arrhythmias when amiodarone given with AMIULSPRIDE, DROPERIDOL, HALOPERIDOL, PHENOTHIAZINES, IMIDAZOID or ZUCLOPENTHIOLS—avoid concomitant use; increased risk of ventricular arrhythmias when amiodarone given with SULFUR.
- Anti-arrhythmics: increased risk of ventricular arrhythmias when amiodarone given with ATAZANAVIR; possible increased risk of bradycardia when amiodarone given with DACLATASVIR and SIMEPREVIR (with sofosbuvir)—see under Amiodarone, p. 88; plasma concentration of amiodarone possibly increased by FOSAPRENAVIR (increased risk of ventricular arrhythmias—avoid concomitant use); plasma concentration of amiodarone possibly increased by INDINAVIR—avoid concomitant use; plasma concentration of amiodarone increased by RITONAVIR (increased risk of ventricular arrhythmias—avoid concomitant use); increased risk of ventricular arrhythmias when amiodarone given with SAAQINUAVIR—avoid concomitant use; possible increased risk of bradycardia when amiodarone given with SOFOSBUVIR—see under Amiodarone, p. 88; avoidance of amiodarone advised by manufacturer of TELAPREVIR (risk of ventricular arrhythmias).
- Antituberculosis: increased risk of ventricular arrhythmias when amiodarone given with ATOMOXETINE.
- Beta-blockers: increased risk of bradycardia, AV block and myocardial depression when amiodarone given with BETABLOCKERS; increased myocardial depression when anti-
Amiodarone

- Beta-blockers (continued)
  - arrhythmics given with: ▶ BETA-BLOCKERS; increased risk of ventricular arrhythmias when amiodarone given with
  - SOTALOL—avoid concomitant use
  - Calcium-channel Blockers: increased risk of bradycardia, AV block and myocardial depression when amiodarone given with ▶ DILTIAZEM or ▶ VERAPAMIL
  - Cardiac Glycosides: amiodarone increases plasma concentration of ▶ DIGOXIN (halve dose of digoxin)
  - Ciclosporin: amiodarone possibly increases plasma concentration of ▶ CICLOSPORIN
  - Ciclosporin: plasma concentration of amiodarone possibly increased by a ▶ COBI STATIST—manufacturer of ciclosporin advises avoid concomitant use
  - Colchicine: amiodarone possibly increases risk of ▶ COLCHICINE
  - Cytotoxics: amiodarone possibly increases the plasma concentration of ▶ AFatinib—manufacturer of afatinib advises separating administration of amiodarone by 6 to 12 hours; possible increased risk of ventricular arrhythmias when amiodarone given with ▶ Bosutinib; amiodarone possibly increases the plasma concentration of ▶ Ibrutinib—reduce dose of ibrutinib (see under ibrutinib, p. 809); avoidance of amiodarone advised by manufacturer of ▶ IDEALIS—possible increased risk of ventricular arrhythmias when amiodarone given with ▶ VANDETANIB—avoid concomitant use; increased risk of ventricular arrhythmias when amiodarone given with ▶ ARSEnic TRIOXide
  - Diuretics: increased cardiac toxicity with amiodarone if hypokalaemia occurs with ▶ ACEATAZOLAMIDE, ▶ LOOPER DIURETICS or ▶ THIAZIDES AND RELATED DIURETICS; amiodarone increases plasma concentration of ▶ EPLERENONE (reduce dose of eplerenone)
  - Fingerlind: possible increased risk of bradycardia when amiodarone given with ▶ FINGERLIND
  - Grapefruit Juice: plasma concentration of amiodarone increased by ▶ GRAPEFRUIT JUICE
  - Ibradina: increased risk of ventricular arrhythmias when amiodarone given with ▶ I布拉DINA
  - Lipid-regulating Drugs: increased risk of myopathy when amiodarone given with ▶ SIMVASTATIN (see under simvastatin, p. 181); separating administration from amiodarone by 12 hours advised by manufacturer of ▶ LOMITAPIDE
  - Lithium: manufacturer of amiodarone advises avoid concomitant use with ▶ LITHIUM (risk of ventricular arrhythmias)
  - Orlistat: plasma concentration of amiodarone possibly decreased by ▶ ORLSTAT
  - Pentamidine Isetionate: increased risk of ventricular arrhythmias when amiodarone given with ▶ PENTAMIDINE ISETIONATE—avoid concomitant use
  - Thyroid Hormones: amiodarone can affect serum concentrations of ▶ THYROID HORMONES—monitor thyroid function closely
  - Ulcer-healing Drugs: plasma concentration of amiodarone increased by ▶ CIMETIDINE

Amisulpride see Antipsychotics

Amiriptyline see Antidepressants, Tricyclic

Amiodipine see Calcium-channel Blockers

Amoxicillin see Penicillins

Amphotericin (continued)

- Ciclosporin: increased risk of nephrotoxicity when amphotericin given with ▶ CICLOSPORIN
- Corticosteroids: increased risk of hypokalaemia when amphotericin given with ▶ CORTICOSTEROIDS—avoid concomitant use unless corticosteroids needed to control reactions
- Cytotoxics: increased risk of ventricular arrhythmias when amphotericin given with ▶ ARSEnic TRIOXide
- Diuretics: increased risk of hypokalaemia when amphotericin given with ▶ LOOP DIURETICS or ▶ THIAZIDES AND RELATED DIURETICS
- Pentamidine Isetionate: possible increased risk of nephrotoxicity when amphotericin given with ▶ PENTAMIDINE ISETIONATE
- Sodium Stibogluconate: possible increased risk of arrhythmias when amphotericin given after ▶ SODIUM STIBOGLUCONATE—manufacturer of sodium stibogluconate advises giving 14 days apart
- Tacrolimus: increased risk of nephrotoxicity when amphotericin given with ▶ TACROLIMUS

Anabolics see Anabolic Steroids

Anabolic Steroids

- Anti-cogulants: anabolic steroids enhance anticoagulant effect of ▶ OUDARINS and ▶ PHENINDIONE
- Antidiabetics: anabolic steroids possibly enhance hypoglycaemic effect of ▶ ANTI-DIABETICS

Anaesthetics, General

NOTE See also Surgery and Long-term Medication, under General Anaesthesia in BNF

- ACE inhibitors: enhanced hypotensive effect when general anaesthetics given with ▶ ACE INHIBITORS
- Adrenergic Neurone Blockers: enhanced hypotensive effect when general anaesthetics given with ▶ ADRENERGIC NEURONE BLOCKERS
- Alpha-blockers: enhanced hypotensive effect when general anaesthetics given with ▶ ALPHA-BLOCKERS
- Naphthyline: increased risk of convulsions when ketamine given with ▶ AMINOPHYLINE
- Analgesics: metabolism of etomidate inhibited by ▶ Fentanyl (consider reducing dose of etomidate); effects of thiopental possibly enhanced by ▶ ASPRIN; effects of intravenous general anaesthetics and volatile liquid general anaesthetics possibly enhanced by ▶ OPIDN ALGASECS
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when general anaesthetics given with ▶ ANGIOTENSIN-II RECEPTOR ANTAGONISTS
- Antibacterials: increased risk of hepatotoxicity when isoflurane given with ▶ SULFAZID—effects of thiopental enhanced by ▶ SULFONAMIDES; hypersensitivity-like reactions can occur when general anaesthetics given with intravenous VANCOMYCIN
- Antidepressants: increased risk of arrhythmias and hypotension when general anaesthetics given with ▶ TRICYCLICs
- Antipsychotics: enhanced hypotensive effect when general anaesthetics given with ▶ ANTI-PSYCHOTICs; effects of thiopental enhanced by ▶ DROPERIDOL
- Anxiety and Hypnotics: increased sedative effect when general anaesthetics given with ▶ ANXIOLYTICS AND HYPNOTICS
- Beta-blockers: enhanced hypotensive effect when general anaesthetics given with ▶ BETA-BLOCKERS
- Calcium-channel Blockers: enhanced hypotensive effect when general anaesthetics or isoflurane given with ▶ CALCIUM-CHANNEL BLOCKERS; general anaesthetics enhance hypotensive effect of ▶ VERAPAMIL (also AV delay)
- Clonidine: enhanced hypotensive effect when general anaesthetics given with ▶ CLONIDINE
- Cytotoxics: nitros oxide increases antifolate effect of ▶ METHOTREKATE—avoid concomitant use
- Diazoxide: enhanced hypotensive effect when general anaesthetics given with ▶ DIAZOXIDE
- Diuretics: enhanced hypotensive effect when general anaesthetics given with ▶ DIURETICS
- Dopaminergics: increased risk of arrhythmias when volatile liquid general anaesthetics given with ▶ CO-BENELDopa, ▶ CO-CARELDOPO or ▶ LEVODOPA
Anaesthetics, General (continued)

- Dopram: increased risk of arrhythmias when volatile liquid general anaesthetics given with
- DOXAPRAM (avoid doxapram for at least 10 minutes after volatile liquid general anaesthetics)
- Memantine: increased risk of CNS toxicity when ketamine given with MEMANTINE (manufacturer of memantine advises avoid concomitant use)
- Methyldopa: enhanced hypotensive effect when general anaesthetics given with METHYLDOPA
- Metoclopramide: effects of thiopental enhanced by METOCLOPRAMIDE
- Moxonidine: enhanced hypotensive effect when general anaesthetics given with MOXONIDINE
- Muscle Relaxants: increased risk of myocardial depression and bradycardia when propofol given with
- SUXAMETHONIUM; volatile liquid general anaesthetics enhance effects of NON-DEPOLARISING MUSCLE RELAXANTS and SUXAMETHONIUM; ketamine enhances effects of ATRACURIUM
- Nitrates: enhanced hypotensive effect when general anaesthetics given with NITRATES
- Oxytocin: oxytocic effect possibly reduced, also enhanced hypotensive effect and risk of arrhythmias when volatile liquid general anaesthetics given with OXYTOCIN
- Phosphodiesterase Type-3 inhibitors: avoid concomitant use with SYMPATHOMIMETICS (risk of ventricular arrhythmias); increased risk of arrhythmias when volatile liquid general anaesthetics given with ADRENERGIC NEURONE BLOCKERS
- Theophylline: increased risk of convulsions when ketamine given with THEOPHYLLINE
- Vasodilator Antihypertensives: enhanced hypotensive effect when general anaesthetics given with HYDRALAZINE, MINOXIDIL or SODIUM NITRITOPRUSSIDE

Anaesthetics, General (Intravenous) see Anaesthetics, General

Anaesthetics, General (volatile liquids) see Anaesthetics, General

Anaesthetics, Local see Bupivacaine, Chloroprocaine, Levobupivacaine, Lidocaine, Prilocaine, and Ropivacaine

Anagrelide

- Clolstol: manufacturer of anagrelide advises avoid concomitant use with CLOSTAZOL
- Prostaglandin Type-E1 Inhibitors: manufacturer of anagrelide advises avoid concomitant use with ENOXIMONE and MILRINONE

Anakinra

- Cytotokins: avoid concomitant use of anakinra with LUMINUMAB, CERTOLIZUMAB PEGOL, GOLIMUMAB or INFILIXIMAB
- Etanercept: avoid concomitant use of anakinra with ETANERCEPT
- Vaccines: risk of generalised infections when anakinra given with live VACCINES—avoid concomitant use

Analgescics see Aspirin, Nefopam, NSAIDs, Opioid Analgesics, and Paracetamol

Angiotensin-II Receptor Antagonists (continued)

- Alpha-blockers: enhanced hypotensive effect when angiotensin-II receptor antagonists given with ALPHA-BLOCKERS
- Anagrelide: General; enhanced hypotensive effect when angiotensin-II receptor antagonists given with GENERAL ANAESTHETICS
- Analgesics: increased risk of renal impairment when angiotensin-II receptor antagonists given with NSAIDS, also hypotensive effect antagonised
- Antibacterials: plasma concentration of losartan and its active metabolite reduced by RIFAMPICIN; possible increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with TRIMETHOPRIM
- Anticoagulants: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with HEPARINS
- Antidepressants: hypotensive effect of angiotensin-II receptor antagonists possibly enhanced by MAOIs
- Antipsychotics: enhanced hypotensive effect when angiotensin-II receptor antagonists given with ANTIPSYCHOTICS
- Anxiolytics and Hypnotics: enhanced hypotensive effect when angiotensin-II receptor antagonists given with ANXIOLYTICS AND HYPNOTICS
- Beta-blockers: enhanced hypotensive effect when angiotensin-II receptor antagonists given with BETA-BLOCKERS
- Calcium-channel Blockers: enhanced hypotensive effect when angiotensin-II receptor antagonists given with CALCIUM-CHANNEL BLOCKERS
- Ciclosporin: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with CICLOSPORIN
- Corticosteroids: hypotensive effect of angiotensin-II receptor antagonists antagonised by CORticosteroids
- Diazoxide: enhanced hypotensive effect when angiotensin-II receptor antagonists given with DIAZOXIDE
- Diuretics: enhanced hypotensive effect when angiotensin-II receptor antagonists given with DIURETICS; increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with POTASSIUM-SPARING DIURETICS AND ALDOSTERONE ANTAGONISTS
- Dopaminergics: enhanced hypotensive effect when angiotensin-II receptor antagonists given with CO-BENELDOPA, CO-CARELDOPA or LEVODOPA
- Lithium: angiotensin-II receptor antagonists reduce excretion of LITHIUM (increased plasma concentration)
- Methyldopa: enhanced hypotensive effect when angiotensin-II receptor antagonists given with METHYLDOPA
- Moxisylyte: enhanced hypotensive effect when angiotensin-II receptor antagonists given with MOXISYLYTE
- Moxonidine: enhanced hypotensive effect when angiotensin-II receptor antagonists given with MOXONIDINE
- Muscle Relaxants: enhanced hypotensive effect when angiotensin-II receptor antagonists given with BACLOFEN or TIZANIDINE
- Nitrates: enhanced hypotensive effect when angiotensin-II receptor antagonists given with NITRATES
- Oestrogens: hypotensive effect of angiotensin-II receptor antagonists antagonised by OESTROGENS
- Potassium Salts: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with KALCIUM SALTS
- Prostaglandins: enhanced hypotensive effect when angiotensin-II receptor antagonists given with PROSTAGLANDINS
- Tacrolimus: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with TACROLIMUS
- Vasodilator Antihypertensives: enhanced hypotensive effect when angiotensin-II receptor antagonists given with HYDRALAZINE, MINOXIDIL or SODIUM NITRITOPRUSSID

Antacids

NOTE Antacids should preferably not be taken at the same time as other drugs since they may impair absorption
- ACE inhibitors: antacids possibly reduce absorption of ACE INHIBITORS; antacids reduce absorption of CAPTOPRIL, ENALAPRIL and FOSINOPRIL

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Antacids (continued)

Analgesics: antacids possibly reduce absorption of
ACETAMIN; alkaline urine due to some antacids increases excretion of ASPIRIN.

Antihelmintics: sodium bicarbonate increases the excretion of DIETHYLCARBAMAZINE.

Antibacterials: antacids reduce absorption of AZITHROMYCIN, CEFACLOR, CIPROFLOXACIN, ISONIAZID, LEVOFLOXACIN, MOXIFLOXACIN, NORFLOXACIN, OFLOXACIN, RIFAMPICIN and TETRACYCLINES; avoid concomitant use of antacids with METHENAMINE; oral magnesium salts (as magnesium trisilicate) reduce absorption of NITROFURANTOIN.

Antiepileptics: antacids reduce absorption of PHENYTOIN, GABAPENTIN and PHENYTOIN.

Antifungals: antacids reduce absorption of ITRACAZOLE and KETOCONAZOLE.

Antihistamines: antacids reduce absorption of FEXOFENADINE.

Antimalarials: antacids reduce absorption of CHLOROQUINE and HYDROXYCHLOROQUINE; oral magnesium salts (as magnesium trisilicate) reduce absorption of PROGUANIL.

Antipsychotics: antacids reduce absorption of PHENOTHIAZINES and SULFURIDE.

Antivirals: antacids reduce absorption of AZATAZANAVIR (give at least 2 hours before or 1 hour after antacids); aluminium hydroxide reduces absorption of DOLUTEGRAVIR—manufacturer of dolutegravir advises give at least 2 hours before or 6 hours after aluminium hydroxide; oral magnesium salts reduce absorption of DOLUTEGRAVIR—manufacturer of dolutegravir advises give at least 2 hours before or 6 hours after aluminium hydroxide; oral magnesium hydroxide reduces absorption of ELVITEGRAVIR (give at least 4 hours apart); oral magnesium salts reduce absorption of RALTEGRAVIR (give at least 4 hours apart); aluminium hydroxide reduces plasma concentration of RALTEGRAVIR—manufacturer of raltegravir advises avoid concomitant use; oral magnesium salts reduce plasma concentration of RALTEGRAVIR—manufacturer of raltegravir advises avoid concomitant use; manufacturer of rilpivirine advises give at least 2 hours before or 4 hours after RILPIVIRINE; antacids reduce absorption of TIPRANAVIR (give at least 2 hours apart)

Bile Acids: antacids possibly reduce absorption of BILE ACIDS.

Bisphosphonates: antacids reduce absorption of BISPHOSPHONATES.

Cardiac Glycosides: antacids possibly reduce absorption of DIGOXIN.

Corticosteroids: antacids reduce absorption of DEFLAZACORT.

Cytotoxics: aluminium hydroxide and oral magnesium salts possibly reduce absorption of ESTRAMUSTINE—manufacturer of estramustine advises avoid concomitant administration; separating administration with antacids by about 12 hours advised by manufacturer of BOSUTINIB; antacids possibly reduce plasma concentration of ERLOTINIB—give antacids at least 4 hours before or 2 hours after erlotinib.

Deferasirox: antacids containing aluminium possibly reduce absorption of DEFERASIROX (manufacturer of deferasirox advises avoid concomitant use)

Diflunisal: antacids possibly reduce absorption of DIFLUNISAL.

Drotrecogin: antacids possibly reduce absorption of DROTRECOGIN.

Eltrombopag: antacids reduce absorption of ELTROMBOPAG (give at least 4 hours apart)

Folates: antacids possibly reduce absorption of FOLIC ACID (manufacturer of folinic acid advises give at least 2 hours apart)

Iron Salts: oral magnesium salts (as magnesium trisilicate) reduce absorption of oral IRON SALTS

Lipid-regulating Drugs: antacids reduce absorption of ROSUVASTATIN.

Lithium: sodium bicarbonate increases excretion of LITHIUM (reduced plasma concentration)

Myophosphonate: antacids reduce absorption of MYOPHOSPHONATE.

Penicillamine: antacids reduce absorption of PENICILLAMINE.

Polyethylene Sulfonate Resin: risk of intestinal obstruction when aluminium hydroxide given with POLYSTYRENE.

Antacids

Polystyrene Sulfonate Resins (continued)

SULFONATE RESINS; risk of metabolic alkalosis when oral magnesium salts given with POLYSTYRENE SULFONATE RESINS

Riociguat: antacids reduce absorption of RIOCIQUAT (give at least 2 hours before or 1 hour after riociguat).

Symptomlimiters: aluminium hydroxide possibly increases absorption of PSEUDOEPHEDRINE.

Thyroid Hormones: antacids possibly reduce absorption of LETHYLOXYRHODIZINE.

Ulcerc Healing Drugs: antacids possibly reduce absorption of LANSOPRAZOLE.

Antazoline see Antihistamines

Antithrombotics see Individual drugs

Antithrombin see Immunoglobulins

Anti-arrhythmics see Adenosine, Amiodarone, Disopyramide, Dronedarone, Flecaïnine, Lidocaïne, and Propafenone

Antibacterials see Individual drugs

Antibiotics (cytotoxic) see Bleomycin, Doxorubicin, Epirubicin, Idrabucin, Mitomycin, Mitoxantrone, and Pixaantrone

Anticoagulants see Apixaban, Argatroban, Bivalirudin, Coumarins, Dabigatran, Danaparoid, Fondaparinux, Heparins, Phenindione, and Rivaroxaban.

Antidepressants see Agomelatine; Antidepressants, SSRI; Antidepressants, Tricyclic; Antidepressants, Tricyclic (related); MAOIs; Mirtazapine; Moclobemide; Reboxetine; St John’s Wort; Venlafaxine.

Antidepressants, Noradrenaline Re-uptake Inhibitors see Reboxetine.

Antidepressants, SSRIs

Note see also Dapoxetine

Alcohol: sedative effects possibly increased when SSRIs given with ALCOHOL.

Aminophylline: fluvoxamine increases plasma concentration of AMINOPHYLLINE (concomitant use should usually be avoided, but where not possible halve aminophylline dose and monitor plasma-aaminophylline concentration)

Anaesthetics, Local: fluvoxamine inhibits metabolism of ROPIVACAINE—avoid prolonged administration of ropivacaine.

Analgesics: increased risk of bleeding when SSRIs given with NSAIDS or ASPIRIN; possible increased serotonergic effects when SSRIs given with FENTANYL; fluoxetine, fluvoxamine, paroxetine and sertraline possibly increase plasma concentration of METHADONE; increased risk of CNS toxicity when SSRIs given with TRAMADOL.

Anti-arrhythmics: manufacturer of citalopram and escitalopram advises avoid concomitant use with AMIODARONE (risk of ventricular arrhythmias); manufacturer of citalopram and escitalopram advises avoid concomitant use with DISOPYRAMIDE (risk of ventricular arrhythmias); manufacturer of citalopram and escitalopram advises avoid concomitant use with DRONEDARONE (risk of ventricular arrhythmias); fluoxetine increases plasma concentration of FLECAINIDE; fluoxetine and paroxetine possibly inhibit metabolism of PROPafenONE.

Antibacterials: manufacturer of citalopram and escitalopram advises avoid concomitant use with intravenous AMIODARONE (risk of ventricular arrhythmias); manufacturer of citalopram and escitalopram advises avoid concomitant use with TELITHROMYCIN (risk of ventricular arrhythmias); possible increased risk of ventricular arrhythmias when citalopram given with TELITHROMYCIN.

Anticoagulants: SSRIs possibly enhance anticoagulant effect of COUMARINS; possible increased risk of bleeding when SSRIs given with DABIGATRAN.

Antidepressants: avoidance of fluvoxamine advised by manufacturer of REBOXETINE; possible increased serotoninergic effects when SSRIs given with DUOXETINE; fluvoxamine inhibits metabolism of DUOXETINE—avoid concomitant use; citalopram, escitalopram, fluvoxamine, paroxetine or sertraline should not be started until 2 weeks after stopping MAOIs, also MAOIs should not be started until at least 1 week after stopping citalopram, escitalopram, fluvoxamine, paroxetine or sertraline; fluoxetine should not
Antidepressants, SSRI

- Antidepressants (continued)

be started until 2 weeks after stopping • MAOI, also MAOIs should not be started until at least 5 weeks after stopping fluoxetine; CNS effects of SSRIs increased by • MAOI (risk of serious toxicity); increased risk of CNS toxicity when escitalopram given with • MOLOBEMIDE, preferably avoid concomitant use; after stopping citalopram, fluvoxamine, paroxetine or sertraline do not start • MOLOBEMIDE for at least 1 week after stopping fluoxetine do not start • MOLOBEMIDE for 5 weeks; increased serotonergic effects when SSRIs given with • ST JOHN’S WORT—avoid concomitant use; fluvoxamine inhibits metabolism of • AGOMELATINE (increased plasma concentration); possible increased serotonergic effects when fluoxetine or fluvoxamine given with • SSRIs increase plasma concentration of some • TRICYCLICS; manufacturer of citalopram and escitalopram advises avoid concomitant use with • TRICYCLICS (risk of ventricular arrhythmias)

- Antiepileptics: SSRIs antagonise anticonvulsant effect of • ANTIPELIEPTICS (convulsive threshold lowered); fluoxetine and fluvoxamine increase plasma concentration of • CARBAMAZEPINE; fluoxetine and fluvoxamine increase plasma concentration of • FOSPHENTYNO; plasma concentration of sertraline possibly reduced by • PHENYTOIN and • PHENOTYNO, also plasma concentration of fosphenytoin and phenytoin possibly increased; plasma concentration of paroxetine reduced by • FOSPHENTYNO, • PHENOBARBITAL, • PHENYTOIN and • PRIMIDONE; fluoxetine and fluvoxamine increase plasma concentration of • PHENOTYNO

- Antifungals: plasma concentration of paroxetine possibly increased by • TERBINAFINE

- Antihistamines: manufacturer of citalopram and escitalopram advises avoid concomitant use with • MIZOLASTINE (risk of ventricular arrhythmias); antihistaminic effect of SSRIs possibly antagonised by • CYPROHEPTADINE

- Antimalarials: avoidance of antidepressants advised by manufacturer of • ARTEMETHER WITH LUMEFANTRINE and • ARTEMIL WITH PIPERAZINE; possible increased risk of ventricular arrhythmias; citalopram or escitalopram given with • ARTEMIL WITH LUMEFANTRINE—avoid concomitant use; possible increased risk of ventricular arrhythmias when citalopram or escitalopram given with • ARTEMIL WITH PIPERAZINE—avoid concomitant use; possible increased risk of ventricular arrhythmias when citalopram or escitalopram given with • CHLOROQUINE; possible increased risk of ventricular arrhythmias when citalopram or escitalopram given with • QUININE—avoid concomitant use

- Antipsychotics: citalopram increases plasma concentration of • DARIFENACIN and • PROCYCLIDINE

- Antipsychotics: avoidance of fluoxetine, fluvoxamine and sertraline advised by manufacturer of • DROPERIDOL (risk of ventricular arrhythmias); manufacturer of citalopram and escitalopram advises avoid concomitant use with • HALOPERIDOL (risk of ventricular arrhythmias); fluoxetine increases plasma concentration of • CLOzapine, • HALOPERIDOL and • RISPERIDONE; fluvoxamine possibly increases plasma concentration of • ASENAPINE and • HALOPERIDOL; paroxetine inhibits metabolism of • PERPHENAZINE (reduce dose of phenerazine); fluoxetine and paroxetine possibly increase plasma concentration of • ARPIpipRAZOLE (reduce dose of aripiprazole—consult aripiprazole product literature); plasma concentration of paroxetine possibly increased by • ASENAPINE; fluvoxamine, paroxetine and sertraline increase plasma concentration of • CLOzapine; citalopram possibly increases plasma concentration of • CLOzapine (increased risk of toxicity); fluoxetine increases plasma concentration of • OLANZAPINE; manufacturer of citalopram and escitalopram advises avoid concomitant use with • PHENOTYNO (risk of ventricular arrhythmias); manufacturer of citalopram and escitalopram advises avoid concomitant use with • PIMOZIDE (risk of ventricular arrhythmias); SSRIs possibly increase plasma concentration of • PIMOZIDE (increased risk of ventricular arrhythmias—avoid concomitant use); paroxetine possibly increases plasma concentration of • RISPERIDONE (increased risk of toxicity)

- Anti-HIV: plasma concentration of paroxetine and sertraline possibly reduced by • DURANAVIR; plasma concentration of SSRIs possibly increased by • RITONAVIR; plasma concentration of paroxetine possibly reduced by • RITONAVIR

- Anticholinergics: fluoxetine increases plasma concentration of • ALPRAZOLAM; fluoxetine increases plasma concentration of • PHENOBARBITAL, also plasma concentration of fosphenytoin increases plasma concentration of some • BENZODIAZEPINES; fluoxetine increases plasma concentration of • MELATONIN—avoid concomitant use; sedative effects possibly increased when sertraline given with • ZOLPIDEM

- Atomoxetine: possible increased risk of convulsions when antidepressants given with • ATOMOXETINE; fluoxetine and paroxetine possibly inhibit metabolism of • ATOMOXETINE

- Beta-blockers: citalopram and escitalopram increase plasma concentration of • METOPROLOL; paroxetine possibly increases the plasma concentration of • METOPROLOL—increased risk of AV block (manufacturer of paroxetine advises avoid concomitant use in cardiac insufficiency); fluvoxamine increases plasma concentration of • PROPRANOLOL; • PROPRANOLOL increases risk of ventricular arrhythmias when citalopram given with • SOTALOL—avoid concomitant use; manufacturer of escitalopram advises avoid concomitant use with • SOTALOL (risk of ventricular arrhythmias)

- Buproprion: plasma concentration of citalopram possibly increased by • BUPROPION

- Calcium-channel Blockers: fluoxetine possibly inhibits metabolism of • NIFEDIPINE (increased plasma concentration)

- Clopidogrel: fluoxetine and fluvoxamine possibly reduce antiplatelet effect of • CLOPIDOGREL

- Dopaminergic: possible increased risk of serotonergic effects when SSRIs given with • DAPoxetine (manufacturer of dapoxetine advises SSRIs should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping SSRIs)

- Dopaminergic: increased risk of CNS toxicity when SSRIs given with • RASAGLINE; fluoxetine should not be started until 2 weeks after stopping • RASAGLINE; fluoxetine should not be started until 2 weeks after stopping • RASAGLINE, also rasagiline should not be started until at least 5 weeks after stopping fluoxetine; avoidance of citalopram and escitalopram when citalopram and escitalopram given with • CHLOROQUINE; increased risk of ventricular arrhythmias when citalopram or escitalopram given with • QUININE—avoid concomitant use

- Dopaminergic: increased risk of toxicity when SSRIs given with • CLOZAPINE, • PERPHENAZINE; • SELEGILINE possibly increased by • CLOZAPINE (increased risk of toxicity)

- Dopaminergic: increased risk of hypertension and CNS excitation when fluvoxamine or sertraline given with • SELEGILINE (selegiline should not be started until 1 week after stopping fluvoxamine or sertraline, avoid fluvoxamine or sertraline for 2 weeks after stopping selegiline); increased risk of hypertension and CNS excitation when fluoxetine or sertraline given with • SELEGILINE (selegiline should not be started until 5 weeks after stopping fluoxetine, avoid fluoxetine for 2 weeks after stopping selegiline)

- Dopaminergic: increased risk of toxicity when SSRIs given with • CLOZAPINE, • PERPHENAZINE; • SELEGILINE possibly increased by • CLOZAPINE (increased risk of toxicity)

- Dopaminergic: increased risk of toxicity when SSRIs given with • CLOZAPINE, • PERPHENAZINE; • SELEGILINE possibly increased by • CLOZAPINE (increased risk of toxicity)

- Dopaminergic: increased risk of toxicity when SSRIs given with • CLOZAPINE, • PERPHENAZINE; • SELEGILINE possibly increased by • CLOZAPINE (increased risk of toxicity)

- Dopaminergic: increased risk of toxicity when SSRIs given with • CLOZAPINE, • PERPHENAZINE; • SELEGILINE possibly increased by • CLOZAPINE (increased risk of toxicity)

- Dopaminergic: increased risk of toxicity when SSRIs given with • CLOZAPINE, • PERPHENAZINE; • SELEGILINE possibly increased by • CLOZAPINE (increased risk of toxicity)

- Dopaminergic: increased risk of toxicity when SSRIs given with • CLOZAPINE, • PERPHENAZINE; • SELEGILINE possibly increased by • CLOZAPINE (increased risk of toxicity)
Antidepressants, SSRI (continued)

- Lipid-regulating Drugs: separating administration from fluoxetine and fluvoxamine by 12 hours advised by manufacturer of LOMITAPIDE
- Lithium: increased risk of CNS effects when SSRIs given with lithium (lithium toxicity reported)
- Methylthioninium: risk of CNS toxicity when SSRIs given with methylthioninium (avoid concomitant use for up to 4 hours after administration)
- Metoclopramide: CNS toxicity reported when SSRIs given with METOCLOPRAMIDE
- Muscle Relaxants: fluvoxamine increases plasma concentration of TIZANIDINE (increased risk of toxicity)—avoid concomitant use
- Parasymptomimetics: paroxetine increases plasma concentration of GALANTAMINE
- Pentamidine isetionate: manufacturer of cilostopram and escitalopram avoids concomitant use with PENTAMIDINE ISETIONATE (risk of ventricular arrhythmias)
- Pirfenidone: fluvoxamine increases plasma concentration of PIRFENIDONE—manufacturer of pirfenidone advises avoid concomitant use
- Pomalidomide: fluvoxamine increases plasma concentration of POMALIDOMIDE
- Ranolazine: paroxetine increases plasma concentration of RANOLAZINE
- Roflumilast: fluvoxamine inhibits the metabolism of ROFLUMILAST
- Sympathomimetics: metabolism of SSRIs possibly inhibited by METHYLPHENIDATE
- Theophylline: fluvoxamine increases plasma concentration of THEOPHYLLINE (concomitant use should usually be avoided, but where not possible halve theophylline dose and monitor plasma— Theophylline concentration)
- Ticagrelor: possible increased risk of bleeding when cilostopram, paroxetine or sertraline given with TICAGRELOR
- Ulcer-healing Drugs: plasma concentration of cilostopram, escitalopram and sertraline increased by Cimetidine; fluvoxamine possibly increases plasma concentration of Lansoprazole; plasma concentration of escitalopram increased by Omeprazole

Antidepressants, SSRI (related) see Duloxetine and Venlafaxine

Antidepressants, Tricyclic

- Adrenergic Neurone Blockers: tricyclics antagonise hypothetensive effect of ADRENERGIC NEURONE BLOCKERS
- Alcohol: increased sedative effect when tricyclics given with ALCOHOL
- Alpha-adrenoceptor Stimulants: avoidance of tricyclics advised by manufacturer of APRACLONIDINE and BRIMONIDINE
- Anaesthetics, General: increased risk of arrhythmias and hypotension when tricyclics given with GENERAL ANAESTHETICS
- Analgesics: increased risk of CNS toxicity when tricyclics given with TRAMADOL—side effects possibly increased when tricyclics given with NEFOPAM; sedative effects possibly increased when tricyclics given with OPIOID ANALGESICS
- Anti-arrhythmics: increased risk of ventricular arrhythmias when tricyclics given with DISOPYRAMIDE or FLECAINIDE; avoidance of tricyclics advised by manufacturer of DRONEDARONE (risk of ventricular arrhythmias); increased risk of arrhythmias when tricyclics given with PRPAFENONE
- Antibacterials: increased risk of ventricular arrhythmias when tricyclics given with MOXIFLOXACIN—avoid concomitant use; possible increased risk of ventricular arrhythmias when tricyclics that prolong the QT interval given with DELAMANID; possible increased risk of ventricular arrhythmias when tricyclics given with TELITHROMYCIN
- Anticoagulants: tricyclics may enhance or reduce anticoagulant effect of COUMARINS
- Antidepressants: avoidance of tricyclics advised by manufacturer of CITOLAPRAM and ESCITALOPRAM (risk of ventricular arrhythmias); possible increased serotonergic

Antidepressants, Tricyclic

- Antidepressants (continued)
  - effects when amitriptyline or clomipramine given with DULOXETINE; increased risk of hypertension and CNS excitation when tricyclics given with MAOIS, tricyclics should not be started until 2 weeks after stopping MAOIs (3 weeks if starting clomipramine or imipramine), also MAOIs should not be started for at least 1–2 weeks after stopping tricyclics (5 weeks in the case of clomipramine or imipramine); after stopping tricyclics do not start MOLOBEMIDE for at least 4 weeks; plasma concentration of some tricyclics increased by SSRIs; plasma concentration of amitriptyline reduced by ST JOHN’S WORT
  - Antiepileptics: tricyclics antagonise anticonvulsant effect of ANTIEPILEPTICS (convulsive threshold lowered); metabolism of tricyclics accelerated by CARBAMAZEPINE (reduced plasma concentration and reduced effect); plasma concentration of tricyclics possibly reduced by FOSPHENYTOIN and PHENOBARBITAL and PRIMIDONE (reduced plasma concentration)
  - Antifungals: plasma concentration of amitriptyline and nortriptyline possibly increased by FLUCONAZOLE; plasma concentration of tricyclics possibly increased by TERTIBAFINE
  - Antihistamines: increased antimuscarinic and sedative effects when tricyclics given with ANTHISTAMINES
  - Antimalarias: avoidance of antidepressants advised by manufacturer of ARTEMETHER with LUMEFANTRINE and ARTEMINIL with PIPERAQUIN
  - Antimuscarinics: increased risk of antimuscarinic side-effects when tricyclics given with ANTIMUSCARINICS
  - Antipsychotics: avoidance of tricyclics advised by manufacturer of DROPERIDOL, FLUPHENAZINE, HALOPERIDOL, SULPIRIDE and ZUCLOPENTHIXOL (risk of ventricular arrhythmias); possible increased antimuscarinic side-effects when tricyclics given with CLOZAPINE; increased risk of antimuscarinic side-effects when tricyclics given with PHENOTHIAZINES; possible increased risk of ventricular arrhythmias when tricyclics given with RISPERIDONE
  - Antivirals: plasma concentration of tricyclics possibly increased by RITONAVIR; increased risk of ventricular arrhythmias when tricyclics given with SQUINAVIR—avoid concomitant use
  - Anxiolytics and Hypnotics: increased sedative effect when tricyclics given with ANXIOLYTICS AND HYPNOTICS
  - Atomoxetine: increased risk of ventricular arrhythmias when tricyclics given with ATOMOXETINE; possible increased risk of convulsions when antidepressants given with ATOMOXETINE
  - Beta-blockers: plasma concentration of imipramine increased by LABELALOL and PROPRANOLOL; increased risk of ventricular arrhythmias when tricyclics given with SOTALOL
  - Bupropion: plasma concentration of tricyclics possibly increased by BUPROPION (possible increased risk of convulsions)
  - Calcium-channel Blockers: plasma concentration of imipramine increased by DILTIAZEM and VERAPAMIL; plasma concentration of tricyclics possibly increased by DILTIAZEM and VERAPAMIL
  - Cannabis Extract: possible increased risk of hypertension and tachycardia when tricyclics given with CANNABIS EXTRACT
  - Clonidine: tricyclics antagonise hypertensive effect of CLONIDINE, also increased risk of hypertension on clonidine withdrawal
  - Cytotoxics: increased risk of ventricular arrhythmias when amitriptyline or clomipramine given with ARSENIC TRIOXIDE
  - Dapoxetine: possible increased risk of serotonin effects when tricyclics given with DAPoxetine (manufacturer of dapoxetine advises tricyclics should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping tricyclics)
  - Disulfiram: metabolism of tricyclics inhibited by DISULFIRAM (increased plasma concentration); concomitant amitriptyline reported to increase DISULFIRAM reaction with alcohol
  - Diuretics: increased risk of postural hypotension when tricyclics given with diuretics
  - Dopaminergics: caution with tricyclics advised by manufacturer of ENTACAPONE; increased risk of CNS toxicity
Antidepressants, Tricyclic (related) (continued)

» Antimuscarnics: possible increased antimuscarinic side-effects when tricyclic-related antidepressants given with

ANTIUSCARNICS

» Antivirals: plasma concentration of trazodone increased by

Ritonavir (increased risk of toxicity); increased risk of ventricular arrhythmias when trazodone given with

SAQUINAVIR—avoid concomitant use; plasma concentration of trazodone possibly increased by TELAPREVIR

» Anticholinergics and hypnotics: increased sedative effect when tricyclic-related antidepressants given with ANTIUSCARNICS AND HYPNOTICS

» Atomoxetine: possible increased risk of convulsions when antidepressants given with

ATOMOXETINE

» Diazoxide: enhanced hypotensive effect when tricyclic-related antidepressants given with

DIAZoxide

» Nitrates: tricyclic-related antidepressants possibly reduce effects of sublingual tablets of

NITRATES (failure to dissolve under tongue owing to dry mouth)

» Vasodilator Antihypertensives: enhanced hypotensive effect when tricyclic-related antidepressants given with

HYDRAZINE or SODIUM NITROPRUSIDE

Antidiabetics

NOTE Other drugs administered orally may need to be taken at least 1 hour before or 4 hours after exenatide injection, or taken with a meal when linsidetate is not administered, to minimise possible interference with absorption

NOTE Other drugs administered orally may need to be taken at least 1 hour before or 4 hours after exenatide injection, or taken with a meal when exenatide is not administered, to minimise possible interference with absorption

ACE Inhibitors: hypoglycaemic effect of insulin, metformin and sulfonylureas possibly enhanced by ACE INHIBITORS

» Alcohol: hypoglycaemic effect of antidiabetics enhanced by

ALCOHOL; increased risk of lactic acidosis when metformin given with

ALCOHOL

» Anabolic Steroids: hypoglycaemic effect of antidiabetics possibly enhanced by ANABOLIC STEROIDS

» Analgesics; effects of sulfonylureas possibly enhanced by

NEOcyn; lixisenatide possibly reduces the absorption of

PARACETAMOL when given 1 to 4 hours before paracetamol

Anti-arrhythmics: hypoglycaemic effect of gliclazide, insulin and metformin possibly enhanced by DISOPYRAMIDE

» Antibacterials: hypoglycaemic effect of acarbose possibly enhanced by

NEOcyn; also severity of gastro-intestinal effects increased; effects of repaglinide enhanced by

CLARITHROMYCIN; effects of glibenclamide possibly enhanced by

NORFLOXACIN; plasma concentration of canagliflozin and nateglinide reduced by

RIFAMPICIN; effects of linagliptin possibly reduced by

RIFAMPICIN; hypoglycaemic effect of repaglinide possibly antagonised by

RIFAMPICIN; effects of sulfonylureas enhanced by

CHLORAPMENIC; metabolism of tolbutamide accelerated by

RIFAMPICIN (reduced effect); metabolism of sulfonylureas possibly accelerated by

RIFAMPICIN (reduced effect); effects of sulfonylureas rarely enhanced by

SULFONAMIDES and TRIMETHOPRIM; hypoglycaemic effect of sulfonylureas possibly enhanced by

TETRACYCLINES; hypoglycaemic effect of repaglinide possibly enhanced by

TRIMETHOPRIM—manufacturer advises avoid concomitant use

» Anticoagulants: exenatide possibly enhances anticoagulant effect of

WARFARIN; hypoglycaemic effect of sulfonylureas possibly enhanced by

COUMARINS, also possible changes to anticoagulant effect

» Antidepressants: hypoglycaemic effect of antidiabetics possibly enhanced by

MAOIS; hypoglycaemic effect of insulin, metformin and sulfonylureas enhanced by

MAOIS

» Antidiabetics: manufacturer of dapagliflozin advises avoid concomitant use with

PIGGLITAZONE

Antiepileptics: tolbutamide transiently increases plasma concentration of

FOSPHENITOIN and PHENYTOIN (possibility of toxicity); plasma concentration of glibenclamide possibly reduced by

TOPIRAMATE; plasma concentration of metformin possibly increased by

TOPIRAMATE

» Antifungals: plasma concentration of pioglitazone, saxagliptin and tolbutamide increased by

KETOCONAZOLE; plasma concentration of
Antidiabetics (continued)
- Antiarrhythmics: reduction in plasma concentration of acarbose; may be avoided concomitantly or a separate dose given
- Antiarrhythmics: reduced plasma concentration of acarbose; may be avoided concomitantly or a separate dose given
- Antiarrhythmics: increased risk of severe arrhythmias in patients treated with antiarrhythmics; do not use concomitantly

Antidiabetics (continued)
- Orlistat: avoidance of concomitant use with ORLISTAT
- Pancreatin: increased risk of severe diarrhea; do not use concomitantly
- Progestogens: hypoglycaemic effect of antidiabetes antagonised by PROGESTOGENS
- Sulfinpyrazone: effects of sulfinpyrazone antagonised by SULFINPYRAZONE
- Teriflunomide: plasma concentration of teriflunomide increased by TERIFLUNOMIDE
- Testosterone: hypoglycaemic effect of antidiabetes antagonised by TESTOSTERONE
- Ulcer-healing Drugs: excretion of metformin reduced by Cimetidine (increased plasma concentration); hypoglycaemic effect of sulfinpyrazone antagonised by Cimetidine

Antiepileptics
- Carbamazepine, Eslicarbazepine, Ethosuximide, Fosphenytoin, Gabapentin, Lacosamide, Lamotrigine, Levetiracetam, Oxcarbazepine, Perampanel, Phenoxybutil, Phenyltoin, Pregabalin, Primidone, Reticaine, Rufinamide, Sodium valproate, Stiripentol, Tiagabine, Topiramate, Valproic acid, Vigabatin, and Zonisamide

Antifungals
- Amphotericin; Antifungals, Imidazole; Antifungals, Triazole; Caspofungin; Fluconosine; Fluorosine; Griseofulvin; Micafungin; Terbinafine

Antifungals, Imidazole
- Alcohol: possibility of disulfiram-like reaction when ketoconazole given with ALCOHOL
- Aliskiren: increased plasma concentration of ALISKIREN
- Alpha-blockers: ketoconazole possibly increases plasma concentration of ALFLOZOSIN; ketoconazole increases plasma concentration of TAMSULOSIN
- Aminophylline: ketoconazole possibly increases plasma concentration of AMINOPHYLLINE
- Analgesics: ketoconazole inhibits metabolism of BUPRENORPHINE (reduce dose of buprenorphine); possible increased risk of ventricular arrhythmias when ketoconazole given with METHADONE—manufacturer of ketoconazole advises avoid concomitant use; ketoconazole increases plasma concentration of OXYCODONE; manufacturer of ketoconazole advises avoid concomitant use with PARACETAMOL
- Antacids: absorption of ketoconazole reduced by ANTACIDS
- Antihelmintics: increased plasma concentration of PRAZIQUANTEL
- Anti-arrhythmics: increased risk of ventricular arrhythmias when ketoconazole given with DISOPYRAMIDE—avoid concomitant use; ketoconazole increases plasma concentration of DRONEDARONE—avoid concomitant use
- Antibacterial: manufacturer of ketoconazole advises avoid concomitant use with CLARITHROMYCIN in severe renal impairment; metabolism of ketoconazole accelerated by RIFAMPICIN (reduced plasma concentration), also plasma concentration of rifampicin may be reduced by ketoconazole; ketoconazole increases plasma concentration of BEDAQUILINE—avoid concomitant use if ketoconazole given for more than 14 days; avoidance of ketoconazole advised by manufacturer of FIDASOMICIN; plasma concentration of ketoconazole possibly reduced by ISONIAZID; ketoconazole increases the plasma concentration of TELITHROMYCIN—avoid in severe renal and hepatic impairment
- Anticoagulants: ketoconazole increases plasma concentration of APIKABAN—manufacturer of apixaban advises avoid concomitant use; miconazole enhances anticoagulant effect of COUMARINS (miconazole oral gel and possibly vaginal and topical formulations absorbed); ketoconazole enhances anticoagulant effect of COUMARINS; ketoconazole increases plasma concentration of DARIGABATAN and RIVAROXABAN—avoid concomitant use
- Antidepressants: avoidance of imidazoles advised by manufacturer of REBOXETINE; ketoconazole increases plasma concentration of MIRTAZAPINE
- Antiinfectives: miconazole enhances hypoglycaemic effect of GLICLIZIDE and GLIPIZIDE—avoid concomitant use;
Avanafil: increased plasma concentration of 
• PLOGLITAZONE, SAXAGLIPTIN and TOLBUTAMIDE; miconazole increases plasma concentration of 
• SULFONLURAEs

Antiepileptics: miconazole possibly increases plasma concentration of CARBABAZEPINE; plasma concentration of ketonazole possibly reduced by CARBABAZEPINE, also plasma concentration of carbamazepine possibly increased; plasma concentration of ketonazole reduced by:
• FOSPHENYTOIN and PHENYTOIN; miconazole enhances anticonvulsant effect of FOSPHENYTOIN and PHENYTOIN (plasma concentration of fosphenytoin and phenytoin increased); ketonazole increases plasma concentration of PERAMPANO

Antifungals: idazoxane possibly antagonise effects of AMPHOTERICIN

Antihistamines: idazoxane possibly inhibit metabolism of:
• MIZOLASTINE (avoid concomitant use)

Antimalarials: avoidance of idazoxane advised by manufacturer of:
• ARTEMETHER WITH LUMEFANTRINE; avoidance of idazoxane advised by manufacturer of:
• ARTEMINMOL WITH PIPERAQUIN (possible risk of ventricular arrhythmias); ketonazole increases plasma concentration of MELDOQUINE

Antimuscarnics: absorption of ketonazole reduced by ANTIMUSCARINICS; ketonazole increases plasma concentration of DARIFENACIN—avoid concomitant use; manufacturer of fesoterodine advises dose reduction when ketonazole given with FESOTERODINE—consult fesoterodine product literature; ketonazole increases plasma concentration of OXYBUTYNIN; ketonazole increases plasma concentration of SOLIFENACIN—see under Solifenacin, p. 670; avoidance of ketonazole advised by manufacturer of:
• TOLTERODINE

Antipsychotics: ketonazole inhibits metabolism of:
• ARIPIPRAZOLE (reduce dose of aripiprazole); ketonazole increases plasma concentration of Lurasidone—avoid concomitant use; increased risk of ventricular arrhythmias when idazoxane given with PIMOZIDE—avoid concomitant use; idazoxane possibly increase plasma concentration of QUIETAPINE—manufacturer of quetiapine advises avoid concomitant use

Antivirals: ketonazole increases plasma concentration of:
• BOCEPREVIR; ketonazole increases the plasma concentration of:
• DACLATASVIR (see under Daclatasvir, p. 544); plasma concentration of both drugs increased when ketonazole given with DARUNAVIR; plasma concentration of ketonazole reduced by:
• EFAVIRENZ; plasma concentration of ketonazole increased by RALTEGRAVIR (also possibly fosamprenavir possibly increased); ketonazole increases plasma concentration of:
• INDINAVIR and MARAVIROC (consider reducing dose of indinavir and maraviroc); plasma concentration of ketonazole reduced by:
• NEVIRAPINE—avoid concomitant use; plasma concentration of ketonazole increased by:
• RITONAVIR (reduce dose of ketonazole); idazoxane possibly increase plasma concentration of SAQUINAVIR; ketonazole increases plasma concentration of:
• SAQUINAVIR—manufacturer of ketonazole advises avoid concomitant use; avoidance of ketonazole advised by manufacturer of:
• SIMPREVIR; plasma concentration of both drugs possibly increased when ketonazole given with TELAPREVIR (increased risk of ventricular arrhythmias)—reduce dose of ketonazole

Antioxidants and Hypotensives: ketonazole increases plasma concentration of:
• ALPRAZOLAM—manufacturer of ketonazole advises avoid concomitant use; ketonazole increases plasma concentration of:
• MIDAZOLAM (risk of prolonged sedation—avoid concomitant use of oral midazolam); ketonazole increases plasma concentration of ZOLPIDEM

Apresitant: ketonazole increases plasma concentration of:
• APREPIVIT

Avanafil: ketonazole increases plasma concentration of:
• AVANAFIL—avoid concomitant use

Antifungals, Imidazole (continued)

• Beta-blockers: ketonazole possibly increases plasma concentration of NADOLOL

Bosentan: ketonazole increases plasma concentration of:
• BOSENTAN

Calcium-channel Blockers: ketonazole inhibits metabolism of:
• FELODIPINE (increased plasma concentration)—manufacturer of ketonazole advises avoid concomitant use; avoidance of ketonazole advised by manufacturer of:
• LERANIDIPINE; ketonazole possibly inhibits metabolism of:
• DIHYDROPRIDINIDES (increased plasma concentration)

Cannabis Extract: ketonazole increases plasma concentration of CANNABIS EXTRACT

Ciclosporin: ketonazole inhibits metabolism of:
• CICLOSPORIN (increased plasma concentration); miconazole possibly inhibits metabolism of:
• CICLOSPORIN (increased plasma concentration)

Cilostazol: ketonazole increases plasma concentration of:
• CILOSTAZOL (see under Cilostazol, p. 206)

Cinacalcet: ketonazole inhibits metabolism of CINACALCET (increased plasma concentration)

Clopidogrel: ketonazole possibly reduces antiplatelet effect of:
• CLOPIDOGREL

Cobicistat: plasma concentration of ketonazole possibly increased by:
• COBICISTAT—manufacturer of cobicistat advises reduce dose of ketonazole

Colchicine: ketonazole possibly increases risk of:
• COLCHICINE toxicity—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)

Corticosteroids: ketonazole possibly inhibits metabolism of:
• CORTICOSTEROIDS; ketonazole increases the plasma concentration of inhaled and oral (and possibly also intranasal and rectal) Budesonide; ketonazole increases plasma concentration of active metabolite of:
• CICLESONIDE; ketonazole possibly increases plasma concentration of inhaled Fluticasone; ketonazole inhibits the metabolism of Methylprednisolone; ketonazole increases plasma concentration of inhaled Mometasone

Cytotoxic: ketonazole inhibits the metabolism of:
• IFOSFAMIDE; possible increased risk of neutropenia when ketonazole given with:
• BRENXTUMIBM VEDOTIN; ketonazole possibly increases the plasma concentration of:
• AFATINIB—manufacturer of afatinib advises separating administration of ketonazole by 6 to 12 hours; ketonazole increases plasma concentration of:
• AXITINIB (reduce dose of axitinib—consult axitinib product literature); ketonazole increases the plasma concentration of:
• BOSTINIB—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; ketonazole increases plasma concentration of:
• BORTezOMIB; CARBOZANTINIB, DABRAFENIB, IDOPOSIDE, IDELALISIB, IMATINIB and PONATINIB; ketonazole increases plasma concentration of:
• CRIZOTINIB; LAPATINIB, NILOTINIB and REGORAFENIB—avoid concomitant use; ketonazole possibly increases plasma concentration of:
• DASATINIB; ketonazole inhibits metabolism of:
• ERLOTINIB and SUNITINIB (increased plasma concentration); ketonazole increases plasma concentration of:
• EVEROLIMUS—manufacturer of ketonazole advises avoid concomitant use; ketonazole increases plasma concentration of:
• IBRUTINIB; reduce dose of ibrutinib (see under ibrutinib, p. 809); ketonazole increases plasma concentration of:
• PAZOPANIB (reduce dose of pazopanib); manufacturer of ruxolitinib advises dose reduction when ketonazole given with:
• RUXOLITINIB—consult ruxolitinib product literature); ketonazole reduces plasma concentration of:
• IRINOTECAN (but concentration of irinotecan increased)—avoid concomitant use; ketonazole increases plasma concentration of:
• VINFLUNINE—manufacturer of vinflunine advises avoid concomitant use
Antifungals, Imidazole (continued)
- Dapoxetine: ketoconazole increases plasma concentration of dapoxetine—manufacturer of dapoxetine advises avoid concomitant use
- Diuretics: ketoconazole increases plasma concentration of diuretics—avoid concomitant use
- Domperidone: manufacturer of ketoconazole advises avoid concomitant use with domperidone (risk of ventricular arrhythmias)
- Ergot Alkaloids: manufacturer of ketoconazole advises avoid concomitant use with ergot alkaloids; increased risk of ergotism when imidazoles given with ergotamine—avoid concomitant use
- Fingolimod: ketoconazole increases plasma concentration of fingolimod
- Fosaprepitant: ketoconazole increases plasma concentration of fosaprepitant
- Hormone Antagonists: manufacturer of ketoconazole advises avoid concomitant use with pasireotide
- SHT-receptor Agonists: ketoconazole increases plasma concentration of almotriptan (increased risk of toxicity); ketocazole increases plasma concentration of eletriptan (risk of toxicity)—avoid concomitant use
- Itraloxifene: ketoconazole increases plasma concentration of itraloxifene—avoid concomitant use
- Ivacafort: ketoconazole increases plasma concentration of ivacafort (see under ivacafort, p. 257)
- Lanthanum: absorption of ketoconazole possibly reduced by lanthanum (give at least 2 hours apart)
- Lenalidomide: ketoconazole possibly increases plasma concentration of lenalidomide (increased risk of toxicity)
- Lipid-regulating Drugs: possible increased risk of myopathy when imidazoles given with atorvastatin; possible increased risk of myopathy when ketoconazole given with atorvastatin—manufacturer of ketoconazole advises avoid concomitant use; increased risk of myopathy when ketoconazole given with simvastatin (avoid concomitant use); possible increased risk of myopathy when miconazole given with simvastatin; ketoconazole increases plasma concentration of lipophilic statins—avoid concomitant use
- Macitentan: ketoconazole increases plasma concentration of macitentan
- Mirabegron: when given with ketoconazole avoid or reduce dose of mirabegron in hepatic or renal impairment—see mirabegron, p. 671
- Nintedanib: ketoconazole increases plasma concentration of nintedanib
- Nintedanib
- Oxycodeone: absorption of ketoconazole possibly reduced by oxycodeone (increased risk of uveitis; manufacturer of oxycodeone advises avoid concomitant use with oxycodeone; itraconazole possibly increases plasma concentration of oxycodeone increases plasma concentration of paricalcitol)
- Anticancer Drugs: concentration of fluorouracil is increased by ketoconazole; rifampicin possibly increases risk of toxicity when ketoconazole given with rifampicin; fluconazole increases plasma concentration of itraconazole—avoid concomitant use
- Aminophylline: fluconazole possibly increases plasma concentration of aminophylline
- Analgesics: fluconazole increases plasma concentration of celecoxib (halve dose of celecoxib); voriconazole increases plasma concentration of diclofenac, ibuprofen and oxycodone; fluconazole increases plasma concentration of parecoxib (reduce dose of parecoxib); voriconazole increases plasma concentration of alfentanil and methadone; fluconazole increases plasma concentration of fentanyl; triazoles possibly increase plasma concentration of methadone (increased risk of ventricular arrhythmias); itraconazole increases plasma concentration of oxycodone
- Antacids: absorption of itraconazole reduced by antacids
- Antiarrhythmics: manufacturer of itraconazole advises avoid concomitant use with disopyramide; avoidance of itraconazole, posaconazole and voriconazole advised by manufacturer of dronedarone
- Antibacterials: plasma concentration of itraconazole increased by clarithromycin; manufacturer of fluconazole advises avoid concomitant use with erythromycin; triazoles possibly increase plasma concentration of rifabutin (increased risk of uveitis—reduce rifabutin dose); posaconazole increases plasma concentration of rifabutin (also plasma concentration of posaconazole reduced); voriconazole increases plasma concentration of rifabutin, also rifabutin reduces plasma concentration of voriconazole (increased dose of voriconazole and also monitor for rifabutin toxicity); fluconazole increases plasma concentration of rifabutin (increased risk of uveitis—reduce rifabutin dose); plasma concentration of itraconazole reduced by rifabutin and rifampicin; manufacturer of itraconazole advises avoid concomitant use; plasma concentration of posaconazole reduced by rifampicin; plasma concentration of voriconazole reduced by rifampicin—avoid concomitant use; metabolism of fluconazole accelerated by rifampicin (reduced plasma concentration); fluconazole possibly increases plasma concentration of bedaquiline—avoid concomitant use if fluconazole given for more than 14 days
- Anticoagulants: avoidance of itraconazole, posaconazole and voriconazole advised by manufacturer of apixaban; fluconazole, itraconazole and voriconazole enhance
Antifungals, Triazole
- Anticoagulants (continued)
  anticoagulant effect of COUMARINS; avoidance of itraconazole advised by manufacturer of dabigatran and rivaroxaban; avoidance of posaconazole and voriconazole advised by manufacturer of rivaroxaban
- Antidepressants: avoidance of triazoles advised by manufacturer of reboxetine; fluconazole possibly increases plasma concentration of amitriptyline and nortriptyline; plasma concentration of voriconazole reduced by ST JOHN’S WORT—avoid concomitant use
- Antibacterials: posaconazole possibly enhances hypoglycaemic effect of glipizide; fluconazole possibly enhances hypoglycaemic effect of Nateglinide; itraconazole possibly enhances hypoglycaemic effect of repaglinide; fluconazole increases plasma concentration of sulfonylureas; voriconazole possibly increases plasma concentration of sulfonylureas
- Antiepileptics: fluconazole possibly increases plasma concentration of clobazam; plasma concentration of voriconazole possibly reduced by carbamazepine; phenobarbital and primidone—avoid concomitant use; plasma concentration of itraconazole and posaconazole possibly reduced by carbamazepine; voriconazole increases plasma concentration of fosphenytoin and phenytoin, also fosphenytoin and phenytoin reduces plasma concentration of voriconazole (increase dose of voriconazole and also monitor for fosphenytoin and phenytoin toxicity); plasma concentration of posaconazole reduced by fosphenytoin and phenytoin; plasma concentration of itraconazole reduced by fosphenytoin and phenytoin; primidone; plasma concentration of itraconazole and posaconazole possibly reduced by phenobarbital; plasma concentration of itraconazole and posaconazole possibly reduced by primidone
- Antifungals: triazoles possibly antagonise effects of AMPHOTERICIN; monitoring for increased voriconazole side effects advised by manufacturer of fluconazole if voriconazole given after fluconazole; plasma concentration of itraconazole increased by micafungin (consider reducing dose of itraconazole); plasma concentration of fluconazole increased by terbinafine
- Antihistamines: itraconazole inhibits metabolism of mizolastine—avoid concomitant use
- Antimalarials: avoidance of triazoles advised by manufacturer of arteether with lumefantrine; avoidance of triazoles advised by manufacturer of arteether with piperaquine (possible risk of ventricular arrhythmias)
- Antimuscarinics: avoidance of itraconazole advised by manufacturer of darifenacine and tolterodine; manufacturer of fesoterodine advises dose reduction when itraconazole given with fesoterodine—consult fesoterodine product literature; itraconazole possibly increases plasma concentration of solifenacin—see under Solifenacin, p. 670
- Antipsychotics: itraconazole possibly increases plasma concentration of haloperidol; voriconazole possibly increases plasma concentration of aripiprazole (reduce dose of aripiprazole—consult aripiprazole product literature); itraconazole, posaconazole and voriconazole possibly increase plasma concentration of lurasidone—avoid concomitant use; voriconazole possibly increases the plasma concentration of lurasidone (see under Lurasidone, p. 315); increased risk of ventricular arrhythmias when triazoles given with pimozide—avoid concomitant use; triazoles possibly increase plasma concentration of quetiapine—manufacturer of quetiapine advises avoid concomitant use; itraconazole possibly increases side-effects of risperidone
- Antivirals: plasma concentration of voriconazole increased or decreased by atazanavir and plasma concentration of atazanavir also reduced; posaconazole increases plasma concentration of atazanavir; itraconazole, posaconazole and voriconazole possibly increase the plasma concentration of daclatasvir—reduce dose of daclatasvir (see under daclatasvir, p. 544); plasma concentration of voriconazole reduced by efavirenz, also plasma concentration of efavirenz increased (increase voriconazole dose and reduce efavirenz dose); plasma concentration of itraconazole and posaconazole reduced by efavirenz; plasma concentration of both drugs may increase when itraconazole given with fosamprenavir; plasma concentration of posaconazole possibly reduced by fosamprenavir; itraconazole increases plasma concentration of indinavir (consider reducing dose of indinavir); fluconazole increases plasma concentration of nevirapine, ritonavir and tipranavir; plasma concentration of itraconazole possibly reduced by nevirapine—consider increasing dose of itraconazole; plasma concentration of voriconazole reduced by ritonavir—avoid concomitant use; combination of itraconazole with ritonavir may increase plasma concentration of either drug (or both); triazoles possibly increase plasma concentration of saquinavir; fluconazole, itraconazole, posaconazole and voriconazole possibly increase plasma concentration of simprevir—manufacturer of simprevir advises avoid concomitant use; plasma concentration of voriconazole possibly affected by telaprevir (possible increased risk of ventricular arrhythmias); plasma concentration of posaconazole possibly increased by telaprevir (increased risk of ventricular arrhythmias); plasma concentration of itraconazole possibly increased by telaprevir; voriconazole increases plasma concentration of zidovudine (increased risk of toxicity)
- Anxiolytics and Hypnotics: itraconazole increases plasma concentration of alprazolam; fluconazole and voriconazole increase plasma concentration of diazepam (risk of prolonged sedation); fluconazole, itraconazole, posaconazole and voriconazole increase plasma concentration of midazolam (risk of prolonged sedation); itraconazole increases plasma concentration of buspirone (reduce dose of buspirone)
- Avanafil: itraconazole and voriconazole possibly increase plasma concentration of avanafil—manufacturer of avanafil advises avoid concomitant use; fluconazole possibly increases plasma concentration of avanafil—see under Avanafil, p. 698
- Bosentan: fluconazole possibly increases plasma concentration of bosentan—avoid concomitant use; itraconazole possibly increases plasma concentration of bosentan
- Calcium-channel Blockers: negative inotropic effect possibly increased when itraconazole given with calcium-channel blockers; itraconazole inhibits metabolism of felodipine (increased plasma concentration); avoidance of itraconazole advised by manufacturer of lercanidipine; itraconazole possibly inhibits metabolism of dihydropyridines (increased plasma concentration)
- Cardiac Glycosides: itraconazole increases plasma concentration of digoxin
- Ciclosporin: fluconazole, itraconazole, posaconazole and voriconazole inhibit metabolism of ciclosporin (increased plasma concentration)
- Clofazimine: itraconazole possibly increases plasma concentration of clofazimine (and clofazimine is a CYP3A inhibitor), itraconazole possibly increases plasma concentration of lurasidone (see under Lurasidone, p. 315); increased risk of ventricular arrhythmias when triazoles given with pimozide—avoid concomitant use; triazoles possibly increase plasma concentration of quetiapine—manufacturer of quetiapine advises avoid concomitant use; itraconazole possibly increases side-effects of risperidone
- Corticosteroids: itraconazole possibly inhibits metabolism of corticosteroids and methylprednisolone; itraconazole increases the plasma concentration of inhaled and oral (and...
Antifungals, Triazole
- Corticosteroids (continued) possibly also intranasal and rectal
- Budesonide; itraconazole increases plasma concentration of inhaled flusolone
- Cytotoxic: itraconazole inhibits metabolism of busulfan (increased risk of toxicity); fluconazole and itraconazole possibly increase side-effects of cyclophosphamide; itraconazole possibly increases the plasma concentration of astemizole; manufacturer of astemizole advises parating administration of itraconazole by 6 to 12 hours; itraconazole possibly increases plasma concentration of axitinib (reduce dose of axitinib—consult axitinib product literature); fluconazole, itraconazole, posaconazole and voriconazole possibly increase the plasma concentration of bosutinib; itraconazole possibly increases plasma concentration of cabozantinib; itraconazole and voriconazole possibly increase plasma concentration of crizotinib; manufacturer of crizotinib advises avoid concomitant use; avoidance of itraconazole advised by manufacturer of dasatinib and temsirolimus (plasma concentration of dasatinib and temsirolimus possibly increased); itraconazole, posaconazole and voriconazole possibly increase plasma concentration of everolimus—manufacturer of everolimus advises avoid concomitant use; itraconazole increases plasma concentration of gefitinib; fluconazole, itraconazole and voriconazole possibly increase the plasma concentration of ifritinib—reduce dose of ifritinib (see under ifritinib, p. 809); avoidance of itraconazole, posaconazole and voriconazole advised by manufacturer of lapatinib; avoidance of itraconazole and voriconazole advised by manufacturer of nilotinib; itraconazole and voriconazole possibly increase plasma concentration of pazopanib; itraconazole and voriconazole possibly increase plasma concentration of ponatinib—consider reducing initial dose of ponatinib (see under ponatinib, p. 814); manufacturer of ruxolitinib advises dose reduction when fluconazole, itraconazole, posaconazole and voriconazole given with ruxolitinib—consult ruxolitinib product literature; itraconazole and voriconazole possibly increase the plasma concentration of cabazitaxel—manufacturer of cabazitaxel advises avoid or consider reducing dose of cabazitaxel; itraconazole and voriconazole possibly increase plasma concentration of docetaxel—manufacturer of docetaxel advises avoid concomitant use or consider reducing docetaxel dose; increased risk of toxicity when itraconazole given with rimodotanec—avoid concomitant use; itraconazole possibly increases plasma concentration of vinblastine, vindesine, vinflunline and vinorelbin toxicity; posaconazole possibly inhibits metabolism of vinblastine and vincristine (increased risk of neurotoxicity); itraconazole increases risk of vincristine toxicity.
- Dapoxetine: manufacturer of dapoxetine advises dose reduction when fluconazole given with dapoxetine (see under dapoxetine, p. 705); avoidance of itraconazole advised by manufacturer of dapoxetine (increased risk of toxicity).
- Diuretics: fluconazole increases plasma concentration of eplerenone (reduce dose of eplerenone); itraconazole increases plasma concentration of eplerenone—avoid concomitant use; plasma concentration of fluconazole increased by hydrochlorothiazide.
- Domperidone: possible increased risk of ventricular arrhythmias when itraconazole or voriconazole given with domperidone—avoid concomitant use.
- Ergot Alkaloids: increased risk of ergotism when voriconazole given with ergometrine—avoid concomitant use; manufacturer of itraconazole advises avoid concomitant use with ergometrine (increased risk of ergotism); increased risk of ergotism when triazoles given with ergotamine—avoid concomitant use.
- SHT-receptor Agonists: itraconazole increases plasma concentration of eletriptan (risk of toxicity)—avoid concomitant use.

Antifungals, Triazole (continued)
- Ibravaine: fluconazole increases plasma concentration of ibravaine—reduce initial dose of ibravaine; itraconazole possibly increases plasma concentration of ibravaine—avoid concomitant use.
- Icavator: itraconazole, posaconazole and voriconazole possibly increase plasma concentration of icavator (see under Icavator, p. 257); fluconazole increases plasma concentration of icavator—avoid concomitant use.
- Lenalidomide: itraconazole possibly increases plasma concentration of lenalidomide (increased risk of toxicity).
- Leukotriene Receptor Antagonists: fluconazole increases plasma concentration of zafirlukast.
- Lipid-regulating Drugs: increased risk of myopathy when itraconazole, posaconazole or voriconazole given with atorvastatin; possible increased risk of myopathy when fluconazole given with atorvastatin or simvastatin; fluconazole increases plasma concentration of fluvastatin—possible increased risk of myopathy; itraconazole increases plasma concentration of rosuvastatin (consult product literature); increased risk of myopathy when itraconazole or posaconazole given with simvastatin (avoid concomitant use); increased risk of myopathy when voriconazole given with simvastatin; avoidance of triazoles advised by manufacturer of lomitapide (plasma concentration of lomitapide possibly increased).
- Mirabegron: when given with itraconazole avoid or reduce dose of mirabegron in hepatic or renal impairment—see Mirabegron, p. 671.
- Oestrogens: plasma concentration of voriconazole increased by oestrogens.
- Progestogens: plasma concentration of voriconazole possibly increased by progestogens.
- Ranolazine: itraconazole, posaconazole and voriconazole possibly increase plasma concentration of ranolazine—manufacturer of ranolazine advises avoid concomitant use.
- Retinoids: fluconazole and voriconazole possibly increase risk of retinoid toxicity.
- Rizoglan: avoidance of itraconazole and voriconazole advised by manufacturer of rizoglan.
- Sildenafil: itraconazole increases plasma concentration of sildenafil—reduce initial dose of sildenafil.
- Sirolimus: fluconazole and posaconazole possibly increase plasma concentration of sirolimus; itraconazole and voriconazole increase plasma concentration of sirolimus—avoid concomitant use.
- Tacrolimus: fluconazole, itraconazole, posaconazole and voriconazole increase plasma concentration of tacrolimus (consider reducing dose of tacrolimus).
- Tadalafil: itraconazole possibly increases plasma concentration of tadalafil.
- Theophylline: fluconazole possibly increases plasma concentration of theophylline.
- Ulcer-healing Drugs: plasma concentration of posaconazole reduced by cimetidine and esomeprazole—manufacturer of posaconazole suspension advises avoid concomitant use; plasma concentration of posaconazole possibly reduced by famotidine, lansoprazole, nizatidine, omeprazole, pantoprazole, rabeprazole and ranitidine—manufacturer of posaconazole suspension advises avoid concomitant use; voriconazole possibly increases plasma concentration of esomeprazole; voriconazole increases plasma concentration of omeprazole (consider reducing dose of omeprazole); absorption of itraconazole reduced by histamine H2-antagonists and proton pump inhibitors.
- Ulipristal: avoidance of itraconazole advised by manufacturer of ulipristal.
- Vardenafil: itraconazole possibly increases plasma concentration of vardenafil—avoid concomitant use.

Antihistamines
- Sedative interactions apply to a lesser extent to the non-sedating antihistamines. Interactions do not generally apply to antihistamines used for topical action (including inhalation).
Antihistamines (continued)

- Alcohol: increased sedative effect when antihistamines given with alcohol (possibly less effect with non-sedating antihistamines)
- Analgesics: sedative effects possibly increased when sedating antihistamines given with opioids, analgesics
- Antacids: absorption of fexofenadine reduced by antacids
- Anti-arrhythmics: increased risk of ventricular arrhythmias when mizolastine given with amiodarone, disopyramide, or flecainide; manufacturer of mizolastine advises avoid concomitant use with propafenone (possible risk of ventricular arrhythmias)
- Antibacterials: manufacturer of lomatadine advises plasma concentration possibly increased by erythromycin; metabolism of mizolastine inhibited by itraconazole—avoid concomitant use; increased risk of ventricular arrhythmias when mizolastine given with moxifloxacin—avoid concomitant use; effects of fexofenadine possibly reduced by rifampicin; metabolism of mizolastine possibly inhibited by macrolides (avoid concomitant use)
- Antidepressants: avoidance of mizolastine advised by manufacturer of citalopram and escitalopram (risk of ventricular arrhythmias); increased antimuscarinic and sedative effects when antihistamines given with MAOIs or tricyclics; manufacturer of promethazine advises avoid for 2 weeks after stopping MAOIs; manufacturer of hydroxyzine advises avoid concomitant use with MAOIs; cyproheptadine possibly antagonises antidepresant effect of SSRIs; possible increased antimuscarinic and sedative effects when antihistamines given with tricyclic-related antidepresants
- Antidiabetics: thomboctye count decreased when ketotifen given with metformin (manufacturer of ketotifen advises avoid concomitant use)
- Antifungals: metabolism of mizolastine inhibited by itraconazole—avoid concomitant use; metabolism of mizolastine possibly inhibited by imidazoles (avoid concomitant use)
- Antimalarials: avoidance of mizolastine advised by manufacturer of artemisomil with piperaquine (possible risk of ventricular arrhythmias)
- Antimuscarinics: increased risk of antimuscarinic side-effects when antihistamines given with antimuscarinics
- Antipsychotics: plasma concentration of chlorpromazine possibly increased by lorazepam; plasma concentration of chlorpromazine possibly increased when antimuscarinics given with MAOIs or tricyclics; increased risk of ventricular arrhythmias when mizolastine given with antimuscarinics possibly reduced effects of antimuscarinics and antihistamines; increased risk of ventricular arrhythmias when mizolastine given with imipramine when antimuscarinics given with manufactured by loratadine advises plasma concentration possibly increased by erythromycin; plasma concentration of active metabolite of fexofenadine reduced by rifampicin
- Anti-arrhythmics: increased risk of ventricular arrhythmias when toterodine given with amiodarone, disopyramide, or flecainide; increased risk of antimuscarinic side-effects when antihistamines given with nefopam
- Anti-arrhythmics: increased risk of ventricular arrhythmias when mizolastine given with amiodarone, disopyramide, or flecainide; increased risk of antimuscarinic side-effects when antihistamines given with nefopam
- Antihistamines: increased sedative effect when antihistamines given with alcohol (possibly increased effect with non-sedating antihistamines)
- Antihistamines, Sedating see Antihistamines
- Antimalarials see Artemether with lumefantrine, artemisomil with piperaquine, chloroquine, hydroxychloroquine, melfloquine, primaquine, proguanil, pyrimethamine, and quinine
- Antimetabolites see Cepacitabine, cladribine, cytarabine, decitabine, fludarabine, fluorouracil, gemcitabine,
- Antimetabolites (continued) Mercaptopurine, methotrexate, pemetrexed, raltitrexed, tegafur, and tioguanine
- Antimuscarinics see Antihistamines
- Antivirals see Ulcer-healing Drugs

Antimuscarinics

- Antidepressants: increased risk of ventricular arrhythmias when mizolastine given with amiodarone, disopyramide, or flecainide—avoid concomitant use; increased risk of antimuscarinic side-effects when antihistamines given with nefopam
- Antihistamines: increased sedative effect when antihistamines given with alcohol (possibly increased effect with non-sedating antihistamines)
- Analgesics: increased sedative effect when antihistamines given with alcohol (possibly less effect with non-sedating antihistamines)
- Antihistamines, Sedating see Antihistamines
- Antimalarials see Artemether with lumefantrine, artemisomil with piperaquine, chloroquine, hydroxychloroquine, melfloquine, primaquine, proguanil, pyrimethamine, and quinine
- Antimetabolites see Cepacitabine, cladribine, cytarabine, decitabine, fludarabine, fluorouracil, gemcitabine,
Antimuscarnics (continued)

- Dopaminergics: antimuscarnics possibly reduce absorption of
  **CO-BENELDOPA, CO-CARELDOPA and LEVODOPA**

- Hormone Antagonists: possible increased risk of bradycardia when ipratropium or oxybutynin given with **PASIRECTIDE**

- Memantine: effects of antimuscarnics possibly enhanced by **MEMANTINE**

- Metoclopramide: antimuscarnics antagonise effects of **METOCLOPRAMIDE** on gastro-intestinal activity

- Nitrates: antimuscarnics possibly reduce effects of sublingual tablets of **NITRATES** (failure to dissolve under tongue owing to dry mouth)

- Parasympathomimetics: antimuscarnics antagonise effects of **PARASYMPATOMIMETICS**

**Antipsychotics**

- Note: Increased risk of toxicity with myelosuppressive drugs

  **Note**: Avoid concomitant use of clozapine with drugs that have a substantial potential for causing agranulocytosis

- ACE Inhibitors: enhanced hypotensive effect when antipsychotics given with **ACE INHIBITORS**

- Adrenergic Neurone Blockers: enhanced hypotensive effect when phenothiazines given with **ADRENERGIC NEURONE BLOCKERS**; higher doses of chlorpromazine antagonise hypotensive effect of **ADRENERGIC NEURONE BLOCKERS**; haloperidol antagonises hypotensive effect of **ADRENERGIC NEURONE BLOCKERS**

- Adsorbents: absorption of phenothiazines possibly reduced by **KAOLIN**

- Alcohol: increased sedative effect when antipsychotics given with **ALCOHOL**

- Alpha-blockers: enhanced hypotensive effect when antipsychotics given with **ALPHA-BLOCKERS**

- Anaesthetics, General: droperidol enhances effects of **THIOPENTAL**; enhanced hypotensive effect when antipsychotics given with **GENERAL ANAESTHETICS**

- Analgesics: possible severe drowsiness when haloperidol given with **ACEMETACIN** or **INDOMETACIN**; increased risk of ventricular arrhythmias when antipsychotics that prolong the QT interval given with **METHADONE**; increased risk of ventricular arrhythmias when amisulpride given with **METHADONE**—avoid concomitant use; increased risk of convulsions when antipsychotics given with **TRAMADOL**; enhanced hypotensive and sedative effects when antipsychotics given with **OPIOID ANALGESICS**

- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when antipsychotics given with **ANGIOTENSIN-II RECEPTOR ANTAGONISTS**

- Antacids: absorption of phenothiazines and sulpiride reduced by **ANTACIDS**

- Anti-arrhythmics: increased risk of ventricular arrhythmias when antipsychotics that prolong the QT interval given with **ANTI-ARRHYTHMICS** that prolong the QT interval; increased risk of ventricular arrhythmias when amisulpride, droperidol, haloperidol, phenothiazines, pimozide or zuclopenthixol given with **AMIODARONE**—avoid concomitant use; increased risk of ventricular arrhythmias when benperidol given with **AMIODARONE**—manufacturer of benperidol advises avoid concomitant use; increased risk of ventricular arrhythmias when sulpiride given with **AMIODARONE** or **DISOPYRAMIDE**; increased risk of ventricular arrhythmias when amisulpride, droperidol, pimozide or zuclopenthixol given with **DISOPYRAMIDE**—avoid concomitant use; possible increased risk of ventricular arrhythmias when haloperidol given with **DISOPYRAMIDE**; increased risk of ventricular arrhythmias when phenothiazines given with **DISOPYRAMIDE**; increased risk of ventricular arrhythmias when clozapine given with **DISOPYRAMIDE**; increased risk of ventricular arrhythmias when zuclopenthixol given with **DISOPYRAMIDE**

- Antibacterials: plasma concentration of lurasidone possibly increased by **CLARITHROMYCIN** and **TELITHROMYCIN**—avoid concomitant use; increased risk of ventricular arrhythmias when pimozide given with **CLARITHROMYCIN** or **MOXIFLOXACIN** or **TELITHROMYCIN**—avoid concomitant use; plasma concentration of quetiapine possibly increased by **CLARITHROMYCIN**—manufacturer of quetiapine advises avoid interactions

**Antipsychotics**

- Antibacterials (continued) concomitant use; plasma concentration of lurasidone possibly increased by **ERYTHROMYCIN** (see under Lurasidone, p. 515); increased risk of ventricular arrhythmias when amisulpride given with **ERYTHROMYCIN**—avoid concomitant use; plasma concentration of clozapine possibly increased by **ERYTHROMYCIN** (possible increased risk of convulsions); possible increased risk of ventricular arrhythmias when pimozide given with **ERYTHROMYCIN**—avoid concomitant use; plasma concentration of quetiapine increased by **ERYTHROMYCIN**—manufacturer of quetiapine advises avoid concomitant use; increased risk of ventricular arrhythmias when sulpiride given with **parenteral** **ERYTHROMYCIN**; increased risk of ventricular arrhythmias when zuclopenthixol given with **parenteral** **ERYTHROMYCIN**—avoid concomitant use; plasma concentration of clozapine increased by **CIPROFLOXACIN**; plasma concentration of olanzapine possibly increased by **CIPROFLOXACIN**; increased risk of ventricular arrhythmias when droperidol, haloperidol, phenothiazines or zuclopenthixol given with **CIPROFLOXACIN**—avoid concomitant use; increased risk of ventricular arrhythmias when benperidol given with **CIPROFLOXACIN**—manufacturer of benperidol advises avoid concomitant use; plasma concentration of aripiprazole possibly reduced by **RIFAMPICIN**; plasma concentration of olanzapine possibly increased by **RIFAMPICIN**; increased risk of ventricular arrhythmias when droperidol, haloperidol, phenothiazines or zuclopenthixol given with **RIFAMPICIN**—avoid concomitant use; increased risk of ventricular arrhythmias when benperidol given with **RIFAMPICIN**—avoid concomitant use; plasma concentration of clozapine possibly reduced by **RIFAMPICIN**; metabolism of haloperidol accelerated by **RIFAMPICIN** (reduced plasma concentration); avoid concomitant use of clozapine with **CHLORMPHENICOL** or **SULFONAMIDES** (increased risk of agranulocytosis); increased risk of ventricular arrhythmias when phenothiazines that prolong the QT interval given with **DELANAMID**; increased risk of ventricular arrhythmias when phenothiazines that prolong the QT interval given with **DELANAMID**; increased risk of ventricular arrhythmias when phenothiazines that prolong the QT interval given with **DELANAMID**; increased risk of ventricular arrhythmias when phenothiazines that prolong the QT interval given with **DELANAMID**; increased risk of ventricular arrhythmias when phenothiazines that prolong the QT interval given with **DELANAMID**; increased risk of ventricular arrhythmias when phenothiazines that prolong the QT interval given with **DELANAMID**; increased risk of ventricular arrhythmias when phenothiazines that prolong the QT interval given with **DELANAMID**

- Antidepressants: plasma concentration of clozapine possibly increased by **CITALOPRAM** (increased risk of toxicity); avoidance of haloperidol, phenothiazines and pimozide advised by manufacturer of **CITALOPRAM** (risk of ventricular arrhythmias); avoidance of haloperidol, phenothiazines and pimozide advised by manufacturer of **CITALOPRAM** (risk of ventricular arrhythmias); plasma concentration of aripiprazole possibly increased by **FLUOXETINE** and **PAROXETINE**—reduce dose of aripiprazole—consult aripiprazole product literature); plasma concentration of lurasidone reduced by **RIFAMPICIN**—avoid concomitant use; plasma concentration of clozapine possibly reduced by **RIFAMPICIN**; metabolism of haloperidol accelerated by **RIFAMPICIN**—avoid concomitant use; increased risk of ventricular arrhythmias when chlorpromazine given with **TELIHROMYCIN**; plasma concentration of quetiapine possibly increased by **TELIHROMYCIN**

- Antidepressants: plasma concentration of clozapine possibly increased by **CITALOPRAM** (increased risk of toxicity); avoidance of haloperidol, phenothiazines and pimozide advised by manufacturer of **CITALOPRAM** (risk of ventricular arrhythmias); avoidance of haloperidol, phenothiazines and pimozide advised by manufacturer of **CITALOPRAM** (risk of ventricular arrhythmias); plasma concentration of aripiprazole possibly increased by **FLUOXETINE** and **PAROXETINE**—reduce dose of aripiprazole—consult aripiprazole product literature); plasma concentration of clozapine, haloperidol and risperidone increased by **FLUOXETINE**; manufacturer of droperidol advises avoid concomitant use with **FLUOXETINE** and **FLUOXAMINE**; **SERTRALINE** and **TRICYCLES** (risk of ventricular arrhythmias); plasma concentration of asenapine and haloperidol possibly increased by **FLUOXAMINE**; plasma concentration of clozapine and olanzapine increased by **FLUOXAMINE**; **FLUOXAMINE**; asenapine possibly increases plasma concentration of **PAROXETINE**; plasma concentration of clozapine increased by **PAROXETINE** and **SERTRALINE**; plasma concentration of risperidone possibly increased by **PAROXETINE** (increased risk of toxicity); metabolism of perphenazine inhibited by **PAROXETINE** (reduce dose of perphenazine); plasma concentration of haloperidol increased by **VENLAFAXINE**; clozapine possibly increases CNS effects of **MADIS**; plasma concentration of pimozide possibly increased by **SSRIS**; increased risk of ventricular arrhythmias—avoid concomitant use; plasma concentration of lurasidone possibly reduced by **ST JOHN’S WORT**—avoid concomitant use; plasma concentration of aripiprazole possibly reduced by **ST JOHN’S WORT** (avoid concomitant use or consider increasing the dose of aripiprazole—consult
Antipsychotics

- Antidepressants (continued)
  - Aripiprazole product literature; manufacturer of fluphenazine, haloperidol, sulpiride and zuclopenthixol advises avoid concomitant use with TRICYCLES (risk of ventricular arrhythmias); increased risk of antimuscarinic side-effects when phenothiazines given with TRICYCLES; possible increased risk of ventricular arrhythmias when risperidone given with TRICYCLES; possible increased antimuscarinic side-effects when clozapine given with TRICYCLES.
  - Antidiabetics: phenothiazines possibly antagonise hypoglycaemic effect of sulfonylureas.
  - Antiepileptics: antipsychotics antagonise anticonvulsant effect of antiepileptics (convulsive threshold lowered); metabolism of haloperidol, olanzapine, quetiapine and risperidone accelerated by CARBAMAZEPINE (reduced plasma concentration); metabolism of clozapine accelerated by CARBAMAZEPINE (reduced plasma concentration); also avoid concomitant use of drugs with substantial potential for causing agranulocytosis; plasma concentration of aripiprazole reduced by CARBAMAZEPINE (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature); plasma concentration of paliperidone reduced by CARBAMAZEPINE; plasma concentration of haloperidol possibly increased by CARBAMAZEPINE and PHENOTHIAZINES; metabolism of haloperidol accelerated by PHENOBARBITAL and PRIMIDONE (reduced plasma concentration).
  - Antipsychotics: metabolism of clozapine and quetiapine accelerated by PHENOBARBITAL and PRIMIDONE (reduced plasma concentration; possible increased risk of ventricular arrhythmias when pimozide given with PHENOBARBITAL—avoid concomitant use; plasma concentration of lurasidone possibly increased by PHENOBARBITAL and PRIMIDONE; plasma concentration of clozapine possibly reduced by PHENOBARBITAL and PRIMIDONE; metabolism of clozapine and quetiapine accelerated by PHENOBARBITAL and PRIMIDONE (reduced plasma concentration; effects of haloperidol possibly reduced by PHENOBARBITAL and PRIMIDONE); plasma concentration of lurasidone possibly increased by PHENOBARBITAL and PRIMIDONE; plasma concentration of clozapine possibly reduced by PHENOBARBITAL and PRIMIDONE; metabolism of clozapine and quetiapine accelerated by PHENOBARBITAL and PRIMIDONE (reduced plasma concentration; increased risk of antimuscarinic side-effects including neutropenia when olanzapine given with SODIUM VALPROATE and VALPROIC ACID; plasma concentration of clozapine possibly increased or decreased by SODIUM VALPROATE and VALPROIC ACID).

- Antimuscarinics: increased risk of antimuscarinic side-effects when clozapine given with ANTIMUSCARINICS; plasma concentration of phenothiazines reduced by ANTIMUSCARINICS; possible increased risk of ventricular arrhythmias when pimozide given with ANTIMUSCARINICS; possible increased risk of ventricular arrhythmias when pimozide given with ARTEMETHER WITH LUMEFANTRINE; avoidance of clozapine advised by manufacturer of ARTEMETHER WITH LUMEFANTRINE; avoidance of droperidol, haloperidol, phenothiazines and pimozide advised by manufacturer of ARTEMETHER WITH LUMEFANTRINE (possible risk of ventricular arrhythmias); increased risk of ventricular arrhythmias when droperidol given with CHLOROQUINE, HYDROXYCHLOROQUINE or QUININE; increased risk of ventricular arrhythmias when haloperidol given with MEFLOQUINE or DRUGS WITH SUBSTANTIAL POTENTIAL FOR CAUSING AGRANULOCYTOSIS.

- Antimalarials: increased risk of antimuscarinic side-effects when mepropazine given with ANTIMUSCARINICS; concentration of chlorpromazine possibly increases or decreases plasma concentration); manufacturer of quetiapine advises avoid concomitant use; plasma concentration of quetiapine increased or decreased by RITONAVIR; plasma concentration of quetiapine increased by FOSAMPRENAVIR, LOPINAVIR, SAQUINAVIR, and TELAPREVIR—avoid concomitant use; plasma concentration of pimozide increased by RITONAVIR, FOSAMPRENAVIR, LOPINAVIR, and SAQUINAVIR and TELAPREVIR (reduced dose of aripiprazole—consult aripiprazole product literature); plasma concentration of quetiapine possibly increased by ATAZANAVIR, DARUNAVIR, RITONAVIR, SAQUINAVIR and TIPRANAVIR; increased sedative effect when nefazodone or mirtazapine given with PHENOTHIAZINES (risk of toxicity); increased risk of toxicity; possible increased risk of ventricular arrhythmias when pimozide given with PHENOTHIAZINES.

- Antivirals: plasma concentration of aripiprazole possibly increased by ATAZANAVIR, DARUNAVIR, FOSAMPRENAVIR, INIDNAVIR, LOPINAVIR, RITONAVIR, SAQUINAVIR and TIPRANAVIR (increased risk of toxicity); increased risk of toxicity; possible increased risk of ventricular arrhythmias when pimozide given with PHENOTHIAZINES; possible increased risk of ventricular arrhythmias when pimozide given with PHENOTHIAZINES; possible increased risk of ventricular arrhythmias when pimozide given with PHENOTHIAZINES; possible increased risk of ventricular arrhythmias when pimozide given with PHENOTHIAZINES.
Antipsychotics (continued)
- Ergot Alkaloids: lurasidone possibly increases plasma concentration of ergot alkaloids (increased risk of toxicity)
- Fosaprepitant: avoidance of pimozide advised by manufacturer of fosaprepitant
- Grapefruit Juice: manufacturer of lurasidone and pimozide avoids concomitant use with grapefruit juice; plasma concentration of quetiapine possibly increased by grapefruit juice—manufacturer of quetiapine advises avoid concomitant use
- Histamine: antipsychotics theoretically antagonise effects of histamine—manufacturer of histamine advises avoid concomitant use
- Hormone Antagonists: manufacturer of droperidol advises avoid concomitant use with tamoxifen (risk of ventricular arrhythmias)
- Ivabradine: increased risk of ventricular arrhythmias when pimozide given with ivabradine
- Lithium: increased risk of extrapyramidal side-effects and possibly neurotoxicity when clozapine, flupentixol, haloperidol, phenothiazines, risperidone or zuclopenthixol given with lithium; possible risk of toxicity when olanzapine given with lithium; extrapyramidal side-effects of quetiapine possibly increased by lithium; increased risk of extrapyramidal side-effects when sulphuride given with lithium
- Memantine: effects of antipsychotics possibly reduced by memantine
- Methylphenidate: enhanced hypotensive effect when antipsychotics given with methylphenidate (also increased risk of extrapyramidal effects)
- Metoclopramide: increased risk of extrapyramidal side-effects when antipsychotics given with metoclopramide
- Moxonidine: enhanced hypotensive effect when antipsychotics given with moxonidine
- Muscle Relaxants: promazone possibly enhances effects of suxamethonium
- Nitrates: enhanced hypotensive effect when phenothiazines given with nitrates
- Penicillamine: avoid concomitant use of clozapine with penicillamine (increased risk of agranulocytosis)
- Pentamidine: increased risk of ventricular arrhythmias when amisulpiride or droperidol given with pentamidine isethionate—avoid concomitant use; increased risk of ventricular arrhythmias when phenothiazines given with pentamidine isethionate
- Sodium Benzoate: haloperidol possibly reduces effects of sodium benzoate
- Sodium Oxbate: antipsychotics possibly enhance effects of sodium oxybate
- Sodium Phenylbutyrate: haloperidol possibly reduces effects of sodium phenylbutyrate
- Sympathomimetics: antipsychotics antagonise hypertensive effect of sympathomimetics; antipsychotic effects of chlorpromazine possibly antagonised by dexamethasone; chlorpromazine possibly reduces effects of lisdekapetamine; side-effects of risperidone possibly increased by methylphenidate
- Tacroplimus: manufacturer of droperidol advises avoid concomitant use with tacroplimus (risk of ventricular arrhythmias)
- Tetrabenazine: increased risk of extrapyramidal side-effects when antipsychotics given with tetrabenzine
- Ulcer-healing Drugs: effects of antipsychotics, chlorpromazine and clozapine possibly enhanced by cimetidine; plasma concentration of clozapine possibly reduced by omeprazole; absorption of sulphuride reduced by sucralfate
- Vasodilator Antihypertensives: enhanced hypotensive effect when phenothiazines given with hydralazine, minoxidil or sodium nitroprusside

Antivirals
- See individual drugs

Anxiolytics and Hypnotics
- ACE Inhibitors: enhanced hypotensive effect when anxiolytics and hypnotics given with ACE inhibitors

- BNF 70

Dopaminergics:
- Diazoxide:
- Desferrioxamine:
- Clonidine:
- Atomoxetine:
- Aprepitant:
- Anxiolytics and Hypnotics
- Antipsychotics
- Cytotoxics:
- Clonidine:
- Cobicitab: plasma concentration of lurasidone possibly increased by cobicitab—avoid concomitant use; plasma concentration of pimozide possibly increased by cobicitab—manufacturer of cobicitab advises avoid concomitant use
- Cytotoxics: avoid concomitant use of clozapine with:
  - Cytotoxics (increased risk of agranulocytosis; possible increased risk of ventricular arrhythmias when haloperidol given with bosutinib; caution with pimozide advised by manufacturer of crizotinib; avoidance of pimozide and quetiapine advised by manufacturer of idealisib; avoidance of pimozide advised by manufacturer of lapatinib; possible increased risk of ventricular arrhythmias when amisulpride, chlorpromazine, haloperidol, pimozide, sulphide or zuclopenthixol given with vandetanib—avoid concomitant use; increased risk of ventricular arrhythmias when antipsychotics that prolong the QT interval given with:
  - Arsenic trioxide; increased risk of ventricular arrhythmias when haloperidol given with arsenic trioxide
- Deferasirox: avoidance of clozapine advised by manufacturer of deferasirox
- Desferrioxamine: manufacturer of levomepromazine advises avoid concomitant use with desferrioxamine; avoidance of prochlorperazine advised by manufacturer of desferrioxamine
- Diazoxide: enhanced hypotensive effect when phenothiazines given with diazoxide
- Diuretics: risk of ventricular arrhythmias with amisulpride increased by hypokalaemia caused by diuretics; risk of ventricular arrhythmias with pimozide increased by hypokalaemia caused by diuretics (avoid concomitant use); enhanced hypotensive effect when phenothiazines given with diuretics
- Dopaminergics: increased risk of extrapyramidal side-effects when antipsychotics given with amantadine; antipsychotics antagonise effects of apomorphine, benzelodopa, cabergoldopa, levodopa and pergolide; antipsychotics antagonise hypoprolactinaemic and antiparkinsonian effects of bromocriptine and cabergoline; manufacturer of amisulpride advises avoid concomitant use of benzelodopa, cabergoldopa and levodopa (antagonism of effect); avoidance of antipsychotics advised by manufacturer of pramipexole, ropinirole and rotigotine (antagonism of effect)
Anxiolytics and Hypnotics (continued)

- Adrenergic Neurone Blockers: enhanced hypertensive effect when anxiolytics and hypnotics given with ADRENERGIC NEURONE BLOCKERS
- Alcohol: increased sedative effect when anxiolytics and hypnotics given with ALCOHOL
- Alpha-blockers: enhanced hypertensive and sedative effects when anxiolytics and hypnotics given with ALPHABLOCKERS
- Aminophylline: effects of benzodiazepines possibly reduced by AMINOPHYLLINE
- Anaesthetics, General: increased sedative effect when anxiolytics and hypnotics given with GENERAL ANAESTHETICS
- Analgesics: when anxiolytics and hypnotics given with ANTIPSYCHOTICS; alprazolam possibly increases plasma concentration of HALOPERIDOL; buspirone increases plasma concentration of HALOPERIDOL; serious adverse events reported with concomitant use of benzodiazepines and CLOZAPINE (causality not established); plasma concentration of midazolam increased by LURASIDONE; increased risk of hypotension, bradycardia and respiratory depression when parenteral benzodiazepines given with intramuscular OLANZAPINE
- Antidepressants: plasma concentration of midazolam possibly increased by ATAZANAVIR—avoid concomitant use of oral midazolam; plasma concentration of oral midazolam increased by BOCEPREVIR—manufacturer of boceprevir advises avoid concomitant use; increased risk of prolonged sedation when midazolam given with EFAVIRENZ—avoid concomitant use; plasma concentration of midazolam possibly increased by FOSAMPRENAVIR, INDINAVIR, RITONAVIR and TELAPREVIR (risk of prolonged sedation—avoid concomitant use of oral midazolam); increased risk of prolonged sedation when alprazolam given with INDINAVIR—avoid concomitant use; plasma concentration of anxiolytics and hypnotics possibly increased by RITONAVIR; plasma concentration of alprazolam, diazepam, flurazepam and zolpidem possibly increased by RITONAVIR (risk of extreme sedation and respiratory depression—avoid concomitant use); plasma concentration of buspirone increased by RITONAVIR (increased risk of toxicity); plasma concentration of midazolam increased by SAQUINAVIR (risk of prolonged sedation—avoid concomitant use of oral midazolam); plasma concentration of oral midazolam increased by SIMEPREVIR
- Aprepitant: plasma concentration of midazolam increased by APREPIANT (risk of prolonged sedation)
- Beta-blockers: enhanced hypertensive effect when anxiolytics and hypnotics given with BETA-BLOCKERS
- Calcium-channel Blockers: enhanced hypertensive effect when anxiolytics and hypnotics given with CALCIUM-CHANNEL BLOCKERS; midazolam increases absorption of LERCANIDIPINE; metabolism of midazolam inhibited by DILTIAZEM and VERAPAMIL (increased plasma concentration with increased sedation); plasma concentration of buspirone increased by DILTIAZEM and VERAPAMIL (reduce dose of buspirone)
- Cardiac Glycosides: alprazolam increases plasma concentration of DOXOZIN (increased risk of toxicity)
- Clonidine: enhanced hypertensive effect when anxiolytics and hypnotics given with CLONIDINE
- Cobimetap: avoidance of oral midazolam advised by manufacturer of COBICISTAT
- Cytotoxics: plasma concentration of midazolam increased by CRIZOTINIB and Nilotinib; avoidance of oral midazolam advised by manufacturer of IDELVISIB
- Deferasirox: plasma concentration of midazolam possibly reduced by DEFERASIROX
- Diazoxide: enhanced hypertensive effect when anxiolytics and hypnotics given with DIAZOXIDE
- Disulfiram: metabolism of benzodiazepines inhibited by DISULFIRAM (increased sedative effects); increased risk of temazepam toxicity when given with DISULFIRAM
- Diuretics: enhanced hypertensive effect when anxiolytics and hypnotics given with DIURETICS; administration of chloral with parenteral TROGEMIDE may displace thyroid hormone from binding sites
- Dopaminergics: benzodiazepines possibly antagonise effects of CO-BENELDOPA, CO-CARELDOPA and LEVODOPA
- Fosaprepitant: plasma concentration of midazolam increased by FOSAPREPIANT (risk of prolonged sedation)
### Interactions

#### Anxiolytics and Hypnotics (continued)
- Grapefruit juice: plasma concentration of oral midazolam possibly increased by GRAPEFRUIT JUICE; plasma concentration of buspirone increased by GRAPEFRUIT JUICE
- Ivaecor: plasma concentration of midazolam increased by IVAECOR
- Lipid-regulating Drugs: plasma concentration of midazolam possibly increased by ATORVASTATIN; separating administration from alprazolam by 12 hours advised by MANUFACTURER OF LOMITAPID
- Lithium: increased risk of neurotoxicity when clonazepam given with LITHIUM
- Lofezidine: increased sedative effect when anxiolytics and hypnotics given with LOFEXIDINE
- Methylodopa: enhanced hypotensive effect when anxiolytics and hypnotics given with METHYLDOPA
- Methylthioninium: possible risk of CNS toxicity when buspirone given with METHYLTHIONIUM—avoid concomitant use (if avoidance not possible, use lowest possible dose of methylthioninium and observe patient for up to 4 hours after administration)
- Moxonidine: enhanced hypotensive effect when anxiolytics and hypnotics given with MOXONIDINE; sedative effects possibly increased when benzodiazepines given with MOXONIDINE
- Muscle Relaxants: increased sedative effect when anxiolytics and hypnotics given with BACLOFEN OR TIZANIDINE
- Nitrates: enhanced hypotensive effect when anxiolytics and hypnotics given with NITRATES
- Oestrone: plasma concentration of melatonin increased by OESTROGENS; plasma concentration of chlordiazepoxide, diazepam and nitrazepam possibly increased by OESTROGENS; plasma concentration of lorazepam, oxazepam and temazepam possibly reduced by OESTROGENS
- Progesterone: plasma concentration of chlordiazepoxide, diazepam and nitrazepam possibly increased by PROGESTOGENS; plasma concentration of lorazepam, oxazepam and temazepam possibly reduced by PROGESTOGENS
- Sodium Oxytate: benzodiazepines enhance effects of SODIUM OXYTE (avoid concomitant use)
- Theophylline: effects of benzodiazepines possibly reduced by THEOPHYLLINE
- Ulcer-healing Drugs: plasma concentration of melatonin increased by CIMETIDINE; metabolism of benzodiazepines, clomethiazole and zaleplon inhibited by CIMETIDINE (increased plasma concentration); metabolism of diazepam possibly inhibited by ESOMEPRAZOLE and OMEPRAZOLE (increased plasma concentration)
- Vasodilator: Antihypertensives: enhanced hypotensive effect when anxiolytics and hypnotics given with HYDRAZONE, MINOXIDIL OR SODIUM NITROPRUSSIDE

#### Apixaban

- Analgesics: increased risk of haemorrhage when anticoagulants given with intravenous DICLOFENAC (avoid concomitant use, including low-dose heparins); increased risk of haemorrhage when anticoagulants given with KETOROLAC (avoid concomitant use, including low-dose heparins)
- Antibacterials: manufacturer of apixaban advises avoid concomitant use with CLARITHROMYCIN and TELITHROMYCIN; plasma concentration of apixaban possibly reduced by RIFAMPICIN—manufacturer of apixaban advises avoid concomitant use when given for treatment of deep-vein thrombosis or pulmonary embolism
- Anticoagulants: increased risk of haemorrhage when apixaban given with other ANTICOAGULANTS (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency); increased risk of haemorrhage when other anticoagulants given with DABIGATRAN and RIVAROXABAN (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)
- Antidepressants: plasma concentration of apixaban possibly reduced by ST JOHN’S WORT—manufacturer of apixaban advises avoid concomitant use when given for treatment of deep-vein thrombosis or pulmonary embolism
- Antifungals: plasma concentration of apixaban possibly reduced by CARBAMAZEPINE—manufacturer of apixaban advises avoid concomitant use when given for treatment of deep-vein thrombosis or pulmonary embolism; plasma concentration of apixaban possibly reduced by FOSPHENOTHIOINE, PHENOBARBITAL, PHENOTYRA and PRIMIDONE
- Antihypertensives: plasma concentration of apixaban possibly reduced by KETOCONAZOLE—manufacturer of apixaban advises avoid concomitant use; manufacturer of apixaban advises avoid concomitant use with ITRAZONAZOLE, POSACONAZOLE AND VORICONAZOLE
- Antivirals: manufacturer of apixaban advises avoid concomitant use with ATAZANAVIR, BOCEPREVIR, DARUNAVIR, FOSAMPRENAVIR, INDINAVIR, LOPINAVIR, RITONAVIR, SAQUINAVIR, TELAPREO AND TIPSANAVIR
- Cobicistat: manufacturer of apixaban advises avoid concomitant use with COBICISTAT
- Sulfapyrazine: increased risk of bleeding when apixaban given with SULFIPYRAZONE

#### Apomorphine

- Antipsychotics: effects of apomorphine antagonised by ANTIPSYCHOTICS
- Dopaminergics: effects of apomorphine possibly enhanced by ENTACAPONE
- 5HT1-receptor Antagonists: possible increased hypotensive effect when apomorphine given with ONDANSETRON—avoid concomitant use
- Memantine: effects of dopaminergics possibly enhanced by METHYLDOPA
- Methylodopa: antiparkinsonian effect of dopaminergics antagonised by METHYLDOPA

#### Apraclonidine

- Antidepressants: manufacturer of apraclonidine advises avoid concomitant use with MAOIS, TRICYCLIC-RELATED ANTIDEPRESSANTS AND TRICYCLICS
- Symptomatologists: manufacturer of apraclonidine advises avoid concomitant use with SYMPATHOMIMETICS

#### Aprepitant

- Antibacterials: plasma concentration of aprepitant possibly increased by CLARITHROMYCIN AND TELITHROMYCIN; plasma concentration of aprepitant reduced by RIFAMPICIN
- Anticoagulants: aprepitant possibly reduces anticoagulant effect of WARFARIN
- Antidepressants: manufacturer of aprepitant advises avoid concomitant use with ST JOHN’S WORT
- Antiadipetics: aprepitant reduces plasma concentration of TOLBUTAMIDE
- Antiepileptics: plasma concentration of aprepitant possibly reduced by CARBAMAZEPINE, FOSPHENOTHIOINE, PHENOBARBITAL, PHENOTYRA AND PRIMIDONE
- Antifungals: plasma concentration of aprepitant increased by KETOCONAZOLE
- Antipsychotics: manufacturer of aprepitant advises avoid concomitant use with PIMOZIDE
- Antivirals: plasma concentration of aprepitant possibly increased by RITONAVIR
- Anxiolytics and Hypnotics: aprepitant increases plasma concentration of MIDAZOLAM (risk of prolonged sedation)
- Avanafil: aprepitant possibly increases plasma concentration of AVANAFIL—see under Avanafil, p. 698
- Calcium-channel Blockers: plasma concentration of both drugs may increase when aprepitant given with DILTIAZEM
- Corticosteroids: aprepitant inhibits metabolism of DEXAMETHASONE AND METHYLPREDNISOLONE (reduce dose of dexamethasone and methylprednisolone)
- Cytotoxics: aprepitant possibly increases the plasma concentration of BOSUTINIB—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; aprepitant possibly increases the plasma concentration of IBRUTINIB—reduce dose of ibritunib (see under Ibrutinib, p. 809)
- Dapoxetine: manufacturer of dapoxetine advises dose reduction when aprepitant given with DAPoxetine (see under Dapoxetine, p. 703)
Aprepitant (continued)

- Oestrogens: aprepiptant possibly causes contraceptive failure of hormonal contraceptives containing **OESTROGENS** (alternative contraception recommended)
- Progestogens: aprepiptant possibly causes contraceptive failure of hormonal contraceptives containing **PROGESTOGENS** (alternative contraception recommended)

**Argatroban**

- Analgesics: increased risk of haemorrhage when anticoagulants given with **ICLODOMAC** (avoid concomitant use, including low-dose heparins); increased risk of haemorrhage when anticoagulants given with **KETOROLAC** (avoid concomitant use, including low-dose heparins)
- Anticoagulants: increased risk of haemorrhage when other anticoagulants given with **APIXABAN**, **DABIGATRAN** and **RIVAROXABAN** (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)

**Aripiprazole** see Antipsychotics

**Arsenic Trioxide**

- Anti-arrhythmics: increased risk of ventricular arrhythmias when arsenic trioxide given with **AMIODARONE** or **DISOPYRAMIDE**
- Antibacterials: increased risk of ventricular arrhythmias when arsenic trioxide given with **CEFTAZIDIME**, **ERYTHROMYCIN**, **LEVOFLOXACIN** or **MOXIFLOXACIN**
- Antidepressants: increased risk of ventricular arrhythmias when arsenic trioxide given with **AMITRIPTYLINE** or **CLOMIPRAMINE**
- Antifungals: increased risk of ventricular arrhythmias when arsenic trioxide given with **AMPHTERICIN**
- Antimalarials: avoidance of arsenic trioxide advised by manufacturer of artenimol with piperaquine
- Antipsychotics: increased risk of ventricular arrhythmias when arsenic trioxide given with **CITALOPRAM**
- Antiarrhythmics: increased risk of ventricular arrhythmias when arsenic trioxide given with **HALOPERIDOL**; avoid concomitant use with **CLOzapine** (increased risk of agranulocytosis)
- Beta-blockers: increased risk of ventricular arrhythmias when arsenic trioxide given with **SOTALOL**
- Cytotoxics: possible increased risk of ventricular arrhythmias when arsenic trioxide given with **VANDΕΤΑΝΙΒ**—avoid concomitant use
- Diuretics: risk of ventricular arrhythmias with arsenic trioxide increased by hypokalaemia caused by **ACETAZOLAMIDE**, **LOOP DIURETICS** or **THIAZIDES AND RELATED DIURETICS**
- Lithium: increased risk of ventricular arrhythmias when arsenic trioxide given with **LITHIUM**

**Artemether with Lumeferantrine**

- Anti-arrhythmics: manufacturer of artemether with lumefantrine advises avoid concomitant use with **AMIODARONE**, **DISOPYRAMIDE** and **FLECAINIDE** (risk of ventricular arrhythmias)
- Antibacterials: manufacturer of artemether with lumefantrine advises avoid concomitant use with **MACROLIDES** and **QUINOLONES**
- Antidepressants: possible increased risk of ventricular arrhythmias when artemether with lumefantrine given with **CITALOPRAM** or **ESCLATOPRAM**—avoid concomitant use; manufacturer of artemether with lumefantrine advises avoid concomitant use with **ANTIDEPRESSANTS**
- Antifungals: manufacturer of artemether with lumefantrine advises avoid concomitant use with **IMIDAZOLINES** and **TRIAZOLES**
- Antimalarials: manufacturer of artemether with lumefantrine advises avoid concomitant use with **ANTIMALARIALS**; increased risk of ventricular arrhythmias when artemether with lumefantrine given with **QUININE**
- Antipsychotics: manufacturer of artemether with lumefantrine advises avoid concomitant use with **ANTIPSYCHOTICS**
- Antivirals: manufacturer of artemether with lumefantrine advises caution with **ATAZANAVIR**, **FOSAMPRENAVIR**, **INDINAVIR**, **LOPINAVIR**, **RITONAVIR**, **SAQUINAVIR** and **TIPRANAVIR**; avoidance of artemether with lumefantrine advised by manufacturer of **BOCERPAN**; plasma concentration of lumefantrine increased when artemether with lumefantrine given with **DARUNAVIR**; plasma concentration of artemether with lumefantrine reduced by **EFAVIREN** and **ETRANIRINE**
- Beta-blockers: manufacturer of artemether with lumefantrine advises avoid concomitant use with **METOPROLOL** and **SOTALOL**
- Cytotoxics: possible increased risk of ventricular arrhythmias when artemether with lumefantrine given with **VANDΕΤΑΝΙΒ**—avoid concomitant use
- Grapefruit Juice: plasma concentration of artemether with lumefantrine possibly increased by **GRAPEFRUIT JUICE**
- Histamine: avoidance of antimalarials advised by manufacturer of **HISTAMINE**
- Ulcer-healing Drugs: manufacturer of artemether with lumefantrine advises avoid concomitant use with **CIMETIDINE**

**Artemisinin with Piperaquine**

*NOTE* Piperaquine has a long half-life; there is a potential for drug interactions to occur for up to 3 months after treatment has been stopped
- Analgesics: manufacturer of artemisinin with piperaquine advises concomitant use with **METHADONE** (possible risk of ventricular arrhythmias)
- Anti-arrhythmics: manufacturer of artemisinin with piperaquine advises concomitant use with **AMIODARONE** and **DISOPYRAMIDE** (possible risk of ventricular arrhythmias)
- Anticoagulants: manufacturer of artemisinin with piperaquine advises concomitant use with **CLOMIDINE** and **MOXIFLOXACIN** (possible risk of ventricular arrhythmias)
- Antipsychotics: manufacturer of artemisinin with piperaquine advises concomitant use with **CITALOPRAM** or **ESCLATOPRAM**—avoid concomitant use; manufacturer of artemisinin with piperaquine advises avoid concomitant use with **ANTIDEPRESSANTS**
- Anti-epileptics: manufacturer of artemisinin with piperaquine advises avoid concomitant use with **CARBAMAZEPINE**, **FOSPHENITOIN**, **PHENOBARBITAL**, **PHENITOIN** and **PRIMIDONE**
- Antifungals: manufacturer of artemisinin with piperaquine advises avoid concomitant use with **IMIDAZOLINES** and **TRIAZOLINES** (possible risk of ventricular arrhythmias)
- Antiadrenalinics: manufacturer of artemisinin with piperaquine advises avoid concomitant use with **MIZOLASTINE** (possible risk of ventricular arrhythmias)
- Antimalarials: avoidance of antimalarials advised by manufacturer of **ARTENIMOL WITH PIPERAQUINE**
- Antipsychotics: manufacturer of artemisinin with piperaquine advises avoid concomitant use with **METOCLOPRAMIDE**
- Beta-blockers: manufacturer of artemisinin with piperaquine advises avoid concomitant use with **SAQUINAVIR** (possible risk of ventricular arrhythmias)
- Cytotoxics: manufacturer of artemisinin with piperaquine advises avoid concomitant use with **ARSENIC TRIOXIDE** (possible risk of ventricular arrhythmias); manufacturer of artemisinin with piperaquine advises avoid concomitant use with **VINBLELINE**
- Grapefruit Juice: manufacturer of artemisinin with piperaquine advises avoid concomitant use with **GRAPEFRUIT JUICE**
Artemisin with Piperaquine (continued)
- Histamine: avoidance of antimalarials advised by manufacturer of HISTAMINE
- Pentamidine isethionate: manufacturer of artemisin with piperaquine advises avoid concomitant use with
- Pentamidine isethionate (possible risk of ventricular arrhythmias)
- Vaccines: antimalarials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF
Ascorbic acid see Vitamins
Asenapine see Antipsychotics
Aspirin
- Adsorbents: absorption of aspirin possibly reduced by KAOLIN
- Anaesthetics, General: aspirin possibly enhances effects of THIOPENTAL
- Analgesics: concomitant use of aspirin with ◆ NSAIDS (increased side-effects); antiplatelet effect of aspirin possibly reduced by IBUPROFEN
- Antacids: excretion of aspirin increased by alkaline urine due to some ANTACIDS
- Anticoagulants: increased risk of bleeding when aspirin given with◆ COUMARINS or◆ PHENINDION (due to antiplatelet effect); aspirin enhances anticoagulant effect of◆ HEPARINS
- Antidepressants: increased risk of bleeding when aspirin given with◆ SSRIS or◆ VENLAFAXINE
- Antiepileptics: aspirin enhances effects of FOSPHENYTIN, PHENYTOIN, SODIUM VALPROATE and VALPROIC ACID
- Clopidogrel: increased risk of bleeding when aspirin given with CLOPIDOGREL
- Corticosteroids: increased risk of gastro-intestinal bleeding and ulceration when aspirin given with CORTICOSTEROIDS, also corticosteroids reduce plasma concentration of salicylate
- Cytotoxics: aspirin reduces excretion of◆ METHOTREXATE (increased risk of toxicity); aspirin possibly reduces renal excretion of PEMETREXED—consult product literature
- Diuretics: increased risk of toxicity when high-dose aspirin given with◆ ACETAZOLAMIDE; aspirin antagonises diuretic effect of SPIRONOLACTONE; possible increased risk of toxicity when high-dose aspirin given with LOOP Diuretics (also possible reduced effect of loop diuretics)
- Iloprost: increased risk of bleeding when aspirin given with ILOPROST
- Leukotriene Receptor Antagonists: aspirin increases plasma concentration of ZAFIRULKAST
- Metoclopramide: rate of absorption of aspirin increased by METOCLOPRAMIDE (enhanced effect)
- Sulfipyrazone: aspirin antagonises effects of SULFOPYRAZONE
Atazanavir
- Antacids: absorption of atazanavir reduced by ANTACIDS (give at least 2 hours before or 1 hour after aspirin)
- Antidepressants: atazanavir possibly increases plasma concentration of◆ AMIODARONE and◆ LIDOCAINE
- Antibacterials: plasma concentration of both drugs increased when atazanavir given with CLARITHROMYCIN; atazanavir increases plasma concentration of◆ Rifabutin (reduce dose of rifabutin); plasma concentration of atazanavir reduced by◆ Rifampicin—avoid concomitant use; avoidance of concomitant atazanavir in severe renal and hepatic impairment advised by manufacturer of◆ Telithromycin
- Antifungals: plasma concentration of atazanavir increased by◆ POSaconazole; atazanavir decreases or increases the plasma concentration of◆ Voriconazole and plasma concentration of atazanavir also reduced
- Antimalarials: caution with atazanavir advised by manufacturer of Artemether with Lumefantrine; atazanavir possibly increases plasma concentration of◆ Quinine (increased risk of toxicity)
- Antimycobacterials: avoidance of atazanavir advised by manufacturer of Daripenam; manufacturer of fosoterodine advises dose reduction when atazanavir given with◆ Fosoterodine—consult fosoterodine product literature
- Antiparkinsonians: increase in plasma concentration of atazanavir also reduced
- Antituberculars: atazanavir possibly increases plasma concentration of◆ Ipyrrole (reduce dose of pyrrole; consult product literature); atazanavir possibly increases plasma concentration of◆ Ethambutol—manufacturer of ethambutol advises avoid concomitant use; atazanavir possibly increases plasma concentration of◆ Ethibon—manufacturer of ethibon advises avoid concomitant use
- Antivirals: plasma concentration of atazanavir reduced by◆ Bosentan; atazanavir increases plasma concentration of◆ Viroptic—manufacturer of viroptic advises avoid concomitant use
- Antiulcer: plasma concentration of atazanavir reduced by◆ Omeprazole (plasma concentration of atazanavir reduced); atazanavir boosted with ritonavir increases plasma concentration of◆ Efavirenz (reduce dose of efavirenz); avoid concomitant use of atazanavir with◆ INIDAVIR; atazanavir increases plasma concentration of◆ Maraviroc (consider reducing dose of maraviroc); plasma concentration of atazanavir possibly reduced by◆ Nevirapine—avoid concomitant use; increased risk of ventricular arrhythmias when atazanavir given with◆ Saquinavir—avoid concomitant use; atazanavir possibly reduces plasma concentration of◆ Telaprevir, also plasma concentration of atazanavir possibly increased; plasma concentration of atazanavir reduced by◆ Tenofovir, also plasma concentration of tenofovir possibly increased; atazanavir increases plasma concentration of◆ TIPRANAVIR (also plasma concentration of atazanavir reduced)
- Antiulcer: plasma concentration of◆ Midazolam—avoid concomitant use of oral midazolam
- Avanafil: atazanavir possibly increases plasma concentration of◆ Avanafil—manufacturer of avanafil advises avoid concomitant use
- Calcium-channel Blockers: atazanavir increases plasma concentration of◆ Diltiazem (reduce dose of diltiazem); atazanavir possibly increases plasma concentration of◆ Verapamil
- Ciclosporin: atazanavir possibly increases plasma concentration of◆ Ciclosporin
- Colchicine: atazanavir possibly increases risk of◆ Colchicine toxicity—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- Cytotoxics: atazanavir possibly increases plasma concentration of◆ Axitinib (reduce dose of axitinib—consult axitinib product literature); atazanavir possibly increases the plasma concentration of◆ Bosutinib—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; atazanavir possibly increases plasma concentration of◆ Crizotinib and◆ Everolimus—manufacturer of crizotinib and everolimus advises avoid concomitant use; atazanavir possibly increases the plasma concentration of◆ Ibrutinib—reduce dose of ibrutinib (see under ibrutinib, p. 809); atazanavir possibly increases plasma concentration of◆ Pazopanib (reduce dose of pazopanib); avoidance of atazanavir advised by manufacturer of◆ Cabazitaxel; atazanavir possibly inhibits metabolism of◆ Pinotocan (increased risk of toxicity)
- Dopamine: avoidance of atazanavir advised by manufacturer of◆ Dopoxetine (increased risk of toxicity)
- Ergot Alkaloids: atazanavir possibly increases plasma concentration of◆ Ergot Alkaloids—avoid concomitant use
- Lipid-regulating Drugs: possible increased risk of myopathy when atazanavir given with◆ Atorvastatin or Pravastatin; atazanavir increases plasma concentration of◆ Rosuvastatin—adjust dose of rosuvastatin (consult product literature); increased risk of myopathy when atazanavir given with◆ Simvastatin (avoid concomitant use)
- Oestrogens: atazanavir increases plasma concentration of◆ Ethinylestradiol
- Orlistat: absorption of atazanavir possibly reduced by◆ Orlistat
- Progestogens: atazanavir increases plasma concentration of◆ Nordestosterone
Atovaquone

- RANOLAZINE—manufacturer of ranolazine advises avoid concomitant use
- SILDENAFIL
- SIROLIUMS
- TACROLIUMS: atovaquone possibly increases plasma concentration of
- TICAGRELOR—manufacturer of ticagrelor advises avoid concomitant use
- Ulcer-healing Drugs: manufacturer of atovaquone advises adjust doses of both drugs when atazanavir given with Cimetidine and Nizatidine—consult atazanavir product literature; plasma concentration of atazanavir reduced by FAMOTIDINE and Ranitidine (adjust doses of both drugs—consult atazanavir product literature); plasma concentration of atazanavir reduced by PROTON PUMP INHIBITORS—avoid or adjust dose of both drugs (consult product literature)

Atenolol see Beta-blockers

Atomoxetine

- Analgesics: increased risk of ventricular arrhythmias when atomoxetine given with METHADONE; possible increased risk of convulsions when atomoxetine given with TRAMADOL
- Anti-arrhythmics: increased risk of ventricular arrhythmias when atomoxetine given with AMIODARONE or DISOPYRAMIDE
- Antibacterials: increased risk of ventricular arrhythmias when atomoxetine given with FLUOXETINE and PAROXETINE; possible increased risk of convulsions when atomoxetine given with ANTIDEPRESSANTS; atomoxetine should not be started until 2 weeks after stopping MADOL, also MAOIs should not be started until at least 2 weeks after stopping atomoxetine; increased risk of ventricular arrhythmias when atomoxetine given with TRICYCLICS
- Antimalarials: increased risk of ventricular arrhythmias when atomoxetine given with MELOQUINE
- Antipsychotics: increased risk of ventricular arrhythmias when atomoxetine given with ANTIPSYCHOTICS that prolong the QT interval
- Beta-blockers: increased risk of ventricular arrhythmias when atomoxetine given with SOTALOL
- Buproprion: possible increased risk of convulsions when atomoxetine given with BUPROPION
- Diuretics: risk of ventricular arrhythmias when atomoxetine increased by Hypokalaemia caused by DIURETICS
- Sympathomimetics, Beta₂: Increased risk of cardiovascular side-effects when atomoxetine given with parenteral SALBUTAMOL

Atozavastatin see Statins

Atracurium see Muscle Relaxants

Atropine see Antimuscarinic Agents

Avanafil

- ACE Inhibitors: avanafil possibly enhances hypotensive effect of ENALAPRIL
- Alpha-blockers: enhanced hypotensive effect when avanafil given with ALPHA-BLOCKERS—when patient is stable on the alpha blocker initiate avanafil at the lowest possible dose
- Antibacterials: plasma concentration of avanafil possibly increased by CLARITHROMYCIN and TELITHROMYCIN—manufacturer of avanafil advises avoid concomitant use; plasma concentration of avanafil increased by ERYTHROMYCIN—see under Avanafil, p. 698; plasma concentration of avanafil possibly reduced by RIFAMPICIN—manufacturer of avanafil advises avoid concomitant use
- Antiepileptics: plasma concentration of avanafil possibly reduced by CARBAMAZEPINE, PHENOBARBITAL and PRIMIDONE—manufacturer of avanafil advises avoid concomitant use
- Antifungals: plasma concentration of avanafil increased by KETOCONAZOLE—avoid concomitant use; plasma concentration of avanafil possibly reduced by FOSAMPRENAVIR—see under Avanafil, p. 698; plasma concentration of avanafil significantly increased by ITRAZONAZOLE; avanafil possibly reduces plasma concentration of avanafil reduced by IFENEPHREN—manufacturer of avanafil advises avoid concomitant use; plasma concentration of avanafil possibly increased by FLUCONAZOLE—see under Avanafil, p. 698; plasma concentration of avanafil possibly increased by IRONAVIR—avoid concomitant use
- Antivirals: plasma concentration of avanafil possibly increased by ATAZANAVIR, INDINAVIR and SAQUINAVIR—manufacturer of avanafil advises avoid concomitant use; plasma concentration of avanafil possibly reduced by TELITROMYCIN—manufacturer of avanafil advises avoid concomitant use; plasma concentration of avanafil possibly increased by HEMIFEPHREN—manufacturer of avanafil advises avoid concomitant use; plasma concentration of avanafil possibly reduced by BOSENTAN—manufacturer of avanafil advises avoid concomitant use
- Calcium-channel Blockers: plasma concentration of avanafil possibly increased by DILTIAZEM and VERAPAMIL—see under Avanafil, p. 698
- Fosaprepitant: plasma concentration of avanafil possibly increased by FOSAPREPITANT
- Grapefruit juice: plasma concentration of avanafil possibly increased by GRAPEFRUIT JUICE—manufacturer of avanafil advises avoid grapefruit juice for 24 hours before avanafil
- Nicardipine: avanafil significantly enhances hypotensive effect of NICORANDIL (avoid concomitant use)
- Nitrates: avanafil significantly enhances hypotensive effect of NITRATES (avoid concomitant use)
- Bosentan: plasma concentration of avanafil significantly increased by bosentan; manufacturer of avanafil advises avoid concomitant use
- Calcium-channel Blockers: plasma concentration of avanafil possibly increased by DILTIAZEM and VERAPAMIL—see under Avanafil, p. 698
- Fosaprepitant: plasma concentration of avanafil possibly increased by FOSAPREPITANT
- Grapefruit juice: plasma concentration of avanafil possibly increased by GRAPEFRUIT JUICE—manufacturer of avanafil advises avoid grapefruit juice for 24 hours before avanafil
- Nicardipine: avanafil significantly enhances hypotensive effect of NICORANDIL (avoid concomitant use)
- Nitrates: avanafil significantly enhances hypotensive effect of NITRATES (avoid concomitant use)
- Bosentan: plasma concentration of avanafil significantly increased by bosentan; manufacturer of avanafil advises avoid concomitant use
- Calcium-channel Blockers: plasma concentration of avanafil possibly increased by DILTIAZEM and VERAPAMIL—see under Avanafil, p. 698
- Fosaprepitant: plasma concentration of avanafil possibly increased by FOSAPREPITANT
- Grapefruit juice: plasma concentration of avanafil possibly increased by GRAPEFRUIT JUICE—manufacturer of avanafil advises avoid grapefruit juice for 24 hours before avanafil
- Nicardipine: avanafil significantly enhances hypotensive effect of NICORANDIL (avoid concomitant use)
- Nitrates: avanafil significantly enhances hypotensive effect of NITRATES (avoid concomitant use)
- Bosentan: plasma concentration of avanafil significantly increased by bosentan; manufacturer of avanafil advises avoid concomitant use

Avanafil see Antimuscarinic Agents

Avanafil see Antimuscarinic Agents
Axitinib
Antifungals (continued)
increased by ITRACONAZOLE (reduce dose of axitinib—consult axitinib product literature)
» Antipsychotics: avoid concomitant use of cytoxotics with
CLOzapine (increased risk of agranulocytosis)
» Antivirals: plasma concentration of axitinib possibly reduced by
ATAZANAVIR, INDINAVIR, RITONAVIR and SAQUINAVIR (reduce dose of axitinib—consult axitinib product literature)
» Corticosteroids: plasma concentration of axitinib possibly decreased by DEXMETHASONE (increase dose of axitinib—consult axitinib product literature)
» Grapefruit juice: plasma concentration of axitinib possibly increased by GRAPEFRUIT JUICE

Azathioprine
ACE Inhibitors: increased risk of anaemia or leucopenia when azathioprine given with Captopril, especially in renal impairment; increased risk of anaemia when azathioprine given with Enalapril, especially in renal impairment
» Allopurinol: enhanced effects and increased toxicity of azathioprine when given with Allopurinol (reduce dose of azathioprine to one quarter of usual dose)
» Antibacterials: increased risk of haematological toxicity when azathioprine given with Sulfamethoxazole (as co-trimoxazole); increased risk of haematological toxicity when azathioprine given with Primithrom (also with co-trimoxazole)
» Anticoagulants: azathioprine possibly reduces anticoagulant effect of Coumarins
» Antivirals: myelosuppressive effects of azathioprine possibly enhanced by Ribavirin
» Febuxostat: avoidance of azathioprine advised by manufacturer of FEBUXOSTAT

Azelastin see Antihistamines
Azilsartan see Angiotensin-II Receptor Antagonists
Azthromycin see Macrolides
Aztreonam
Anticoagulants: aztreonam possibly enhances anticoagulant effect of Coumarins
» Vaccines: antibacterials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF

Baclofen see Muscle Relaxants
Bambuterol see Sympathomimetics, Beta3
Basiliximab
Antipsychotics: avoid concomitant use of cytoxotics with CLOzapine (increased risk of agranulocytosis)
» Vaccines: risk of generalised infections when monoclonal antibodies given with live VACCINES—avoid concomitant use

BCG Vaccine see Vaccines
Beclometasone see Corticosteroids
Bedaquiline
Antibacterials: plasma concentration of bedaquiline possibly increased by CIPROFLOXACIN, CLARITHROMYCIN and ERYTHROMYCIN—avoid concomitant use if ciprofloxacin, clarithromycin and erythromycin given for more than 14 days; manufacturer of bedaquiline advises avoid concomitant use with MOXIFLOXACIN; plasma concentration of bedaquiline possibly reduced by Rifabutin—manufacturer of bedaquiline advises avoid concomitant use; plasma concentration of bedaquiline reduced by Rifampicin—manufacturer of bedaquiline advises avoid concomitant use; possible increased risk of ventricular arrhythmias when bedaquiline given with Clofazimine
» Antidepressants: plasma concentration of bedaquiline possibly reduced by St John’s Wort—manufacturer of bedaquiline advises avoid concomitant use
» Antiepileptics: plasma concentration of bedaquiline possibly reduced by Carbamazepine, Fosphenytoin and Phenytoin—manufacturer of bedaquiline advises avoid concomitant use
» Antifungals: plasma concentration of bedaquiline increased by Ketoconazole—avoid concomitant use if ketoconazole given for more than 14 days; plasma concentration of bedaquiline possibly increased by Fluconazole—avoid concomitant use if fluconazole given for more than 14 days

Bedaquiline (continued)
» Antivirals: plasma concentration of bedaquiline possibly reduced by Efavirenz and Etravirine—manufacturer of bedaquiline advises avoid concomitant use; plasma concentration of bedaquiline possibly increased by Ritonavir—avoid concomitant use if ritonavir given for more than 14 days
» Vaccines: antibacterials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF

Bee Venom Extracts
ACE Inhibitors: possible severe anaphylactoid reaction when bee venom extracts given with ACE INHIBITORS

Belimumab
Antipsychotics: avoid concomitant use of cytoxotics with CLOzapine (increased risk of agranulocytosis)
» Vaccines: risk of generalised infections when monoclonal antibodies given with live VACCINES—avoid concomitant use

Bendamustine
Antipsychotics: avoid concomitant use of cytoxotics with CLOzapine (increased risk of agranulocytosis)

Bendroflumethiazide see Diuretics
Benperidol see Antipsychotics
Benzodiazepines see Anxiolytics and Hypnotics
Benzthiazide see Diuretics
Benzylpenicillin see Penicillins

Beta-blockers
NOTE Since systemic absorption may follow topical application of beta-blockers to the eye the possibility of interactions, in particular, with drugs such as verapamil should be borne in mind
» ACE Inhibitors: enhanced hypotensive effect when beta-blockers given with ACE INHIBITORS
» Adrenergic Neurone Blockers: enhanced hypotensive effect when beta-blockers with ADRENERGIC NEURONE BLOCKERS
» Alcohol: enhanced hypotensive effect when beta-blockers given with ALCOHOL
» Aldesleukin: enhanced hypotensive effect when beta-blockers given with ALDESLEUKIN
» Alpha-blockers: enhanced hypotensive effect when beta-blockers given with ALPHA-BLOCKERS, also increased risk of first-dose hypotension with post-synaptic alpha-blockers such as prazosin
» Anaesthetics, General: enhanced hypotensive effect when beta-blockers given with GENERAL ANAESTHETICS
» Anaesthetics, Local: propranolol increases risk of BUPIVACAINE toxicity
» Analgesics: hypotensive effect of beta-blockers antagonised by NSAIDS; plasma concentration of esmolol possibly increased by MORPHINE
» Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when beta-blockers given with ANGIOTENSIN-II RECEPTOR ANTAGONISTS
» Anti-arrhythmics: increased myocardial depression when beta-blockers given with ANTI-ARRHYTHMICS; increased risk of ventricular arrhythmias when sotalol given with AMIODARONE, DISOPYRAMIDE or DROPERIDOL—avoid concomitant use; increased risk of bradycardia, AV block and myocardial depression when beta-blockers given with AMIODARONE; plasma concentration of metoprolol and propranolol possibly increased by DROPERIDOL; increased risk of myocardial depression and bradycardia when beta-blockers given with AMIODARONE; plasma concentration of metoprolol and propranolol possibly increased by FLECAINIDE; propranolol increases risk of LIDOCAINE toxicity; nadolol possibly increases risk of LIDOCAINE toxicity; plasma concentration of metoprolol and propranolol increased by PROPafenone
» Antibacterials: increased risk of ventricular arrhythmias when sotalol given with MOXIFLOXACIN—avoid concomitant use; metabolism of bisoprolol and propranolol accelerated by Rifampicin (plasma concentration significantly reduced); plasma concentration of carvedilol, celiprolol and metoprolol reduced by Rifampicin; plasma concentration of oral timolol possibly reduced by Rifampicin; increased risk of ventricular arrhythmias when sotalol given with DELAMANID
» Antidepressants: plasma concentration of metoprolol increased by CITALOPRAM and ESCITALOPRAM; Increased risk of
Beta-blockers

- Antidepressants (continued)
  - ventricular arrhythmias when sotalol given with
  - CITALOPRAM—avoid concomitant use; avoidance of sotalol advised by manufacturer of CITALOPRAM (risk of ventricular arrhythmias); plasma concentration of propranolol increased by FLUVOXAMINE; plasma concentration of metoprolol possibly increased by PAROXETINE—increased risk of AV block (manufacturer of paroxetine advises avoid concomitant use in cardiac insufficiency); plasma concentration of propranolol increased by ATOMOXETINE; possible increased risk of ventricular arrhythmias when sotalol given with MAOIS; increased risk of ventricular arrhythmias when sotalol given with TRICYCLICS;
  - Antiarrhythmics: beta-blockers may mask warning signs of bradycardia (such as tremor) when betablockers given with CICLOSPORIN increased risk of ventricular arrhythmias when beta-blockers given with beta-blockers enhance hypoglycaemic effect of ANTIARRHYTHMICS; beta-blockers increase when propranolol given with concomitant use; plasma concentration of both drugs may increased risk of ventricular arrhythmias; plasma concentration of sotalol increased by hypokalaemia caused by ARSENIC TRIOXIDE; enhanced hypotensive effect when beta-blockers given with severe hypotension and heart failure when beta-blockers given with increased peripheral vasoconstriction when beta-blockers given with MIRABEGRON increased risk of ventricular arrhythmias when beta-blockers given with MEFLOQUINE increased risk of ventricular arrhythmias when sotalol given with TOLTERODINE;
  - Antipsychotics: increased risk of ventricular arrhythmias when sotalol given with DROPERIDOL or ZUCLOPENTHIXOL—avoid concomitant use; possible increased risk of ventricular arrhythmias when sotalol given with HALOPERIDOL—avoid concomitant use; plasma concentration of both drugs may increased when propranolol given with CHLORPROMAZINE; increased risk of bradycardia when beta-blockers given with AMISULPRIDE, PHENTHIazines, FIMOZIDE or ATMOTEXetine; possible increased risk of ventricular arrhythmias when sotalol given with RISPERIDONE;
  - Antivirals: beta-blockers may mask warning signs of bradycardia (such as tremor) when beta-blockers given with CITALOPRAM increased risk of ventricular arrhythmias when beta-blockers given with beta-blockers enhance hypoglycaemic effect of ANTIDEPRESSANTS; beta-blockers increase when propranolol given with concomitant use; plasma concentration of both drugs may increased risk of ventricular arrhythmias; plasma concentration of sotalol increased by hypokalaemia caused by ARSENIC TRIOXIDE; enhanced hypotensive effect when beta-blockers given with severe hypotension and heart failure when beta-blockers given with increased peripheral vasoconstriction when beta-blockers given with MIRABEGRON increased risk of ventricular arrhythmias when beta-blockers given with MEFLOQUINE increased risk of ventricular arrhythmias when sotalol given with TOLTERODINE;
  - Antihistamines: increased risk of ventricular arrhythmias when sotalol given with MIZOLATINE—avoid concomitant use; antiarrhythmics: avoidance of metoprolol and sotalol advised by manufacturer of ARTEMETHER WITH LUMEFANTRINE; avoidance of sotalol advised by manufacturer of ARTEMETHIN WITH PIPERAQUINE (possible risk of ventricular arrhythmias); increased risk of bradycardia when beta-blockers given with MEFLQUINE;
  - Antimigraine: increased risk of ventricular arrhythmias when sotalol given with a Tolterodine
  - Antipsychotics: increased risk of ventricular arrhythmias when sotalol given with DROPERIDOL or ZUCLOPENTHIXOL—avoid concomitant use; possible increased risk of ventricular arrhythmias when sotalol given with HALOPERIDOL—avoid concomitant use; plasma concentration of both drugs may increased when propranolol given with CHLORPROMAZINE; increased risk of bradycardia when beta-blockers given with AMISULPRIDE, PHENTHIazines, FIMOZIDE or ATMOTEXetine; possible increased risk of ventricular arrhythmias when sotalol given with RISPERIDONE;
  - Antivirals: beta-blockers may mask warning signs of bradycardia (such as tremor) when beta-blockers given with CITALOPRAM increased risk of ventricular arrhythmias when beta-blockers given with beta-blockers enhance hypoglycaemic effect of ANTIDEPRESSANTS; beta-blockers increase when propranolol given with concomitant use; plasma concentration of both drugs may increased risk of ventricular arrhythmias; plasma concentration of sotalol increased by hypokalaemia caused by ARSENIC TRIOXIDE; enhanced hypotensive effect when beta-blockers given with severe hypotension and heart failure when beta-blockers given with increased peripheral vasoconstriction when beta-blockers given with MIRABEGRON increased risk of ventricular arrhythmias when beta-blockers given with MEFLOQUINE increased risk of ventricular arrhythmias when sotalol given with TOLTERODINE;
  - Antihistamines: increased risk of ventricular arrhythmias when sotalol given with MIZOLATINE—avoid concomitant use; antiarrhythmics: avoidance of metoprolol and sotalol advised by manufacturer of ARTEMETHER WITH LUMEFANTRINE; avoidance of sotalol advised by manufacturer of ARTEMITHIN WITH PIPERAQUINE (possible risk of ventricular arrhythmias); increased risk of bradycardia when beta-blockers given with MEFLQUINE;
  - Antimigraine: increased risk of ventricular arrhythmias when sotalol given with a Tolterodine
Bexarotene (continued)
• Lipid-regulating Drugs: plasma concentration of bexarotene increased by • GEMFIBROZIL — avoid concomitant use
Bezafibrate see Fibrates
Bicalutamide
• Anticoagulants: bicalutamide possibly enhances anticoagulant effect of COUMARINS
• Lipid-regulating Drugs: separating administration from bicalutamide by 12 hours advised by manufacturer of LOMITAPID
Bezafibrate see Antidiabetics
Bilastine see Antihistamines
Bile Acid Sequestrants see Colesevelam, Colestipol, and Colestyramine
Bile Acids
• Antacids: absorption of bile acids possibly reduced by ANTACIDS
• Ciclosporin: ursodeoxycholic acid increases absorption of CICLOSPORIN
• Lipid-regulating Drugs: absorption of bile acids possibly reduced by COLESTIROL and COLESTYRAMINE
Bisoprolol see Beta-blockers
Bisphosphonates
• Antacids: absorption of bisphosphonates reduced by ANTACIDS
• Antibacterials: increased risk of hypocalcaemia when bisphosphonates given with AMINOGLYCOSIDES
• Calcium Salts: absorption of bisphosphonates reduced by CALCIUM SALTS
• Cytotoxics: sodium clodronate increases plasma concentration of ESTRAMUSTINE
• Iron Salts: absorption of bisphosphonates reduced by oral IRON SALTS
Bivalirudin
• Analgesics: increased risk of haemorrhage when anticoagulants given with intravenous DICLOFENAC (avoid concomitant use, including low-dose heparins); increased risk of haemorrhage when anticoagulants given with • KETOROLAC (avoid concomitant use, including low-dose heparins)
• Anticoagulants: increased risk of haemorrhage when other anticoagulants given with • APIXABAN, • DABIGATRAN and • RIVAROXABAN (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)
Bleomycin
• Antipsychotics: avoid concomitant use of cytotoxics with CLOzapine (increased risk of agranulocytosis)
• Cardiac Glycosides: bleomycin possibly reduces absorption of DIGOXIN tablets
• Cytotoxics: increased risk of pulmonary toxicity when bleomycin given with • BRENTHUIMAB VEDOTIN—avoid concomitant use; increased pulmonary toxicity when bleomycin given with • CISPLATIN
Boceprevir
• Alpha-blockers: boceprevir possibly increases plasma concentration of DOXAZOSIN and TAMISULOSIN—manufacturer of boceprevir advises avoid concomitant use
• Analgesics: possible increased risk of prolonged sedation and respiratory depression when boceprevir given with BUPRENORPHINE; boceprevir possibly affects plasma concentration of METHADONE
• Antibacterials: manufacturer of boceprevir advises avoid concomitant use with • RIFAMPICIN (plasma concentration of boceprevir possibly reduced)
• Anticoagulants: avoidance of boceprevir advised by manufacturer of APIXABAN
• Antiepilptics: manufacturer of boceprevir advises avoid concomitant use with • CARBAMAZEPINE, • FOSPHENYTOIN, • PHENOBARBITAL, • PHENOTYON and • PRIMIDONE (plasma concentration of boceprevir possibly reduced)
• Antifungals: plasma concentration of boceprevir increased by KETOCONAZOLE
• Antimalarials: manufacturer of boceprevir advises avoid concomitant use with • ARTEMETHER with LUMEFAOTINE
Boceprevir (continued)
• Antipsychotics: boceprevir possibly increases plasma concentration of • LURASIDONE—avoid concomitant use; manufacturer of boceprevir advises avoid concomitant use with • PIMOZIDE; boceprevir possibly increases plasma concentration of • QUETIAPINE—manufacturer of quetiapine advises avoid concomitant use
• Antivirals: boceprevir reduces plasma concentration of • ATAZANAVIR; boceprevir possibly increases the plasma concentration of • DACLATASVIR—reduce dose of daclatasvir (see under Daclatasvir, p. 544); avoid concomitant use of boceprevir with • DARUNAVIR; effects of both drugs possibly reduced when boceprevir given with ETRAVIRINE; avoidance of boceprevir advised by manufacturer of • ROSAMPRENAVIR, • NEVIRAPINE and • TIPRANAVIR; manufacturers advise avoid concomitant use of boceprevir with • LOPINAVIR; boceprevir increases plasma concentration of MARAVIROC (consider reducing dose of maraviroc); plasma concentration of both drugs reduced when boceprevir given with • RITONAVIR
• Antioxidants and Hypnotics: boceprevir increases plasma concentration of orai • MIDAZOLAM—manufacturer of boceprevir advises avoid concomitant use
• Cardiac Glycosides: boceprevir possibly increases side-effects of DIGOXIN
• Ciclosporin: boceprevir increases plasma concentration of CICLOSPORIN
• Cilostazol: boceprevir possibly increases plasma concentration of • CILOSTAZOL (see under Cilostazol, p. 206)
• Cobicistat: avoidance of boceprevir advised by manufacturer of COBICISTAT
• Cytotoxics: boceprevir possibly increases the plasma concentration of • BOSUTINIB—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; manufacturer of boceprevir advises avoid concomitant use with • DASATINIB, • ERLOTINIB, • Gefitinib, • IMATINIB, • LAPATINIB, • Nilotinib, • Pazopanib, • Sorafenib and • SUNITINIB; manufacturer of ruxolitinib advises dose reduction when boceprevir given with a RUXOLITINIB—consult ruxolitinib product literature
• Domperidone: possible increased risk of ventricular arrhythmias when boceprevir given with • DOMPERIDONE—avoid concomitant use
• Ergot Alkaloids: manufacturer of boceprevir advises avoid concomitant use with • ERGOT ALKALOIDS
• Lipid-regulating Drugs: boceprevir increases plasma concentration of • ATORVASTATIN (reduce dose of atorvastatin); boceprevir increases plasma concentration of • PRAVASTATIN; manufacturers advise avoid concomitant use of boceprevir with • SIMVASTATIN
• Protonpump inhibitors: boceprevir increases plasma concentration of DROSPIRENONE (increased risk of toxicity)
• Sirolimus: boceprevir increases plasma concentration of • SIROLIMUS (increased risk of toxicity—reduce sirolimus dose)
• Tacrolimus: boceprevir increases plasma concentration of • TACROLIMUS (reduce dose of tacrolimus)
Bortezomib
• Antibacterials: plasma concentration of bortezomib reduced by • RIFAMPICIN—manufacturer of bortezomib advises avoid concomitant use
• Antidepressants: plasma concentration of bortezomib possibly reduced by • ST JOHN'S WORT—manufacturer of bortezomib advises avoid concomitant use
• Antiepilptics: plasma concentration of bortezomib possibly reduced by • CARBAMAZEPINE, • FOSPHENYTOIN, • PHENOBARBITAL, • PHENOTYON and • PRIMIDONE—manufacturer of bortezomib advises avoid concomitant use
• Antifungals: plasma concentration of bortezomib reduced by • KETOCONAZOLE
• Antipsychotics: avoid concomitant use of cytotoxics with • CROZAPINE (increased risk of agranulocytosis)
Bosantan
• Antibacterials: plasma concentration of bosantan reduced by • RIFAMPICIN—avoid concomitant use
• Anticoagulants: manufacturer of bosantan recommends monitoring anticoagulant effect of COUMARINS
Appendix 1 Interactions

Bosentinib (continued)
- Antipsychotics: possible increased risk of ventricular arrhythmias when bosutinib given with ▶ HALOPERIDOL; avoid concomitant use of cytoxics with ▶ CLOzapine (increased risk of agranulocytosis)
- Antifungals: plasma concentration of bosutinib possibly increased by ▶ ATAZANAVIR, ▶ BOCEPREVIR, ▶ DARunavir, ▶ FOsamPrenavir, ▶ INIDinavir, ▶ RITOnavir, ▶ SAQuINavir and ▶ Telaprevir—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; plasma concentration of bosutinib possibly reduced by ▶ EFAtreN and ▶ STRAvinir—manufacturer of bosutinib advises avoid concomitant use
- Aprepitant: plasma concentration of bosutinib possibly increased by ▶ APRePitanT—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib
- Beta-blockers: possible increased risk of ventricular arrhythmias when bosutinib given with ▶ Sotalol
- Bosentin: plasma concentration of bosutinib possibly reduced by ▶ Bosentin—manufacturer of bosutinib advise concomitant use
- Calcium-channel Blockers: plasma concentration of bosutinib possibly increased by ▶ DilTiazem and ▶ Verapamil—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib
- Cytoxics: plasma concentration of bosutinib possibly increased by ▶ MatINib—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib
- Domperidone: manufacturer of bosutinib advises avoid concomitant use with ▶ Domperidone (risk of ventricular arrhythmias)
- Fosaprepitant: plasma concentration of bosutinib possibly increased by ▶ FOSaprepitanT—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib
- Grapefruit juice: plasma concentration of bosutinib possibly increased by ▶ Grapefruit Juice—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib
- Modafinil: plasma concentration of bosutinib possibly reduced by ▶ Modafinil—manufacturer of bosutinib advises avoid concomitant use
- Ulcer-healing Drugs: plasma concentration of bosutinib reduced by ▶ Lansoprazole

Brentuximab vedotin
- Antibacterials: effects of brentuximab vedotin possibly reduced by ▶ Rifampicin
- Antifungals: possible increased risk of neutropenia when brentuximab vedotin given with ▶ KetoCONAZOLE
- Antipsychotics: avoid concomitant use of cytoxics with ▶ CLOzapine (increased risk of agranulocytosis)
- Cytoxics: increased risk of pulmonary toxicity when brentuximab vedotin given with ▶ Bleomycin—avoid concomitant use
- Vaccines: risk of generalised infections when monoclonal antibodies given with live ▶ Vaccines—avoid concomitant use

Brimonidine
- Antidepressants: manufacturer of brimonidine advises avoid concomitant use with ▶ MAOIs, TRICYClic-RELATED ANtiDEPressants and TRiCylcics

Brinzolamide see Diuretics

Bromocriptine
- Alcohol: tolerance of bromocriptine reduced by ▶ Alcohol
- Antiparkinsonian: possible increased risk of ventricular arrhythmias when bromocriptine given with ▶ MOXYflUCOXIN; plasma concentration of bromocriptine possibly reduced by ▶ RifabUTIN—manufacturer of bromocriptine advises avoid concomitant use
- Antidepressants: manufacturer of bromocriptine advises avoid concomitant use
- Antiepileptics: plasma concentration of bromocriptine possibly reduced by ▶ CarbAMAZEPINE, ▶ PhoenYtoin, ▶ PheNobarbital, ▶ Phenytoin and ▶ PrimOdone—manufacturer of bromocriptine advises avoid concomitant use
- Antifungals: plasma concentration of bromocriptine increased by ▶ KetoCONAZOLE—manufacturer of bromocriptine advises avoid or consider reducing dose of bromocriptine; plasma concentration of bromocriptine possibly increased by ▶ Macrolides (increased risk of toxicity)
- Antipsychotics: possible increased risk of ventricular arrhythmias when bromocriptine given with ▶ ChlorOquine and ▶ HydroxyChloroquine
- Beta-blockers: possible increased risk of ventricular arrhythmias when bromocriptine given with ▶ Haloperidol; avoid concomitant use of cytoxics with ▶ Clozapine (increased risk of agranulocytosis)
- Antifungals: plasma concentration of bromocriptine possibly increased by ▶ KetoCONAZOLE—manufacturer of bromocriptine advises avoid or consider reducing dose of bromocriptine; plasma concentration of bromocriptine possibly increased by ▶ Fluconazole, ▶ Itraconazole, ▶ Posaconazole and ▶ Voriconazole—manufacturer of bromocriptine advises avoid or consider reducing dose of bromocriptine
- Antimalarials: possible increased risk of ventricular arrhythmias when bromocriptine given with ▶ HydroxyChloroquine and ▶ ChlorOquine and ▶ ChlorOquine

Bosentinib (continued)
- Antidiabetics: increased risk of hepatotoxicity when bosutinib given with ▶ GlibenClamide—avoid concomitant use
- Antifungals: plasma concentration of bosentan increased by ▶ KetoConazole; plasma concentration of bosentan possibly increased by ▶ FlucOnazole—avoid concomitant use; plasma concentration of bosentan possibly increased by ▶ ItraConazole
- Antivirals: avoidance of bosentan advised by manufacturer of ▶ EnteGravir and ▶ TiraPreviN; bosentan possibly reduces plasma concentration of ▶ Indinavir; plasma concentration of bosentan increased by ▶ Lopinavir and ▶ RitoNavir (consider reducing dose of bosentan); bosentan possibly reduces plasma concentration of ▶ Telaprevir, also plasma concentration of bosentan possibly increased
- Avanafil: bosentan possibly reduces plasma concentration of ▶ AvanaFil—manufacturer of avanafil advises avoid concomitant use
- Ciclosporin: plasma concentration of bosentan increased by ▶ Ciclosporin (also plasma concentration of ciclosporin reduced—avoid concomitant use)
- Cobicistat: avoidance of bosentan advised by manufacturer of ▶ Cobicistat
- Cytotoxics: bosentan possibly reduces plasma concentration of ▶ BosuTinib—manufacturer of bosutinib advises avoid concomitant use
- Lipid-regulating Drugs: bosentan reduces plasma concentration of ▶ SimvasTatin
- Oestrogens: bosentan possibly causes contraceptive failure of hormonal contraceptives containing ▶ Oestrogen (alternative contraception recommended)
- Progestogens: bosentan possibly causes contraceptive failure of hormonal contraceptives containing ▶ Progestogens (alternative contraception recommended)
- Rifampicin: bosentan reduces plasma concentration of ▶ RifOGiCat
- Sildenafil: bosentan reduces plasma concentration of ▶ SildenaFil, also plasma concentration of bosentan increased
- Tadalafil: bosentan reduces plasma concentration of ▶ TadaFalin

Bosentinib
- Analgesics: possible increased risk of ventricular arrhythmias when bosutinib given with ▶ Methadone
- Antacids: manufacturer of bosutinib advises separating administration with ▶ Antacids by about 12 hours
- Anti-arthritis: possible increased risk of ventricular arrhythmias when bosutinib given with ▶ AmiodaronE and ▶ Disopyramide; plasma concentration of bosutinib possibly increased by ▶ Dronedarone—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib
- Antituberculotics: plasma concentration of bosutinib possibly increased by ▶ CiproflOXacin; ▶ ClariThromycin, ▶ EryTHromycin and ▶ Telithromycin—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; possible increased risk of ventricular arrhythmias when bosutinib given with ▶ MOXiflucOXin; plasma concentration of bosutinib possibly reduced by ▶ Rifabutin—manufacturer of bosutinib advises avoid concomitant use; plasma concentration of bosutinib reduced by ▶ Rifampicin—manufacturer of bosutinib advises avoid concomitant use
- Antidepressants: plasma concentration of bosutinib possibly reduced by ▶ St John’s Wort—manufacturer of bosutinib advises avoid concomitant use
- Antiepileptics: plasma concentration of bosutinib possibly reduced by ▶ CarbamazEpine, ▶ Fosphenytoin, ▶ PhenoBarbital, ▶ Phenytoin and ▶ PrimOdone—manufacturer of bosutinib advises avoid concomitant use
- Anti-fungals: plasma concentration of bosutinib increased by ▶ KetoConazole—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib, plasma concentration of bosutinib possibly increased by ▶ Fluconazole, ▶ Itraconazole, ▶ Posaconazole and ▶ Voriconazole—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib
- Antimalarials: possible increased risk of ventricular arrhythmias when bosutinib given with ▶ ChloroQuine and ▶ HydroxyChloroQuine
Interactions (Appendix 1 Interactions)

Bromocriptine (continued)
- Sympathomimetics: risk of toxicity when bromocriptine given with MOCLOBEMIDE; manufacturer of bromocriptine advises avoid concomitant use with MOCLOBEMIDE; bromocriptine possibly increases plasma concentration of TRICYCLICS (possible increased risk of convulsions)

Antiepileptics: plasma concentration of bromocriptine reduced by CARBAMAZEPINE, FOSPHENYTOIN and PHENYTOIN; metabolism of bromocriptine inhibited by SODIUM VALPROATE and VALPROIC ACID
- Antivirals: metabolism of bromocriptine accelerated by EFAVIRENZ (reduced plasma concentration); plasma concentration of bromocriptine reduced by RITONAVIR
- Atomoxetine: possible increased risk of convulsions when bromocriptine given with ATOMOXETINE
- Dopaminergics: increased risk of side-effects when bromocriptine given with AMANTADINE, CO-BENEDELPA, CO-CARELDOPA or LEVODOPA
- Hormone Antagonists: bromocriptine possibly inhibits metabolism of TAMOXIFEN to active metabolite (avoid concomitant use)
- Methylthioninium: possible risk of CNS toxicity when bromocriptine given with METHYLTHIONINIUM—avoid concomitant use (if avoidance not possible, use lowest possible dose of methylthioninium and observe patient for up to 4 hours after administration)

Buspirone see>Anxiolytics and Hypnotics

Busulfan
- Analgesics: metabolism of intravenous busulfan possibly inhibited by PARACETAMOL (manufacturer of intravenous busulfan advises caution within 72 hours of paracetamol)
- Antibacterials: plasma concentration of busulfan increased by METRONIDAZOLE (increased risk of toxicity)
- Antiepileptics: plasma concentration of busulfan possibly reduced by FOSPHENYTOIN and PHENYTOIN
- Antifungals: metabolism of busulfan inhibited by ITRACONAZOLE (increased risk of toxicity)
- Antipsychotics: avoid concomitant use of cytoxotics with CLOzapine (increased risk of agranulocytosis)
- Cytotoxic: increased risk of hepatotoxicity when busulfan given with TIOGUANINE

Butyrophenones see Antipsychotics

Cabazitaxel
- Antibacterials: plasma concentration of cabazitaxel possibly increased by CLARITHROMYCIN and TELITHROMYCIN—manufacturer of cabazitaxel advises avoid or consider reducing dose of cabazitaxel; manufacturer of cabazitaxel advises avoid concomitant use with rifabutin; plasma concentration of cabazitaxel reduced by Rifampicin—manufacturer of cabazitaxel advises avoid or consider reducing dose of cabazitaxel
- Antidepressants: manufacturer of cabazitaxel advises avoid concomitant use with ST JOHN’S WORT
- Antiepileptics: plasma concentration of cabazitaxel possibly increased by ITRACONAZOLE and voriconazole—manufacturer of cabazitaxel advises avoid or consider reducing dose of cabazitaxel
- Antipsychotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis)

Cabergoline
- Antibacterials: plasma concentration of cabergoline increased by ERYTHROMYCIN (increased risk of toxicity); plasma concentration of cabergoline possibly increased by MACROLIDES (increased risk of toxicity)
- Antipsychotics: hypoprolactinaemic and antiparkinsonian effects of cabergoline antagonised by ANTIPSYCHOTICS
- Memantine: effects of dopaminergics possibly enhanced by MEMPANTINE
- Methyl dopa: antiparkinsonian effect of dopaminergics antagonised by METHYLDOPA
- Metoclopramide: hypoprolactinaemic effect of cabergoline antagonised by METOCLOPRAMIDE

Cabozantinib
- Antibacterials: plasma concentration of cabozantinib possibly increased by CLARITHROMYCIN and ERYTHROMYCIN; plasma concentration of cabozantinib reduced by rifampicin—avoid concomitant use
- Antidepressants: plasma concentration of cabozantinib potentially reduced by ST JOHN’S WORT—manufacturer of cabozantinib advises avoid concomitant use
- Antiepileptics: plasma concentration of cabozantinib possibly increased by CARBAMAZEPINE, FOSPHENYTOIN, PHENOBARBITAL, PHENYTOIN and PRIMIDONE—avoid concomitant use
- Antifungals: plasma concentration of cabozantinib increased by ITRACONAZOLE; plasma concentration of cabozantinib possibly increased by ITRACONAZOLE
- Antipsychotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis)
- Calcium salts: plasma concentration of calcium citrate increased by GRAPFUIT JUICE

Caffeine citrate
- Aminophylline: manufacturer of caffeine citrate advises avoid concomitant use with AMINOPHYLLINE
- Anti-arrhythmics: caffeine citrate antagonises anti-arrhythmic effect of ADENOSINE—manufacturer of adenosine advises avoid caffeine citrate for at least 12 hours before adenosine
- Antiepileptics: plasma concentration of caffeine citrate reduced by FOSPHENYTOIN and PHENYTOIN; caffeine citrate possibly antagonises effects of PHENOBARBITAL and PRIMIDONE
- Theophylline: manufacturer of caffeine citrate advises avoid concomitant use with THEOPHYLLINE
- Ulcer-healing Drugs: plasma concentration of caffeine citrate increased by CIMETIDINE

Calcitriol see Vitamins

Calcium Salts

NOTE see also Antacids
- Antibacterials: calcium salts reduce absorption of CIPROFLOXACIN and TETRACYCLINE
- Antivirals: calcium salts reduce absorption of DOLUTEGRAVIR—manufacturer of dolutegravir advises give at least 2 hours before or 6 hours after calcium salts; manufacturer of rilpivirine advises give calcium salts 2 hours before or 4 hours after RILPIVIRINE
- Bisphosphonates: calcium salts reduce absorption of BISPHOSPHONATES
- Cardiac Glycosides: large intravenous doses of calcium salts can precipitate arrhythmias when given with CARDIAC GLYCOSIDES
- Corticosteroids: absorption of calcium salts reduced by CORTICOSTEROIDS
Calcium channel blockers: note Dihydropyridine calcium channel blockers include amlodipine, felodipine, isradipine, lacidipine, lercanidine, nicardipine, nifedipine, and nimodipine

- ACE inhibitors: enhanced hypertensive effect when calcium channel blockers given with ACE INHIBITORS
- Adrenergic Neurone Blockers: enhanced hypertensive effect when calcium channel blockers given with ADRENERGIC NEURONE BLOCKERS
- Alcohol: enhanced hypertensive effect when calcium channel blockers given with ALCOHOL; verapamil possibly increases plasma concentration of ALCOHOL
- Aldesleukin: enhanced hypertensive effect when calcium channel blockers given with ALDESLEUKIN
- Alfentanil: verapamil increases plasma concentration of ALFENTANIL
- Alpha-blockers: verapamil increases plasma concentration of TAMSULOSIN; enhanced hypertensive effect when calcium channel blockers given with ALPHA-BLOCKERS, also increased risk of first-dose hypotension with post-synaptic alpha-blockers such as prazosin
- Amphotericin: calcium channel blockers possibly increase plasma concentration of AMINOPHYLLINE (enhanced effect); diltiazem increases plasma concentration of AMINOPHYLLINE; verapamil increases plasma concentration of AMINOPHYLLINE (enhanced effect)
- Analgesics: increased hypertensive effect of calcium-channel blockers antagonised by NSAIDS; diltiazem inhibits metabolism of ALFENTANIL (risk of prolonged or delayed respiratory depression)
- Angiotensin-II Receptor Antagonists: enhanced hypertensive effect when calcium-channel blockers given with ANGIOTENSIN-II RECEPTOR ANTAGONISTS
- Anti-arrhythmics: increased risk of bradyarrhythmia, AV block and myocardial depression when diltiazem or verapamil given with AMIODARONE; increased risk of myocardial depression and asystole when verapamil given with DISOPYRAMIDE or FLECAINIDE; increased risk of bradyarrhythmia and myocardial depression when diltiazem and verapamil given with DRONEDARONE; nifedipine increases plasma concentration of DRONEDARONE
- Antidiabetics: metabolism of calcium-channel blockers possibly inhibited by CLARITHROMYCIN, ERYTHROMYCIN and TELITHROMYCIN (increased risk of side-effects); manufacturer of lercanidine advises avoid concomitant use with ERYTHROMYCIN; metabolism of diltiazem, nicardipine, nifedipine, and verapamil accelerated by RIFAMPICIN (plasma concentration significantly reduced); metabolism of isradipine and nicardipine possibly accelerated by RIFAMPICIN (possible significantly reduced plasma concentration); plasma concentration of felodipine possibly reduced by RIFAMPICIN; avoidance of verapamil advised by manufacturer of FIDAXOMICIN
- Anticoagulants: verapamil possibly increases plasma concentration of DABIGATRAN (see under Dabigatran Etxelate, p. 117)
- Antidepressants: metabolism of nifedipine possibly inhibited by FLUOXETINE (increased plasma concentration); diltiazem and verapamil increase plasma concentration of IMIPRAMINE; Calcium-channel blockers
- Antidepressants: enhanced hypertensive effect when calcium-channel blockers given with MAOIS; plasma concentration of nifedipine reduced by ST JOHN'S WORT; plasma concentration of amlodipine and felodipine possibly reduced by ST JOHN'S WORT; plasma concentration of verapamil significantly reduced by ST JOHN'S WORT; diltiazem and verapamil possibly increase plasma concentration of tricyclics
- Antihypertotics: glucose tolerance occasionally impaired when nifedipine given with INSULIN
- Antiepileptics: effects of dihydropyridines, nicardipine and nifedipine possibly inhibited by CARBAMAZEPINE; effects of felodipine and isradipine reduced by CARBAMAZEPINE; effects of diltiazem and verapamil possibly increase plasma concentration of CARBAMAZEPINE, FOSPHENOTIN and PHENOTHIN (plasma concentration of nimodipine possibly reduced); effects of felodipine and verapamil reduced by FOSPHENOTIN; manufacturer of isradipine advises avoid concomitant use with FOSPHENOTIN, PHENOBARBITAL, PHENOTHIN and PRIMIDONE; diltiazem increases plasma concentration of PHENOBARBITAL and PRIMIDONE (plasma concentration of nimodipine reduced); effects of felodipine and verapamil reduced by PHENOTHIN
- Antifungals: metabolism of dihydropyridines possibly inhibited by ITRACONAZOLE and KETOCONAZOLE (increased plasma concentration); metabolism of fosphenytoin is inhibited by KETOCONAZOLE (increased plasma concentration)—manufacturer of ketoconazole advises avoid concomitant use; manufacturer of lercanidine advises avoid concomitant use with ITRACONAZOLE and KETOCONAZOLE; negative inotropic effect possibly increased when calcium-channel blockers given with ITRACONAZOLE; metabolism of felodipine inhibited by ITRACONAZOLE (increased plasma concentration); plasma concentration of nifedipine increased by NICAFUNGIN
- Antimarialarials: possible increased risk of bradyarrhythmia when calcium-channel blockers given with MEFLOQUINE
- Antimicrobials: avoidance of verapamil advised by manufacturer of DARIFENACIN; verapamil increases plasma concentration of SOLIFENACIN
- Antipsychotics: enhanced hypertensive effect when calcium-channel blockers given with ANTIPSYCHOTICS; diltiazem increases the plasma concentration of LURASIDONE (see under Luzasidone, p. 315); verapamil possibly increases the plasma concentration of LURASIDONE (see under Luzasidone, p. 315)
- Antivirals: plasma concentration of verapamil possibly increased by ATAZANAVIR; plasma concentration of diltiazem increased by ATAZANAVIR (reduce dose of diltiazem); plasma concentration of diltiazem reduced by LAMINIREN; manufacturer of lercanidine advises avoid concomitant use with RITONAVIR; plasma concentration of calcium-channel blockers possibly increased by RITONAVIR; caution with diltiazem, felodipine, nicardipine, nifedipine and verapamil advised by manufacturer of TELAPREVID; plasma concentration of amlodipine increased by TELAPREVID (consider reducing dose of amlodipine)
- Anxiolytics and Hypnotics: enhanced hypertensive effect when calcium-channel blockers given with ANXIOLYTICS AND HYPNOTICS; diltiazem and verapamil inhibit metabolism of MIDAZOLAM (increased plasma concentration with increased sedation); absorption of lercanidine increased by MIDAZOLAM; diltiazem and verapamil increase plasma concentration of BUSPIRONE (reduce dose of buspirone)
- Aprepitant: plasma concentration of both drugs may increase when diltiazem given with APREPIVAT
- Avanafil: diltiazem and verapamil possibly increase plasma concentration of AVANAFIL—see under Avanafil, p. 698
- Beta-blockers: enhanced hypertensive effect when calcium-channel blockers given with Beta-blockers; increased risk of
Interactions

Calcium-channel Blockers
- Beta-blockers (continued)
  AV block and bradycardia when diltiazem given with beta-blockers; asystole, severe hypotension and heart failure when verapamil given with beta-blockers (see under Verapamil, p. 156); possible severe hypotension and heart failure when nifedipine given with beta-blockers
- Calcium-channel Blockers: plasma concentration of both drugs may increase when diltiazem given with rifampicin
- Candesartan: diltiazem, lercanidipine and nifedipine increase plasma concentration of diltiazem; verapamil increases plasma concentration of diltiazem, also increased risk of AV block and bradycardia; nifedipine possibly increases plasma concentration of diltiazem
- Ciclosporin: diltiazem, nicardipine and verapamil increase plasma concentration of ciclosporin; combination of lercanidipine with ciclosporin may increase plasma concentration of either drug (or both)—avoid concomitant use; plasma concentration of nifedipine possibly increased by ciclosporin (increased risk of toxicity including gingival hyperplasia)
- Clocastazol: diltiazem increases plasma concentration of clocastazol (consider reducing dose of clocastazol)
- Clonidine: enhanced hypotensive effect when calcium-channel blockers are antagonised by corticosteroids; diltiazem increases plasma concentration of methylprednisolone
- Cytotoxics: verapamil possibly increases plasma concentration of doxorubicin; verapamil possibly increases the plasma concentration of afatinib—manufacturer of afatinib advises separating administration of verapamil by 6 to 12 hours; diltiazem and verapamil possibly increase the plasma concentration of bosutinib—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; possible increased risk of bradycardia when diltiazem or verapamil given with everolimus (consider reducing the dose of everolimus—consult everolimus product literature); diltiazem and verapamil possibly increase the plasma concentration of ibritinib—reduce dose of ibritinib (see under ibritinib, p. 809); nifedipine possibly inhibits metabolism of vincristine
- Dapoxetine: manufacturer of dapoxetine advises dose reduction when diltiazem and verapamil given with dapoxetine (see under Dapoxetine, p. 705)
- Diazoxide: enhanced hypotensive effect when calcium-channel blockers given with diazoxide
- Diuretics: enhanced hypotensive effect when calcium-channel blockers given with diuretics; diltiazem and verapamil increase plasma concentration of eplerenone (reduce dose of eplerenone)
- Dopaminergics: enhanced hypotensive effect when calcium-channel blockers given with co-beneldopa, co-careldopa or levodopa
- Fingolimod: possible increased risk of bradycardia when diltiazem or verapamil given with fingolimod
- Fosaprepitant: plasma concentration of both drugs may increase when diltiazem given with fosaprepitant
- Grapefruit juice: plasma concentration of felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimoipidine and verapamil increased by grapefruit juice; plasma concentration of amlopidine possibly increased by grapefruit juice
- Hormone Antagonists: diltiazem and verapamil increase plasma concentration of dutasteride; possible increased risk of bradycardia when diltiazem or verapamil given with pasireotide
- Ibrivanadine: diltiazem and verapamil increase plasma concentration of ibrivanadine—avoid concomitant use
- Lenalidomide: verapamil possibly increases plasma concentration of lenalidomide (increased risk of toxicity)
- Lipid-regulating Drugs: diltiazem increases plasma concentration of atorvastatin—possible increased risk of myopathy; plasma concentration of verapamil increased by atorvastatin, also possible increased risk of myopathy (consider reducing dose of atorvastatin); possible increased risk of myopathy when amiodipine and diltiazem given with atorvastatin
- Simvastatin: see under Simvastatin, p. 181; increased risk of myopathy when verapamil given with simvastatin (see under Simvastatin, p. 181); separating administration from amiodipine and lacidipine by 12 hours advised by manufacturer of lomitapide; avoidance of diltiazem and verapamil advised by manufacturer of lomitapide (plasma concentration of lomitapide possibly increased)
- Lithium: neurotoxicity may occur when diltiazem or verapamil given with lithium without increased plasma concentration of lithium
- Magnesium (parenteral): profound hypotension reported with concomitant use of nifedipine and magnesium in pre-eclampsia
- Methylodopa: enhanced hypotensive effect when calcium-channel blockers given with methylodopa
- Moxisylyte: enhanced hypotensive effect when calcium-channel blockers given with moxisylyte
- Moxifloxacin: enhanced hypotensive effect when calcium-channel blockers given with moxifloxacin
- Muscle Relaxants: verapamil enhances effects of non-depolarising muscle relaxants and suxamethonium; enhanced hypotensive effect when calcium-channel blockers given with tacrolimus or tizanidine; manufacturer of verapamil advises avoid concomitant use of intravenous dantrolene; possible increased risk of ventricular arrhythmias when diltiazem given with intravenous dantrolene—manufacturer of dantrolene advises avoid concomitant use; calcium-channel blockers possibly enhance effects of non-depolarising muscle relaxants
- Nitrates: enhanced hypotensive effect when calcium-channel blockers given with nitrates
- Oestrogens: hypotensive effect of calcium-channel blockers antagonised by oestrogens
- Prostaglandins: enhanced hypotensive effect when calcium-channel blockers given with alprostadil
- Ranolazine: diltiazem and verapamil increase plasma concentration of ranolazine (consider reducing dose of ranolazine)
- Sildenafil: enhanced hypotensive effect when amiodipine given with sildenafil
- Sirolimus: diltiazem increases plasma concentration of sirolimus; plasma concentration of both drugs increased when verapamil given with sirolimus; nicardipine possibly increases plasma concentration of sirolimus
- Sulfipyrazone: plasma concentration of verapamil reduced by sulfipyrazone
- Tacrolimus: diltiazem, nicardipine and nifedipine increase plasma concentration of tacrolimus
- Theophylline: calcium-channel blockers possibly increase plasma concentration of theophylline (enhanced effect); diltiazem increases plasma concentration of theophylline; verapamil increases plasma concentration of theophylline (enhanced effect)
- Ticagrelor: diltiazem increases plasma concentration of ticagrelor
- Ulcer-healing Drugs: metabolism of calcium-channel blockers possibly inhibited by cimetidine (increased plasma concentration); plasma concentration of isradipine increased by cimetidine. (halve dose of isradipine)
- Ulipristal: avoidance of verapamil advised by manufacturer of ulipristal
- Vanadefil: enhanced hypotensive effect when nifedipine given with vanadefil
- Vasodilator Antihypertensives: enhanced hypotensive effect when calcium-channel blockers given with hydralazine, minoxidil of sodium nitroprusside
Carbamazepine (continued)
- Anti-arrhythmics: carbamazepine possibly reduces plasma concentration of DRONEDARONE—avoids concomitant use
- Antibacterials: plasma concentration of carbamazepine increased by CLARITHROMYCIN (consider reducing dose of carbamazepine); plasma concentration of carbamazepine increased by ERYTHROMYCIN; plasma concentration of carbamazepine reduced by RIFABUTIN; carbamazepine accelerates metabolism of DOXYCYCLINE (reduced effect); carbamazepine possibly reduces plasma concentration of BEDAQUILINE—manufacturer of bedaquiline advises avoid concomitant use; avoidance of carbamazepine advised by manufacturer of DELAMANDI; plasma concentration of carbamazepine increased by ISONIAZID (also possibly increased isoniazid hepatotoxicity); carbamazepine reduces plasma concentration of TELITHROMYCIN (avoid during and for 2 weeks after carbamazepine)
- Anticoagulants: carbamazepine possibly reduces plasma concentration of APIXABAN—manufacturer of apixaban advises avoid concomitant use when given for treatment of deep-vein thrombosis or pulmonary embolism; carbamazepine accelerates metabolism of COUMARINS (reduced anticoagulant effect); carbamazepine possibly reduces plasma concentration of DABIGATRAN—manufacturer of dabigatran advises avoid concomitant use; carbamazepine possibly reduces plasma concentration of RIVAROXaban, manufacturer of rivaroxaban advises monitor for signs of thrombosis
- Antidepressants: carbamazepine possibly reduces plasma concentration of ROBENOXINE; plasma concentration of carbamazepine increased by FLUOXETINE and FLUVOXAMINE; carbamazepine reduces plasma concentration of MIANERIN, MIRTAZAPINE and Trazodone; anticonvulsant effect of antiepileptics possibly antagonised by MAIDS and TRICYCLIC-RELATED ANTIDEPRESSANTS (convulsive threshold lowered); manufacturer of carbamazepine advises avoid for 2 weeks after stopping MAIDS, also antagonism of anticonvulsant effect; anticonvulsant effect of antiepileptics antagonised by SSRIS and TRICYCLICS (convulsive threshold lowered); plasma concentration of carbamazepine possibly reduced by ST JOHN’S WORT; carbamazepine accelerates metabolism of TRICYCLICS (reduced plasma concentration and reduced effect)
- Antiepileptics: carbamazepine possibly reduces plasma concentration of ESILCARAZEPINE but risk of side-effects increased; carbamazepine possibly reduces plasma concentration of ETHOSUXIMIDE and RITABINE; plasma concentration of both drugs often reduced when carbamazepine given with FOSPHENYTOIN or PHENYTOIN, also plasma concentration of fosphenytoin or phenytoin may be increased; carbamazepine often reduces plasma concentration of LAMOTRIGINE, also plasma concentration of an active metabolite of carbamazepine sometimes raised (but evidence is conflicting); possible increased risk of carbamazepine toxicity when given with LEVETIRACEM; plasma concentration of carbamazepine sometimes reduced by OCARBAZEPINE (but concentration of an active metabolite of carbamazepine may be increased), also plasma concentration of an active metabolite of oxcarbazepine often reduced; carbamazepine reduces plasma concentration of PERAMPANEL (see under Perampanel, p. 398); carbamazepine possibly increases plasma concentration of PHENOBARBITAL and PRIMIDONE; plasma concentration of both drugs possibly reduced when carbamazepine given with RUFINAMIDE; carbamazepine reduces plasma concentration of SODIUM VALPROATE and VALPROIC ACID, also plasma concentration of active metabolite of carbamazepine increased; plasma concentration of carbamazepine increased by STRIPENTROL; carbamazepine reduces plasma concentration of TIAGABINE and ZONISAMIDE; carbamazepine often reduces plasma concentration of TOPIRAMATE
- Antifungals: plasma concentration of carbamazepine possibly increased by KETOCONAZOLE, also plasma concentration of ketoconazole possibly reduced; plasma concentration of carbamazepine possibly increased by FLUCONAZOLE and
Interactions

Cytotoxics
- Carbamazepine
  - Antifungals (continued)
    - MICONAZOLE; carbamazepine possibly reduces plasma concentration of ITRACONAZOLE and POSaconazole; carbamazepine possibly reduces plasma concentration of DOXORUBICIN, DRUGS REDUCED WHEN CARBAMAZEPINE GIVEN WITH ARTENIOL WITH PIPERAZINE, antiepileptic effect of antiepileptics antagonised by MEfloquine
  - Antipyschotics: anticonvulsant effect of antiepileptics antagonised by ANTIPSYCHOTICS (convulsive threshold lowered); carbamazepine accelerates metabolism of DAUNORUBICIN, OLANZAPINE, QUETIAPINE and RISPERIDONE (reduced plasma concentration); carbamazepine reduces plasma concentration of ARIPIRAZOLE (avoid concomitant use or consider increasing the dose of aripiprazole — consult aripiprazole product literature); carbamazepine accelerates metabolism of CLOZAPINE (reduced plasma concentration), also as concomitant use of drugs reduced when carbamazepine given with EFAVIRENZ; carbamazepine possibly reduces plasma concentration of LURASIDONE — avoid concomitant use; carbamazepine reduces plasma concentration of PALPERIDONE
  - Antivirals: avoidance of carbamazepine advised by manufacturer of BOCEPREVIR and RILPIVIRINE (plasma concentration of boceprevir and rilpivirine possibly reduced); carbamazepine possibly reduces plasma concentration of DAKLADASVIR and ETARINIMOL WITH PIPERAQUINE, manufacturer of daclatasvir advises avoid concomitant use; carbamazepine often reduces plasma concentration of SOFOSBUVIR, TIPRANAVIR and NEVIRAPINE; plasma concentration of both drugs reduced when carbamazepine given with EFAVIRENZ; carbamazepine possibly reduces plasma concentration of INDIANAVIR, also plasma concentration of carbamazepine possibly increased; carbamazepine reduces plasma concentration of NEVIRAPINE; plasma concentration of carbamazepine possibly increased by RITONAVIR
  - Anxiolytics and Hypnotics: carbamazepine often reduces plasma concentration of CLONAZEPAM; carbamazepine reduces plasma concentration of MIDAZOLAM
  - Aprepitant: carbamazepine possibly reduces plasma concentration of APREPI TANT
  - Avanafil: carbamazepine possibly reduces plasma concentration of AVANAFIL — manufacturer of avanafil advises avoid concomitant use
  - Bupropion: carbamazepine reduces plasma concentration of BUPROPION
  - Calcium-channel Blockers: carbamazepine reduces effects of FELODIPINE and HRADIPINE; carbamazepine probably reduces effects of DIONYDROPHRIDINES, NICARDIPINE and NIFEDIPINE; avoidance of carbamazepine advised by manufacturer of NIMODIPINE (plasma concentration of nimodipine possibly reduced); effects of carbamazepine enhanced by DILTIAZEM and VERAPAMIL
  - Cannabis Extract: carbamazepine possibly reduces plasma concentration of CANNABIS EXTRACT — manufacturer of cannabis extract advises avoid concomitant use
  - Ciclosporin: carbamazepine accelerates metabolism of CICLOSPORIN (reduced plasma concentration)
  - Clopidogrel: carbamazepine possibly reduces antplatelet effect of CLOPIDOGREL
  - Cobicistat: carbamazepine possibly reduces plasma concentration of Cobicistat — manufacturer of cobicistat advises avoid concomitant use
  - Corticosteroids: carbamazepine accelerates metabolism of CORTICOSTEROIDS (reduced effect)
  - Cytoxics: carbamazepine possibly decreases plasma concentration of AXITINIB (increase of axitinib — consult axitinib product literature); carbamazepine possibly reduces plasma concentration of BORTezOmiB, BOSUTINIB, CRizOTINIB, IBUrITINIB, IDEALISIB and PONATINIB — manufacturer of carbamazepine

Corticosteroids
- Carbamazepine
  - Cytoxotics (continued)
    - bortezomib, bosutinib, crizotinib, ibritinib, idelisib and ponatinib advises avoid concomitant use; carbamazepine possibly reduces plasma concentration of CARBOZANTINIB — avoid concomitant use; avoidance of carbamazepine advised by manufacturer of CABAZITAXEL, DABRAFENIB, GETINIBIN and VEmurafenib; avoidance of carbamazepine advised by manufacturer of DASatinib, VANDetanIB and VISMODEGIB (plasma concentration of dasatinib, vandetanib and vismodegib possibly reduced); carbamazepine reduces plasma concentration of IMATINIB and LAPATINIB — avoid concomitant use; carbamazepine possibly reduces plasma concentration of Eribulin; carbamazepine reduces plasma concentration of IRINotecan and its active metabolite; manufacturer of procarbazine advises possible increased risk of hypersensitivity reactions when carbamazepine given with PROCARBAZINE
  - Diuretics: increased risk of hyponatraemia when carbamazepine given with DIURETICS; plasma concentration of carbamazepine increased by ETALOLAMIDE; carbamazepine reduces plasma concentration of Fingolimod
  - Fosaprepitant: carbamazepine possibly reduces plasma concentration of FOSAPREPI tant
  - Hormone Antagonists: carbamazepine possibly reduces plasma concentration of ABLERATONE — manufacturer of abiraterone advises avoid concomitant use; metabolism of carbamazepine inhibited by DANAZOL (increased risk of toxicity); carbamazepine possibly accelerates metabolism of TOREMIFENE (reduced plasma concentration)
  - HTR2-receptor Antagonists: carbamazepine accelerates metabolism of ONDANSETRON (reduced effect)
  - Ivacator: carbamazepine possibly reduces plasma concentration of IVCATOR — manufacturer of ivacator advises avoid concomitant use
  - Lipid-regulating Drugs: carbamazepine reduces plasma concentration of SIMVASTATIN — consider increasing dose of simvastatin
  - Lithium: neurotoxicity may occur when carbamazepine given with LITHIUM without increased plasma concentration of lithium
  - Mirtazapine: avoidance of carbamazepine advised by manufacturer of MACITENANT
  - Muscle Relaxants: carbamazepine antagonises muscle relaxant effect of NON-DEPOLARISING MUSCLE RELAXANTS (accelerated recovery from neuromuscular blockade)
  - Oestrogens: carbamazepine accelerates metabolism of OESTROGENS; reduced contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings — see Contraceptive Interactions in BNF
  - Orlistat: possible increased risk of convulsions when carbamazepine given with ORLISTAT
  - Progestogens: carbamazepine accelerates metabolism of PROGESTOGENS (reduced contraceptive effect with combined oral contraceptives, progestogen-only oral contraceptives, contraceptive patches, vaginal rings, etonogestrel-releasing implant, and emergency hormone contraception — see Contraceptive Interactions in BNF)
  - Retinoids: plasma concentration of carbamazepine possibly reduced by ISOTRETININ
  - Roflumilast: carbamazepine possibly inhibits effects of ROFLUMILAST — manufacturer of roflumilast advises avoid concomitant use
  - Theophylline: carbamazepine accelerates metabolism of THEOPHYLLINE (reduced effect)
  - Thyroid Hormones: carbamazepine accelerates metabolism of THYROID HORMONES (may increase requirements for thyroid hormones in hypothyroidism)
  - Tibolone: carbamazepine accelerates metabolism of TIBOLONE (reduced plasma concentration)
  - Ticagrelor: carbamazepine possibly reduces plasma concentration of TICAGRELOR
Cardiac Glycosides (continued)
▶ Corticosteroids: increased risk of hypokalaemia when cardiac glycosides given with CORTICOSTEROIDS
▶ Cytotoxics: absorption of digoxin tablets possibly reduced by BLEMOMICIN, CARMUSTINE, CYCLOPHOSPHAMIDE, CYTARABINE, DOXORUBICIN, MELPHALAN, METHOTREXATE, PROCARBAZINE and WINCristine; possible increased risk of bradycardia when digoxin given with CRZOTINIB; manufacturer of digoxin advises give IBUTRINT at least 6 hours before or after ibritinib; plasma concentration of digoxin increased by VANDETANIB—possibly increased risk of bradycardia
▶ Diuretics: increased cardiac toxicity with cardiac glycosides if hypokalaemia occurs with ACETAZOLAMIDE, LOOP DIURETICS or THIACID Diuretics; plasma concentration of digoxin possibly increased by POTASSIUM CARBONATE; plasma concentration of digoxin increased by SPIRONOLACTONE
▶ Ivermectin: plasma concentration of digoxin increased by IVACANTORF
▶ Lenalidomide: plasma concentration of digoxin possibly increased by LENALIDOMIDE
▶ Lipid-regulating Drugs: absorption of cardiac glycosides possibly reduced by COLESTIPOL and COLESTYRAMINE; plasma concentration of digoxin possibly increased by ATORVASTATIN
▶ Mirabegron: plasma concentration of digoxin increased by MIRABEGRON—reduce initial dose of digoxin
▶ Muscle Relaxants: risk of ventricular arrhythmias when cardiac glycosides given with SUXAMETHONIUM; possible increased risk of bradycardia when cardiac glycosides given with TIZANIDINE
▶ Penicillamine: plasma concentration of digoxin possibly increased by PENICILLAMINE
▶ Ranolazine: plasma concentration of digoxin increased by RANOLAZINE
▶ Sympathomimetics, Beta:-; plasma concentration of digoxin possibly reduced by SALBUTAMOL
▶ Ticagrelor: plasma concentration of digoxin increased by TICAgRELOR
▶ Tolbutamide: plasma concentration of digoxin increased by TOlvapTaN (increased risk of toxicity)
▶ Ulcer-healing Drugs: plasma concentration of digoxin possibly slightly increased by PROTON PUMP INHIBITORS; absorption of cardiac glycosides possibly reduced by SUCARLAfTE
▶ Ulipristal: manufacturer of ulipristal advises give digoxin at least 1.5 hours before or after ULIPRISTAL
Carmustine
▶ Antipsychotics: avoid concomitant use of carmustine with CLOzapine (increased risk of agranulocytosis)
▶ Cardiac Glycosides: carmustine possibly reduces absorption of DIOXIN tablets
▶ Ulcer-healing Drugs: myelosuppressive effects of carmustine possibly enhanced by CIMERTIDINE
Carbapenems see Ertaopenem, Imipenem with Cilastatin, and Meropenem
Carbonic Anhydride Inhibitors see Diuretics
Carboplatin see Platinum Compounds
Carboprost see Prostaglandins
Cardiac Glycosides
▶ ACE inhibitors: plasma concentration of digoxin possibly increased by CAPTOPRIL
▶ Alpha-blockers: plasma concentration of digoxin increased by PRAZOSIN
▶ Aminoglycosides: absorption of digoxin possibly reduced by SULFASALAZINE
▶ Analgesics: plasma concentration of cardiac glycosides possibly increased by NSAIDS, also possible exacerbation of heart failure and reduction of renal function
▶ Antacids: absorption of digoxin possibly reduced by ANTACIDS
▶ Anti-arrhythmics: plasma concentration of digoxin increased by AMIODARONE, DRONEDARONE and PROPAFENONE (halve dose of digoxin)
▶ Antibacterials: plasma concentration of digoxin possibly increased by CEFOTAXIM, CEPHALOSPORIN, TEETTHROXIM and TRIMETHOPRIM; absorption of digoxin reduced by NEOMYCIN; plasma concentration of digoxin possibly increased by RIFAMPICIN; plasma concentration of digoxin increased by MACROLIDES (increased risk of toxicity)
▶ Antidepressants: plasma concentration of digoxin reduced by ST JOHN'S WORT—avoid concomitant use
▶ Anti-diabetics: plasma concentration of digoxin possibly reduced by ACARBOS, plasma concentration of digoxin increased by CANAGLIFLOZIN and SITAGLITIEN
▶ Antiepileptics: plasma concentration of digoxin possibly reduced by FOSPHENYTOIN and PHENTYNOl
▶ Antifungals: increased cardiac toxicity with cardiac glycosides if hypokalaemia occurs with AMPHOTERIEIN; plasma concentration of digoxin increased by ITRAConAZOLE
▶ Antimalarials: plasma concentration of digoxin possibly increased by CHLOROQUINE and HYDROXYCHLOROQUINE; possible increased risk of bradycardia when digoxin given with MELOQUEINE; plasma concentration of digoxin increased by QUININE
▶ Antimuscarinics: plasma concentration of digoxin possibly increased by DARIFENACIN
▶ Antivirals: side-effects of digoxin possibly increased by BOCePREVIR; plasma concentration of digoxin increased by DAclTASVIR, ETARVirINE, SIMEPREVIR and TELAPREVeR; plasma concentration of digoxin possibly increased by RITONAVIR
▶ Anxiolytics and Hypnotics: plasma concentration of digoxin increased by ALPRAZOLAM (increased risk of toxicity)
▶ Beta-blockers: increased risk of AV block and bradycardia when cardiac glycosides given with BETABLOCKERS
▶ Calcium Salts: arrhythmias can be precipitated when cardiac glycosides given with large intravenous doses of CALCIUM SALTS
▶ Calcium-channel Blockers: plasma concentration of digoxin increased by DILTiazEM, LERCaPIDINE and NICaPIDINE; plasma concentration of digoxin possibly increased by NIFEDiPINE; plasma concentration of digoxin increased by VERAPAMI, also increased risk of AV block and bradycardia
▶ Ciclosporin: plasma concentration of digoxin increased by CICLOSPORINE (increased risk of toxicity)
▶ Cobicistat: plasma concentration of digoxin possibly increased by CObICISTAT—reduce initial dose of digoxin
▶ Colchicine: possible increased risk of myopathy when digoxin given with COLECHINE

Appendix 1 Interactions
Catumaxomab (continued)  
- Vaccines: risk of generalised infections when monoclonal antibodies given with live vaccines—avoid concomitant use

Cefadroxil see Cephalosporins

Cefalexin see Cephalosporins

Cefixime see Cephalosporins

Cefotaxime see Cephalosporins

Cefuroxime see Cephalosporins

Cefaclor see Cephalosporins

Ceftaroline see Cephalosporins

Chloramphenicol see Chloramphenicol

Chloral see Chloral

Ciclosporin see Ciclosporin

Ceftadoline see Cephalosporins

Ceftriaxone see Cephalosporins

Cefuroxime see Cephalosporins

Celiprolol see Beta-blockers

Cephalosporins
  - Antacids: absorption of cefaclor reduced by antacids
  - Antibacterials: possible increased risk of nephrotoxicity when cefuroxime given with aminoglycosides
  - Anticoagulants: cefuroxime possibly increases plasma concentration of warfarin
  - Teriflunomide: plasma concentration of cefuroxime increased by teriflunomide
  - Vaccines: antibacterials inactivate oral typhoid vaccine—see under Typhoid Vaccine in BNF

Certilzumab pegol
  - Abacavir: avoid concomitant use of certilzumab pegol with abacavir
  - Anakinra: avoid concomitant use of certilzumab pegol with anakinra
  - Antipsychotics: avoid concomitant use of cytoxan with cer tilzumab pegol
  - Vaccines: risk of generalised infections when monoclonal antibodies given with live vaccines—avoid concomitant use

Cetuximab
  - Antibacterials: metabolism of cetuximab accelerated by rifampicin (reduced plasma concentration)
  - Anticoagulants: monoclonal antibodies possibly enhance anticoagulant effect of coumarins
  - Teriflunomide: plasma concentration of cefuroxime increased by teriflunomide
  - Vaccines: antibacterials inactivate oral typhoid vaccine—see under Typhoid Vaccine in BNF

Chloroquine (continued)  
- Agalsidase alfa and beta: chloroquine possibly inhibits effects of agalsidase alfa and beta (manufacturers of agalsidase alfa and beta advise avoid concomitant use)
- Antacids: absorption of chloroquine reduced by antacids
- Anthelmintics: chloroquine reduces plasma concentration of praziquantel—consider increasing praziquantel dose when given for systemic infections
- Anti-arrhythmics: increased risk of ventricular arrhythmias when chloroquine given with amiodarone—avoid concomitant use
- Antibacterials: increased risk of ventricular arrhythmias when chloroquine given with moxiﬂoxacin—avoid concomitant use
- Antidepressants: possible increased risk of ventricular arrhythmias when chloroquine given with citalopram and escitalopram
- Antimalarials: avoidance of antimalarials advised by manufacturer of arte mether with lumefantrine; increased risk of convulsions when chloroquine given with mefloquine
- Antipsychotics: increased risk of ventricular arrhythmias when chloroquine given with bosutinib
- Histamine: avoidance of antiarrhythmials advised by manufacturer of histamine
- Lanthanum: absorption of chloroquine possibly reduced by lanthanum (give at least 2 hours apart)
- Laronidase: chloroquine possibly inhibits effects of Laronidase (manufacturer of laronidase advises avoid concomitant use)
- Parasymptomathetics: chloroquine has potential to increase symptoms of myasthenia gravis and thus diminish effect of neostigmine and pyridostigmine
- Ulcer-healing Drugs: metabolism of chloroquine inhibited by cimetidine (increased plasma concentration)
- Vaccines: antimalarials inactivate oral typhoid vaccine—see under Typhoid Vaccine in BNF

Chlorothiazide see Diuretics

Chlorphenamine see Antihistamines

Chlorpromazine see Antipsychotics

Chlorotope see Diuretics

Chloroquine see Antimalarials

Ciclosporin see Ciclosporin

Ciclosporin
  - Anticoagulants: metabolism of ciclosporin possibly inhibited by rifampicin (reduced plasma concentration)
  - Anticoagulants: monoclonal antibodies possibly enhance anticoagulant effect of coumarins
  - Antidepressants: monoclonal antibodies possibly enhance effects of sulfonylureas
  - Antiepileptics: ciclosporin increases plasma concentration of fosphenytoin and phenytoin (increased risk of toxicity); metabolism of ciclosporin possibly accelerated by phenobarbital and primidone (reduced plasma concentration)
  - Antipsychotics: avoid concomitant use of ciclosporin with clozapine (increased risk of agranulocytosis)
  - Ciclosporin: ciclosporin possibly reduces plasma concentration of ciclosporin
  - Clopidogrel: ciclosporin possibly reduces antiplatelet effect of clopidogrel
  - Hydroxocobalamin: ciclosporin reduces response to hydroxocobalamin
  - Tacrolimus: ciclosporin possibly increases plasma concentration of tacrolimus
  - Vaccines: antibacterials inactivate oral typhoid vaccine—see under Typhoid Vaccine in BNF

Chlorozapine see Antidepressants

Chlorpromazine see Antipsychotics

Ciclosporin see Ciclosporin
Ciclosporin

- Antibacterials (continued)
  - CHLORMPHENICOL and TELITROMYCIN; increased risk of myopathy when ciclosporin given with DAFTOMYCIN (preferably avoid concomitant use); avoidance of ciclosporin advised by manufacturer of FIDAXOMICIN; metabolism of ciclosporin possibly inhibited by MACROLIDES (increased plasma concentration); increased risk of nephrotoxicity when ciclosporin given with TRIMETHOPRIM, also plasma concentration of ciclosporin reduced by intravenous trimethoprim
- Anticoagulants: ciclosporin possibly increases plasma concentration of dabigatran—manufacturer of dabigatran advises avoid concomitant use
- Antidepressants: plasma concentration of ciclosporin reduced by ST JOHN'S WORT—avoid concomitant use
- Antidiabetics: ciclosporin possibly enhances hypoglycaemic effect of REPAGLINIDE
- Antiepileptics: metabolism of ciclosporin accelerated by CARBAMAZEPINE, OXFENITOIN, PHENOBARBITAL, PHENYTOIN and PRIMIDONE (reduced plasma concentration); plasma concentration of ciclosporin possibly reduced by OXCARBAZEPINE
- Antifungals: metabolism of ciclosporin inhibited by FLUCONAZOLE, ITRACONAZOLE, KETOCONAZOLE, POSaconazole and VORICONAZOLE (increased plasma concentration); metabolism of ciclosporin possibly inhibited by MICONAZOLE (increased plasma concentration); increased risk of nephrotoxicity when ciclosporin given with FENITOIN; ciclosporin possibly increases plasma concentration of CASPOFUNGIN (manufacturer of caspofungin recommends monitoring liver enzymes); plasma concentration of ciclosporin possibly reduced by GRISEOFULVIN and TERBINAFINE; plasma concentration of ciclosporin possibly increased by MICAFUNGIN
- Antimalarials: plasma concentration of ciclosporin increased by CHLOROQUINE and HYDROXYCHLOROQUINE (increased risk of toxicity)
- Antimucosarins: avoidance of ciclosporin advised by manufacturer of TARIFENACIN
- Antivirals: increased risk of nephrotoxicity when ciclosporin given with ACICLOVIR or VALACICLOVIR; plasma concentration of ciclosporin possibly increased by AZANAVIR and RITONAVIR; plasma concentration of ciclosporin increased by FOSAMPRENISIDE; plasma concentration of ciclosporin possibly reduced by EFAVIRENZ; plasma concentration of both drugs increased when ciclosporin given with SAAQUINAVIR; plasma concentration of both drugs increased when ciclosporin given with TELAPREVIR (reduce dose of ciclosporin)
- Beta-blockers: plasma concentration of ciclosporin increased by CARVEDIOL
- Bile Acids: absorption of ciclosporin increased by URSODEOXYCHOLIC ACID
- Bosenat: ciclosporin increases plasma concentration of BOSENTAN (also plasma concentration of ciclosporin reduced—avoid concomitant use)
- Calcium-channel Blockers: combination of ciclosporin with LERCANIDIPINE may increase plasma concentration of either drug (or both)—avoid concomitant use; plasma concentration of ciclosporin increased by DILTIAZEM, NICARDIPINE and VERAPAMIL; ciclosporin possibly increases plasma concentration of NIFEDIPINE (increased risk of toxicity including gingival hyperplasia)
- Cardiac Glycosides: ciclosporin increases plasma concentration of DIGOXIN (increased risk of toxicity)
- Colchicine: possible increased risk of nephrotoxicity and myotoxicity when ciclosporin given with COLCHICINE—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- Colestilan: manufacturer of colestilan advises give ciclosporin at least 1 hour before or 3 hours after COLESTILAN
- Corticosteroids: plasma concentration of ciclosporin increased by high-dose METHYLPREREDINOSOLONE (risk of convulsions); ciclosporin increases plasma concentration of PREREDINOSOLONE

Ciclosporin (continued)

- Cytotoxics: increased risk of nephrotoxicity when ciclosporin given with MELPHALAN; increased risk of neurotoxicity when ciclosporin given with DOXORUBICIN; ciclosporin increases plasma concentration of EPURUBICIN and IDARUBICIN; ciclosporin reduces excretion of MITOXANTRONE (increased plasma concentration); risk of toxicity when ciclosporin given with METHOTREXATE; ciclosporin possibly increases the plasma concentration of APATINIB—manufacturer of apatinib advises separating administration of ciclosporin by 6 to 12 hours; caution with ciclosporin advised by manufacturer of CRIZOTINIB; ciclosporin increases plasma concentration of EVEROLUSIN (consider reducing the dose of everolimus—consult everolimus product literature); plasma concentration of ciclosporin possibly increased by IMatinib; in vitro studies suggest a possible interaction between ciclosporin and Docetaxel (consult docetaxel product literature); ciclosporin possibly increases plasma concentration of Etoposide (increased risk of toxicity)
- Dexrazoxane: increased risk of immunosupression with ciclosporin advised by manufacturer of Dexrazoxane
- Diuretics: plasma concentration of ciclosporin possibly increased by ACETAZOLAMIDE; increased risk of hyperkalaemia when ciclosporin given with POTASSIUM-SPARING DIURETICS AND ALDOSTERONE ANTAGONISTS; increased risk of nephrotoxicity and possibly hypermagnesaemia when ciclosporin given with THIAZIDES AND RELATED DIURETICS
- Grapefruit juice: plasma concentration of ciclosporin increased by GRAPEFRUIT JUICE (increased risk of toxicity)
- Hormone Antagonists: metabolism of ciclosporin inhibited by PHENOBARBITAL, PHENOBARBITAL and PHENOBARBITAL; ciclosporin advised by manufacturer of Mifepristone; plasma concentration of ciclosporin possibly increased by DANAZOL (increased plasma concentration); plasma concentration of ciclosporin reduced by LANREOTIDE and OCTREOTIDE; plasma concentration of ciclosporin possibly reduced by PASREOTIDE
- Lenalidomide: ciclosporin possibly increases plasma concentration of LENALIDOMIDE (increased risk of toxicity)
- Lipid-regulating Drugs: absorption of ciclosporin reduced by COLESEVELAM; increased risk of renal impairment when ciclosporin given with BEZAFIBRATE or FENOBIBRATE; increased risk of myopathy when ciclosporin given with ATORVASTATIN (see under Atorvastatin, p. 179); increased risk of myopathy when ciclosporin given with FLUVASTATIN or PRAVASTATIN; increased risk of myopathy when ciclosporin given with ROSUVASTATIN or SIMVASTATIN (avoid concomitant use); plasma concentration of both drugs may increase when ciclosporin given with EZETIMIBE; separating administration from ciclosporin by 12 hours advised by manufacturer of LOMITAPIDE
- Manipol: possible increased risk of nephrotoxicity when ciclosporin given with MANIPOL
- Metoclopramide: plasma concentration of ciclosporin increased by METOCLOPROMIDE
- Mifamurtide: avoidance of ciclosporin advised by manufacturer of MIFAMURTIDE
- Modafinil: plasma concentration of ciclosporin reduced by MODAFINIL
- Oestrogens: plasma concentration of ciclosporin possibly increased by OESTROGENS
- Orlstat: absorption of ciclosporin possibly reduced by ORLISTAT
- Potassium Salts: increased risk of hyperkalaemia when ciclosporin given with POTASSIUM SALTS
- Progestogens: plasma concentration of ciclosporin possibly increased by PROGESTOGENS
- Ranolazine: plasma concentration of both drugs may increase when ciclosporin given with RANOLAZINE
- Sevelamer: plasma concentration of ciclosporin possibly reduced by SEVELAMER
- Sirolimus: ciclosporin increases plasma concentration of SIROLIMUS
- Sulfipyrazole: plasma concentration of ciclosporin reduced by SYLFINPYRAZONE
- Tacrolimus: plasma concentration of ciclosporin increased by SYLFINPYRAZONE
- Tuglakolyne: plasma concentration of ciclosporin increased by SYLFINPYRAZONE
- Trilostane: plasma concentration of ciclosporin increased by SYLFINPYRAZONE
Ciclesonin (continued)

- Ticagrelor: ciclesonin increases plasma concentration of TICAGRELOR
- Ulcer-healing Drugs: plasma concentration of ciclesonin possibly increased by CLONIDINE; plasma concentration of ciclesonin possibly affected by OMPERAZOLE
- Vitamins: plasma concentration of ciclesonin possibly affected by VITAMIN E

Clidrocin

- Antidepressants: avoidance of cildrocin advised by manufacturer of ANAGRELIDE

Clindamycin

- Antibiotics: plasma concentration of clindamycin possibly increased by CLARITHROMYCIN (see under Cilostazol, p. 206); plasma concentration of clindamycin increased by ERYTHROMYCIN (see under Cilostazol, p. 206)
- Anti-infectivals: plasma concentration of clindamycin increased by KETOCONAZOLE (see under Cilostazol, p. 206)
- Antifungals: plasma concentration of clindamycin increased by ITRACONAZOLE (see under Cilostazol, p. 206)

Clonidine

- Anxiolytics and Hypnotics: enhanced hypotensive effect when clonidine given with GENERAL ANAESTHETICS
- Analgesics: hypotensive effect of clonidine antagonised by NSAIDS
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when clonidine given with ANGIOTENSIN-II RECEPTOR ANTAGONISTS
- Antidepressants: enhanced hypotensive effect when clonidine given with MAOIS; hypotensive effect of clonidine possibly antagonised by MIRTAZAPINE; hypotensive effect of clonidine antagonised by TRICYCLES, also increased risk of hypertension on clonidine withdrawal
- Anti-psychotics: enhanced hypotensive effect when clonidine given with PHENOTHIAZINES
- Anxiolytics and Hypnotics: enhanced hypotensive effect when clonidine given with ANXIOLYTICS AND HYPNOTICS
- Beta-blockers: increased risk of withdrawal hypertension when clonidine given with BETA-BLOCKERS (withdraw beta-blockers several days before slowly withdrawing clonidine)
- Calcium-channel Blockers: enhanced hypotensive effect when clonidine given with CALCIUM-CHANNEL BLOCKERS
- Corticosteroids: hypotensive effect of clonidine antagonised by CORTICOSTEROIDS
- Cytoxics: possible increased risk of bradycardia when clonidine given with CRIZOTINIB
- Diazoxide: enhanced hypotensive effect when clonidine given with DIAZoxide
- Diuretics: enhanced hypotensive effect when clonidine given with DIURETICS
- Dopaminergics: enhanced hypotensive effect when clonidine given with CO-BENELDOPA, CO-CARBDOPA or LEVODopa
- Histamine: avoidance of clonidine advised by manufacturer of HISTAMINE
- Methylprednisolone: enhanced hypotensive effect when clonidine given with METHYLDOPIA
- Moxisylyte: enhanced hypotensive effect when clonidine given with MOXISLYTE
- Monoxidine: enhanced hypotensive effect when clonidine given with MONOXIDINE
- Muscle Relaxants: enhanced hypotensive effect when clonidine given with BACLOFEN or TIZANIDINE
- Nitrates: enhanced hypotensive effect when clonidine given with NITRATES
- Oestrogens: hypotensive effect of clonidine antagonised by OESTROGENS
- Prostaglandins: enhanced hypotensive effect when clonidine given with ALPROSTADIL
- Symphathomimetics: possible risk of hypertension when clonidine given with ADRENALINE (EPINEPHRINE) or NORADRENALINE (NOREPINEPHRINE); serious adverse events reported with concomitant use of clonidine and METHYLPHENIDATE (causality not established)
- Vasodilator Antihypertensives: enhanced hypotensive effect when clonidine given with HYDRAZINE, MINOXIDIL or SODIUM NITROPRUSSIDE

Clomipramine

- Antidepressants: increased risk of bleeding when clopidogrel given with NSAIDS or ASPIRIN
- Antibiotics: antplatelet effect of clopidogrel possibly reduced by CHLORAMPHENICOL, CIPROFLOXACIN and ERYTHROMYCIN
- Anticoagulants: manufacturer of clopidogrel advises avoid concomitant use with WARFARIN; antplatelet action of clopidogrel enhances anticoagulant effect of COUMARINS and PHENINDIONE; increased risk of bleeding when clopidogrel given with HEPARINS
- Antidepressants: antplatelet effect of clopidogrel possibly reduced by FLUXOTIN, FLUVOXAMINE and MOLOBEMIDE
- Antiepileptics: antplatelet effect of clopidogrel possibly reduced by CARBAMAZEPINE and OXCARBAMAZEPINE
- Antifungals: antplatelet effect of clopidogrel possibly reduced by FLUCONAZOLE, ITRACONAZOLE, KETOCONAZOLE and VORICONAZOLE

Clomipramine (continued)

- ACE Inhibitors: enhanced hypotensive effect when clonidine given with ACE INHIBITORS; previous treatment with clonidine possibly delays antihypertensive effect of CAPTOPRIL
- Adrenergic Neurone Blockers: enhanced hypotensive effect when clonidine given with ADRENERGIC NEURONE BLOCKERS
- Alcohol: enhanced hypotensive effect when clonidine given with ALCOHOL
- Aldehydes: enhanced hypotensive effect when clonidine given with ALDEHYDES
- Alpha-blockers: enhanced hypotensive effect when clonidine given with ALPHA-BLOCKERS
Co-beneldopa (continued)  
▶ Vasodilator Antihypertensives: enhanced hypotensive effect when co-beneldopa given with HYDRAZALINE, MINOXIDIL or SODIUM NITROPRUSSIDE  

Co-beneldopa (continued)  
▶ Vasodilator Antihypertensives: enhanced hypotensive effect when co-beneldopa given with HYDRAZALINE, MINOXIDIL or SODIUM NITROPRUSSIDE  

Clobidogrel (continued)  
▶ Antivirals: antiplatelet effect of clobidogrel possibly reduced by • ETARVIRINE  

Clopipamide: increased risk of bleeding when clobidogrel given with • DIPYRIDAMOLE  

Cloprostenol: increased risk of bleeding when cloprostenol given with • ILOPROST  

Lipid-regulating Drugs: clobidogrel increases plasma concentration of • ROSUVASTATIN—adjust dose of rosuvastatin (even with product literature)  

Prasugrel: possible increased risk of bleeding when clopidogrel given with • PRASUGREL  

Ulcet-healing Drugs: antiplatelet effect of clobidogrel possibly reduced by • CIMETIDINE, LANOSPORAZOLE, PANTOPRAZOLE and RABEPRAZOLE; antiplatelet effect of clopidogrel reduced by • ESOMEPRAZOLE and • OMEPRAZOLE  

Clobazam see Antipsychotics  

Co-amoxiclav see Penicillins  

Co-beneldopa  
▶ ACE inhibitors: enhanced hypotensive effect when co-beneldopa given with • ACE INHIBITORS  
▶ Adrenergic Neurone Blockers: enhanced hypotensive effect when co-beneldopa given with • ADRENERGIC NEURONE BLOCKERS  
▶ Alpha-blockers: enhanced hypotensive effect when co-beneldopa given with • ALPHA-BLOCKERS  
▶ Anaesthetics, General: increased risk of arrhythmias when co-beneldopa given with • VOLATILE LIQUID GENERAL ANAESTHETICS  
▶ Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when co-beneldopa given with • ANGIOTENSIN-II RECEPTOR ANTAGONISTS  
▶ Antidepressants: effects of co-beneldopa possibly reduced by • ISONIAZID  
▶ Antidepressants: risk of hypertensive crisis when co-beneldopa given with • MAOIS, avoid co-beneldopa for at least 2 weeks after stopping MAOIs; increased risk of side-effects when co-beneldopa given with • MOCLOBEMIDE  
▶ Antiepileptics: effects of co-beneldopa possibly reduced by • FOSPHENYTOIN and • PHENYTOIN  
▶ Antimuscarinics: absorption of co-beneldopa possibly reduced by • ANTIMUSCARINICS  
▶ Antipsychotics: effects of co-beneldopa antagonised by • ANTIPSYCHOTICS; avoidance of co-beneldopa advised by manufacturer of • AMISULPRIDE (antagonism of effect)  
▶ Anxiolytics and Hypnotics: effects of co-beneldopa possibly antagonised by • BENZODIAZEPINES  
▶ Beta-blockers: enhanced hypotensive effect when co-beneldopa given with • BETA-BLOCKERS  
▶ Bupropion: increased risk of side-effects when co-beneldopa given with • BUPROPION  
▶ Calcium-channel Blockers: enhanced hypotensive effect when co-beneldopa given with • CALCIUM-CHANNEL BLOCKERS  
▶ Clonidine: enhanced hypotensive effect when co-beneldopa given with • CLONIDINE  
▶ Diazoxide: enhanced hypotensive effect when co-beneldopa given with • DIAZOXIDE  
▶ Diuretics: enhanced hypotensive effect when co-beneldopa given with • DIURETICS  
▶ Dopaminergics: enhanced effects and increased toxicity of co-beneldopa when given with • SELEGILINE (reduce dose of co-beneldopa)  
▶ Iron Salts: absorption of co-beneldopa possibly reduced by • oral IRON SALTS  
▶ Memantine: effects of dopaminergics possibly enhanced by • MEMANTINE  
▶ Methyldopa: enhanced hypotensive effect when co-beneldopa given with • METHYLDOPA; antiparkinsonian effect of dopaminergics antagonised by • METHYLDOPA  
▶ Monoxidine: enhanced hypotensive effect when co-beneldopa given with • MONOXIDINE  
▶ Muscle Relaxants: possible agitation, confusion and hallucinations when co-beneldopa given with • BACLOFEN  
▶ Nitrates: enhanced hypotensive effect when co-beneldopa given with • NITRATES  

Co-beneldopa (continued)  
▶ Vasodilator Antihypertensives: enhanced hypotensive effect when co-beneldopa given with HYDRAZALINE, MINOXIDIL or SODIUM NITROPRUSSIDE  

Cobicistat  
▶ Alpha-blockers: cobicistat possibly increases plasma concentration of • ALFUSIZON—manufacturer of cobicistat advises avoid concomitant use  
▶ Anti-arrhythmics: cobicistat possibly increases plasma concentration of • AMIODARONE—manufacturer of cobicistat advises avoid concomitant use  
▶ Antibacterials: plasma concentration of cobicistat reduced by • RIFABUTIN (adjust dose—consult product literature); plasma concentration of cobicistat possibly reduced by • RIFAMPCIN—manufacturer of cobicistat advises avoid concomitant use  
▶ Anticoagulants: avoidance of cobicistat advised by manufacturer of • APIXABAN; cobicistat possibly enhances anticoagulant effect of • RIVAROXABAN—avoid concomitant use  
▶ Antidepressants: plasma concentration of cobicistat possibly reduced by • ST JOHN’S WORT—manufacturer of cobicistat advises avoid concomitant use  
▶ Antiepileptics: plasma concentration of cobicistat possibly reduced by • CARBAMAZEPINE, • FOSPHENYTOIN, • PHENOGRABARTIAL, • PHENTHOIN and • PRIMIDONE—manufacturer of cobicistat advises avoid concomitant use  
▶ Antifungals: cobicistat possibly increases plasma concentration of • ITRACONAZOLE and • KETOCONAZOLE—manufacturer of cobicistat advises reduce dose of itraconazole and ketoconazole  
▶ Antipsychotics: cobicistat possibly increases plasma concentration of • Lurasidone—avoid concomitant use; cobicistat possibly increases plasma concentration of • PIMOZIDE—manufacturer of cobicistat advises avoid concomitant use  
▶ Antivirals: manufacturer of cobicistat advises avoid concomitant use with • BOCEPREVIR; cobicistat possibly increases the plasma concentration of • Daclatasvir—reduce dose of daclatasvir (see under Daclatasvir, p. 544); cobicistat possibly increases plasma concentration of • MARAVIROC (reduce dose of maraviroc); avoidance of cobicistat advised by manufacturer of • NEVIRAPINE; cobicistat possibly increases plasma concentration of • SIMPEPREVIR—manufacturer of simeprevir advises avoid concomitant use; plasma concentration of both drugs reduced when cobicistat given with • Tipranavir (avoid concomitant use)  
▶ Anxiolytics and Hypnotics: manufacturer of cobicistat advises avoid concomitant use with • ORAL • MIDAZOLAM  
▶ Bosentan: manufacturer of cobicistat advises avoid concomitant use with • BOSENTAN  
▶ Cardiac Glycosides: cobicistat possibly increases plasma concentration of • Digoxin—reduce initial dose of digoxin  
▶ Cytoxotics: cobicistat possibly increases the plasma concentration of • Ibrutinib—reduce dose of ibrutinib (see under Ibrutinib, p. 809)  
▶ Concomitant use of sildenafil for pulmonary arterial
Cobicistat

- Sildenafil (continued)
  - hypertension or reduce dose of sildenafil for erectile dysfunction—consult cobicistat product literature
- Sympathomimetics, Beta: manufacturer of cobicistat advises avoid concomitant use with salmeterol
- Tadalafil: cobicistat possibly increases plasma concentration of tadalafil (consult cobicistat product literature)
- Vardenafil: cobicistat possibly increases plasma concentration of vardenafil (consult cobicistat product literature)

Co-careldopa

- ACE Inhibitors: enhanced hypotensive effect when co-careldopa given with ACE INHIBITORS
- Adrenergic Neurone Blockers: enhanced hypotensive effect when co-careldopa given with ADRENERGIC NEURONE BLOCKERS
- Alpha-blockers: enhanced hypotensive effect when co-careldopa given with ALPHA-BLOCKERS
- Anaesthetics, General: increased risk of arrhythmias when co-careldopa given with volatile liquid general anaesthetics
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when co-careldopa given with ANGIOTENSIN-II RECEPTOR ANTAGONISTS
- Antidepressants: effects of co-careldopa possibly reduced by ISONIAZID
- Antidepressants: risk of hypertensive crisis when co-careldopa given with MAOIS, increased risk of side-effects when co-careldopa given with moclobumide
- Antiepileptics: effects of co-careldopa possibly reduced by fosphenytoin and phenytoin
- Antimuscarnics: absorption of co-careldopa possibly reduced by antimuscarinics
- Antipsychotics: effects of co-careldopa antagonised by antipsychotics; avoidance of co-careldopa advised by manufacturer of amisulpride (antagonism of effect)
- Anxiolytics and Hypnotics: effects of co-careldopa possibly antagonised by benzodiazepines
- Beta-blockers: enhanced hypotensive effect when co-careldopa given with beta-blockers
- Bupropion: increased risk of side-effects when co-careldopa given with bupropion
- Calcium-channel Blockers: enhanced hypotensive effect when co-careldopa given with calcium-channel blockers
- Clonidine: enhanced hypotensive effect when co-careldopa given with clonidine
- Diazoxide: enhanced hypotensive effect when co-careldopa given with diazoxide
- Diuretics: enhanced hypotensive effect when co-careldopa given with diuretics
- Dopaminergics: enhanced effects and increased toxicity of co-careldopa when given with selegiline (reduce dose of co-careldopa)
- Iron Salts: absorption of co-careldopa possibly reduced by oral iron salts
- Memantine: effects of dopaminergics possibly enhanced by memantine
- Methyldopa: enhanced hypotensive effect when co-careldopa given with methyldopa; antiparkinsonian effect of dopaminergics antagonised by methyldopa
- Moxonidine: enhanced hypotensive effect when co-careldopa given with moxonidine
- Muscle Relaxants: possible agitation, confusion and hallucinations when co-careldopa given with baclofen
- Nitrates: enhanced hypotensive effect when co-careldopa given with nitrates
- Vasodilator: Antihypertensives: enhanced hypotensive effect when co-careldopa given with hydralazine, minoxidil or sodium nitroprusside

Codeine see Opioid Analgesics

Co-fluampicil see Penicillins

Colchicine

- Anti-arrhythmics: possible increased risk of colchicine toxicity when given with amiodarone

Colchicine (continued)

- Antibacterials: possible increased risk of colchicine toxicity when given with azithromycin, clarithromycin, erythromycin and telithromycin—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- Antifungals: possible increased risk of colchicine toxicity when given with itraconazole and ketoconazole—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- Antivirals: possible increased risk of colchicine toxicity when given with atazanavir, indinavir, ritonavir and telaprevir—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- Calcium-channel Blockers: possible increased risk of colchicine toxicity when given with diltiazem and verapamil—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- Cardiac Glycosides: possible increased risk of myopathy when colchicine given with digoxin
- Ciclosporin: possible increased risk of nephrotoxicity and myotoxicity when colchicine given with ciclosporin—suspend or reduce dose of ciclosporin (avoid concomitant use in hepatic or renal impairment)
- Grapefruit Juice: possible increased risk of colchicine toxicity when given with grapefruit juice
- Lipid-regulating Drugs: possible increased risk of myopathy when colchicine given with fibrates or statins

Colecalficeral see Vitamins

Colesevelam

NOTE Other drugs should be taken at least 4 hours before or after colesevelam to reduce possible interference with absorption

- Antidiabetics: colesevelam reduces absorption of glimepiride and glipizide; colesevelam reduces absorption of glipizide—manufacturer of glimepiride advises give at least 4 hours before colesevelam; manufacturer of canagliflozin advises give bile acid sequestrants at least 1 hour after or 4–6 hours before canagliflozin
- Antiepileptics: colesevelam possibly reduces absorption of fosphenytoin and phenytoin
- Ciclosporin: colesevelam reduces absorption of ciclosporin
- Lipid-regulating Drugs: bile acid sequestrants possibly reduce absorption of lomitapide (give at least 4 hours apart)
- Oestrogens: colesevelam reduces absorption of ethinylestradiol
- Thyroid Hormones: colesevelam reduces absorption of levothyroxine

Colestipol

NOTE Other drugs should be taken at least 1 hour before or 3 hours after colestipol to reduce possible interference with absorption

- Ciclosporin: manufacturer of colestipol advises give ciclosporin at least 1 hour before or 3 hours after colestipol
- Mycophenolate: manufacturer of colestipol advises give mycophenolate at least 1 hour before or 3 hours after colestipol
- Tacrolimus: manufacturer of colestipol advises give tacrolimus at least 1 hour before or 3 hours after colestipol
- Mycophenolate: manufacturer of colestipol advises give mycophenolate at least 1 hour before or 3 hours after colestipol

Colestipol (continued)

- Antibacterials: colestipol possibly reduces absorption of tetracycline
- Antidiabetics: manufacturer of canagliflozin advises give bile acid sequestrants at least 1 hour after or 4–6 hours before canagliflozin
- Bile Acids: colestipol possibly reduces absorption of bile acids
- Cardiac Glycosides: colestipol possibly reduces absorption of cardiac glycosides
- Diuretics: colestipol reduces absorption of thiazides and related diuretics (give at least 2 hours apart)
Corticosteroids

Antibacterials: corticosteroids possibly reduce absorption of LOMITAPIDE (give at least 4 hours apart)

Thyroid Hormones: corticosteroids reduce absorption of THYROID HORMONES

NOTE Other drugs should be taken at least 1 hour before or 4–6 hours after corticosteroids to reduce possible interference with absorption

Analgesics: corticosteroids increase the excretion of MELOXICAM; corticosteroids reduce absorption of PARACETAMOL

Anti-infectives: corticosteroids may enhance or reduce anticoagulant effect of COUMARINS and PHENIDINE

Antidiabetics: corticosteroids may enhance or reduce hypoglycaemic effect of ANTI DIABETICS

Antiepileptics: corticosteroids possibly reduce absorption of SODIUM VALPROATE and VALPROIC ACID

Bile Acids: corticosteroids possibly reduce absorption of BILE ACIDS

Cardiac Glycosides: corticosteroids possibly reduce absorption of CARDIAC GYCOSES

Diuretics: corticosteroids reduce absorption of THIAZIDES and RELATED DIURETICS (give at least 2 hours apart)

Lipid-regulating Drugs: bile acid sequestrants possibly reduce absorption of LOMITAPIDE (give at least 4 hours apart)

Myophenolate: corticosteroids reduce absorption of MYCOPHENOLATE

Ranolazine: corticosteroids reduce absorption of RANOLAZINE (manufacturer of ranolazine advises avoid concomitant administration)

Terfenadine: corticosteroids significantly decreases effect of TERFLUNOMIDE (enhanced elimination)—avoid unless drug elimination desired

Cardiac Glycosides: corticosteroids reduce absorption of CARDIAC GYCOSES

Thyroid Hormones: corticosteroids reduce absorption of THYROID HORMONES

Contraceptives, oral

NOTE Interactions do not generally apply to corticosteroids used for topical application (including inhalation) unless specified

ACE inhibitors: corticosteroids antagonise hypotensive effect of ACE INHIBITORS

Adrenergic Neurone Blockers: corticosteroids antagonise hypotensive effect of ADRENERGIC NEURONE BLOCKERS

Aldesleukin: avoidance of corticosteroids advised by manufacturer of ADELSEUKIN

Alpha-blockers: corticosteroids antagonise hypotensive effect of ALPHA-BLOCKERS

Aminophylline: increased risk of hypokalaemia when corticosteroids given with AMINOPHYLLINE

Analgesics: increased risk of gastro-intestinal bleeding and ulceration when corticosteroids given with NSAIDS; increased risk of gastro-intestinal bleeding and ulceration when corticosteroids given with ASPIRIN, also corticosteroids reduce plasma concentration of salicylate

Angiotensin-II Receptor Antagonists: corticosteroids antagonise hypertensive effect of ANGIOTENSIN-II RECEPTOR ANTAGONISTS

Antacids: absorption of deflazacort reduced by ANTACIDS

Anthelmintics: dexamethasone increases plasma concentration of active metabolite of ALBENDAZOLE; continuous use of dexamethasone possibly reduces plasma concentration of PRAZIQUANTEL

Antibacterials: plasma concentration of methylprednisolone possibly increased by CLARITHROMYCIN; metabolism of METHYLPREDNISOLONE possibly increased by cabozantinib

Anticoagulants: plasma concentration of CABOZANTINIB possibly increased by INHIBITORS

Anticoagulants: corticosteroids may enhance or reduce anticoagulant effect of ANTI COAGULANTS

Antidepressants: corticosteroids may enhance or reduce antidepressant effect of ANTI DEPRESSANTS

Antihistamines: plasma concentration of ANTIHISTAMINES possibly increased by INHIBITORS

Antiepileptics: metabolism of dexamethasone possibly increased by INHIBITORS

Antiparkinsonians: corticosteroids antagonise hypotensive effect of ANTIPARKINSONIANS

Antituberculous: increased risk of active metabolite of ISONIAZID when given with corticosteroids

Antivirals: plasma concentration of antiviral possibly increased by INHIBITORS

Anticoagulants: metabolism of corticosteroids possibly inhibited by INHIBITORS

Antiplatelet Agents: metabolism of corticosteroids possibly inhibited by INHIBITORS

Anticoagulants: metabolism of corticosteroids possibly inhibited by INHIBITORS

Anticoagulants: increased risk of hypokalaemia when corticosteroids given with INHIBITORS

Anticoagulants: metabolism of corticosteroids possibly inhibited by INHIBITORS

Antiarrhythmics: metabolism of corticosteroids possibly inhibited by INHIBITORS

Anticoagulants: increased risk of hypokalaemia when corticosteroids given with INHIBITORS

Lipid-regulating Drugs: corticosteroids antagonise hypotensive effect of LIPID-REGULATING DRUGS

Anticoagulants: metabolism of corticosteroids possibly inhibited by INHIBITORS

Anticoagulants: metabolism of corticosteroids possibly inhibited by INHIBITORS

Anticoagulants: increased risk of hypokalaemia when corticosteroids given with INHIBITORS

Anticoagulants: metabolism of corticosteroids possibly inhibited by INHIBITORS

Anticoagulants: increased risk of hypokalaemia when corticosteroids given with INHIBITORS

Anticoagulants: metabolism of corticosteroids possibly inhibited by INHIBITORS
Appendix 1 Interactions

Corticosteroids (continued)

- Diuretics: corticosteroids antagonise diuretic effect of DIURETICS; increased risk of hypokalaemia when corticosteroids given with Aacetazolamide, Loop Diuretics or related diuretics
- Fosaprepitant: metabolism of dexamethasone and methylprednisolone inhibited by Fosaprepitant (reduce dose of dexamethasone and methylprednisolone)
- Grapefruit juice: plasma concentration of oral budesonide increased by Grapefruit Juice—avoid concurrent use or separate administration by as much as possible and consider reducing oral budesonide dose
- Histamine: avoidance of corticosteroids advised by manufacturer of HISTAMINE
- Metyldopa: corticosteroids antagonise hypotensive effect of METHYLDOPA
- Mifamurtide: avoidance of corticosteroids advised by manufacturer of MIFAMURTIDE
- Mileprolone: effect of corticosteroids (including inhaled corticosteroids) may be reduced for 3–4 days after MIFEPRISTONE
- Moxonidine: corticosteroids antagonise hypotensive effect of MOXONIDINE
- Muscle Relaxants: corticosteroids possibly antagonise effects of pancuronium and vecuronium
- Nitrates: corticosteroids antagonise hypotensive effect of NITRATES
- Oestrogens: plasma concentration of corticosteroids increased by oral contraceptives containing OESTROGENS
- Sodium Benzoate: corticosteroids possibly reduce effects of SODIUM BENZOATE
- Sodium Phenytoin: corticosteroids possibly reduce effects of SODIUM PHENYTOIN
- Somatropin: corticosteroids may inhibit growth-promoting effect of SOMATROPIN
- Sympathomimetics: metabolism of dexamethasone accelerated by SYMPATHOMIMETICS
- Theophylline: increased risk of hypokalaemia when corticosteroids given with high doses of THEOPHYLLINE
- Vaccines: high doses of corticosteroids impair immune response to VACCINES—avoid concomitant use with live vaccines
- Vasodilator Antihypertensives: corticosteroids antagonise hypotensive effect of HYDRAZALINE, MINOXIDIL and SODIUM NITROPRUSSIDES

Co-trimoxazole see Trimethoprim and Sulfamethoxazole Co-trimoxazole

Note: Change in patient’s clinical condition, particularly associated with liver disease, intercurrent illness, or drug administration, necessitates more frequent testing. Major changes in diet (especially involving salads and vegetables) and in alcohol consumption may also affect antiarrhythmic control

- Alcohol: antiarrhythmic control with co-trimoxazole may be affected by major changes in consumption of ALCOHOL
- Alopurinol: antiarrhythmic effect of co-trimoxazole possibly enhanced by ALOPURINOL
- Anabolic Steroids: antiarrhythmic effect of co-trimoxazole possibly enhanced by ANABOLIC STEROIDS
- Analgesics: antiarrhythmic effect of co-trimoxazole possibly enhanced by NSAIDS; increased risk of haemorrhage when antiarrhythmics given with INTRAVENOUS DICLOFENAC (avoid concomitant use, including low-dose heparins); increased risk of haemorrhage when antiarrhythmics given with KETOROLAC (as avoid concomitant use, including low-dose heparins); increased risk of bleeding when co-trimoxazole given with TRAMADOL; increased risk of bleeding when co-trimoxazole given with ASPIRIN (due to antplatelet effect); antiarrhythmic effect of co-trimoxazole possibly enhanced by prolonged regular use of PARACETAMOL
- Anthelmintics: antiarrhythmic effect of co-trimoxazole possibly enhanced by IVERMECTIN; antiarrhythmic effect of co-trimoxazole possibly enhanced by LEVAMISOLE

Cumarins (continued)

- Anti-arrhythmics: metabolism of coumarins inhibited by AMIODARONE
- Anti-arrhythmics: metabolism of coumarins inhibited by DISOPYRAMIDE; anticoagulant effect of coumarins possibly enhanced by DIPRENALONE and PROPafenone
- Anticoagulants: experience in anticoagulant clinics suggests that INR may be altered; plasma concentration of warfarin possibly enhanced by RIFAMYCINS (reduced anticoagulant effect)
- Anticoagulants: increased risk of haemorrhage when other anticoagulants given with APREPITANT, DABIGATRAN and RIVAROXABAN (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)
- Antidepressants: anticoagulant effect of warfarin possibly enhanced by SSRI; anticoagulant effect of coumarins possibly enhanced by ST JOHN’S WORT (avoid concomitant use); anticoagulant effect of warfarin enhanced by MIRTAZAPINE; anticoagulant effect of co-trimoxazole may be enhanced or reduced by TRICYCLICS
- Antidiabetics: anticoagulant effect of warfarin possibly enhanced by CARBAMAZEPINE, PHENOBARBITAL and PRIMIDONE (reduced anticoagulant effect); plasma concentration of warfarin reduced by ERLIBARbezEPINE; metabolism of coumarins accelerated by ORIFIA and RIFAPENTON (possibility of reduced anticoagulant effect, but enhancement also reported); anticoagulant effect of coumarins possibly enhanced by SODIUM VALPROATE and VALPROIC ACID
- Antifungals: anticoagulant effect of co-trimoxazole enhanced by FLUCONAZOLE, ITRACONAZOLE, VORICONAZOLE and MICONAZOLE (miconazole oral gel and possibly vaginal and topical formulations absorbed); anticoagulant effect of coumarins reduced by GRISEOFULVIN
- Antimalarials: isolated reports that anticoagulant effect of warfarin may be enhanced by PROGUANIIL; plasma concentration of both drugs increased when warfarin given with QUININE
- Antivirals: anticoagulant effect of warfarin may be enhanced or reduced by ATAZANAVIR, NEVIRAPINE and RITONAVIR and plasma concentration of coumarins possibly affected by AMIODARONE; anticoagulant effect of warfarin enhanced or reduced by TELAPREVIR
- Anxiolytics and Hypnotics: anticoagulant effect of coumarins may transiently be enhanced by CHLORAL
- Aprepitant: anticoagulant effect of warfarin possibly reduced by Aprepitant
- Azathioprine: anticoagulant effect of coumarins possibly enhanced by AZATHIOPRINE
- Bosentan: monitoring anticoagulant effect of coumarins recommended by manufacturer of BOSENTAN
### Coumarins (continued)
- Clodigorel: anticoagulant effect of coumarins enhanced due to antiplatelet action of Clodigorel; avoidance of warfarin advised by manufacturer of Clodigorel.
- Corticosteroids: anticoagulant effect of coumarins may be enhanced or reduced by corticosteroids (high-dose corticosteroids enhance anticoagulant effect).
- Cranberry Juice: anticoagulant effect of coumarins possibly enhanced by Cranberry Juice—avoid concomitant use.
- Cytoxotics: anticoagulant effect of coumarins possibly enhanced by Entacapone.
- Dipyridamole: anticoagulant effect of coumarins enhanced due to antiplatelet action of Dipyridamole.
- Disulfiram: anticoagulant effect of coumarins enhanced by Disulfiram.
- Dopaminergics: anticoagulant effect of warfarin enhanced by Entacapone.
- Enteral Foods: anticoagulant effect of coumarins antagonised by vitamin K (present in some Enteral Foods).
- Fosaprepitant: anticoagulant effect of warfarin possibly reduced by Fosaprepitant.
- Glucosamine: anticoagulant effect of warfarin enhanced by Glucosamine.
- Hormone Antagonists: anticoagulant effect of coumarins possibly enhanced by Bicalutamide and Toremifene, metabolism of coumarins inhibited by Danazol (enhanced anticoagulant effect); plasma concentration of coumarins possibly reduced by Enzalutamide; anticoagulant effect of coumarins enhanced by FLUTAMIDE and TAMOXIFEN.
- Iloprost: anticoagulant effect of coumarins possibly enhanced by Iloprost.
- Lactulose: anticoagulant effect of coumarins possibly enhanced by Lactulose.
- Leflunomide: anticoagulant effect of warfarin enhanced by Leflunomide.
- Leukotriene Receptor Antagonists: anticoagulant effect of warfarin enhanced by Zafirlukast.
- Levozinc: anticoagulant effect of coumarins enhanced by Levozinc.
- Lipid-regulating Drugs: anticoagulant effect of coumarins may be enhanced or reduced by Colestyramine; anticoagulant effect of warfarin may be transiently reduced by ATORVASTATIN; anticoagulant effect of coumarins enhanced by FIBRATES and FLUVASTATIN; anticoagulant effect of coumarins possibly enhanced by Ezetimibe and Rosuvastatin; anticoagulant effect of coumarins can be enhanced by Simvastatin; anticoagulant effect of warfarin possibly enhanced by Lomitapide.
- Memantine: anticoagulant effect of warfarin possibly enhanced by Memantine.
- Oestroges: anticoagulant effect of coumarins may be enhanced or reduced by Oestroges.
- Orlisat: monitoring anticoagulant effect of coumarins recommended by manufacturer of Orlisat.
- Prasugrel: possible increased risk of bleeding when coumarins given with Prasugrel.
- Progestogens: anticoagulant effect of coumarins may be enhanced or reduced by Progestogens.
- Raloxifene: anticoagulant effect of coumarins antagonised by Raloxifene.
- Retinoids: anticoagulant effect of coumarins possibly reduced by Acitretin; anticoagulant effect of coumarins enhanced by Sulfynpyrazone.
- Sulfinpyrazone: anticoagulant effect of coumarins enhanced by Sulfinpyrazone.
- Testosterone: anticoagulant effect of coumarins enhanced by Testosterone.
- Thyroid Hormones: anticoagulant effect of coumarins enhanced by Thyroid Hormones.
- Ubidecarenone: anticoagulant effect of warfarin may be enhanced or reduced by Ubidecarenone.
- Ulcer-healing Drugs: metabolism of coumarins inhibited by Cimetidine (enhanced anticoagulant effect); anticoagulant effect of coumarins possibly reduced by Esomeprazole and Omeprazole; anticoagulant effect of coumarins may be enhanced by Pantoprazole; absorption of coumarins possibly reduced by Sucralfate (reduced anticoagulant effect).
- Vaccines: anticoagulant effect of warfarin possibly enhanced by Influenza Vaccine.
- Vitamins: anticoagulant effect of coumarins possibly enhanced by Vitamin E; anticoagulant effect of coumarins antagonised by Vitamin K.

### Cranberry Juice
- Anticoagulants: cranberry juice possibly enhances anticoagulant effect of Coumarins—avoid concomitant use.

### Crizotinib
- Analgesics: manufacturer of crizotinib advises caution with Alfentanil and Fentanyl.
- Anti-bacterials: plasma concentration of crizotinib possibly increased by clarithromycin and telithromycin—manufacturer of crizotinib advises avoid concomitant use; plasma concentration of crizotinib possibly reduced by Rifabutin—manufacturer of crizotinib advises avoid concomitant use; plasma concentration of crizotinib reduced by Rifampicin—manufacturer of crizotinib advises avoid concomitant use.
- Antidepressants: plasma concentration of crizotinib possibly reduced by ST John’s Wort—manufacturer of crizotinib advises avoid concomitant use.
- Antiepileptics: plasma concentration of crizotinib possibly reduced by Carbamazepine, fosphenytoin, phenobarbital, phenytoin and Primidone—manufacturer of crizotinib advises avoid concomitant use.
- Antifungals: plasma concentration of crizotinib increased by Ketoconazole—avoid concomitant use; plasma concentration of crizotinib possibly increased by Itraconazole and Voriconazole—manufacturer of crizotinib advises avoid concomitant use.
- Antimalarials: possible increased risk of bradycardia when crizotinib given with Mefloquine.
- Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis); manufacturer of crizotinib advises caution with Pimozide.
- Antivirals: plasma concentration of crizotinib possibly increased by Atazanavir, Indinavir, Ritonavir and Saquinavir—manufacturer of crizotinib advises avoid concomitant use.
- Antiulcerative: plasma concentration of crizotinib possibly reduced by Carbaazepine, Fosphenytoin, Phenobarbital, Phenytoin and Primidone—manufacturer of crizotinib advises avoid concomitant use.
- Antibacterials: plasma concentration of crizotinib possibly increased by clarithromycin and telithromycin—manufacturer of crizotinib advises avoid concomitant use; plasma concentration of crizotinib possibly reduced by Rifabutin—manufacturer of crizotinib advises avoid concomitant use; plasma concentration of crizotinib reduced by Rifampicin—manufacturer of crizotinib advises avoid concomitant use.
- Anti-bacterials: plasma concentration of crizotinib possibly increased by clarithromycin and telithromycin—manufacturer of crizotinib advises avoid concomitant use; plasma concentration of crizotinib possibly reduced by Rifabutin—manufacturer of crizotinib advises avoid concomitant use; plasma concentration of crizotinib reduced by Rifampicin—manufacturer of crizotinib advises avoid concomitant use.
- Antiepileptics: plasma concentration of crizotinib possibly reduced by Carbamazepine, Fosphenytoin, Phenobarbital, Phenytoin and Primidone—manufacturer of crizotinib advises avoid concomitant use.
- Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis); manufacturer of crizotinib advises caution with Pimozide.
- Antivirals: plasma concentration of crizotinib possibly increased by Atazanavir, Indinavir, Ritonavir and Saquinavir—manufacturer of crizotinib advises avoid concomitant use.
- Antiulcerative: plasma concentration of crizotinib possibly reduced by Carbaazepine, Fosphenytoin, Phenobarbital, Phenytoin and Primidone—manufacturer of crizotinib advises avoid concomitant use.
- Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis); manufacturer of crizotinib advises caution with Pimozide.
- Antivirals: plasma concentration of crizotinib possibly increased by Atazanavir, Indinavir, Ritonavir and Saquinavir—manufacturer of crizotinib advises avoid concomitant use.
- Antiulcerative: plasma concentration of crizotinib possibly reduced by Carbaazepine, Fosphenytoin, Phenobarbital, Phenytoin and Primidone—manufacturer of crizotinib advises avoid concomitant use.
Cytarabine: see Cyproheptadine

Cyclizine: see Antihistamines

Cyclophosphamide
- Antifungals: side-effects of cyclophosphamide possibly increased by flucloxacillin and itraconazole.
- Anticoagulants: avoid concomitant use of cyclophosphamide with anticoagulants or using heparin to maintain catheter patency; increased risk of haemorrhage when anticoagulants given with 
  - warfarin
- Cardiac Glycosides: increased risk of agranulocytosis.
- Antibacterials: increased risk of CNS toxicity when cycloserine given with
  - chloramphenicol
- Vaccines: antibacterials inactivate oral typhoid vaccine.

Cyclophosphamide enhance effects of

Cycloserine
- Alcohol: increased risk of convulsions when cycloserine given with
  - alcohol
- Antibacterials: increased risk of CNS toxicity when cycloserine given with
  - isoniazid
- Vaccines: antibacterials inactivate oral typhoid vaccine.

Cyproheptadine: see Antihistamines

Cytarabine
- Antifungals: cytarabine possibly reduces plasma concentration of fuflcyclosine.
- Anticoagulants: avoid concomitant use of cytoxics with
  - warfarin
- Cardiac Glycosides: cytarabine possibly reduces absorption of digoxin tablets.
- Cytotoxics: increased toxicity when high-dose cyclophosphamide given with
  - pentostatin

Muscle Relaxants: cyclophosphamide enhances effects of

Cyclophosphamide enhance effects of

Cycloserine
- Alcohol: increased risk of convulsions when cycloserine given with
  - alcohol
- Antibacterials: increased risk of CNS toxicity when cycloserine given with
  - isoniazid
- Vaccines: antibacterials inactivate oral typhoid vaccine.

Cyproheptadine: see Antihistamines

Cytarabine
- Antifungals: cytarabine possibly reduces plasma concentration of flucytosine.
- Antipsychotics: avoid concomitant use of cytoxics with
  - clozapine
- Cardiac Glycosides: cytarabine possibly reduces absorption of digoxin tablets.
- Cytotoxics: intracellular concentration of cytarabine increased by fluorouracil.

Cytotoxic: see individual drugs

Dabigatran
- Analgesics: possible increased risk of bleeding when dabigatran given with
  - NSAIDs
- Antibacterials: increased risk of haemorrhage when anticoagulants given with intravenous
  - diclofenac
- Antibacterials: plasma concentration of dabigatran reduced by
  - Amodarone
- Drug interactions: dabigatran reduced by
  - Dronedarone
- Antibacterials: possible increased risk of bleeding when dabigatran given with clindamycin.
- Anticoagulants: plasma concentration of dabigatran reduced by
  - Rifampicin
- Antibacterials: possible increased risk of bleeding when dabigatran given with
  - Ampicillin
- Anticoagulants: increased risk of haemorrhage when dabigatran given with other
  - Anticoagulants: avoid concomitant use except when switching with another anticoagulant or using heparin to maintain catheter patency.
- Antidepressants: possible increased risk of bleeding when dabigatran given with
  - SSRIs
- Anticoagulants: manufacturer of dabigatran advises avoid concomitant use.

Dabrafenib
- Antibacterials: manufacturer of dabrafenib advises avoid concomitant use with
  - rifampicin
- Anticoagulants: dabrafenib reduces plasma concentration of
  - warfarin
- Antidepressants: manufacturer of dabrafenib advises avoid concomitant use with
  - ketoconazole
- Anticoagulants: dabrafenib reduces plasma concentration of
  - warfarin
- Antidepressants: manufacturer of dabrafenib advises avoid concomitant use with
  - ketoconazole
- Anticoagulants: dabrafenib reduces plasma concentration of
  - warfarin
- Antidepressants: manufacturer of dabrafenib advises avoid concomitant use with
  - ketoconazole
- Anticoagulants: dabrafenib reduces plasma concentration of
  - warfarin
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  - ketoconazole
- Anticoagulants: dabrafenib reduces plasma concentration of
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  - ketoconazole
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- Anticoagulants: dabrafenib reduces plasma concentration of
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- Antidepressants: manufacturer of dabrafenib advises avoid concomitant use with
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  - ketoconazole
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  - warfarin
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  - ketoconazole
- Anticoagulants: dabrafenib reduces plasma concentration of
  - warfarin
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  - ketoconazole
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  - warfarin
- Antidepressants: manufacturer of dabrafenib advises avoid concomitant use with
  - ketoconazole
- Anticoagulants: dabrafenib reduces plasma concentration of
  - warfarin
- Antidepressants: manufacturer of dabrafenib advises avoid concomitant use with
  - ketoconazole
- Anticoagulants: dabrafenib reduces plasma concentration of
  - warfarin
- Antidepressants: manufacturer of dabrafenib advises avoid concomitant use with
Daclatasvir
- Antiepileptics (continued)
  - PRIMIDONE — manufacturer of daclatasvir advises avoid concomitant use
- Antigenas: plasma concentration of daclatasvir increased by
  - KETOCONAZOLE — reduce dose of daclatasvir (see under Daclatasvir, p. 544); plasma concentration of daclatasvir possibly increased by
  - ERGOTRALFONAZOLE, POSaconazole and VORICONAZOLE — reduce dose of daclatasvir (see under Daclatasvir, p. 544)
- Antivirals: plasma concentration of daclatasvir increased by
  - ATAZANAVIR and TELAPREVIR — reduce dose of daclatasvir (see under Daclatasvir, p. 544); plasma concentration of daclatasvir possibly increased by
  - BOCEprevir — reduce dose of daclatasvir (see under Daclatasvir, p. 544); manufacturer of daclatasvir advises avoid concomitant use with DUNAVIR and LOPINAVIR (plasma concentration of daclatasvir possibly increased); plasma concentration of daclatasvir reduced by
  - EFAVIRENZ — increase dose of daclatasvir (see under Daclatasvir, p. 544); manufacturer of daclatasvir advises avoid concomitant use with
  - Cobicitstat: plasma concentration of daclatasvir possibly increased by
  - COBICISTAT — reduce dose of daclatasvir (see under Daclatasvir, p. 544)
- Corticosteroids: plasma concentration of daclatasvir possibly reduced by
  - DEXAMETHASONE — manufacturer of daclatasvir advises avoid concomitant use
- Lipid-regulating Drugs: daclatasvir increases plasma concentration of
  - Rosuvastatin

Dactinomycin
- Antipsychotics: avoid concomitant use of cytoxics with
  - Clozapine (increased risk of agranulocytosis)
- Vitamins: dactinomycin possibly reduces effects of
  - Calcitriol, Alfacalcidol, Ergocalciferol, Paricalcitol and Vitamin D

Dairy Products
- Antibacterials: dairy products reduce absorption of
  - Ciprofloxacin and Norfloxacin; dairy products reduce absorption of Tetracyclines (except doxycycline and minocycline)
- Corticosteroids: dairy products possibly reduce plasma concentration of
  - Mercaptopurine — manufacturer of mercaptopurine advises give at least 1 hour before or 2 hours after dairy products
- Anticoagulants: dairy products possibly reduce absorption of
  - Dapoxetine (give at least 4 hours apart)

Dalfetarin see Heparins

Danaparoid
- Analgesics: increased risk of haemorrhage when anticoagulants given with intravenous DICLOFENAC (avoid concomitant use, including low-dose heparin); increased risk of haemorrhage when anticoagulants given with
  - Ketorolac (avoid concomitant use, including low-dose heparin)
- Anticoagulants: increased risk of haemorrhage when other anticoagulants given with
  - Apixaban, Dabigatran and Rivaroxaban (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)

Danazol
- Anticoagulants: danazol inhibits metabolism of
  - Coumarins (enhanced anticoagulant effect)
- Antiepileptics: danazol inhibits metabolism of
  - Carbamazepine (increased risk of toxicity)
- Ciclosporin: danazol inhibits metabolism of
  - Ciclosporin (increased plasma concentration)
- Lipid-regulating Drugs: possible increased risk of myopathy when danazol given with
  - Simvastatin — avoid concomitant use
  - Tacrolimus: danazol possibly increases plasma concentration of
  - Tacrolimus

Dantrolene see Muscle Relaxants

Dapagliflozin see Antidiabetics

Dapoxetine
- Alcohol: increased sedative effect when dapoxetine given with
  - Alcohol
- Analgesics: possible increased risk of serotonic effects when dapoxetine given with
  - Tramadol (manufacturer of dapoxetine advises tramadol should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping tramadol)
- Antibacterials: manufacturer of dapoxetine advises dose reduction when dapoxetine given with Clarithromycin and erythromycin (see under Dapoxetine, p. 703); manufacturer of dapoxetine advises avoid concomitant use with
  - Telithromycin (increased risk of toxicity)
- Antidepressants: possible increased risk of serotonergic effects when dapoxetine given with
  - SSRI, St John’s Wort,
  - DULoxetine, TRICYCLICS and venlafaxine (manufacturer of dapoxetine advises SSRIs, St John’s wort, duloxetine, tricyclics and venlafaxine should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping SSRIs, St John’s wort, duloxetine, tricyclics and venlafaxine); increased risk of serotonergic effects when dapoxetine given with
  - MAOIs (MAOIs should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping MAOIs)
- Antifungals: plasma concentration of dapoxetine increased by
  - KETOCONAZOLE — manufacturer of dapoxetine advises avoid concomitant use; manufacturer of dapoxetine advises dose reduction when dapoxetine given with
  - Fluconazole (see under Dapoxetine, p. 705); manufacturer of dapoxetine advises avoid concomitant use with
  - Itraconazole (increased risk of toxicity)
- Antivirals: manufacturer of dapoxetine advises avoid concomitant use with
  - Atazanavir, Ritonavir and Saquinavir (increased risk of toxicity); manufacturer of dapoxetine advises dose reduction when dapoxetine given with
  - Fosamprenavir (see under Dapoxetine, p. 705)
- Aprepitant: manufacturer of dapoxetine advises dose reduction when dapoxetine given with aprepitant (see under Dapoxetine, p. 705)
- Calcium-channel Blockers: manufacturer of dapoxetine advises dose reduction when dapoxetine given with
  - Diltiazem and verapamil (see under Dapoxetine, p. 705)
- SHT: receptor ago: possible increased risk of serotonergic effects when dapoxetine given with
  - SHT, agonists (manufacturer of dapoxetine advises SHT, agonists should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping SHT, agonists)
- Lithium: possible increased risk of serotonergic effects when dapoxetine given with
  - Lithium (manufacturer of dapoxetine advises lithium should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping lithium)
- Sildenafil: manufacturer of dapoxetine advises avoid concomitant use with
  - Sildenafil
  - Tadalafil: manufacturer of dapoxetine advises avoid concomitant use with tadalafil
  - Vardenafil: manufacturer of dapoxetine advises avoid concomitant use with
  - Vardenafil

Dapsone
- Antibacterials: plasma concentration of dapsone reduced by
  - Rifampicin; plasma concentration of both drugs may increase when dapsone given with trimethoprim
- Antivirals: increased risk of ventricular arrhythmias when dapsone given with
  - Saquinavir — avoid concomitant use
- Vaccines: antibacterials inactivate oral typhoid vaccine — see under Typhoid Vaccine in BNF

Daptomycin
- Ciclosporin: increased risk of myopathy when daptomycin given with
  - Ciclosporin (preferably avoid concomitant use)
- Lipid-regulating Drugs: increased risk of myopathy when daptomycin given with
  - Fibric acid or Statins (preferably avoid concomitant use)
Daptomycin (continued)
- Antibacterials: inactivate ORAL TYPHOID VACCINE — see under Typhoid Vaccine in BNF
Darifenacin see Antimuscarinics

Darunavir
- Antibacterials: darunavir possibly increases plasma concentration of LIDOCAINE — avoid concomitant use
- Antibacterials: darunavir increases plasma concentration of • Rifabutin (reduce dose of rifabutin); plasma concentration of darunavir significantly reduced by • Rifampicin — avoid concomitant use
- Anticoagulants: avoidance of darunavir advised by manufacturer of Apixaban and Rivaroxaban
- Antidepressants: darunavir possibly reduces plasma concentration of PAROXETINE and SERTRALINE; plasma concentration of darunavir reduced by • ST JOHN’S WORT — avoid concomitant use
- Antiepileptics: plasma concentration of darunavir possibly reduced by CARBAMAZEPINE, FOSPHENYTOIN, PHENOBARBITAL, PHENYTOIN and PRIMIDONE
- Antifungals: plasma concentration of both drugs increased when darunavir given with KETOCONAZOLE
- Antimalarials: plasma concentration of lumefantrine increased when darunavir given with ARTEMETHER with LUMEFANTRINE; darunavir possibly increases plasma concentration of • Quinine (increased risk of toxicity)
- Antipsychotics: darunavir possibly increases plasma concentration of • Aripiprazole (reduce dose of aripiprazole—consult aripiprazole product literature); manufacturer of darunavir advises take DIDANOSINE 1 hour before or 2 hours after darunavir; plasma concentration of darunavir reduced by • Efavirenz (adjust dose—consult product literature); plasma concentration of both drugs increased when darunavir given with INDINAVIR; plasma concentration of darunavir reduced by • Lopinavir, also plasma concentration of lopinavir increased (avoid concomitant use); darunavir increases plasma concentration of • Maraviroc (consider reducing dose of maraviroc); increased risk of rash when darunavir given with Raltegravir; plasma concentration of darunavir reduced by • Saquinavir; plasma concentration of both drugs increased when darunavir given with • Simperevir — manufacturer of simperervir advises avoid concomitant use
- Antipsychotics: darunavir possibly increases plasma concentration of • Bosutinib—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; darunavir possibly increases plasma concentration of • Everolimus—manufacturer of everolimus advises avoid concomitant use; darunavir possibly increases the plasma concentration of • Ibrutinib—reduce dose of ibrutinib (see under ibrutinib, p. 809)
- Ergot Alkaloids: increased risk of ergotism when darunavir given with • Ergot Alkaloids—manufacturer of darunavir advises avoid concomitant use
- Lipid-regulating Drugs: possible increased risk of myopathy when darunavir given with ATORVASTATIN; darunavir possibly increases plasma concentration of PRAVASTATIN; darunavir increases plasma concentration of • Rosuvastatin—adjust dose of rosuvastatin (consult product literature); avoidance of darunavir advised by manufacturer of • Lomitapide (plasma concentration of lomitapide possibly increased)
- Oritistat: absorption of darunavir possibly reduced by • Ursolidat
- Ranolazine: darunavir possibly increases plasma concentration of • Ranolazine—manufacturer of ranolazine advises avoid concomitant use

Dasatinib
- Antibacterials: manufacturer of dasatinib advises avoid concomitant use with CLARITHROMYCIN, ERYTHROMYCIN and TELITHROMYCIN (plasma concentration of dasatinib possibly increased); metabolism of dasatinib accelerated by • Rifampicin (reduced plasma concentration—avoid concomitant use)
- Antiepileptics: manufacturer of dasatinib advises avoid concomitant use with CARBAMAZEPINE, FOSPHENYTOIN, PHENOBARBITAL, PHENYTOIN and PRIMIDONE (plasma concentration of dasatinib possibly increased)
- Antifungals: plasma concentration of dasatinib possibly increased by KETOCONAZOLE; manufacturer of dasatinib advises avoid concomitant use with IRAFONAZOLE (plasma concentration of dasatinib possibly increased)
- Antipsychotics: avoid concomitant use of cytotoxics with • Clozapine (increased risk of agranulocytosis)
- Antivirals: avoidance of dasatinib advised by manufacturer of • Boceprevir; manufacturer of dasatinib advises avoid concomitant use with • Ritonavir (plasma concentration of dasatinib possibly increased)
- Grapefruit Juice: manufacturer of dasatinib advises avoid concomitant use with • Grapefruit Juice (plasma concentration of dasatinib possibly increased)
- Lipid-regulating Drugs: dasatinib possibly increases plasma concentration of SIMVASTATIN
- Ulcer-healing Drugs: plasma concentration of dasatinib possibly reduced by FAMOTIDINE

Decitabine
- Antipsychotics: avoid concomitant use of cytotoxics with • Clozapine (increased risk of agranulocytosis)

Deferasirox
- Aminophyline: deferasirox increases plasma concentration of • Aminophyline (consider reducing dose of aminophyline)
- Antacids: absorption of deferasirox possibly reduced by • Antacids containing aluminium (manufacturer of deferasirox advises avoid concomitant use)
- Antibacterials: plasma concentration of deferasirox reduced by • Rifampicin
- Antidiabetics: deferasirox increases plasma concentration of • Repaglinide
- Antipsychotics: manufacturer of deferasirox advises avoid concomitant use with • Clozapine
- Anxietytics and Hypnotics: deferasirox possibly reduces plasma concentration of • Midazolam
- Muscle Relaxants: manufacturer of deferasirox advises avoid concomitant use with • Tizanidine
- Theophylline: deferasirox increases plasma concentration of • Theophylline (consider reducing dose of theophylline)

Diferiprone
- Antacids: absorption of deferiprone possibly reduced by • Antacids containing aluminium (manufacturer of deferiprone advises avoid concomitant use)

Deflazacort see Corticosteroids

Delamanid
- Analgesics: increased risk of ventricular arrhythmias when delamanid given with • Methadone
- Anti-arrhythmics: increased risk of ventricular arrhythmias when delamanid given with • Amiodarone or • Disopyramide
- Antibacterials: possible increased risk of ventricular arrhythmias when delamanid given with • Clarithromycin and • erythromycin; Increased risk of ventricular arrhythmias when delamanid given with • moxifloxacin; plasma concentration of delamanid reduced by • Rifampicin; delamanid increases plasma concentration of ethambutol
- Antidepressants: possible increased risk of ventricular arrhythmias when delamanid given with • Tricyclics that prolong the QT interval
- Antiepileptics: manufacturer of delamanid advises avoid concomitant use with • Carbamazepine
- Antipsychotics: increased risk of ventricular arrhythmias when delamanid given with • Droperidol, Haloperidol or • Pipemid; increased risk of ventricular arrhythmias when delamanid given with • phenothiazines that prolong the QT interval
Delamanid

- Antivirals: plasma concentration of delamanid increased by LOPINAVIR and RITONAVIR; increased risk of ventricular arrhythmias when delamanid given with NIFEDIPINE.
- Beta-blockers: increased risk of ventricular arrhythmias when delamanid given with METOPROLOL.
- Cytotoxics: increased risk of ventricular arrhythmias when delamanid given with ARSENIC TRIOXIDE or VINFLUNINE; possible increased risk of ventricular arrhythmias when delamanid given with VINBLASTINE, VINCRISTINE, VINDESINE and VINORELBINE.
- Domperidone: possible increased risk of ventricular arrhythmias when delamanid given with DOMPERIDONE.
- Pentamidine isetionate: increased risk of ventricular arrhythmias when delamanid given with PENTAMIDINE.

Isetionate

- Vaccines: antibacterials inactivate ORAL TYPHOID VACCINE; see under Typhoid Vaccine in BNF.

Demeclocycline see Tetracyclines

Desferrioxamine

- Antipsychotics: avoidance of desferrioxamine advised by manufacturer of LEVOMEPROMAZINE; manufacturer of desferrioxamine advises concomitant use with PROCHLORPERAZINE.

Desflurane see Anaesthetics, General

Desloratadine see Antihistamines

Desmosprin

- Analgesics: effects of desmosprin enhanced by INDOMETACIN.
- Loperamide: plasma concentration of oral desmosprin increased by LOPERAMIDE.

Desogestrel see Progestogens

Dexamethasone see Corticosteroids

Dexamfetamine see Symptomatics

Dexibuprofen see NSAIDs

Dextropropoxyphene see Opioid Analgesics

Diazepam see Anxiolytics and Hypnotics

Diazoxide

- ACE Inhibitors: enhanced hypotensive effect when diazoxide given with ACE INHIBITORS.
- Adrenergic Neurone Blockers: enhanced hypotensive effect when diazoxide given with ADRENERGIC NEURONE BLOCKERS.
- Alcohol: enhanced hypotensive effect when diazoxide given with ALCOHOL.
- Aldesleukin: enhanced hypotensive effect when diazoxide given with ALDESLEUKIN.
- Alpha-blockers: enhanced hypotensive effect when diazoxide given with ALPHA-BLOCKERS.
- Anaesthetics, General: enhanced hypotensive effect when diazoxide given with GENERAL ANAESTHETICS.
- Analgesics: hypotensive effect of diazoxide antagonised by NSAIDS.
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when diazoxide given with ANGIOTENSIN-II RECEPTOR ANTAGONISTS.
- Antidepressants: enhanced hypotensive effect when diazoxide given with MAOI or TRICYCLIC-RELATED ANTIDEPRESSANTS.
- Antidiabetics: diazoxide antagonises hypoglycaemic effect of ANTIDIABETICS.
- Antiepileptics: diazoxide reduces plasma concentration of FOSFENYPHTHALIN and PHENTHOIN, also effect of diazoxide may be reduced.
- Antipsychotics: enhanced hypotensive effect when diazoxide given with PHENOTHIAZINES.

Diacyclavine see Antimuscarnics

Didanosine

- NOTE Antacids in tablet formulation might affect absorption of other drugs—give at least 2 hours apart.
- Allopurinol: plasma concentration of didanosine increased by ALLOPURINOL (risk of toxicity)—avoid concomitant use.
- Analgesics: plasma concentration of didanosine possibly reduced by METHADONE.
- Antimicrobials: manufacturer of norfloxacin advises give didanosine at least 2 hours before or after NORFLOXACIN.
- Antivirals: didanosine tablets reduce absorption of ATAZANAVIR (give at least 2 hours before or 1 hour after didanosine tablets); manufacturer of darunavir advises take didanosine 1 hour before or 2 hours after DARUNAVIR; plasma concentration of didanosine increased by GANCICLOVIR and VALGANCICLOVIR; didanosine tablets reduce absorption of INDINAVIR (give at least 1 hour apart); increased risk of side-effects when didanosine given with RIBAVIRIN—avoid concomitant use; manufacturer of ritonavir advises give didanosine 2 hours before or 4 hours after RILPIVIRINE; manufacturer of rilpivirine advises didanosine and RITONAVIR should be taken 2.5 hours apart; increased risk of side-effects when didanosine given with STAVUDINE; plasma concentration of didanosine increased by TENOFIVIR (increased risk of toxicity)—avoid concomitant use; plasma concentration of didanosine reduced by TIPRANAVIR—manufacturer of tipranavir advises tipranavir and didanosine capsules should be taken at least 1 hour apart.
- Cytotoxics: increased risk of toxicity when didanosine given with HYDROXYCARBAMIDE—avoid concomitant use.
- Orlistat: absorption of didanosine possibly reduced by ORLISTAT.

Dienogest see Progestogens

Diethylcarbamazine

- Antacids: excretion of diethylcarbamazine increased by SODIUM BICARBONATE.

Digoxin see Cardiac Glycosides

Dihydrocodeine see Opioid Analgesics

Dihydrotachysterol see Vitamins

Diltiazem see Calcium-channel Blockers

Dimethyl sulfoxide

- Analgesics: avoid concomitant use of dimethyl sulfoxide with SUINDAC.

Dinoprost see Prostaglandins
Disopyramide (continued)

- Antivirals: plasma concentration of disopyramide possibly increased by ritonavir (increased risk of toxicity); increased risk of ventricular arrhythmias when disopyramide given with saquinavir—avoid concomitant use; avoidance of disopyramide advised by manufacturer of telaprevir (risk of ventricular arrhythmias).
- Atomoxetine: increased risk of ventricular arrhythmias when disopyramide given with atomoxetine.
- Beta-blockers: increased myocardial depression when anti-arrhythmics given with beta-blockers; increased risk of ventricular arrhythmias when disopyramide given with sotalol—avoid concomitant use.
- Calcium-channel blockers: increased risk of myocardial depression and asystole when disopyramide given with verapamil.
- Cytotoxics: possible increased risk of ventricular arrhythmias when disopyramide given with bosutinib; possible increased risk of ventricular arrhythmias when disopyramide given with vanetupib—avoid concomitant use; increased risk of ventricular arrhythmias when disopyramide given with arsenic trioxide.
- Diuretics: increased cardiac toxicity with disopyramide if hypokalaemia occurs with acetazolamide; loop diuretics or thiazides and related diuretics.
- Fingolimod: possible increased risk of bradyarrhythmia when disopyramide given with fingolimod.
- Ixabradine: increased risk of ventricular arrhythmias when disopyramide given with ivabradine.
- Nitrates: disopyramide reduces effects of sublingual tablets of nitrates (failure to dissolve under tongue owing to dry mouth).
- Pentamidine isetionate: possible increased risk of ventricular arrhythmias when disopyramide given with pentamidine isetionate.
- Ranolazine: avoidance of disopyramide advised by manufacturer of ranolazine.
- Sildenafil: manufacturer of disopyramide advises avoid concomitant use with sildenafil (risk of ventricular arrhythmias).
- Tadalafil: manufacturer of disopyramide advises avoid concomitant use with tadalafil (risk of ventricular arrhythmias).
- Vardenafil: manufacturer of disopyramide advises avoid concomitant use with vardenafil (risk of ventricular arrhythmias).

Disulfiram

- Alcohol: disulfiram reaction when disulfiram given with alcohol.
- Aminophylline: disulfiram inhibits metabolism of aminophylline (increased risk of toxicity).
- Antibacterials: psychotic reaction reported when disulfiram given with metronidazole; CNS effects of disulfiram possibly increased by isoniazid.
- Anticoagulants: disulfiram enhances anticoagulant effect of coumarins.
- Antidepressants: increased disulfiram reaction with alcohol reported with concomitant amitriptyline; disulfiram inhibits metabolism of tricyclics (increased plasma concentration).
- Antiepileptics: disulfiram inhibits metabolism of fosphenytoin and phenytoin (increased risk of toxicity).
- Anxietytics and Hypnotics: disulfiram increases risk of temazepam toxicity; disulfiram inhibits metabolism of benzodiazepines (increased sedative effects).
- Paraldehyde: risk of toxicity when disulfiram given with paraldehyde.
- Theophylline: disulfiram inhibits metabolism of theophylline (increased risk of toxicity).

Diuretics

- Note: Since systemic absorption may follow topical application of brinzolamide to the eye, the possibility of interactions should be borne in mind.
- Note: Since systemic absorption may follow topical application of dorzolamide to the eye, the possibility of interactions should be borne in mind.
Diuretics (continued)
- ACE inhibitors: enhanced hypotensive effect when diuretics given with ACE INHIBITORS; increased risk of severe hyperkalaemia when potassium-sparing diuretics and aldosterone antagonists given with ACE INHIBITORS.
- Adrenergic α-Blockers: enhanced hypotensive effect when diuretics given with ADRENERGIC NEURONE BLOCKERS.
- Alcohol: enhanced hypotensive effect when diuretics given with ALCOHOL.
- Allspironil: increased risk of hypokalaemia when thiazides and related diuretics given with ALLOPURINOL especially in renal impairment.
- Alpha-blockers: enhanced hypotensive effect when diuretics given with ALPHA-BLOCKERS, also increased risk of first-dose hypotension with post-synaptic alpha-blockers such as prazosin.
- Aminophylline: increased risk of hypokalaemia when acetazolamide, loop diuretics or thiazides and related diuretics given with AMINOALKALOIDS.
- Anaesthetics: enhanced hypotensive effect when diuretics given with GENERAL ANAESTHETICS.
- Analgesics: diuretics increase risk of nephrotoxicity of NSAIDS, also antagonism of diuretic effect; diuretic effect of potassium canrenoate possibly antagonised by NSAIDS; possible increased risk of hyperkalaemia when potassium-sparing diuretics and aldosterone antagonists given with NSAIDS; furosemide possibly increases the excretion of ACEMETACIN; effects of diuretics antagonised by INDOMETACIN and KETOCONAZOLE; increased risk of hyperkalaemia when potassium-sparing diuretics and aldosterone antagonists given with INDOMETACIN; occasional reports of reduced renal function when triamterene given with INDOMETACIN—avoid concomitant use; increased risk of toxicity when acetazolamide given with high-dose ASPRIN; diuretic effect of spironolactone antagonised by ASPRIN; possible increased risk of toxicity when loop diuretics given with high-dose ASPRIN (also possible reduced effect of loop diuretics).
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when diuretics given with ANGIOTENSIN-II RECEPTOR ANTAGONISTS; increased risk of hyperkalaemia when potassium-sparing diuretics and aldosterone antagonists given with ANGIOTENSIN-II RECEPTOR ANTAGONISTS.
- Anti-arrhythmics: hypokalaemia caused by acetazolamide, loop diuretics or thiazides and related diuretics increases cardiac toxicity with DISOPRIMIDE; hypokalaemia caused by acetazolamide, loop diuretics or thiazides and related diuretics increases cardiac toxicity with FLECAINIDE; hypokalaemia caused by acetazolamide, loop diuretics or thiazides and related diuretics action of LIDOCAINE.
- Antibacterials: plasma concentration of eplerenone increased by CLARITHROMYCIN and TELITHROMYCIN—avoid concomitant use; plasma concentration of eplerenone increased by ERYTHROMYCIN (reduce dose of eplerenone); plasma concentration of eplerenone reduced by RIFAMPICIN—avoid concomitant use; avoidance of diuretics advised by manufacturer of LYMCEFCLINE; increased risk of oto toxicity when loop diuretics given with AMINOLUCOSIDES, POLYMIXINS OR VANCOMYCIN; acetazolamide antagonises effects of diuretics given with COLCHICINES; plasma concentration of eplerenone increased by TRIMETHOPRIM; increased risk of hyperkalaemia when spironolactone given with TRIMETHOPRIM; increased risk of hyperkalaemia when eplerenone given with TRIMETHOPRIM.
- Antidepressants: possible increased risk of hypokalaemia when loop diuretics or thiazides and related diuretics given with REBOXETINE; enhanced hypotensive effect when diuretics given with CLONIDINE.
- Antiemetics: increased risk of hyperkalaemia when diuretics given with antiemetics.
- Antidiabetics: enhanced hypotensive effect when diuretics given with ANTI DIABETICS.
- Antiarrhythmics: diuretics increase risk of ventricular arrhythmias with AMISULPRIDE; enhanced hypotensive effect when diuretics given with PHENOTHIAZINES; hypokalaemia caused by diuretics increases risk of ventricular arrhythmias with PIMOZIDE (avoid concomitant use).
- Antitussives: plasma concentration of eplerenone increased by RITONAVIR—avoid concomitant use; plasma concentration of eplerenone increased by SAQUINAVIR (reduce dose of eplerenone).
- Anti-inflammatory: diuretics increase risk of nephrotoxicity with ANTIINFLAMMATORY DRUGS.
- Antihypertensives: plasma concentration of eplerenone possibly increased by CLONIDINE and ZANAMIVIR; furosemide with parenteral CHLORAL may displace thyroid hormone from binding sites.
- Antihistamines: plasma concentration of eplerenone increased by CYCLOSPORIN—avoid concomitant use; plasma concentration of eplerenone increased by CYCLOSPORIN.
- Antiinfectives: plasma concentration of eplerenone increased by SULPHASALAZINE, also increased risk of first-dose hypotension with post-synaptic alpha-blockers such as prazosin.
- Antiparkinson: plasma concentration of eplerenone increased by CARBAMAZEPINE; acetalazolamide increases plasma concentration of CARBAMAZEPINE; effects of furosemide antagonised by FOSPHENYTOIN and PHENYTOIN; acetalazolamide possibly increases plasma concentration of FOSPHENYTOIN and PHENYTOIN; increased risk of osteomalacia when thiazides and related diuretics given with CARBAMAZEPINE; hyperkalaemia when thiazides and related diuretics antagonise action of DIURETICS; increased risk of postural hypotension when diuretics given with TRICYCLIC ANTI DEPRESSANTS; plasma concentration of eplerenone increased by DISOPYRAMIDE.
- Antineoplastic: plasma concentration of eplerenone possibly increased by DAPAGLIFLOZIN; diuretics increase cardiac toxicity with ANTI NEOPLASTIC DRUGS.
- Antipyretics: plasma concentration of eplerenone increased by IBU PROFEN and IBU PROFEN.
- Anti-Parkinson: plasma concentration of eplerenone increased by IBU PROFEN and IBU PROFEN.
- Anti-convulsants: plasma concentration of eplerenone possibly increased by PHENYTOIN; plasma concentration of eplerenone increased by CANAGLIFLOZIN; reduced effect of loop diuretics given with CANAGLIFLOZIN; diuretic effect of loop diuretics and thiazides and related diuretics possibly enhanced by DAPAGLIFLOZIN.
- Antiparkinson: plasma concentration of eplerenone increased by CARBAMAZEPINE; plasma concentration of eplerenone increased by CARBAMAZEPINE; effects of furosemide antagonised by FOSPHENYTOIN and PHENYTOIN; acetalazolamide possibly increases plasma concentration of TOPIRAMATE; avoidance of carbonic anhydrase inhibitors in children advised by manufacturer of ZONISAMIDE.
- Antitussives: plasma concentration of eplerenone increased by RITONAVIR—avoid concomitant use; plasma concentration of eplerenone increased by SAQUINAVIR (reduce dose of eplerenone).
- Antihistamines: diuretics increase risk of nephrotoxicity with ANTIINFLAMMATORY DRUGS.
- Administration of parenteral furosemide with CHLORAL may displace thyroid hormone from binding sites.
- Antihistamines: plasma concentration of eplerenone increased by CYCLOSPORIN—avoid concomitant use; plasma concentration of eplerenone increased by CYCLOSPORIN.
- Anti-infectives: plasma concentration of eplerenone increased by SULPHASALAZINE, also increased risk of first-dose hypotension with post-synaptic alpha-blockers such as prazosin.
- Antihypertensives: plasma concentration of eplerenone possibly increased by CLONIDINE and ZANAMIVIR; furosemide with parenteral CHLORAL may displace thyroid hormone from binding sites.
- Antihistamines: plasma concentration of eplerenone increased by CYCLOSPORIN—avoid concomitant use; plasma concentration of eplerenone increased by CYCLOSPORIN.
- Anti-Parkinson: plasma concentration of eplerenone possibly increased by DAPAGLIFLOZIN; diuretics increase cardiac toxicity with ANTI NEOPLASTIC DRUGS.
- Antipyretics: plasma concentration of eplerenone increased by IBU PROFEN and IBU PROFEN.
- Anti-convulsants: plasma concentration of eplerenone possibly increased by PHENYTOIN; plasma concentration of eplerenone increased by CANAGLIFLOZIN; reduced effect of loop diuretics given with CANAGLIFLOZIN; diuretic effect of loop diuretics and thiazides and related diuretics possibly enhanced by DAPAGLIFLOZIN.
- Antiparkinson: plasma concentration of eplerenone increased by CARBAMAZEPINE; plasma concentration of eplerenone increased by CARBAMAZEPINE; effects of furosemide antagonised by FOSPHENYTOIN and PHENYTOIN; acetalazolamide possibly increases plasma concentration of TOPIRAMATE; avoidance of carbonic anhydrase inhibitors in children advised by manufacturer of ZONISAMIDE.
- Antitussives: plasma concentration of eplerenone increased by RITONAVIR—avoid concomitant use; plasma concentration of eplerenone increased by SAQUINAVIR (reduce dose of eplerenone).
- Anti-Parkinson: plasma concentration of eplerenone possibly increased by DAPAGLIFLOZIN; diuretics increase cardiac toxicity with ANTI NEOPLASTIC DRUGS.
- Antipyretics: plasma concentration of eplerenone increased by IBU PROFEN and IBU PROFEN.
- Anti-convulsants: plasma concentration of eplerenone possibly increased by PHENYTOIN; plasma concentration of eplerenone increased by CANAGLIFLOZIN; reduced effect of loop diuretics given with CANAGLIFLOZIN; diuretic effect of loop diuretics and thiazides and related diuretics possibly enhanced by DAPAGLIFLOZIN.
- Antiparkinson: plasma concentration of eplerenone increased by CARBAMAZEPINE; plasma concentration of eplerenone increased by CARBAMAZEPINE; effects of furosemide antagonised by FOSPHENYTOIN and PHENYTOIN; acetalazolamide possibly increases plasma concentration of TOPIRAMATE; avoidance of carbonic anhydrase inhibitors in children advised by manufacturer of ZONISAMIDE.
- Antitussives: plasma concentration of eplerenone increased by RITONAVIR—avoid concomitant use; plasma concentration of eplerenone increased by SAQUINAVIR (reduce dose of eplerenone).
- Anti-Parkinson: plasma concentration of eplerenone possibly increased by DAPAGLIFLOZIN; diuretics increase cardiac toxicity with ANTI NEOPLASTIC DRUGS.
- Antipyretics: plasma concentration of eplerenone increased by IBU PROFEN and IBU PROFEN.
- Anti-convulsants: plasma concentration of eplerenone possibly increased by PHENYTOIN; plasma concentration of eplerenone increased by CANAGLIFLOZIN; reduced effect of loop diuretics given with CANAGLIFLOZIN; diuretic effect of loop diuretics and thiazides and related diuretics possibly enhanced by DAPAGLIFLOZIN.
- Antiparkinson: plasma concentration of eplerenone increased by CARBAMAZEPINE; plasma concentration of eplerenone increased by CARBAMAZEPINE; effects of furosemide antagonised by FOSPHENYTOIN and PHENYTOIN; acetalazolamide possibly increases plasma concentration of TOPIRAMATE; avoidance of carbonic anhydrase inhibitors in children advised by manufacturer of ZONISAMIDE.
Appendix 1 Interactions

Diuretics

Corticosteroids (continued)
acacetazolamide, loop diuretics or thiazides and related diuretics given with CORTICOSTEROIDS

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotocics: alkaline urine due to acetazolamide increases excretion of METHOTREXATE; hypocalcaemia caused by acetazolamide, loop diuretics or thiazides and related diuretics increases risk of ventricular arrhythmias with</td>
<td></td>
</tr>
<tr>
<td>ARSENIC TROXIDE; avoidance of spironolactone advised by manufacturer of MITOTANE (antagonism of effect); increased risk of nephrotoxicity and ototoxicity when diuretics given with PLATINUM COMPOUNDS</td>
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<tr>
<td>Diazoxide: enhanced hypotensive and hyperglycaemic effects when diuretics given with DIAZoxide</td>
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<tr>
<td>Diuretics: increased risk of hypokalaemia when loop diuretics or thiazides and related diuretics given with ACETAZOLAMIDE; profound diuresis possible when metolazone given with FUROSEMIDE; increased risk of hypokalaemia when thiazides and related diuretics given with LOOP DIURETICS</td>
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<tr>
<td>Dopaminergics: enhanced hypotensive effect when diuretics given with CO-BENEDOPA, CO-CARELDOPA or LEVODOPA</td>
<td></td>
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<tr>
<td>Hormone Antagonists: increased risk of hypercalcaemia when thiazides and related diuretics given with TOREMIFENE</td>
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<tr>
<td>Lipid-regulating Drugs: absorption of thiazides and related diuretics reduced by COLESTIPOL and COLESTYRAMINE (give at least 2 hours apart)</td>
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</tr>
<tr>
<td>Lithium: loop diuretics and thiazides and related diuretics reduce excretion of LITHIUM (increased plasma concentration and risk of toxicity)—loop diuretics safer than thiazides; potassium-sparing diuretics and aldosterone antagonists reduce excretion of LITHIUM (increased plasma concentration and risk of toxicity); acetazolamide increases the excretion of LITHIUM</td>
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<tr>
<td>Methylpiperazine: enhanced hypotensive effect when diuretics given with MOXISLYTE</td>
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<tr>
<td>Moxonidine: enhanced hypotensive effect when diuretics given with MOXONIDINE</td>
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<tr>
<td>Muscle Relaxants: enhanced hypotensive effect when diuretics given with BACLOFEN or TIZANIDINE</td>
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<tr>
<td>Nitrates: enhanced hypotensive effect when diuretics given with NITRATES</td>
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<tr>
<td>Oestrogens: diuretic effect of diuretics antagonised by OESTROGENS</td>
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<tr>
<td>Potassium Salts: increased risk of hypercalcaemia when potassium-sparing diuretics and aldosterone antagonists given with POTASSIUM SALTS</td>
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<tr>
<td>Progestogens: risk of hypercalcaemia when potassium-sparing diuretics and aldosterone antagonists given with DROSPIRENONE (monitor serum potassium during first cycle)</td>
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<tr>
<td>Prostaglandins: enhanced hypotensive effect when diuretics given with ALPROSTALID</td>
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<tr>
<td>Sympathomimetics, Beta: increased risk of hypokalaemia when acetazolamide, loop diuretics or thiazides and related diuretics given with high doses of BETA,SYMPATHOMIMETICS</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus: increased risk of hyperkalaemia when potassium-sparing diuretics and aldosterone antagonists given with TACROLIMUS</td>
<td></td>
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<tr>
<td>Theophylline: increased risk of hypokalaemia when acetazolamide, loop diuretics or thiazides and related diuretics given with THEOPHYLLINE</td>
<td></td>
</tr>
<tr>
<td>Vasodilator Antihypertensives: enhanced hypotensive effect when diuretics given with HYDRAZINE, MINOXIDIL or SODIUM NITROPRUSIDE</td>
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<tr>
<td>Vitamins: increased risk of hypercalcaemia when thiazides and related diuretics given with ALFACALCICOL, CALCITRIOL, COLECALCIFEROL, DIHYDROTACHysterol, ERGOCALCIFEROL, PARICALCITOL or VITAMIN D</td>
<td></td>
</tr>
</tbody>
</table>

Antacids: absorption of dolutedegravir reduced by ALUMINIUM HYDROXIDE and ORAL MAGNESIUM SALTS—manufacturer of dolutedegravir advises give at least 2 hours before or 6 hours after aluminium hydroxide and oral magnesium salts

Antibacterials: plasma concentration of dolutedegravir reduced by RIFAMPICIN (see under Dolutedegravir, p. 1186)

Antidepressants: manufacturer of dolutedegravir advises avoid concomitant use with ST JOHN'S WORT

Antiepileptics: manufacturer of dolutedegravir advises avoid concomitant use with CARBAMAZEPINE, FOSPHENYTOIN, OXCARBAZEPINE, PHENOBARBITAL, PHENYTOIN and PRIMIDONE

Antivirals: plasma concentration of dolutedegravir reduced by EFAVIRENZ, ETRAVIRINE and TIPRANAVIR (see under Dolutedegravir, p. 1186); plasma concentration of dolutedegravir reduced by FOSAMPRENAVIR; plasma concentration of dolutedegravir possibly reduced by NEVIRAPINE (see under Dolutedegravir, p. 1186)

Calcium Salts: absorption of dolutedegravir reduced by CALCIUM SALTS—manufacturer of dolutedegravir advises give at least 2 hours before or 6 hours after calcium salts

Iron Salts: absorption of dolutedegravir reduced by oral IRON SALTS—manufacturer of dolutedegravir advises give at least 2 hours before or 6 hours after oral iron salts

Docetaxel

Antibacterials: plasma concentration of docetaxel possibly increased by CLARITHROMYCIN and TELITHROMYCIN—manufacturer of docetaxel advises avoid concomitant use or consider reducing docetaxel dose

Antifungals: in vitro studies suggest a possible interaction between docetaxel and KETOCONAZOLE (consult docetaxel product literature); plasma concentration of docetaxel possibly increased by ITRACONAZOLE and VORICONAZOLE—manufacturer of docetaxel advises avoid concomitant use or consider reducing docetaxel dose

Antipsychotics: avoid concomitant use of cytoxotics with CLOZAPINE (increased risk of agranulocytosis)

Antivirals: plasma concentration of docetaxel possibly increased by INDINAVIR, RITONAVIR and SAQUINAVIR—manufacturer of docetaxel advises avoid concomitant use or consider reducing docetaxel dose

Ciclosporin: in vitro studies suggest a possible interaction between docetaxel and CICLOSPORIN (consult docetaxel product literature)

Cytotoxics: possible increased risk of neutropenia when docetaxel given with LAPTANIB; plasma concentration of docetaxel increased by SORAFENIB

Dolutedegravir

Antacids: absorption of dolutedegravir reduced by ALUMINIUM HYDROXIDE and ORAL MAGNESIUM SALTS—manufacturer of dolutedegravir advises give at least 2 hours before or 6 hours after aluminium hydroxide and oral magnesium salts

Antibacterials: plasma concentration of dolutedegravir reduced by RIFAMPICIN (see under Dolutedegravir, p. 1186)

Antidepressants: manufacturer of dolutedegravir advises avoid concomitant use with CARBAMAZEPINE, FOSPHENYTOIN, OXCARBAZEPINE, PHENOBARBITAL, PHENYTOIN and PRIMIDONE

Antivirals: plasma concentration of dolutedegravir reduced by EFAVIRENZ, ETRAVIRINE and TIPRANAVIR (see under Dolutedegravir, p. 1186); plasma concentration of dolutedegravir reduced by FOSAMPRENAVIR; plasma concentration of dolutedegravir possibly reduced by NEVIRAPINE (see under Dolutedegravir, p. 1186)

Calcium Salts: absorption of dolutedegravir reduced by CALCIUM SALTS—manufacturer of dolutedegravir advises give at least 2 hours before or 6 hours after calcium salts

Iron Salts: absorption of dolutedegravir reduced by oral IRON SALTS—manufacturer of dolutedegravir advises give at least 2 hours before or 6 hours after oral iron salts

Dorperazone Analgesics: effects of dorperazone on gastro-intestinal activity antagonised by OPIOID ANALGESICS

Antibacterials: possible increased risk of ventricular arrhythmias when dorperazone given with CLARITHROMYCIN or TELITHROMYCIN—or VORICONAZOLE—avoid concomitant use; plasma concentration of dorperazone increased by ERITHROMYCIN (increased risk of ventricular arrhythmias—avoid concomitant use); possible increased risk of ventricular arrhythmias when dorperazone given with DELAMANID

Antifungals: avoidance of dorperazone advised by manufacturer of KETOCONAZOLE (risk of ventricular arrhythmias); possible increased risk of ventricular arrhythmias when dorperazone given with ITRACONAZOLE or VORICONAZOLE—avoid concomitant use

Antimalaria: avoidance of dorperazone advised by manufacturer of ARTEMISININ WITH PIPERQUIN (possible risk of ventricular arrhythmias)

Antimuscarinics: effects of dorperazone on gastro-intestinal activity antagonised by ANTIMUSCARINICS

Antivirals: possible increased risk of ventricular arrhythmias when dorperazone given with BOCEPREVIR, RITONAVIR, SAQUINAVIR or TELAPREVIR—avoid concomitant use

Cobicistat: possible increased risk of ventricular arrhythmias when dorperazone given with Cobicistat—avoid concomitant use

Cytotoxics: avoidance of dorperazone advised by manufacturer of ROSUVASTATIN (risk of ventricular arrhythmias)
Dopamine see Sympathomimetics
Dopaminergics see Amantadine, Apomorphine, Bromocriptine, Cabergoline, Entacapone, Levodopa, Pergolid, Pramipexole, Quinagolide, Rasagiline, Ropinirole, Rotigotine, Selegiline, and Toclapon
Dopexamine see Sympathomimetics
Dorzolamide see Diuretics
Doxepin see Antidepressants, Tricyclic
Doxapram
- Aminophylline: increased CNS stimulation when doxapram given with AMINOPHYLLINE
  - Anaesthetics, General: increased risk of arrhythmias when doxapram given with VOLATILE LIQUID GENERAL ANAESTHETICS (avoid doxapram for at least 10 minutes after volatile liquid general anaesthetics)
  - Antibacterials: effects of doxapram enhanced by MAOIS
  - Antidepressants: increased risk of hypertension when doxapram given with SYMPATHOMIMETICS
  - Theophylline: increased CNS stimulation when doxapram given with THEOPHYLLINE
Doxazosin see Alpha-blockers
Doxepin see Antidepressants, Tricyclic
Doxorubicin see Cytotoxics
Doxorubicin see Antidepressants, Tricyclic
Doxapram (continued)
- Aminephrine: increased CNS stimulation when doxapram given with AMINOPHYLLINE
  - Anaesthetics, General: increased risk of arrhythmias when doxapram given with VOLATILE LIQUID GENERAL ANAESTHETICS (avoid doxapram for at least 10 minutes after volatile liquid general anaesthetics)
  - Antibacterials: effects of doxapram enhanced by MAOIS
  - Antidepressants: increased risk of hypertension when doxapram given with SYMPATHOMIMETICS
  - Theophylline: increased CNS stimulation when doxapram given with THEOPHYLLINE
Dronedarone see Cardiac Glycosides
Dronedarone (continued)
- Antiarrhythmics: plasma concentration of drozdarone possibly reduced by KETOCONAZOLE—avoid concomitant use; manufacturer of drozdarone advises avoid concomitant use with ITRA
  - Antiarrhythmics: increased risk of ventricular arrhythmias when anti-arrhythmics that prolong the QT interval given with ANTIPSYCHOTICS that prolong the QT interval; manufacturer of drozdarone advises avoid concomitant use with PHENOTHIAZINES (risk of ventricular arrhythmies)
  - Antivirals: manufacturer of drozdarone advises avoid concomitant use with RITONAVIR; increased risk of ventricular arrhythmias when drozdarone given with
  - CYP450 3A4 inhibitors: drozdarone possibly increases plasma concentration of METOTR accrued and PRPRANOLOL; increased risk of ventricular arrhythmias when drozdarone given with SOTALOL—avoid concomitant use
  - Calcium-channel Blockers: plasma concentration of drozdarone increased by NIFEDIPINE; increased risk of hypotension with drozdarone given with
  - Cardiac Glycosides: drozdarone increases plasma concentration of DIGOXIN (risk of ventricular arrhythmias)
  - CYP450 3A4 inhibitors: drozdarone possibly increases plasma concentration of BOSUTINIB—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; drozdarone possibly increases the plasma concentration of IBURITINIB—reduce dose of ibritinib (see under ibritinib, p. 909)
  - Fingolimod: possible increased risk of hypotension with drozdarone given with FINGOLIMOD
  - Grapefruit Juice: plasma concentration of drozdarone increased by GRAPEFRUIT JUICE—avoid concomitant use
  - Lipid-regulating Drugs: drozdarone possibly increases plasma concentration of ATORVASTATIN; drozdarone increases plasma concentration of ROSUVA STATIN—adjust dose of rosuvastatin; increased risk of hypotension with drozdarone given with SIMVASTATIN; avoidance of drozdarone advised by manufacturer of LOMITAPIDE (plasma concentration of lomitapide possibly increased)
  - Sirolimus: manufacturer of drozdarone advises caution with SIROLIMUS
  - Tacrolimus: manufacturer of drozdarone advises caution with TACROLIMUS
Droperidol see Antiemetics
Drospirenone see Progestogens
Duloxetine
- Analgesics: possible increased serotonergic effects when SSRI-related antidepressants given with FENTANYL; possible increased serotonergic effects when duloxetine given with PETHIDINE or TRAMADOL
  - Antiarrhythmics: metabolism of duloxetine inhibited by CIPROFLOXACIN;—avoid concomitant use
  - Anticoagulants: possible increased risk of bleeding when SSRI-related antidepressants given with DABIGATRAN
  - Antidepressants: metabolism of duloxetine inhibited by FLUVAXMIDINE—avoid concomitant use; possible increased serotonergic effects when duloxetine given with SSRIs, ST JOHN’S WORT, AMITRIPTYLINE, CLOMIPRAMINE, MOCLOBEMIDE or VENLAFAXINE; duloxetine should not be started until 2 weeks after stopping; MAOIS, also MAOIs should not be started until at least 5 days after stopping duloxetine; after stopping SSRIs-related antidepressants do not start MOCLOBEMIDE for at least 1 week
  - Antimalarials: avoidance of antidepressants advised by manufacturer of ARTEMETHER WITH LUMEFANTRINE and ARTEMIMOL WITH PIPERAQIUNE
Efavirenz (continued)

- **Antivirals:** plasma concentration of **SAQUINAVIR**; efavirenz reduces plasma concentration of **TELAPREVIR**—increase dose of telaprevir
- **Anxiolytics and Hypnotics:** increased risk of prolonged sedation when efavirenz given with **MIDAZOLAM**—avoid concomitant use
- **Atovaquone:** efavirenz reduces plasma concentration of **ATOVACUONE**—avoid concomitant use
- **Avanafil:** efavirenz possibly reduces plasma concentration of **AVANAFIL**—manufacturer of avanafil advises avoid concomitant use
- **Bupropion:** efavirenz accelerates metabolism of **BUPROPION** (reduced plasma concentration)
- **Calcium-channel Blockers:** efavirenz reduces plasma concentration of **DILTIAZEM**
- **Ciclosporin:** efavirenz possibly reduces plasma concentration of **CICLOSPORIN**
- **Cytotoxics:** efavirenz possibly reduces plasma concentration of **BOSUTINIB**—manufacturer of bosutinib advises avoid concomitant use
- **Ergot Alkaloids:** increased risk of ergotism when efavirenz given with **ERGOT ALKALOIDS**—avoid concomitant use
- **Grapefruit Juice:** plasma concentration of efavirenz possibly increased by **GRAPEFRUIT JUICE**
- **Lipid-regulating Drugs:** efavirenz reduces plasma concentration of **ATORVASTATIN**, **PRAVASTATIN** and **SIMVASTATIN**
- **Orlistat:** absorption of efavirenz possibly reduced by **ORLISTAT**
- **Progestogens:** efavirenz possibly reduces contraceptive effect of **PROGESTOGENS**
- **Tacrolimus:** efavirenz possibly affects plasma concentration of **TACROLIMUS**

Elotrubbogain

- **Antacids:** absorption of elotrubbogain reduced by **ANTACIDS** (give at least 4 hours apart)
- **Antivirals:** plasma concentration of elotrubbogain possibly reduced by **LOPINAVIR**
- **Calcium Salts:** absorption of elotrubbogain possibly reduced by **CALCIUM SALTS** (give at least 4 hours apart)
- **Dairy Products:** absorption of elotrubbogain possibly reduced by **DAIRY PRODUCTS** (give at least 4 hours apart)
- **Iron Salts:** absorption of elotrubbogain possibly reduced by **IRON SALTS** (give at least 4 hours apart)
- **Lipid-regulating Drugs:** elotrubbogain increases plasma concentration of **ROSUVASTATIN**—adjust dose of rosuvastatin (consult product literature)
- **Selenium:** absorption of elotrubbogain possibly reduced by **SELENIUM** (give at least 4 hours apart)
- **Zinc:** absorption of elotrubbogain possibly reduced by **ZINC** (give at least 4 hours apart)

Elivtegravir

- **Antacids:** absorption of elivtegravir reduced by **ALUMINIUM HYDROXIDE** and **ORAL MAGNESIUM SALTS** (give at least 4 hours apart)
- **Antibacterials:** plasma concentration of elivtegravir reduced by **rifabutin** also plasma concentration of active metabolite of rifabutin increased—reduce dose of rifabutin; manufacturer of elivtegravir advises avoid concomitant use with ****
- **Antileptics:** manufacturer of elivtegravir advises avoid concomitant use with ****
- **Antidepressants:** manufacturer of elivtegravir advises avoid concomitant use with **ST JOHNS WORT**
- **Antivirals:** avoidance of efavirenz advised by manufacturer of ****
- **Bosentan:** manufacturer of elivtegravir advises avoid concomitant use with ****
- **Calcium Salts:** absorption of elivtegravir possibly reduced by **CALCIUM SALTS** (give at least 4 hours apart)
- **Ciclosporin:** efavirenz reduces plasma concentration of **CICLOSPORIN**
- **Cytotoxic:** efavirenz possibly reduces plasma concentration of **BOSUTINIB**—manufacturer of bosutinib advises avoid concomitant use
- **Dairy Products:** absorption of elivtegravir possibly reduced by **DAIRY PRODUCTS** (give at least 4 hours apart)
- **Iron Salts:** absorption of elivtegravir possibly reduced by **IRON SALTS** (give at least 4 hours apart)
- **Methylthioninium:** manufacturer of elivtegravir advises avoid concomitant use
- **Atovaquone:** efavirenz reduces plasma concentration of **ATOVACUONE**—avoid concomitant use
- **Avanafil:** efavirenz possibly reduces plasma concentration of **AVANAFIL**—manufacturer of avanafil advises avoid concomitant use
- **Bupropion:** efavirenz accelerates metabolism of **BUPROPION** (reduced plasma concentration)
- **Calcium-channel Blockers:** efavirenz reduces plasma concentration of **DILTIAZEM**
- **Ciclosporin:** efavirenz possibly reduces plasma concentration of **CICLOSPORIN**
- **Cytotoxic:** efavirenz possibly reduces plasma concentration of **BOSUTINIB**—manufacturer of bosutinib advises avoid concomitant use
- **Ergot Alkaloids:** increased risk of ergotism when efavirenz given with **ERGOT ALKALOIDS**—avoid concomitant use
- **Grapefruit Juice:** plasma concentration of efavirenz possibly increased by **GRAPEFRUIT JUICE**
- **Lipid-regulating Drugs:** efavirenz reduces plasma concentration of **ATORVASTATIN**, **PRAVASTATIN** and **SIMVASTATIN**
- **Orlistat:** absorption of efavirenz possibly reduced by **ORLISTAT**
- **Progestogens:** efavirenz possibly reduces contraceptive effect of **PROGESTOGENS**
- **Tacrolimus:** efavirenz possibly affects plasma concentration of **TACROLIMUS**
- **Antacids:** absorption of elotrubbogain reduced by **ANTACIDS** (give at least 4 hours apart)
- **Antivirals:** plasma concentration of elotrubbogain possibly reduced by **LOPINAVIR**
- **Calcium Salts:** absorption of elotrubbogain possibly reduced by **CALCIUM SALTS** (give at least 4 hours apart)
- **Dairy Products:** absorption of elotrubbogain possibly reduced by **DAIRY PRODUCTS** (give at least 4 hours apart)
- **Iron Salts:** absorption of elotrubbogain possibly reduced by **IRON SALTS** (give at least 4 hours apart)
- **Lipid-regulating Drugs:** elotrubbogain increases plasma concentration of **ROSUVASTATIN**—adjust dose of rosuvastatin (consult product literature)
- **Selenium:** absorption of elotrubbogain possibly reduced by **SELENIUM** (give at least 4 hours apart)
- **Zinc:** absorption of elotrubbogain possibly reduced by **ZINC** (give at least 4 hours apart)
Elvitegravir (continued)  
> Progestogens: elvitegravir increases plasma concentration of NORGESTIMATE

Emagliflozin see Antidiabetics

Emtricitabine  
Antiviral, manufacturer of emtricitabine advises avoid concomitant use with LAMIVUDINE  
> Orlistat: absorption of emtricitabine possibly reduced by ORLISTAT

Enalapril see ACE Inhibitors

Enfuvirtide  
Orlistat: absorption of enfuvirtide possibly reduced by ORLISTAT

Enoxaparin see Heparins

Enoximone see Phosphodiesterase Inhibitors

Entacapone  
> Anti-coagulants: entacapone enhances anti-coagulant effect of WARFARIN

> Anti-depressants: manufacturer of entacapone advises caution with MOCLOBEMIDE, TRICYCLICS and VENLAFAXINE; avoid concomitant use of entacapone with non-selective MAOIS

Dopaminergics: entacapone possibly enhances effects of APOMORPHINE; entacapone possibly reduces plasma concentration of RASAGILINE; manufacturer of entacapone advises max. dose of 10 mg SELEGILINE if used concomitantly

Iron Salts: absorption of entacapone reduced by oral IRON SALTS

Memesantine: effects of dopaminergics possibly enhanced by MEMANTINE

Methyldopa: entacapone possibly enhances effects of METHYLDOPA; antiparkinsonian effect of dopaminergics antagonised by METHYLDOPA

Sympathomimetics: entacapone possibly enhances effects of ADRENALINE (EPINEPHRINE), DOBUTAMINE, DOPAMINE and NORADRENALINE (NOREPINEPHRINE)

Enteral Foods  
> Anti-coagulants: the presence of vitamin K in some enteral feeds can antagonise the anti-coagulant effect of COUMARINS and PHENINDIONE

> Antiepileptics: enteral feeds possibly reduce absorption of FOSPHENYTOIN and PHENYTOIN

Enzalutamide  
> Anti-bacterials: manufacturer of enzalutamide advises avoid concomitant use with RIFAMPICIN

> Anticoagulants: enzalutamide possibly reduces plasma concentration of COUMARINS

Lipid-regulating Drugs: plasma concentration of enzalutamide increased by GEMFIBROZIL—manufacturer of enzalutamide advises avoid concomitant use or halve dose of enzalutamide

Ephedrine see Sympathomimetics

Epinephrine  
> NOTE Epinephrine interactions as for adrenaline, see under sympathomimetics

Epirubicin  
> Anti-psychotics: avoid concomitant use of cytotoxics with CLOzapine (increased risk of agranulocytosis)

Cloclosporin: plasma concentration of epirubicin increased by CICLOSPORIN

Ulcer-healing Drugs: plasma concentration of epirubicin increased by CIMETIDINE

Eplerenone see Diuretics

Eprosartan see Angiotensin-II Receptor Antagonists

Epifibatide  
> Iloprost: increased risk of bleeding when epifibatide given with ILOPROST

Ergocalciferol see Vitamins

Ergometrine see Ergot Alkaloids

Ergot Alkaloids  
> Anti-bacterials: increased risk of ergotism when ergometrine given with MACROLIDES or ERYTHROMYCIN—avoid concomitant use; increased risk of ergotism when ergometrine given with TETRACYCLINES

Ergot Alkaloids (continued)  
> Anti-depressants: possible risk of hypertension when ergotamine given with REBOXETINE

> Anti-fungals: avoidance of ergot alkaloids advised by manufacturer of KETOCONAZOLE; avoidance of ergotamine advised by manufacturer of TRICLOROANIL (increased risk of ergotism); increased risk of ergotism when ergometrine given with VORICONAZOLE—avoid concomitant use; increased risk of ergotism when ergotamine given with IMIDAZOLES or TRIAZOLEs; avoid concomitant use

Anti-psychotics: plasma concentration of ergot alkaloids possibly increased by LURASIDONE (increased risk of toxicity)

Anti-virals: plasma concentration of ergot alkaloids possibly increased by ATAZANAVIR—avoid concomitant use; avoidance of ergot alkaloids advised by manufacturer of BOCREPRAVIR and TELAPREVIR; increased risk of ergotism when ergot alkaloids given with DARUNAVIR—manufacturer of darunavir advises avoid concomitant use; increased risk of ergotism when ergot alkaloids given with EFAVIRENZ—avoid concomitant use; increased risk of ergotism when ergotamine given with FOSAMPRENAVIR, INDINAVIR, RITONAVIR or SAQUINAVIR—avoid concomitant use; increased risk of ergotism when ergometrine given with INDINAVIR or RITONAVIR—avoid concomitant use

Beta-blockers: increased peripheral vasocostriction when ergotamine given with BETA-BLOCKERS

Cobicistat: plasma concentration of ergot alkaloids possibly increased by COBICISTAT—manufacturer of cobicistat advises avoid concomitant use

Cytotoxics: caution with ergot alkaloids advised by manufacturer of CHIZOTINIB; avoidance of ergotamine advised by manufacturer of IDELALISIB

5HT-receptor Agonists: increased risk of vasospasm when ergotamine given with ALMOTRIPTAN, RIZATRIPTAN, SUMATRIPTAN or ZOLMITRIPTAN (avoid ergotamine for 6 hours after almotriptan, rizatRIPTan, sumatriptan or zolmitriptan, avoid almotriptan, rizatRIPTan, sumatriptan or zolmitriptan for 24 hours after ergotamine); increased risk of vasospasm when ergotamine given with ELETRIPTAN, FROVATRIPTAN or NARATRIPTAN (avoid ergotamine for 24 hours after eletriptan, frovatriptan or naranatriptan, avoid eletriptan, frovatrIPAIN or naranatriptan for 24 hours after ergotaine)

Sympathomimetics: increased risk of ergotism when ergotamine given with SYMPATHOMIMETICS

Ticagrelor: plasma concentration of ergot alkaloids possibly increased by TICAGRELOR

Ulcer-healing Drugs: increased risk of ergotism when ergotamine given with CIMETIDINE—avoid concomitant use

Ergotamine see Ergot Alkaloids

Eribulin  
> Anti-bacterials: plasma concentration of eribulin possibly reduced by RIFAMPICIN

> Anti-depressants: plasma concentration of eribulin possibly reduced by ST JOHN’S WORT's

Antiepileptics: plasma concentration of eribulin possibly reduced by CARBAMAZEPINE, FOSPHENYTOIN and PHENYTOIN

Anti-psychotics: avoid concomitant use of cytotoxics with CLOzapine (increased risk of agranulocytosis)

Erlotinib  
> Analgesics: increased risk of bleeding when erlotinib given with NSAIDS

> Anti-cids: plasma concentration of erlotinib possibly reduced by ANTACIDS—give antacids at least 4 hours before or 2 hours after erlotinib

> Anti-bacterials: plasma concentration of erlotinib increased by CIPROFLOXACIN; metabolism of erlotinib accelerated by RIFAMPICIN (reduced plasma concentration)

> Anti-coagulants: increased risk of bleeding when erlotinib given with COUMARINS

> Anti-fungals: metabolism of erlotinib inhibited by KETOCONAZOLE (increased plasma concentration)

Anti-psychotics: avoid concomitant use of cytotoxics with CLOzapine (increased risk of agranulocytosis)

Anti-virals: avoidance of erlotinib advised by manufacturer of BOCREPRAVIR
Erlotinib (continued)

- Cytotoxic: plasma concentration of erlotinib possibly increased by CAPECITABINE
- Ulcer-healing Drugs: manufacturer of erlotinib advises avoid concomitant use with Cimetidine, Esomeprazole,
  Famotidine, Lansoprazole, Nizatidine, Pantoprazole and Rabeprazole; plasma concentration of erlotinib reduced by Ranitidine—manufacturer of erlotinib advises give at least 2 hours before or 10 hours after ranitidine; plasma concentration of erlotinib reduced by Omeprazole—manufacturer of erlotinib advises avoid concomitant use

Ertapenem
- Antiepileptics: carbapenems reduce plasma concentration of Sodium Valproate and Valproic Acid—avoid concomitant use
- Vaccines: antibacterials inactivate Oral Typhoid Vaccine—see under Typhoid Vaccine in BNF

Erythromycin see Macrolides

Escitalopram see Antidepressants, SSRI

Escarbazepine
- Antiepileptics: escarbazepine reduces plasma concentration of Warfarin
- Antidepressants: anticongestant effect of antiepileptics possibly antagonised by MAOIs and Tricyclic-Related Antidepressants (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by SSRIs and Tricyclics (convulsive threshold lowered)
- Antiepileptics: plasma concentration of escarbazepine possibly reduced by Carbamazepine but risk of side-effects increased; plasma concentration of escarbazepine reduced by Phenytoin and Phenytoin, also plasma concentration of fosphenytoin and phenytoin increased; manufacturer of escarbazepine advises avoid concomitant use with Oxcarbazepine
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by Mefloquine
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by Antipsychotics (convulsive threshold lowered)
- Lipid-regulating Drugs: escarbazepine reduces plasma concentration of Rosuvastatin; escarbazepine reduces plasma concentration of Simvastatin—consider increasing dose of simvastatin
- Oestrogens: escarbazepine accelerates metabolism of Oestrogens
- Progestogens: escarbazepine accelerates metabolism of Progestogens
- Antiepileptics: reduced contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF
- Orlistat: possible increased risk of convulsions when antiepileptics given with Orlistat
- Progestogens: escarbazepine accelerates metabolism of Progestogens
- Antiepileptics: reduced contraceptive effect with combined oral contraceptives, progestogen-only oral contraceptives, contraceptive patches, vaginal rings, etonogestrel-releasing implant, and emergency hormonal contraception—see Contraceptive Interactions in BNF

Esmolol see Beta-blockers

Esomeprazole see Proton Pump Inhibitors

 Estradiol see Oestrogens

 Estramustine
- Antacids: absorption of estramustine possibly reduced by Aluminium Hydroxide and Oral Magnesium Salts—manufacturer of estramustine advises avoid concomitant administration
- Antipsychotics: avoid concomitant use of cytotoxics with Clozapine (increased risk of agranulocytosis)
- Bisphosphonates: plasma concentration of estramustine increased by Sodium Clodronate
- Calcium Salts: absorption of estramustine reduced by Calcium Salts (manufacturer of estramustine advises avoid concomitant administration)

Estradiol see Oestrogens

Estrone see Oestrogens

Etanercept
- Abatacept: avoid concomitant use of etanercept with Abatacept

Etenostradiol see Oestrogens

Ethosuximide
- Antibacterials: metabolism of ethosuximide inhibited by Isoniazid (increased plasma concentration and risk of toxicity)
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by MAOIs and Tricyclic-Related Antidepressants (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by SSRIs and Tricyclics (convulsive threshold lowered)
- Antiepileptics: plasma concentration of ethosuximide possibly reduced by Carbamazepine, Phenobarbital, and Primidone; plasma concentration of ethosuximide possibly reduced by Phenytoin and Phenytion, also plasma concentration of fosphenytoin and phenytoin increased; plasma concentration of ethosuximide possibly increased by Sodium Valproate and Valproic Acid
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by Mefloquine
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by Antipsychotics (convulsive threshold lowered)
- Orlistat: possible increased risk of convulsions when antiepileptics given with Orlistat

Etodolac see NSAIDs

Etomate see Anaesthetics, General

Etonogestrel see Progestogens

Etosapide
- Anticoagulants: etosapide possibly enhances anticoagulant effect of Coumarins
- Antiepileptics: plasma concentration of etosapide possibly reduced by Phenytoin, Phenobarbital, Phenytion and Primidone
- Antifungals: plasma concentration of etosapide increased by Ketoconazole
- Antipsychotics: avoid concomitant use of cytotoxics with Clozapine (increased risk of agranulocytosis)
- Atovaquone: plasma concentration of etosapide possibly increased by Atovaquone
- Ciclosporin: plasma concentration of etosapide possibly increased by Ciclosporin (increased risk of toxicity)

Etoricoxib see NSAIDs

Etravirine
- Antibacterials: etravirine reduces plasma concentration of Clarithromycin (but concentration of an active metabolite increased), also plasma concentration of etravirine increased; plasma concentration of both drugs reduced when etravirine given with Rifabutin; manufacturer of etravirine advises avoid concomitant use with Rifamycin; etravirine possibly reduces plasma concentration of Bedaquiline—manufacturer of bedaquiline advises avoid concomitant use
- Antidepressants: manufacturer of etravirine advises avoid concomitant use with St John’s Wort
- Antiepileptics: manufacturer of etravirine advises avoid concomitant use with Carbamazepine, Fosphenytoin, Phenobarbital, Phenytion and Primidone
- Antimalarials: etravirine reduces plasma concentration of Artemether with Lumefantrine
- Antivirals: effects of both drugs possibly reduced when etravirine given with Bictegravir; avoidance of etravirine advised by manufacturer of Dolutegravir (plasma concentration of dolutegravir possibly reduced); etravirine reduces the plasma concentration of Dolutegravir (see under Dolutegravir, p. 557); plasma concentration of etravirine possibly reduced by Efavirenz and Nevirapine—
Etravirine
- Antivirals (continued)
  avoid concomitant use; etravirine increases plasma concentration of ciclosporin (consider reducing dose of ciclosporin); etravirine possibly reduces plasma concentration of tizanidine—avoid concomitant use; etravirine possibly reduces plasma concentration of maraviroc; avoidance of etravirine advised by manufacturer of simprevir; plasma concentration of etravirine reduced by
  tizanidine, also plasma concentration of tipranavir increased (avoid concomitant use)
  cardiac glycosides: etravirine increases plasma concentration of digoxin
  clopidogrel: etravirine possibly reduces antiplatelet effect of
  clopidogrel
  cytoxotics: etravirine possibly reduces plasma concentration of
  bosutinib—manufacturer of bosutinib advises avoid concomitant use
  lipid-regulating Drugs: etravirine possibly reduces plasma concentration of atorvastatin
  orlistat: absorption of etravirine possibly reduced by
  orlistat
  sildenafil: etravirine reduces plasma concentration of sildenafil

Everolimus
- ACE inhibitors: increased risk of angioedema when everolimus given with
  ACE INHIBITORS
- Antibacterials: plasma concentration of everolimus possibly increased by
  clarithromycin and telithromycin—manufacturer of everolimus advises avoid concomitant use; plasma concentration of everolimus increased by
  erythromycin (consider the reducing the dose of everolimus—consult everolimus product literature); plasma concentration of everolimus reduced by
  rifampicin (avoid concomitant use or consider increasing the dose of everolimus—consult everolimus product literature)
- Antidepressants: plasma concentration of everolimus possibly reduced by st john’s wort—manufacturer of everolimus advises avoid concomitant use
- Antifungals: plasma concentration of everolimus increased by
  ketoconazole—manufacturer of ketoconazole advises avoid concomitant use; plasma concentration of everolimus possibly increased by
  itraconazole, posaconazole and voriconazole—manufacturer of everolimus advises avoid concomitant use
- Antipsychotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis)
- Antivirals: plasma concentration of everolimus possibly increased by
  atazanavir, darunavir, indinavir, ritonavir and saquinavir—manufacturer of everolimus advises avoid concomitant use
- Calcium-channel Blockers: plasma concentration of both drugs may increase when everolimus given with
  verapamil (consider reducing the dose of everolimus—consult everolimus product literature)
- Ciclosporin: plasma concentration of everolimus increased by
  cyclosporin (consider reducing the dose of everolimus—consult everolimus product literature)
- Cytoxotics: plasma concentration of everolimus increased by
  imatinib (consider reducing the dose of everolimus—consult everolimus product literature)
- Grapefruit Juice: manufacturer of everolimus advises avoid concomitant use with grapefruit juice

Exemestane
- Antibacterials: plasma concentration of exemestane possibly reduced by rifampicin

Exenatide see Antidiabetics

Ezetimibe
- Anticoagulants: ezetimibe possibly enhances anticoagulant effect of
  coumadins
- Ciclosporin: plasma concentration of both drugs may increase when ezetimibe given with
  ciclosporin
- Lipid-regulating Drugs: ezetimibe increases plasma concentration of
  rosuvastatin—adjust dose of rosuvastatin (consult product literature); increased risk of cholelithiasis

Famotidine see Histamine H2-antagonists

Fampridine
- Ulcer-healing Drugs: manufacturer of fampridine advises avoid concomitant use with
  cimetidine

Fexofenadine see Antihistamines

Fenofibrate see Fibrates

Fenoprofen see NSAIDs

Fentanyl see Opioid Analgesics

Ferrous Gluconate see Iron salts

Ferrous Sulphate see Iron salts

Fesoterodine see Antimuscarinics

Fexofenadine see Antihistamines

Fibrates
- Antibacterials: increased risk of myopathy when fibrates given with
  daptomycin (preferably avoid concomitant use)
- Anticoagulants: fibrates enhance anticoagulant effect of
  coumadins and
  phenindione
- Antidiabetics: fibrates may improve glucose tolerance and have an additive effect with
  insulin or sulfonylureas;
  gemfibrozil possibly enhances hypoglycaemic effect of
  nateglinide; increased risk of severe hypoglycaemia when gemfibrozil given with
  repaglinide—avoid concomitant use
  ciclosporin: increased risk of renal impairment when bezafibrate or fenofibrate given with
  ciclosporin
  colchicine: possible increased risk of myopathy when fibrates given with
  colchicine
  cytoxotics: gemfibrozil increases plasma concentration of
darafenib; gemfibrozil increases plasma concentration of
  bexarotene—avoid concomitant use
- Hormone Antagonists: gemfibrozil increases plasma concentration of
  enzalutamide—manufacturer of enzalutamide advises avoid concomitant use or half dose of enzalutamide
- Leukotriene Receptor Antagonists: gemfibrozil increases plasma concentration of montelukast
- Lipid-regulating Drugs: increased risk of myopathy when fibrates given with
  atorvastatin, fluvastatin or pravastatin (preferably avoid concomitant use); increased risk of myopathy when fibrates given with
  rosuvastatin (see under Rosuvastatin, p. 180); possible increased risk of myopathy when bezafibrate given with
  simvastatin (see under Simvastatin, p. 181); possible increased risk of myopathy when ciprofibrate given with
  simvastatin (see under Simvastatin, p. 181); increased risk of myopathy when gemfibrozil given with
  simvastatin (avoid concomitant use); increased risk of cholelithiasis and gallbladder disease when fibrates given with ezetimibe—discontinue if suspected; increased risk of myopathy when fibrates given with
  statins; reduce maximum dose of fenofibrate when given with
  statins—see under Fenofibrate, p. 175

Fidaxomicin
- Anti-arrhythmics: manufacturer of fidaxomicin advises avoid concomitant use with
  amiodarone and dronedarone
- Antibacterials: manufacturer of fidaxomicin advises avoid concomitant use with
  clarithromycin and erythromycin
- Antifungals: manufacturer of fidaxomicin advises avoid concomitant use with
  ketoconazole
- Calcium-channel Blockers: manufacturer of fidaxomicin advises avoid concomitant use with
  verapamil
- Ciclosporin: manufacturer of fidaxomicin advises avoid concomitant use with
  ciclosporin
- Vaccines: antibacterials inactivate
  oral typhoid vaccine—see under Typhoid Vaccine in BNF
Filgrastim
- Cytotoxics: neutropenia possibly exacerbated when filgrastim given with capecitabine, fluorouracil or tegafur

Fingolimod
- Anti-arrhythmics: possible increased risk of bradycardia when fingolimod given with amiodarone, disopyramide or dronedarone
- Antidepressants: plasma concentration of fingolimod possibly reduced by St John's Wort—manufacturer of fingolimod advises avoid concomitant use
- Antiepileptics: plasma concentration of fingolimod reduced by carbamazepine
- Antifungals: plasma concentration of fingolimod increased by ketconazole
- Beta-blockers: possible increased risk of bradycardia when fingolimod given with beta-blockers
- Calcium-channel Blockers: possible increased risk of bradycardia when fingolimod given with diltiazem or verapamil

Flavonoids see Antimuscarinics

Flecainide
- Anaesthetics, Local: increased myocardial depression when anti-arrhythmics given with bupivacaine, levobupivacaine, prilocaine or ropivacaine
- Anti-arrhythmics: increased myocardial depression when anti-arrhythmics given with other anti-arrhythmics; plasma concentration of flecainide increased by amiodarone (halve dose of flecainide)
- Antidepressants: plasma concentration of flecainide increased by fluoxetine; increased risk of ventricular arrhythmias when flecainide given with fluoxetine
- Antihistamines: increased risk of ventricular arrhythmias when flecainide given with mizolastine—avoid concomitant use
- Antimalarials: avoidance of flecainide advised by manufacturer of arteether with lumefantrine (risk of ventricular arrhythmias); plasma concentration of flecainide increased by quinine
- Antimuscarinics: increased risk of ventricular arrhythmias when flecainide given with folterodine
- Antipsychotics: increased risk of ventricular arrhythmias when anti-arrhythmics that prolong the QT interval given with antipsychotics that prolong the QT interval; increased risk of arrhythmias when flecainide given with clozapine
- Antivirals: plasma concentration of flecainide possibly increased by fosamprenavir, indinavir, lopinavir and ritonavir (increased risk of ventricular arrhythmias—avoid concomitant use); increased risk of ventricular arrhythmias when flecainide given with saquinavir—avoid concomitant use; caution with flecainide advised by manufacturer of lularitrevir (risk of ventricular arrhythmias)
- Beta-blockers: increased risk of myocardial depression and bradycardia when flecainide given with beta-blockers; increased myocardial depression when anti-arrhythmics given with beta-blockers
- Calcium-channel Blockers: increased risk of myocardial depression and asystole when flecainide given with verapamil
- Diuretics: increased cardiac toxicity with flecainide if hyponatraemia occurs with acetazolamide, loop diuretics or triazoles and related diuretics
- Ulcer-healing Drugs: metabolism of flecainide inhibited by cimetidine (increased plasma concentration)

Fluoxacillin see Penicillins
Fluconazole see Antifungals, Triazole

Flucytosine
- Antifungals: renal excretion of flucytosine decreased and cellular uptake increased by amphotericin (toxicity possibly increased)
- Cytotoxics: plasma concentration of flucytosine possibly reduced by cytarabine

Fludarabine
- Antipsychotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis)
- Cytotoxics: fludarabine increases intracellular concentration of cytarabine; increased pulmonary toxicity when

Fludarabine (continued)
- Cytotoxics (continued) fludarabine given with pentostatin (unacceptably high incidence of fatalities)
- Dipyridamole: effects of fludarabine possibly reduced by dipyridamole

Fluudrocortisone see Corticosteroids

Fluorides
- Calcium Salts: absorption of fluorides reduced by calcium salts

Fluouracil
- Antibacterials: metabolism of fluorouracil inhibited by metronidazole (increased toxicity)
- Anticoagulants: fluorouracil enhances anticoagulant effect of coumarins
- Antiepileptics: fluorouracil possibly inhibits metabolism of fosphenytoin and phenytoin (increased risk of toxicity)
- Antipsychotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis)
- Fibrates: neutropenia possibly exacerbated when fluouracil given with filgrastim
- Folates: toxicity of fluorouracil increased by folinic acid—avoid concomitant use
- Lipoglitazin: neutropenia possibly exacerbated when fluorouracil given with lipoglitazin
- Pegfilgrastim: neutropenia possibly exacerbated when fluorouracil given with pegfilgrastim
- Temoporfin: increased skin photosensitivity when topical fluorouracil used with temoporfin
- Ulcer-healing Drugs: metabolism of fluorouracil inhibited by cimetidine (increased plasma concentration)

Fluoxetine see Antidepressants, SSRI
Flupenthixol see Antipsychotics
Fluphenazine see Antipsychotics
Flurazepam see Anxiolytics and Hypnotics
Flurbiprofen see NSAIDs

Flutamide
- Anticoagulants: flutamide enhances anticoagulant effect of coumarins

Fluticasone see Corticosteroids
Fluvastatin see Statins
Fluvoxamine see Antidepressants, SSRI

Folates
- Aminosaliclyates: absorption of folic acid possibly reduced by sulphasalazine
- Antacids: absorption of folic acid possibly reduced by antacids (manufacturer of folic acid advises give at least 2 hours apart)
- Antiepileptics: folates possibly reduce plasma concentration of fosphenytoin, phenobarbital, phenytoin and primidone
- Cytotoxics: folic acid increases toxicity of capecitabine, fluorouracil and tegafur—avoid concomitant use; avoidance of folates advised by manufacturer of raltitrexed

Folic Acid see Folates
Folinic Acid see Folates

Fondaparinux
- Analgesics: increased risk of haemorrhage when anticoagulants given with intravenous diclofenac (avoid concomitant use, including low-dose heparins); increased risk of haemorrhage when anticoagulants given with ketorolac (avoid concomitant use, including low-dose heparins)
- Anticoagulants: increased risk of haemorrhage when other anticoagulants given with apixaban, dabigatran and rivaroxaban (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)

Formoterol see Sympathomimetics, Beta2
Fosamprenavir
Note Fosamprenavir is a prodrug of amprenavir
- Analgesics: fosamprenavir reduces plasma concentration of methadone
- Anti-arrhythmics: fosamprenavir possibly increases plasma concentration of amiodarone, flecainide and propafenone (increased risk of ventricular arrhythmias—
Fosamprenavir
- Anti-arrhythmics (continued)
  avoid concomitant use; fosamprenavir possibly increases plasma concentration of • LIDOCAINE—avoid concomitant use
- Antibacterials: fosamprenavir increases plasma concentration of • RIFAPTIN (reduce dose of rifapentin); plasma concentration of fosamprenavir significantly reduced by • RIFAMPICIN—avoid concomitant use; avoidance of concomitant fosamprenavir in severe renal and hepatic impairment advised by manufacturer of • TELITHROMYCIN
- Anti-coagulants: avoidance of fosamprenavir advised by manufacturer of APIXABAN and RIVAROXABAN; fosamprenavir may enhance or reduce anticoagulant effect of COUMARINS
- Antidepressants: plasma concentration of fosamprenavir reduced by • ST JOHN’S WORT—avoid concomitant use
- Antiepileptics: plasma concentration of fosamprenavir possibly reduced by • CARBAMAZEPINE, PHENOBARBITAL and PRIMIDONE
- Anti-fungals: fosamprenavir increases plasma concentration of • KETOCONAZOLE (also plasma concentration of fosamprenavir possibly increased); plasma concentration of both drugs may increase when fosamprenavir given with • ITRACONAZOLE; fosamprenavir possibly reduces plasma concentration of • POSANOCAZOLE
- Antimalarials: caution with fosamprenavir advised by manufacturer of ARTEMETHER WITH LUMEFANTRINE; fosamprenavir possibly increases plasma concentration of • QUININE (increased risk of toxicity)
- Antimuscarinics: avoidance of fosamprenavir advised by manufacturer of DARIFENACIN and TOLTERODINE
- Antivirals: fosamprenavir possibly increases plasma concentration of • ARIPIZOLE (reduce dose of aripiprazole—consult aripiprazole product literature); fosamprenavir increases plasma concentration of • PIMOZIDE (increased risk of ventricular arrhythmias—avoid concomitant use); fosamprenavir possibly increases plasma concentration of • QUETIAPINE—manufacturer of quetiapine advises avoid concomitant use
- Antivirals: manufacturer of fosamprenavir advises avoid concomitant use with • BOCEPREVIR and • RALTEGRAVIR; fosamprenavir reduces plasma concentration of • DULUTEGRAVIR; plasma concentration of fosamprenavir increased by • ETARIVIRINE (consider reducing dose of fosamprenavir); plasma concentration of fosamprenavir reduced by • LOPINAVIR, effect on lopinavir plasma concentration not predictable—avoid concomitant use; plasma concentration of fosamprenavir reduced by • MARAVIROC—avoid concomitant use; plasma concentration of fosamprenavir possibly reduced by • NEVIRAPINE—avoid unboosted fosamprenavir; manufacturers advise avoid concomitant use of fosamprenavir with • TELAPREVIR; plasma concentration of fosamprenavir reduced by • TIPRANAVIR
- Anxiolytics and Hypnotics: fosamprenavir possibly increases plasma concentration of • MIDAZOLAM (risk of prolonged sedation)—avoid concomitant use of oral midazolam)
- Avanafil: fosamprenavir possibly increases plasma concentration of • AVANAFIL—see under Avanafil, p. 698
- Ciclosporin: fosamprenavir increases plasma concentration of • CICLOSPORIN
- Cytotoxics: fosamprenavir possibly increases the plasma concentration of • BOSONIN—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; fosamprenavir possibly increases the plasma concentration of • IBRUTINIB—reduce dose of ibritunib (see under ibritunib, p. 809)
- Dapoxetine: manufacturer of dapoxetine advises dose reduction when fosamprenavir given with • DAPOXETINE (see under Dapoxetine, p. 703)
- Ergot Alkaloids: increased risk of ergotism when fosamprenavir given with • ERGOTAMINE—avoid concomitant use
- Lipid-regulating Drugs: possible increased risk of myopathy when fosamprenavir given with • ATORVASTATIN; possible increased risk of myopathy when fosamprenavir given with • ROSUVASTATIN—manufacturer of rosuvastatin advises avoid concomitant use; possible increased risk of myopathy when fosamprenavir given with • SIMVASTATIN—avoid concomitant

Fosamprenavir
- Lipid-regulating Drugs (continued)
  use; avoidance of fosamprenavir advised by manufacturer of • LOMITAPIDE (plasma concentration of lomitapide possibly increased)
- Orlistat: absorption of fosamprenavir possibly reduced by • ORLISTAT
- Ranolazine: fosamprenavir possibly increases plasma concentration of • RANOLAZINE—manufacturer of ranolazine advises avoid concomitant use
- Sildenafil: fosamprenavir possibly increases plasma concentration of • SILDENAFIL
- Tacrolimus: fosamprenavir increases plasma concentration of • TACROLIMUS
- Vardenafil: fosamprenavir possibly increases plasma concentration of • VARDENAFIL

Fosaprepitant
- Antibacterials: plasma concentration of fosaprepitant possibly increased by • CLARITHROMYCIN and • TELITHROMYCIN; plasma concentration of fosaprepitant reduced by • RIFAMPICIN
- Anti-coagulants: fosaprepitant possibly reduces anticoagulant effect of • WARFARIN
- Antidepressants: manufacturer of fosaprepitant advises avoid concomitant use with • ST JOHN’S WORT
- Anti-diabetics: fosaprepitant reduces plasma concentration of • TOLBUTAMIDE
- Antiepileptics: plasma concentration of fosaprepitant possibly reduced by • CARBAMAZEPINE, PHENOBARBITAL, PHENYTOIN and • PRIMIDONE
- Anti-fungals: plasma concentration of fosaprepitant increased by • KETOCONAZOLE
- Antipsychotics: manufacturer of fosaprepitant advises avoid concomitant use with • PIMOZIDE
- Antivirals: plasma concentration of fosaprepitant possibly increased by • RITONAVIR
- Anxiolytics and Hypnotics: fosaprepitant increases plasma concentration of • MIDAZOLAM (risk of prolonged sedation)
- Avanafil: fosaprepitant possibly increases plasma concentration of • AVANAFIL
- Calcium-channel Blockers: plasma concentration of both drugs may increase when fosaprepitant given with • DILTIAZEM
- Corticosteroids: fosaprepitant inhibits metabolism of • DEXAMETHASONE and • METHYLPHENIDYLINE (reduce dose of dexamethasone and methylphenidylsline)
- Cytotoxics: fosaprepitant possibly increases the plasma concentration of • BOSUTINIB—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; fosaprepitant possibly increases plasma concentration of • IBRUTINIB
- Lipid-regulating Drugs: separating administration from fosaprepitant by 12 hours advised by manufacturer of • LOMITAPIDE
- Oestrogens: fosaprepitant possibly causes contraceptive failure of hormonal contraceptives containing • OSTREGENS (alternative contraception recommended)
- Progestogens: fosaprepitant possibly causes contraceptive failure of hormonal contraceptives containing • PROGESTEGENS (alternative contraception recommended)

Foscarnet
- Pentamidine isethionate: increased risk of hypocaemia when foscarnet given with • PARENTERAL • PENTAMIDINE ISETHONATE

Fosfomycin
- Metoclopramide: plasma concentration of fosfomycin reduced by • METOCLOPRAMIDE
- Vaccines: antibacterials inactivate • ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF

Fosinopril see ACE Inhibitors

Fosphenytoin
- Alcohol: plasma concentration of fosphenytoin possibly reduced by chronic heavy consumption of • ALCOHOL
- Aminophylline: plasma concentration of both drugs reduced when fosphenytoin given with • AMINOPHYLLINE
- Analgesics: excretion of fosphenytoin possibly reduced by • ACETAMIN (increased risk of toxicity); fosphenytoin possibly
Interactions

Fosphenytoin

- Analgesics (continued)
  - accelerates metabolism of FENTANYL (reduced effect); fosphenytoin accelerates metabolism of METHADONE (reduced effect and risk of withdrawal effects); fosphenytoin possibly increases risk of FENTHION toxicity; effects of fosphenytoin enhanced by ASPIRIN; fosphenytoin possibly accelerates metabolism of PARACETAMOL (also isolated reports of hepatotoxicity)

- Anthelmintics: fosphenytoin reduces plasma concentration of:
  - ALBENDAZOLE and PRAZIQUANTEL—consider increasing albendazole and praziquantel dose when given for systemic infections; plasma concentration of fosphenytoin possibly increased by LEVAMISOLE

- Anti-arrhythmics: metabolism of fosphenytoin inhibited by:
  - AMIODARONE (increased plasma concentration); fosphenytoin reduces plasma concentration of DISOPRIMADI; fosphenytoin possibly reduces plasma concentration of:
    - DRONEDARONE—avoid concomitant use

- Antibacterials: metabolism of fosphenytoin inhibited by:
  - CLARITHROMYCIN (increased plasma concentration); metabolism of fosphenytoin possibly inhibited by:
    - METRONIDAZOLE (increased plasma concentration); plasma concentration of fosphenytoin increased or decreased by:
      - CIPROFLOXACIN; fosphenytoin accelerates metabolism of:
        - DOXYCYCLINE (reduced plasma concentration); fosphenytoin possibly reduces plasma concentration of:
          - BEDAQUILINE—manufacturer of bedaquiline advises avoid concomitant use; plasma concentration of fosphenytoin increased by:
            - CHLORAMPHENICOL (increased risk of toxicity); metabolism of fosphenytoin possibly inhibited by:
              - SONIDAZO (increased risk of toxicity); metabolism of fosphenytoin accelerated by:
                - RIFAMYCINS (reduced plasma concentration); plasma concentration of fosphenytoin possibly increased by:
                  - SULFONAMIDES; fosphenytoin reduces plasma concentration of:
                    - TELITHROMYCIN (avoid during and for 2 weeks after fosphenytoin); plasma concentration of fosphenytoin increased by:
                      - TRIMETHOPRIM (also increased antifolate effect)

- Anticoagulants: fosphenytoin possibly reduces plasma concentration of:
  - APYXABAN; fosphenytoin accelerates metabolism of:
    - COUMARINS (possibility of reduced anticoagulant effect, but enhancement also reported); fosphenytoin possibly reduces plasma concentration of:
      - DARIGRAZIN—manufacturer of darigrazin advises avoid concomitant use; fosphenytoin possibly reduces plasma concentration of:
        - RIVAROXABAN—manufacturer of rivaroxaban advises monitor for signs of thrombosis

- Antidepressants: plasma concentration of fosphenytoin increased by:
  - FLUDEXTORIN; fosphenytoin reduces plasma concentration of:
    - MIASERRIN, MIRTAZAPINE and PAROXETINE; plasma concentration of fosphenytoin possibly increased by:
      - SERTRALINE, also plasma concentration of sertraline possibly reduced; anticonvulsant effect of:
        - antiepileptics possibly antagonised by:
          - MADOS and TRICYCLIC-RELATED ANTIPSYCHOTICS (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by:
            - SSRIS and TRICYCLICS (convulsive threshold lowered); plasma concentration of fosphenytoin possibly reduced by:
              - ST JOHN'S WORT—avoid concomitant use; fosphenytoin possibly reduces plasma concentration of:
                - TRICYCLICS

- Antidiabetics: plasma concentration of fosphenytoin transiently increased by:
  - TOLBUTAMIDE (possibility of toxicity)

- Antiepileptics: plasma concentration of both drugs often reduced when fosphenytoin given with:
  - CARBAMAZEPINE, also plasma concentration of:
    - ESLICARBZEPINE, also plasma concentration of fosphenytoin may be increased;
      - fosphenytoin reduces plasma concentration of:
        - ESICARBZEPINE, also plasma concentration of fosphenytoin increased;
          - plasma concentration of fosphenytoin possibly increased by:
            - ETHOSUXIMIDE possibly reduced; fosphenytoin reduces plasma concentration of:
              - LAMOTRIGINE, TIAGABINE and ZONISAMIDE; plasma concentration of fosphenytoin increased by:
                - OXCARBAZEPINE, also plasma concentration of an active metabolite of oxcarbazepine reduced; fosphenytoin reduces
Fosphenytoin (continued)

- Calcium-channel Blockers: fosphenytoin reduces effects of
  feleodipine and verapamil; avoidance of fosphenytoin advised by manufacturer of isradipine; avoidance of fosphenytoin advised by manufacturer of nimodipine (plasma concentration of nimodipine possibly reduced); plasma concentration of fosphenytoin increased by diltiazem but also effect of diltiazem reduced
- Cardiovascular Extract: fosphenytoin possibly reduces plasma concentration of abiretroplina—manufacturer of abiretroplina advises reduced concomitant use; fosphenytoin possibly accelerates metabolism of toremifene
- SHTS-receptor Antagonists: fosphenytoin accelerates metabolism of ondasertorin (reduced effect)
- Pancitria: fosphenytoin possibly reduces plasma concentration of vacatorin—manufacturer of vacatorin advises avoid concomitant use

Fosphenytoin (continued)

- Leflunomide: plasma concentration of fosphenytoin possibly increased by leflunomide
- Lipid-regulating Drugs: absorption of fosphenytoin possibly reduced by colesevelam; combination of fosphenytoin with fluvastatin may increase plasma concentration of either drug (or both)
- Lithium: neurotoxicity may occur when fosphenytoin given with lithium without increased plasma concentration of lithium
- Macitentan: avoidance of fosphenytoin advised by manufacturer of macitentan
- Modafinil: plasma concentration of fosphenytoin possibly increased by modafinil
- Muscle Relaxants: long-term use of fosphenytoin reduces effects of non-depolarising muscle relaxants (but acute use of fosphenytoin might increase effects of non-depolarising muscle relaxants)
- Oestrogens: fosphenytoin accelerates metabolism of
  oestrogens (reduced contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF)
- Orlistat: possible increased risk of convulsions when antiepileptics given with orlistat
- Progestogens: fosphenytoin accelerates metabolism of
  progestogens (reduced contraceptive effect with combined oral contraceptives, progestogen-only oral contraceptives, contraceptive patches, vaginal rings, etonogestrel-releasing implant, and emergency hormonal contraception—see Contraceptive Interactions in BNF)
- Roluplumast: fosphenytoin possibly inhibits effects of roluplumast (manufacturer of roluplumast advises avoid concomitant use)
- Sulfonpyrazone: plasma concentration of fosphenytoin increased by sulfinpyrazone
- Symptomimetics: plasma concentration of fosphenytoin increased by methylphenidate
- Tacrolimus: fosphenytoin reduces plasma concentration of tacrolimus, also plasma concentration of fosphenytoin possibly increased
- Theophylline: plasma concentration of both drugs reduced when fosphenytoin given with theophylline
- Thyroid Hormones: fosphenytoin accelerates metabolism of
  thyroid hormones (may increase requirements in hypothyroidism), also plasma concentration of fosphenytoin possibly increased
- Tbilonol: fosphenytoin accelerates metabolism of tibolone
- Ticagrelor: fosphenytoin possibly reduces plasma concentration of ticagrelor
- Ulcer-healing Drugs: metabolism of fosphenytoin inhibited by
  cimetidine (increased plasma concentration); effects of fosphenytoin enhanced by esomeprazole; effects of fosphenytoin possibly enhanced by omeprazole; absorption of fosphenytoin reduced by sucralfate
- Ulipristal: avoidance of fosphenytoin advised by manufacturer of ulipristal (contraceptive effect of ulipristal possibly reduced)
- Vaccines: effects of fosphenytoin enhanced by influenza vaccine
- Vitamins: fosphenytoin possibly increases requirements for alfalcaldidol, calcitriol, colecalciferol, dihydrotachysterol, ergocalciferol, paricalcitol or vitamin D

Fosaprepitant see SH7—receptor Agonists (under HT)
Furosemide see Diuretics
Fusidic Acid

- Antivirals: plasma concentration of both drugs increased when fusidic acid given with ritonavir—avoid concomitant use; plasma concentration of both drugs may increase when fusidic acid given with saquinavir
- Lipid-regulating Drugs: risk of myopathy and rhabdomyolysis when fusidic acid given with statins—avoid concomitant use and for 7 days after last fusidic acid dose
- Sugammadex: fusidic acid possibly reduces response to sugammadex
**Fusidic Acid** (continued)
- Vaccines: antibacterials inactivate **oral typhoid vaccine**—see under Typhoid Vaccine in BNF

**Gabapentin**
- Analgesics: bioavailability of gabapentin increased by **anticonvulsants**
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by **MAOIs** and **tricyclic-related antidepressants** (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by **SSRIs** and **tricyclics** (convulsive threshold lowered)
- Antimalarias: anticonvulsant effect of antiepileptics antagonised by **antipsychotics** (convulsive threshold lowered)
- Orlistat: possible increased risk of convulsions when antiepileptics given with **orlistat**

**Galcantamine** see Parasympathomimetics

**Ganciclovir**
- **NOTE**: Increased risk of myelosuppression with other myelosuppressive drugs—consult product literature
- Antibacterials: increased risk of convulsions when ganciclovir given with **imipenem with cilastatin**
- Antivirals: ganciclovir possibly increases plasma concentration of **didanosine**; profound myelosuppression when ganciclovir given with **zidovudine** (if possible avoid concomitant administration, particularly during initial ganciclovir therapy)
- MycopHENolate: plasma concentration of ganciclovir possibly increased by **mycophenolate**, also plasma concentration of inactive metabolite of mycophenolate possibly increased
- Tacrolimus: possible increased risk of nephrotoxicity when ganciclovir given with **tacrolimus**

**Gefitinib**
- Antibacterials: plasma concentration of gefitinib reduced by **rifampicin**—avoid concomitant use
- Anticoagulants: gefitinib possibly enhances anticoagulant effect of **warfarin**
- Antidepressants: manufacturer of gefitinib advises avoid concomitant use with **st john’s wort**
- Antiepileptics: manufacturer of gefitinib advises avoid concomitant use with carbamazepine, fosphenytoin, phenobarbital, phenytoin and primidone
- Antifungals: plasma concentration of gefitinib increased by **itraconazole**
- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)
- Antiretrovirals: avoidance of gefitinib advised by manufacturer of **boceprevir**
- Ulcer-healing Drugs: plasma concentration of gefitinib reduced by **ranitidine**

**Gemcitabine**
- Anticoagulants: gemcitabine possibly enhances anticoagulant effect of **warfarin**
- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)

**Gentamicin** see Aminoglycosides

**Gestodene** see Progestogens

**Glibenclamide** see Antidiabetics

**Gliclazide** see Antidiabetics

**Glimepiride** see Antidiabetics

**Glipizide** see Antidiabetics

**Glucosamine**
- Anticoagulants: glucosamine enhances anticoagulant effect of **warfarin** (avoid concomitant use)

**Glyceril Trinitrate** see Nitrates

**Glycopyronium** see Antimuscarinics

**Golimumab** (continued)
- Anakinra: avoid concomitant use of golimumab with **anakinra**
- Antipsychotics: avoid concomitant use of cytotoxics with **clozapine** (increased risk of agranulocytosis)
- Vaccines: risk of generalised infections when monoclonal antibodies given with live **vaccines**—avoid concomitant use

**Granisetron** see 5HT3-receptor Antagonists (under HT)

**Grapefruit Juice**
- Alcohol: grapefruit juice reduces plasma concentration of **aliskiren**—avoid concomitant use
- Antiarrhythmics: grapefruit juice increases plasma concentration of active metabolite of **albendazole**; grapefruit juice increases plasma concentration of **pradaxa**—avoid concomitant use
- Antidepressants: grapefruit juice possibly increases plasma concentration of **sertraline**
- Antihistamines: grapefruit juice reduces plasma concentration of **bilstain**
- Antimalarials: grapefruit juice possibly increases plasma concentration of **artemether with lumefantrine**; avoidance of grapefruit juice advised by manufacturer of **artemimol with piperaquine**
- Antipsychotics: avoidance of grapefruit juice advised by manufacturer of **lurasidone and pimozone**; grapefruit juice possibly increases plasma concentration of **quetiapine**—manufacturer of quetiapine advises avoid concomitant use
- Antivirals: grapefruit juice possibly increases plasma concentration of **efavirenz**
- Anxiolytics and Hypnotics: grapefruit juice possibly increases plasma concentration of **oral midazolam**; grapefruit juice increases plasma concentration of **bispirono**
- Avanafil: grapefruit juice possibly increases plasma concentration of **avanafil**—manufacturer of avanafil advises avoid grapefruit juice for 24 hours before avanafil
- Calcium-channel Blockers: grapefruit juice possibly increases plasma concentration of **amlodipine**; grapefruit juice increases plasma concentration of **felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine and verapamila**
- Ciclosporin: grapefruit juice increases plasma concentration of **ciclosporin** (increased risk of toxicity)
- Colchicine: grapefruit juice possibly increases risk of **colchicine** toxicity
- Corticosteroids: grapefruit juice increases plasma concentration of **oral budesonide**—avoid concurrent use or separate administration by as much as possible and consider reducing oral budesonide dose
- Cytotoxics: grapefruit juice possibly increases plasma concentration of **axitinib, cabozantinib and ponatinib**; grapefruit juice possibly increases the plasma concentration of **bosutinib**—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; grapefruit juice possibly increases plasma concentration of **crizotinib** and **vinflunine**—manufacturer of crizotinib and vinflunine advises avoid concomitant use; avoidance of grapefruit juice advised by manufacturer of **dasatinib** (plasma concentration of dasatinib possibly increased); avoidance of grapefruit juice advised by manufacturer of **everolimus, ibrutinib**
- Lapatinib, nilotinib and pazopanib
- Ivabradine: grapefruit juice increases plasma concentration of **ivabradine**
- Ivaftor: grapefruit juice possibly increases plasma concentration of **ivaftor**—manufacturer of ivafator advises avoid concomitant use
- Lipid-regulating Drugs: grapefruit juice possibly increases plasma concentration of **atorvastatin**; grapefruit juice increases plasma concentration of **simvastatin**—avoid concomitant use; avoidance of grapefruit juice advised by manufacturer of **lomitapide**
- Pirfenidone: avoidance of grapefruit juice advised by manufacturer of **pirfenidone**
Grapefruit Juice (continued)
- Ranolazine: grapefruit juice possibly increases plasma concentration of RANOLAZINE — manufacturer of ranolazine advises avoid concomitant use
- Sildenafil: grapefruit juice possibly increases plasma concentration of SILDENAFIL
- Sirolimus: grapefruit juice increases plasma concentration of SIROLIUMS — avoid concomitant use
- Tacrolimus: grapefruit juice increases plasma concentration of TACROLIMUS
- Tadalafil: grapefruit juice possibly increases plasma concentration of TADALAFIL
- Tolvaptan: grapefruit juice increases plasma concentration of TOLVAPTAN — avoid concomitant use
- Vardenafil: grapefruit juice possibly increases plasma concentration of VARDENAFIL — avoid concomitant use

Griseofulvin
- Alcohol: griseofulvin possibly enhances effects of ALCOHOL
- Anticoagulants: griseofulvin reduces anticoagulant effect of COUMARINS
  - Antiepileptics: absorption of griseofulvin reduced by PHENOBARBITAL and PHENYTOIN (reduced effect)
  - Cimetidine: griseofulvin possibly reduces plasma concentration of CICLOSPORIN
  - Oestrogens: anecdotal reports of contraceptive failure and menstrual irregularities when griseofulvin given with OESTROGENS
  - Progestogens: anecdotal reports of contraceptive failure and menstrual irregularities when griseofulvin given with PROGESTOGENS

Guanethidine
- see Adrenergic Neurone Blockers

Haemophilus Vaccine
- see Vaccines

Haloperidol
- see Antipsychotics

Heparin
- see Heparins

Heparins
- ACE inhibitors: increased risk of hyperkalaemia when heparins given with ACE INHIBITORS
- Alikiren: increased risk of hyperkalaemia when heparins given with ALIKIREN
- Analgesics: possible increased risk of bleeding when heparins given with NSAIDS; increased risk of haemorrhage when anticoagulants given with intravenous DICLOFENAC (avoid concomitant use, including low-dose heparins); increased risk of haemorrhage when anticoagulants given with KETOROLAC (avoid concomitant use, including low-dose heparins); anticoagulant effect of heparins enhanced by ASPIRIN and ANGIOTENSIN-ll Receptor Antagonists: increased risk of hyperkalaemia when heparins given with ANGIOTENSIN-ll RECEPTOR ANTAGONISTS
- Anticoagulants: increased risk of haemorrhage when other anticoagulants given with APIXABAN, DABIGATRAN and RIVAROXABAN (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)
- Clopidogrel: increased risk of bleeding when heparins given with CLOPIDOGREL
- Dipyridamole: anticoagulant effect of heparins enhanced by DIPYRIDAMOLE
- Iloprost: anticoagulant effect of heparins possibly enhanced by ILOPROST
- Nitrites: anticoagulant effect of heparins reduced by infusion of GLYCERYL TRINITRATE

Hepatitis Vaccines
- see Vaccines

Histamine (continued)
- Antimalarials: manufacturer of histamine advises avoid concomitant use with ANTIMALARIALS
- Antipsychotics: effects of histamine theoretically antagonised by ANTIPSYCHOTICS — manufacturer of histamine advises avoid concomitant use
- Antihistamines: effects of histamine theoretically antagonised by ANTIHISTAMINES — manufacturer of histamine advises avoid concomitant use

Histamine H2-antagonists
- Alpha-blockers: cimetidine and ranitidine antagonise effects of TOLAZOLINE
- Aminophylline: cimetidine inhibits metabolism of AMINOPHYLLINE (increased plasma concentration)
- Analgesics: cimetidine inhibits metabolism of OPIOID ANALGESICS (increased plasma concentration)
- Anthelmintics: cimetidine possibly enhances effects of ALBENDAZOLE; cimetidine possibly inhibits metabolism of MEBENDAZOLE (increased plasma concentration); cimetidine increases plasma concentration of PRAZIQUANTEL
- Anti-arrhythmics: cimetidine increases plasma concentration of AMIODARONE and PROPafenone; cimetidine inhibits metabolism of FLECAINIDE (increased plasma concentration); cimetidine increases plasma concentration of LIDOCAINE (increased risk of toxicity)
- Antibacterials: cimetidine increases plasma concentration of ERYTHROMYCIN (increased risk of toxicity, including deafness); cimetidine inhibits metabolism of METRONIDAZOLE (increased plasma concentration); metabolism of cimetidine accelerated by RIFAMPICIN (reduced plasma concentration)
- Anticoagulants: cimetidine inhibits metabolism of COUMARINS (enhanced anticoagulant effect)
- Antidepressants: cimetidine increases plasma concentration of CITALOPRAM, ESCITALOPRAM, MIRTAZAPINE and SERTRALINE; cimetidine inhibits metabolism of AMITRIPTYLINE, DOXEPIN, IMIPRAMINE and NORTRIPTYLINE (increased plasma concentration); cimetidine increases plasma concentration of MOXOLEMIDE (halve dose of moxolamide); cimetidine possibly increases plasma concentration of TOLAZOLINE; cimetidine inhibits metabolism of lithium (increased plasma concentration); cimetidine enhances hypoglycaemic effect of SULfonylureas
- Antiepileptics: cimetidine inhibits metabolism of CARBAMAZEPINE, FOSFOHENOTOIN, PHENYTOIN, SODIUM VALPROATE and VALPROIC ACID (increased plasma concentration)
- Antifungals: histamine H2—antagonists reduce absorption of ITRACONAZOLE and KETOCONAZOLE; cimetidine reduces plasma concentration of POSaconazole — manufacturer of posaconazole suspension advises avoid concomitant use; famotidine, nizatidine and ranitidine possibly reduce plasma concentration of POSaconazole — manufacturer of posaconazole suspension advises avoid concomitant use; cimetidine increases plasma concentration of TELFENACINE
- Antihistamines: manufacturer of loratadine advises cimetidine possibly increases plasma concentration of LORATADINE; cimetidine increases plasma concentration of HYDROXYZINE
- Antimalarials: avoidance of cimetidine advised by manufacturer of ARTEMETHER with LUMEFANTRINE; cimetidine inhibits metabolism of CHLOROQUINE, HYDROXYCHLOROQUINE and QUININE (increased plasma concentration)
- Antipsychotics: cimetidine possibly enhances effects of ANTIPSYCHOTICS, CHLORPROMAZINE and CLOzapine
- Antivirals: manufacturer of atazanavir advises adjust doses of both drugs when cimetidine and nizatidine given with ATAZANAVIR (adjust doses of both drugs—consult atazanavir product literature); famotidine and ranitidine reduce the plasma concentration of ATAZANAVIR (adjust doses of both drugs—consult atazanavir product literature); famotidine increases plasma concentration of ATAZANAVIR

Appendix 1 Interactions 1199
Histamine H₂-antagonists
- Antivirals (continued)
concentration of Raltegravir; avoidance of histamine H₂-antagonists for 12 hours before or 4 hours after Rilpivirine advised by manufacturer of rilpivirine—consult product literature; cimetidine possibly increases plasma concentration of Saquinavir
  "Anxiolytics and Hypnotics: cimetidine inhibits metabolism of Benzodiazepines, Clomethiazole and Zaleplon (increased plasma concentration); cimetidine increases plasma concentration of MELATONIN"
- Beta-blockers: cimetidine increases plasma concentration of Labetalol, Metoprolol and Propranolol; cimetidine possibly increases plasma concentration of Oral Timolol
- Caffeine citrate: cimetidine increases plasma concentration of Caffeine
- Calcium-channel Blockers: cimetidine possibly inhibits metabolism of Calcium-channel blockers (increased plasma concentration); cimetidine increases plasma concentration of Sradipine (halve dose of isradipine)
- Ciclosporin: cimetidine possibly increases plasma concentration of Ciclosporin
- Clopidogrel: cimetidine possibly reduces antiplatelet effect of Clopidogrel
- Cytostatics: cimetidine possibly enhances myelosuppressive effects of Carmustine and Lomustine; cimetidine reduces plasma concentration of Doxorubicin; cimetidine increases plasma concentration of Epirubicin; cimetidine inhibits metabolism of Capecitabine, Fluorouracil and Tegafur (increased plasma concentration); famotidine possibly reduces plasma concentration of Dasatinib; avoidance of cimetidine, famotidine and nizatidine advised by manufacturer of Erlotinib; ranitidine reduces plasma concentration of Erlotinib—manufacturer of erlotinib advises give at least 2 hours before or 10 hours after ranitidine; ranitidine reduces plasma concentration of Gefitinib; histamine H₂-antagonists possibly reduce absorption of Lapatinib; histamine H₂-antagonists possibly reduce absorption of Pazopanib—manufacturer of pazopanib advises give at least 2 hours before or 10 hours after histamine H₂-antagonists
- Dopaminergics: cimetidine reduces excretion of Pramipexole (increased plasma concentration)
- Ergot Alkaloids: increased risk of ergotism when cimetidine given with Ergotamine—avoid concomitant use
- Famipridine: avoidance of cimetidine advised by manufacturer of Famipride
- Histamine: histamine H₂-antagonists theoretically antagonise effects of Histamine—manufacturer of histamine advises avoid concomitant use
- Hormone Antagonists: absorption of cimetidine possibly delayed by Octreotide
- SHT₁-receptor Agonists: cimetidine inhibits metabolism of Zolmitriptan (reduce dose of zolmitriptan)
- Lipid-regulating Drugs: separating administration from cimetidine and ranitidine by 12 hours advised by manufacturer of Lomitapide
- Roflumilast: cimetidine inhibits the metabolism of Roflumilast
- Sildenafil: cimetidine increases plasma concentration of Sildenafil—consider reducing dose of sildenafil for erectile dysfunction
- Sympathomimetics: cimetidine possibly inhibits metabolism of Dobutamine
- Theophylline: cimetidine inhibits metabolism of Theophylline (increased plasma concentration)
- Thyroid Hormones: cimetidine reduces absorption of Levothyroxine

Hormone Antagonists see Antimuscarinics

Hormone Antagonists see Abiraterone, Bicalutamide, Danazol, Dutasteride, Enzalutamide, Exemestane, Flu tamide, Lane reotide, Octreotide, Pasireotide, Tamoxifen, and Toremifene

SHT₁-receptor Agonists
- Antibacterials: plasma concentration of eletriptan increased by Clarithromycin and Erythromycin (risk of toxicity)
### Interactions

<table>
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<tr>
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#### Hydrochlorothiazide
See Diuretics

#### Hydrocortisone
See Corticosteroids

#### Hydroflumethiazide
See Diuretics

#### Hydromorphone
See Opioid Analgesics

#### Hydrotalcite
See Antacids

#### Hydroxocobalamin
- Antibacterials: response to hydroxocobalamin reduced by Chloramphenicol

#### Hydroxyaminophenol

#### Hydroxybenzoxazine

#### Hydroxychloroquine
- Adsorbs: absorption of hydroxychloroquine reduced by
  - KaoLyn

#### Hydroxyzine
See Antihistamines

#### Ibrutinib
- Anti-arrrhythmics: plasma concentration of ibrutinib possibly
  - Increased by CYP3A4 inhibitors
  - Decreased by CYP3A4 inducers
- Antivirals: plasma concentration of ibrutinib possibly
  - Increased by
  - Arenaviruses
  - Bunyaviruses
  - Filoviruses
  - Orthomyxoviruses
  - Picornaviruses
  - Reoviruses
  - Retroviruses
  - Sendaviruses
  - Togaviruses
  - Thermoviruses
  - Coronaviruses

#### Iloprost
See Prostanoids

#### Iloprost
See Prostanoids

#### Iodine

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Ibosafamide (continued)

- Antifungals: metabolism of ibosafamide inhibited by KETOCONAZOLE.
- Antipsychotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis).
- Cytotoxics: increased risk of toxicity when ibosafamide given with cisplatin.

Iloprost

- Analgesics: increased risk of bleeding when iloprost given with NSAIDS or ASPIRIN.
- Anticoagulants: iloprost possibly enhances anticoagulant effect of coumarins and heparins; increased risk of bleeding when iloprost given with phenindione.
- Epithelial: increased risk of bleeding when iloprost given with etipifibatide.
- Tirofiban: increased risk of bleeding when iloprost given with tirofiban.

Imatinib

- Analgesics: manufacturer of imatinib advises caution with paracetamol.
- Antibacterials: plasma concentration of imatinib reduced by rifampicin—avoid concomitant use.
- Anticoagulants: manufacturer of imatinib advises replacement of warfarin with a heparin (possibility of enhanced warfarin effect).
- Antidepressants: plasma concentration of imatinib reduced by St John’s Wort—avoid concomitant use.
- Antiepileptics: plasma concentration of imatinib reduced by carbamazepine, fosphenytoin, oxcarbazepine and phenytoin—avoid concomitant use.
- Antifungals: plasma concentration of imatinib increased by bosutinib—manufacturer of bosutinib advises replacement of ifosfamide and normal immunoglobulin; anti-d immunoglobulin might impair immune response to vacciniam might impair immune response to anti-d immunoglobulin with normal immunoglobulin; anti-d immunoglobulin might impair immune response to vac.</p>
Indinavir

Antipsychotics (continued)

- *Quetiapine*: manufacturer of quetiapine advises avoid concomitant use
- *Aripiprazole*: avoid concomitant use of indinavir with
- *Azaprazole*: plasma concentration of both drugs increased when indinavir given with *Darunavir*; absorption of indinavir reduced by *Didanosine* tablets (give at least 1 hour apart); plasma concentration of indinavir reduced by *Efavirenz* and *Nevirapine*; plasma concentration of indinavir possibly reduced by *Etravirine*—avoid concomitant use; indinavir increases plasma concentration of *Maraviroc* (consider reducing dose of maraviroc); plasma concentration of indinavir increased by *Ritonavir*; indinavir increases plasma concentration of *Saquinavir*
- *Acetaminophen*: increased risk of prolonged sedation when indinavir given with *Alprazolam*—avoid concomitant use; indinavir possibly increases plasma concentration of *Midazolam* (risk of prolonged sedation—avoid concomitant use of oral midazolam)
- *Ato伐quone*: plasma concentration of indinavir possibly reduced by *Ato伐quone*
- *Avanaflu*: indinavir possibly increases plasma concentration of *Avanafil*—manufacturer of avanafil advises avoid concomitant use
- *Bosentan*: plasma concentration of indinavir possibly reduced by *Bosentan*
- *Ciclosporin*: indinavir increases plasma concentration of *Ciclosporin*
- *Colchicine*: indinavir possibly increases risk of *Colchicine* toxicity—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- *Corticosteroids*: plasma concentration of indinavir possibly reduced by *Dexamethasone*
- *Cytosines*: indinavir possibly increases plasma concentration of *Axitinib* (reduce dose of axitinib—consult axitinib product literature); indinavir possibly increases the plasma concentration of *Bosutinib* and *Cabazitaxel*—manufacturer of bosutinib and cabazitaxel advises avoid or consider reducing dose of bosutinib and cabazitaxel; indinavir possibly increases plasma concentration of *Crizotinib* and *Everolimus*—manufacturer of crizotinib and everolimus advises avoid concomitant use; indinavir possibly increases the plasma concentration of *Ibrutinib*—reduce dose of ibrutinib (see under ibrutinib, p. 809); indinavir possibly increases plasma concentration of *Pazopanib* (reduce dose of pazopanib); indinavir possibly increases plasma concentration of *Ponatinib*—consider reducing initial dose of ponatinib (see under ponatinib, p. 814); manufacturer of ruxolitinib advises dose reduction when indinavir given with *Ruxolitinib*—consult ruxolitinib product literature; indinavir possibly increases plasma concentration of *Docetaxel*—manufacturer of docetaxel advises avoid concomitant use or consider reducing docetaxel dose
- *Ergot Alkaloids*: increased risk of ergotism when indinavir given with *Ergometrine* or *Ergotamine*—avoid concomitant use
- *SH1-Receptor Agonists*: indinavir increases plasma concentration of *Eleptrafin* (risk of toxicity)—avoid concomitant use
- *Lipid-Regulating Drugs*: possible increased risk of myopathy when indinavir given with *Atorvastatin*; possible increased risk of myopathy when indinavir given with *Rosuvastatin*—manufacturer of rosuvastatin advises avoid concomitant use; increased risk of myopathy when indinavir given with *Simvastatin* (avoid concomitant use); avoidance of indinavir advised by manufacturer of *Lomitapide* (plasma concentration of lomitapide possibly increased)
- *Orlistat*: absorption of indinavir possibly reduced by *Orlistat*
- *Ranolazine*: indinavir possibly increases plasma concentration of *Ranolazine*—manufacturer of ranolazine advises avoid concomitant use
- *Sildenafil*: indinavir increases plasma concentration of *Sildenafil*—reduce initial dose of sildenafil

Indinavir (continued)

- *Tadalafil*: indinavir possibly increases plasma concentration of *Tadalafil*
- *Vardenafil*: indinavir increases plasma concentration of *Vardenafil*—avoid concomitant use
- *Indomethacin*: see NSAIDs
- *Inodoramin*: see Alpha-blockers

Infliximab

- *Abatacept*: avoid concomitant use of infliximab with *Abatacept*
- *Anakinra*: avoid concomitant use of infliximab with *Anakinra*
- *Antipsychotics*: avoid concomitant use of infliximab with *Antipsychotics*

Interferons

- *Interferon Alfa*: see Interferons
- *Interferon Gamma*: see Interferons

Iron Salts

- *Antacids*: absorption of oral iron salts reduced by *oral Magnesium Salts* (as magnesium trisilicate)
- *Antibacterials*: oral iron salts reduce absorption of *Ciprofloxacin*, *Levofloxacin*, *Moxifloxacin* and *Ofloxacin*; oral iron salts reduce absorption of *Norfloxacin* (give at least 2 hours apart); oral iron salts reduce absorption of *Tetracyclines*, also absorption of oral iron salts reduced by *Tetracyclines*
- *Antivirals*: oral iron salts reduce absorption of *Dolutegravir*—manufacturer of dolutegravir advises give at least 2 hours before or 6 hours after oral iron salts
Iron Salts (continued)

- Bisphosphonates: oral iron salts reduce absorption of
  BISPHOSPHONATES
- Calcium Salts: absorption of oral iron salts reduced by CALCIUM SALTS
- Dopaminergic: oral iron salts possibly reduce absorption of
  CO-BENELDOPA, CO-CARELDOPA and LEVODOPA; oral iron salts reduce absorption of ENTACAPONE
- Eltrombopag: oral iron salts possibly reduce absorption of
  ELTROMOPAG (give at least 4 hours apart)
- Methyldopa: oral iron salts antagonise hypnotic effect of
  METHYLDOPA
- Mycophenolate: oral iron salts reduce absorption of
  MYCOPHENOLATE
- Penicillamine: oral iron salts reduce absorption of
  PENICILLAMINE
- Thyroid Hormones: oral iron salts reduce absorption of
  LEVOTHYROXINE (give at least 2 hours apart)
- Trientine: absorption of oral iron salts reduced by TRIENTINE
- Zinc: oral iron salts reduce absorption of ZINC, also absorption of
  oral iron salts reduced by zinc

Isocarboxazid see MAOIs
Isoflurane see Anaesthetics, General
Isomethyptene see Sympathomimetics
Isoniazid
- Aminophylline: isoniazid possibly increases plasma concentration of
  AMINOPHYLLINE
- Anaesthetics, General: increased risk of hepatotoxicity when
  isoniazid given with ISOFLURANE
- Analgesics: avoidance of isoniazid advised by manufacturer of
  PETHIDINE
- Antacids: absorption of isoniazid reduced by ANTACIDS
- Antibacterials: increased risk of hepatotoxicity when isoniazid given with
  RIFAMPICIN; increased risk of CNS toxicity when
  isoniazid given with CYCLOSERINE
- Antiepileptics: isoniazid increases plasma concentration of
  CARBAMAZEPINE (also possibly increased isoniazid
  hepatotoxicity); isoniazid inhibits metabolism of
  ETHOSUXIMIDE (increased plasma concentration and risk
  of toxicity); isoniazid possibly inhibits metabolism of
  PHENOBARBITAL and PHENTHYON (increased risk of toxicity)
- Antifungals: isoniazid possibly reduces plasma concentration of
  KETOCONAZOLE
- Anxiolytics and Hypnotics: isoniazid inhibits the metabolism of
  DIAZEPAM
- Corticosteroids: plasma concentration of isoniazid possibly reduced by
  CORTICOSTEROIDS
- Disulfiram: isoniazid possibly increases CNS effects of
  DISULFiram
- Dopaminergic: isoniazid possibly reduces effects of
  CO-BENELDOPA, CO-CARELDOPA and LEVODOPA
- Lipid-regulating Drugs: separating administration from
  isoniazid by 12 hours advised by manufacturer of
  LOMITAPIDE
- Theophylline: isoniazid possibly increases plasma concentration of
  THEOPHYLLINE
- Vaccines: antibacterials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF

Isosorbide Dinitrate see Nikrates
Isosorbide Mononitrate see Nikrates
Isotsrinoin see Betains
Isradipine see Calcium-channel Blockers
Itraconazole see Antifungals, Triazole
Ivabradine
- Anti-arrhythmics: increased risk of ventricular arrhythmias
  when ivabradine given with AMIODARONE or DISOPYRAMIDE
- Antibacterials: plasma concentration of ivabradine possibly increased by
  CLARITHROMYCIN and TELITHROMYCIN—avoid concomitant use; increased risk of ventricular arrhythmias
  when ivabradine given with ERYTHROMYCIN—avoid concomitant use
- Antiepileptics: plasma concentration of ivabradine reduced by
  ST JOHN’S WORT—avoid concomitant use
- Antifungals: plasma concentration of ivabradine increased by
  FLUCONAZOLE—avoid concomitant use; plasma concentration of ivabradine increased by
  FLUCONAZOLE—reduce initial dose of ivabradine; plasma concentration of
  ivabradine possibly increased by ITRACONAZOLE—avoid concomitant use
- Antimalarials: increased risk of ventricular arrhythmias when
  ivabradine given with MELOquine
- Antipsychotics: increased risk of ventricular arrhythmias when
  ivabradine given with PIMozide
- Antivirals: plasma concentration of ivabradine possibly increased by
  RITONAVIR—avoid concomitant use
- Beta-blockers: increased risk of ventricular arrhythmias when
  ivabradine given with SOTALOL
- Calcium-channel Blockers: plasma concentration of ivabradine
  increased by DILTIAZEM and VERAPAMIL—avoid concomitant use
- Grapefruit Juice: plasma concentration of ivabradine increased by
  GRAPEFRUIT JUICE
- Pentamidine Isethionate: increased risk of ventricular arrhythmias when
  ivabradine given with PENTAMIDINE ISETIONATE

Ivacaftor
- Antibacterials: plasma concentration of ivacaftor possibly increased by
  CLARITHROMYCIN, ERYTHROMYCIN and
  TELITHROMYCIN (see under Ivermectin, p. 257); plasma concentration of ivacaftor possibly reduced by
  RIFABUTIN—manufacturer of ivacaftor advises avoid concomitant use; plasma concentration of ivacaftor reduced by
  RIFAMPICIN—manufacturer of ivacaftor advises avoid concomitant use
- Antidepressants: plasma concentration of ivacaftor possibly reduced by
  ST JOHN’S WORT—manufacturer of ivacaftor advises avoid concomitant use
- Antiepileptics: plasma concentration of ivacaftor possibly increased by
  CARBAMAZEPINE, FOSFENOTHION,
  PHENOBARBITAL, PHENYTOIN and PRIMIDONE—manufacturer of ivacaftor advises avoid concomitant use
- Antifungals: plasma concentration of ivacaftor increased by
  FLUCONAZOLE and KETOCONAZOLE (see under Ivermectin, p. 257); plasma concentration of ivacaftor possibly increased
  by ITRACONAZOLE, POSACONAZOLE and VORICONAZOLE (see under Ivermectin, p. 257)
- Anxiolytics and Hypnotics: ivacaftor increases plasma concentration of
  MIDAZOLAM
- Cardiac Glycosides: ivacaftor increases plasma concentration of
  DIGOXIN
- Grapefruit Juice: plasma concentration of ivacaftor possibly increased by
  GRAPEFRUIT JUICE—manufacturer of ivacaftor advises avoid concomitant use
- Lipid-regulating Drugs: separating administration from
  ivacaftor by 12 hours advised by manufacturer of
  LOMITAPIDE
- Ivermectin
- Anthelmintics: plasma concentration of ivermectin possibly increased by
  LEVAMISOLE
- Anticoagulants: ivermectin possibly enhances anticoagulant
  effect of COUMARINS
- Japanese Encephalitis Vaccine see Vaccines
- Kaolin
- Analgesics: kaolin possibly reduces absorption of
  ASPRIN
- Antibacterials: kaolin possibly reduces absorption of
  TETRACYCLINES
- Antimalarials: kaolin reduces absorption of CHLOROQUINE and
  HYDROXYCHLOROQUINE
- Antipsychotics: kaolin possibly reduces absorption of
  PHENOTHIAZINES
- Ketoamine see Anaesthetics, General
- Ketoconazole see Antifungals, Imidazole
- Ketoprofen see NSAIDs
- Ketorolac see NSAIDs
- Ketotifen see Antihistamines
- Labetalol see Beta-blockers
- Lacidipine see Calcium-channel Blockers
- Lacosamide
- Antidepressants: anticonvulsant effect of antiepileptics
  possibly antagonised by MAOIs and TRICYCLIC-RELATED
  ANTIDEPRESSANTS (convulsive threshold lowered);
Interactions

Lacosamide
- Antidepressants (continued)
  - Anticonvulsant effect of antiepileptics antagonised by
    - SSRIS
  - TRICYCLICS (convulsive threshold lowered)
  - Antimalarials: anticonvulsant effect of antiepileptics antagonised by
  - ANTIPSYCHOTICS (convulsive threshold lowered)
  - Orlistat: possible increased risk of convulsions when antiepileptics given with
  - ORLISTAT

Lactulose
- Anticoagulants: lactulose possibly enhances anticoagulant effect of COUMARINS

Lamivudine
- Antibacterials: plasma concentration of lamivudine increased by
  - TRIMETHOPRIM (as co-trimoxazole)—avoid concomitant use of high-dose co-trimoxazole
- Antivirals: avoidance of lamivudine advised by manufacturer of EMTRICITABINE
- Antimyelomas: manufacturer of lamivudine advises avoid concomitant use with
  - CLADRIBINE
- Orlistat: absorption of lamivudine possibly reduced by
  - ORLISTAT

Lamotrigine
- Antibacterials: plasma concentration of lamotrigine reduced by
  - RIFAMPICIN
  - Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by
    - MAOI S
  - TRICYCLIC-RELATED ANTIDEPRESSANTS (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by
    - SSRIS
  - TRICYCLICS (convulsive threshold lowered)
  - Antiepileptics: plasma concentration of lamotrigine often reduced by
    - CARBAMAZEPINE, also plasma concentration of an active metabolite of carbamazepine sometimes raised (but evidence is conflicting); plasma concentration of lamotrigine reduced by
      - FOSPHENYTOIN, PHENOBARBITAL, PHENYTOIN and PRIMIDONE; plasma concentration of lamotrigine increased by
        - SODIUM VALPROATE and
        - VALPROIC ACID (increased risk of toxicity—reduce lamotrigine dose)
  - Antimalarials: anticonvulsant effect of antiepileptics antagonised by
    - MELOQUINE
  - Antipsychotics: anticonvulsant effect of antiepileptics antagonised by
    - ANTIPSYCHOTICS (convulsive threshold lowered)
  - Antivirals: plasma concentration of lamotrigine possibly reduced by
    - RITONAVIR
  - Oestrogens: plasma concentration of lamotrigine reduced by
    - OESTROGENS—consider increasing dose of lamotrigine
  - Orlistat: possible increased risk of convulsions when antiepileptics given with
    - ORLISTAT
  - Progestogens: plasma concentration of lamotrigine possibly increased by
    - DESGESTREL

Lanreotide
- Antidiabetics: lanreotide possibly reduces requirements for
  - ANTIDIABETICS
  - Ciclosporin: lanreotide reduces plasma concentration of
    - CICLOSPORIN

Lansoprazole
- see Proton Pump Inhibitors

Lanthanum
- Antibacterials: lanthanum possibly reduces absorption of
  - QUINOLONES (give at least 2 hours before or 4 hours after lanthanum)
- Antifungals: lanthanum possibly reduces absorption of
  - KETOCONAZOLE (give at least 2 hours apart)
- Antimalarials: lanthanum possibly reduces absorption of
  - CHLOROQUINE and HYDROXYCHLOROQUINE (give at least 2 hours apart)
  - Thyroid Hormones: lanthanum reduces absorption of
    - LEVOTHYROXINE (give at least 2 hours apart)

Lapatinib
- Antidepressants: manufacturer of lapatinib advises avoid concomitant use with
  - RIFABUTIN, RIFAMPICIN and
  - TELITHROMYCIN
  - Antidiabetics: manufacturer of lapatinib advises avoid concomitant use with
  - ST JOHN'S WORT
  - Antimalarials: manufacturer of lapatinib advises avoid concomitant use with
    - PAPAYLINDA
  - Antipsychotics: manufacturer of lapatinib advises avoid concomitant use with
    - CARBAMAZEPINE—avoid concomitant use; manufacturer of lapatinib advises avoid concomitant use with
      - FOSPHENYTOIN and
      - PHENYTOIN
  - Antifungals: plasma concentration of lapatinib increased by
    - KETOCONAZOLE—avoid concomitant use; manufacturer of lapatinib advises avoid concomitant use with
      - ITRACONAZOLE, POSACONAZOLE and VORICONAZOLE
  - Antipsychotics: avoid concomitant use of cytotoxics with
    - CLOZAPINE (increased risk of agranulocytosis); manufacturer of lapatinib advises avoid concomitant use with
      - PIMOZIDE
    - Antivirals: avoidance of lapatinib advised by manufacturer of
      - BOCEPREVIR; manufacturer of lapatinib advises avoid concomitant use with
        - RITONAVIR and SAQUINAVIR
  - Cytoxics: lapatinib increases plasma concentration of
    - PAZOPANIB; possible increased risk of neutropenia when lapatinib given with
      - DOCETAXEL; increased risk of neutropenia when lapatinib given with
        - PACLITAXEL; lapatinib increases plasma concentration of active metabolite of
          - IRINOTECAN—consider reducing dose of irinotecan
  - Grapefruit juice: manufacturer of lapatinib advises avoid concomitant use with
    - GRAPEFRUIT JUICE
  - Lipid-regulating Drugs: separating administration from lapatinib by 12 hours advised by manufacturer of
    - LOMITAPIDE
  - Ulcer-healing Drugs: absorption of lapatinib possibly reduced by
    - HISTAMINE H 2-ANTAGONISTS and PROTON PUMP INHIBITORS

Laronidase
- Antimalarials: effects of laronidase possibly inhibited by
  - CHLOROQUINE and HYDROXYCHLOROQUINE (manufacturer of laronidase advises avoid concomitant use)

Leflunomide
- NOTE: Increased risk of toxicity with other haematotoxic and hepatotoxic drugs
  - Antifungals: plasma concentration of active metabolite of leflunomide possibly increased by
    - RIFAMPICIN
  - Anticoagulants: leflunomide possibly enhances anticoagulant effect of WARFARIN
  - Antidiabetics: leflunomide possibly enhances hypoglycaemic effect of
    - TOLBUTAMIDE
  - Antiepileptics: leflunomide possibly increases plasma concentration of
    - FOSPHENYTOIN and PHENYTOIN
  - Antidepressants: leflunomide possibly increases plasma concentration of
    - HYDROXYCHLOROQUINE
- Cytoxics: risk of toxicity when leflunomide given with
  - METHOTREXATE
  - Lipid-regulating Drugs: the effect of leflunomide is significantly decreased by
    - COLESTYRAMINE (enhanced elimination)—avoid unless drug elimination desired
  - Vaccines: risk of generalised infections when leflunomide given with live
    - VACCINES—avoid concomitant use

Lenalidomide
- Antifungals: plasma concentration of lenalidomide possibly increased by
  - CLARITHROMYCIN (increased risk of toxicity)
  - Antiepileptics: plasma concentration of lenalidomide possibly increased by
    - ITRACONAZOLE and KETOCONAZOLE (increased risk of toxicity)
  - Calcium-channel Blockers: plasma concentration of lenalidomide possibly increased by
    - VERAPAMIL (increased risk of toxicity)
  - Cardiac Glycosides: lenalidomide possibly increases plasma concentration of
    - DIGOXIN
  - Ciclosporin: plasma concentration of lenalidomide possibly increased by
    - CICLOSPORIN (increased risk of toxicity)

Lercanidipine
- see Calcium–channel Blockers

Leukoatriene Receptor Antagonists
- Aminophylline: zafirlukast possibly increases plasma concentration of
  - AMINOPHYLLINE, also plasma concentration of zafirlukast reduced
- Analgesics: plasma concentration of zafirlukast increased by
  - ASPIRIN
- Antifungals: plasma concentration of zafirlukast reduced by
  - ERYTHROMYCIN
Levodopa (continued) • Buproprion: increased risk of side effects when levodopa given with BUPROPION • Calcium-channel blockers: enhanced hypotensive effect when levodopa given with CALCIUM-CHANNEL BLOCKERS • Clonidine: enhanced hypotensive effect when levodopa given with CLONIDINE • Diazoxide: enhanced hypotensive effect when levodopa given with DIAZOXIDE • Diuretics: enhanced hypotensive effect when levodopa given with DIURETICS • Dopaminergics: enhanced effects and increased toxicity of levodopa when given with SELEGILINE (reduce dose of levodopa) • Iron salts: absorption of levodopa possibly reduced by oral IRON SALTS • Memantine: effects of dopaminergics possibly enhanced by MEMANTINE • Methylphenidate: enhanced hypotensive effect when levodopa given with METHYLPREDNISOLONE • Muscle relaxants: possible agitation, confusion and hallucinations when levodopa given with BACLOFEN • Nitrates: enhanced hypotensive effect when levodopa given with NITRATES • Vasodilators: Antihypertensives: enhanced hypotensive effect when levodopa given with HYDRAZINE, MINOXYDIL or SODIUM NITROPRUSSIDE • Vitamins: effects of levodopa reduced by PYRIDOXINE when given without dopa-decarboxylase inhibitor Levofoxaclin see Quinolones Levolofolic Acid see Folicates Levomepromazine see Antipsychotics Levonorgestrel see Progestogens Levothryoxine see Thyroid Hormones Lidocaine • NOTE Interactions less likely when lidocaine used topically • Anaesthetics, local: increased myocardial depression when anti-arrhythmics given with BUPIVACAINE, LEVOBUPIVACAINE, PRilocaine or Ropivacaine • Anti-arrhythmics: increased myocardial depression with other ANTI-ARRHYTHMICS • Antipsychotics: increased risk of ventricular arrhythmias when anti-arrhythmics that prolong the QT interval given with ANTIPSYCHOTICS that prolong the QT interval • Antivirals: plasma concentration of lidocaine possibly increased by ATAZANAVIR and LOPINAVIR; plasma concentration of lidocaine possibly increased by DARUNAVIR and FOSAMPRENAVIR—avoid concomitant use; increased risk of ventricular arrhythmias when lidocaine given with SAQUNAVIR—avoid concomitant use; caution with intravenous lidocaine advised by manufacturer of TELAPREIV • Beta-blockers: increased myocardial depression when anti-arrhythmics given with BETA-BLOCKERS; possible increased risk of lidocaine toxicity when given with NADOLOL; increased risk of lidocaine toxicity when given with PROPRANOLOL • Diuretics: action of lidocaine antagonised by hydralazine caused by ACETAZOLAMIDE; LOOP DIURETICS or THIAZIDES AND RELATED DIURETICS • Muscle relaxants: neuromuscular blockade enhanced and prolonged when lidocaine given with SUXAMETHONIUM • Uter-healing drugs: plasma concentration of lidocaine increased by CIMETIDINE (increased risk of toxicity) Linagliptin see Antidiabetics Linezolid • NOTE Linezolid is a reversible, non-selective MAO inhibitor—see interactions of MAOIs • Antibacterials: plasma concentration of linezolid reduced by RIFAMPICIN (possible therapeutic failure of linezolid) • Vaccines: antibacterials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF Liotyroidine see Thyroid Hormones
**Lipophilic Drugs** see Colesevelam, Colestipol, Colestevam, Ezetimibe, Fibrates, Lomitapide, Nicotinic Acid, and Statins

**Liganduretics** see Antidiabetics

**Lidexamifetamine** see Symptomatomics

**Lisinopril** see ACE Inhibitors

**Lithium**
- ACE Inhibitors: excretion of lithium reduced by ACE INHIBITORS (increased plasma concentration)
- Aminophylline: excretion of lithium increased by AMINOPHYLLINE (reduced plasma concentration)
- Analgesics: excretion of lithium reduced by NSAIDS (increased risk of toxicity); excretion of lithium reduced by KETOROLAC (increased risk of toxicity)—avoid concomitant use
- Angiotensin-II Receptor Antagonists: excretion of lithium reduced by AMIODARONE (risk of ventricular arhythmias)
- Antacids: excretion of lithium increased by SODIUM BICARBONATE (reduced plasma concentration)
- Anti-arrhythmics: avoidance of lithium advised by manufacturer of AMIODARONE (risk of ventricular arrhythmias)
- Antibacterials: increased risk of lithium toxicity when given with METRONIDAZOLE
- Antidepressants: possible increased serotonergic effects when lithium given with VENLAFAXINE; increased risk of CNS effects when lithium given with SSRIS (lithium toxicity reported); risk of toxicity when lithium given with TRICYCLICS
- Anti-epileptics: neurotoxicity may occur when lithium given with CARBAMAZEPINE, PHENOTHYLAN or PHENYTOIN without increased plasma concentration of lithium; plasma concentration of lithium possibly affected by TOPIRAMATE
- Antipsychotics: increased risk of extrapyramidal side-effects and possibly neurotoxicity when lithium given with CLOzapine, FLUPENTIXOL, HALOPERIDOL, PHENOTHIAZINES; RISPERIDONE or ZUCLOPENTIXOL; possible risk of toxicity when lithium given with OLanzapine; lithium possibly increases extrapyramidal side-effects of QUETIAPINE; increased risk of extrapyramidal side-effects when lithium given with SULPIRIDE
- Anxiolytics and Hypnotics: increased risk of neurotoxicity when lithium given with CLONAZEPAM
- Calcium-channel Blockers: neurotoxicity may occur when lithium given with DILTIAZEM or VERAPAMIL without increased plasma concentration of lithium
- Cytotoxics: increased risk of ventricular arrhythmias when lithium given with ARSENIC TRIOXIDE
- Dapoxetine: possible increased risk of serotonergic effects when lithium given with DAPoxetine (manufacturer of dapoxetine advises lithium should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping lithium)
- Diuretics: excretion of lithium increased by ACETAZOLAMIDE; excretion of lithium reduced by LOOP DIURETICS and THIURAM DERIVATIVES; diuretics; excretion of lithium reduced by POTASSIUM-SPARING DIURETICS and ALDOSTERONE ANTAGONISTS (increased plasma concentration and risk of toxicity)
- SAH, reuser of lithium: possible risk of toxicity when lithium given with SUMATRIPTAN
- Methylprena: neurotoxicity may occur when lithium given with METHYLPRENA without increased plasma concentration of lithium
- Muscle Relaxants: lithium enhances effects of MUSCLE RELAXANTS; hyperkinesis caused by lithium possibly aggravated by BACLOFEN
- Parasympathomimetics: lithium antagonises effects of NEOSTIGMINE

**Lithium** (continued)
- Theophylline: excretion of lithium increased by THEOPHYLLINE (reduced plasma concentration)

**Lixisenatide** see Antidiabetics

**Lofepramine** see Antidepressants, Tricyclic

**Lofexidine**
- Alcohol: increased sedative effect when lofexidine given with ALCOHOL
- Anxiolytics and Hypnotics: increased sedative effect when lofexidine given with ANXIOLYSES AND HYPNOTICS

**Lomipstatted**
- Alcohol: manufacturer of lomitapide advises avoid concomitant use with ALCOHOL
- Anti-arrhythmics: manufacturer of lomitapide advises separating administration from AMIODARONE by 12 hours; manufacturer of lomitapide advises avoid concomitant use with DRONEDARONE (plasma concentration of lomitapide possibly increased)
- Anti-bacterials: manufacturer of lomitapide advises separating administration from AZITHROMYCIN and COPIAZINE by 12 hours; manufacturer of lomitapide advises avoid concomitant use with CLARITHROMYCIN, ERYTHROMYCIN and TELITHROMYCIN (plasma concentration of lomitapide possibly increased)
- Anticoagulants: lomitapide possibly enhances anticoagulant effect of WARFARIN
- Antidepressants: manufacturer of lomitapide advises separating administration fromFLUKETINE and FLUVAXAMINE by 12 hours
- Antidiabetics: manufacturer of lomitapide advises separating administration from LINAGLITIPIN by 12 hours
- Anti-fungals: plasma concentration of lomitapide increased by KETONACAZOLE—avoid concomitant use; manufacturer of lomitapide advises avoid concomitant use with FRIAIZOLEs (plasma concentration of lomitapide possibly increased)
- Antivirals: manufacturer of lomitapide advises avoid concomitant use with DARUNAVIR, FOSAMPRENAVIR, INDINAVIR, LOPINAVIR, RITONAVIR, SQUINAVIR, TELAPREVAR and TIPRANNRAVIR (plasma concentration of lomitapide possibly increased)
- Anxiolytics and Hypnotics: manufacturer of lomitapide advises separating administration from ALPRAZOLAM by 12 hours
- Calcium-channel Blockers: manufacturer of lomitapide advises separating administration from AMLODIPINE and LACIDIPINE by 12 hours; manufacturer of lomitapide advises avoid concomitant and with DILTIAZEM and VERAPAMIL (plasma concentration of lomitapide possibly increased)
- Ciclosporin: manufacturer of lomitapide advises separating administration from CICLOSPORIN by 12 hours
- Clostazol: manufacturer of lomitapide advises separating administration from CLOSTAZOL by 12 hours
- Cytotoxics: manufacturer of lomitapide advises separating administration from LAPATINIB, NILOTINIB and PAZOPANIB by 12 hours
- Fosaprepitant: manufacturer of lomitapide advises separating administration from FOSAPREPINT by 12 hours
- Grapefruit Juice: manufacturer of lomitapide advises avoid concomitant use with GRAPEFRUIT JUICE
- Hormone Antagonists: manufacturer of lomitapide advises separating administration from BICALUTAMIDE by 12 hours
- Ivacaftor: manufacturer of lomitapide advises separating administration from IVACAOIT by 12 hours
- Lidipid-regulating Drugs: lomitapide increases plasma concentration of ATORVASTATIN—manufacturer of lomitapide advises reduce dose of atorvastatin by half or separate administration by 12 hours; lomitapide increases plasma concentration of SIMVASTATIN (see under Simvastatin, p. 181); absorption of lomitapide possibly reduced by BILE ACID SEQUESTRANTS (gave at least 4 hours apart)
- Oestrogens: manufacturer of lomitapide advises separating administration from OESTROGENS by 12 hours
- Ranolazine: manufacturer of lomitapide advises separating administration from RANOLAZINE by 12 hours
- Tacrolimus: manufacturer of lomitapide advises separating administration from TACROLIMUS by 12 hours
- Ticagrelor: manufacturer of lomitapide advises separating administration from TICAGRELOR by 12 hours
Eltrombopag:

Corticosteroids: lopinavir possibly reduces plasma concentration of ELTROMBOPAG

Bosentan:

Corticosteroids: lopinavir possibly reduces plasma concentration of ELTROMBOPAG

Cytotoxic:

Interactions do not apply to small amounts of erythromycin used topically

Loratadine see Antihistamines

Lorazepam see Anxiolytics and Hypnotics

Losartan see Angiotensin-II Receptor Antagonists

Lurasidone see Antipsychotics

Lymecycline see Tetracyclines

Macitentan

NOTE Some manufacturers suggest taking other oral medication 1 hour before or 1 hour after macrogols to reduce possible interference with absorption

Macrolides

NOTE See also Telithromycin

Interactions do not apply to small amounts of erythromycin used topically

Amitriptyline: clarithromycin possibly increases plasma concentration of AMITRIPTYLINE; erythromycin increases plasma concentration of AMITRIPTYLINE (also erythromycin may reduce absorption of oral amitriptyline)

Analgesics: erythromycin increases plasma concentration of ALFENTANIL; clarithromycin possibly increases plasma concentration of FENTANYL

Antacids: absorption of erythromycin reduced by ANTAGICS

Anti-arrhythmics: increased risk of ventricular arrhythmias when parenteral erythromycin given with AMIODARONE—avoid concomitant use; azithromycin possibly increases plasma concentration of DISOPYRAMIDE (increased risk of toxicity); erythromycin increases plasma concentration of DISOPYRAMIDE (increased risk of toxicity); clarithromycin possibly increases plasma concentration of DISOPYRAMIDE (increased risk of toxicity); erythromycin increases plasma concentration of DRONEDARONE (increased risk of ventricular arrhythmias)—avoid concomitant use

Antibacterials: increased risk of ventricular arrhythmias when parenteral erythromycin given with MOXIFLOXACIN—avoid concomitant use; increased risk of side-effects including neutropenia when azithromycin given with rifabutin clarify that clarithromycin increases plasma concentration of RIFABUTIN (increased risk of toxicity—reduce rifabutin dose); erythromycin possibly increases plasma concentration of RIFABUTIN (increased risk of toxicity—reduce rifabutin dose); clarithromycin and erythromycin possibly increase plasma concentration of BEDAQUILINE—avoid concomitant use if clarithromycin and erythromycin given for more than 14 days; possible increased risk of ventricular arrhythmias

Lopixil

Anxiolytics and Hypnotics

Loratadine see Antihistamines

Lorazepam see Anxiolytics and Hypnotics

Losartan see Angiotensin-II Receptor Antagonists

Lurasidone see Antipsychotics

Lymecycline see Tetracyclines

Macitentan

NOTE Some manufacturers suggest taking other oral medication 1 hour before or 1 hour after macrogols to reduce possible interference with absorption

Macrolides

NOTE See also Telithromycin

Interactions do not apply to small amounts of erythromycin used topically

Amitriptyline: clarithromycin possibly increases plasma concentration of AMITRIPTYLINE; erythromycin increases plasma concentration of AMITRIPTYLINE (also erythromycin may reduce absorption of oral amitriptyline)

Analgesics: erythromycin increases plasma concentration of ALFENTANIL; clarithromycin possibly increases plasma concentration of FENTANYL

Antacids: absorption of erythromycin reduced by ANTAGICS

Anti-arrhythmics: increased risk of ventricular arrhythmias when parenteral erythromycin given with AMIODARONE—avoid concomitant use; azithromycin possibly increases plasma concentration of DISOPYRAMIDE (increased risk of toxicity); erythromycin increases plasma concentration of DISOPYRAMIDE (increased risk of toxicity); clarithromycin possibly increases plasma concentration of DISOPYRAMIDE (increased risk of toxicity); erythromycin increases plasma concentration of DRONEDARONE (increased risk of ventricular arrhythmias)—avoid concomitant use

Antibacterials: increased risk of ventricular arrhythmias when parenteral erythromycin given with MOXIFLOXACIN—avoid concomitant use; increased risk of side-effects including neutropenia when azithromycin given with rifabutin clarify that clarithromycin increases plasma concentration of RIFABUTIN (increased risk of toxicity—reduce rifabutin dose); erythromycin possibly increases plasma concentration of RIFABUTIN (increased risk of toxicity—reduce rifabutin dose); clarithromycin and erythromycin possibly increase plasma concentration of BEDAQUILINE—avoid concomitant use if clarithromycin and erythromycin given for more than 14 days; possible increased risk of ventricular arrhythmias
Macrolides
- Antibacterials (continued) when clarithromycin and erythromycin given with
  - DELAMANID; avoidance of clarithromycin and erythromycin advised by manufacturer of FIDAXOMICIN; plasma concentration of clarithromycin reduced by rifampicins
- Anticagulants: avoidance of clarithromycin advised by manufacturer of APIXABAN; clarithromycin and erythromycin enhance anticoagulant effect of COUMARINS; erythromycin possibly increases anticoagulant effect of COUMARINS; possible increased risk of bleeding when clarithromycin given with DABIGATRAN
- Antidepressants: avoidance of macrolides advised by manufacturer of REBOXETINE; avoidance of intravenous erythromycin advised by manufacturer of OTACLOPRAM and ESCITALOPRAM (risk of ventricular arrhythmias); clarithromycin possibly increases plasma concentration of TRAZODONE
- Antidiabetics: clarithromycin enhances effects of REPAGLINDINE
- Antiepileptics: clarithromycin increases plasma concentration of CARBAMAZEPINE (consider reducing dose of carbamazepine); erythromycin increases plasma concentration of CARBAMAZEPINE; clarithromycin inhibits metabolism of FOSPHENYTOIN and PHENYTOIN (increased plasma concentration); erythromycin possibly inhibits metabolism of SODIUM VALPROATE and VALPROIC ACID (increased plasma concentration)
- Antibacterials: avoidance of concomitant clarithromycin in severe renal impairment advised by manufacturer of KETOCONAZOLE; avoidance of erythromycin advised by manufacturer of FLUCONAZOLE; clarithromycin increases plasma concentration of ITRACONAZOLE
- Antihistamines: manufacturer of loratadine advises erythromycin possibly increases plasma concentration of LORATADINE; macrolides possibly inhibit metabolism of MILOZASTINE (avoid concomitant use); erythromycin inhibits metabolism of MILOZASTINE—avoid concomitant use
- Antimalarials: avoidance of macrolides advised by manufacturer of ARTEMETHER WITH LUMEFANTRINE; avoidance of macrolides advised by manufacturer of ARTENINOL WITH PIPERAQUNE (possible risk of ventricular arrhythmias)
- Antimuscarinics: erythromycin possibly increases plasma concentration of DAFENINAC; manufacturer of fosoterodine advises dose reduction when clarithromycin given with FOSTERODINE—consult product literature; avoidance of clarithromycin and erythromycin advised by manufacturer of TOLERODINE
- Antipsychotics: avoidance of macrolides advised by manufacturer of DROPERIDOL (risk of ventricular arrhythmias); increased risk of ventricular arrhythmias when parenteral erythromycin given with ZUCLOPENTHIXOL—avoid concomitant use; increased risk of ventricular arrhythmias when erythromycin given with AMISULPRIDE—avoid concomitant use; erythromycin possibly increases plasma concentration of clozapine (possible increased risk of convulsions); clarithromycin possibly increases plasma concentration of LURASIDONE—avoid concomitant use; erythromycin possibly increases the plasma concentration of LURASIDONE (see under Lurasidone, p. 515); increased risk of ventricular arrhythmias when clarithromycin given with PIMOZIDE—avoid concomitant use; possible increased risk of ventricular arrhythmias when erythromycin given with PIMOZIDE—avoid concomitant use; clarithromycin possibly increases plasma concentration of quetiapine—manufacturer of quetiapine advises avoid concomitant use; erythromycin increases plasma concentration of quetiapine—manufacturer of quetiapine advises avoid concomitant use; clarithromycin possibly increases plasma concentration of dalf lazatavir—reduce dose of dalf lazatavir (see under Dalf lazatavir, p. 544); plasma concentration of clarithromycin reduced by efavirenz, also plasma concentration of active

Macrolides
- Antivirals (continued) metabolite of clarithromycin increased; plasma concentration of clarithromycin reduced by ETARAVIRINE and NEVIRAPINE (but concentration of an active metabolite increased), also plasma concentration of etravirine and nevirapine increased; clarithromycin possibly increases plasma concentration of MARAVIROC (consider reducing dose of maraviroc); avoidance of clarithromycin and erythromycin advised by manufacturer of RUDANIPINE; clarithromycin increases plasma concentration of rilpivirine (possibly increased); clarithromycin increases plasma concentration of azithromycin and erythromycin possibly increased by RITONAVIR; plasma concentration of clarithromycin increased by RITONAVIR (reduce dose of clarithromycin in renal impairment); increased risk of ventricular arrhythmias when erythromycin given with SAQUINAVIR—avoid concomitant use; plasma concentration of both drugs possibly increased when clarithromycin given with SAQUINAVIR and TELAPREVIR (increased risk of ventricular arrhythmias); plasma concentration of both drugs possibly increased when erythromycin given with SIMPEPREVIR—manufacturer of simprevir advises avoid concomitant use; clarithromycin possibly increases plasma concentration of SIMPEPREVIR—manufacturer of simprevir advises avoid concomitant use; plasma concentration of both drugs possibly increased when erythromycin given with TELAPREVIR (increased risk of ventricular arrhythmias); plasma concentration of clarithromycin increased by TIPRANAVIR (reduce dose of clarithromycin in renal impairment), also clarithromycin increases plasma concentration of tipranavir; clarithromycin tablets reduce absorption of ZIDOVIDINE (give at least 2 hours apart)
- Anxiolytics and Hypnotics: clarithromycin and erythromycin inhibit metabolism of MIDAZOLAM (increased plasma concentration with increased sedation); erythromycin increases plasma concentration of BUSPIRONE (reduce dose of busipirone); erythromycin inhibits the metabolism of ZOPICLONE
- Aprepitant: clarithromycin possibly increases plasma concentration of aprepitant
- Atomoxetine: increased risk of ventricular arrhythmias when parenteral erythromycin given with ATOMOXETINE
- Avanafil: clarithromycin possibly increases plasma concentration of AVANAFIL—manufacturer of avanafil advises avoid concomitant use; possible increased risk of erythromycin increased; plasma concentration of AVANAFIL—see under Avanafil, p. 698
- Calcium-channel Blockers: clarithromycin and erythromycin possibly inhibit metabolism of CALCIUM-CHANNEL BLOCKERS (increased risk of side-effects); avoidance of erythromycin advised by manufacturer of LERANDIPINE
- Cardiac Glycosides: macrolides increase plasma concentration of DIGOXIN (increased risk of toxicity)
- Ciclosporin: macrolides possibly inhibit metabolism of CICLOSPORIN (increased plasma concentration); clarithromycin and erythromycin inhibit metabolism of CICLOSPORIN (increased plasma concentration)
- Cilostazol: clarithromycin possibly increases plasma concentration of CILOSTAZOL (see under Cilostazol, p. 206); erythromycin increases plasma concentration of CILOSTAZOL (see under Cilostazol, p. 206)
- Clomiprod: erythromycin possibly reduces antiplatelet effect of CLOPIDOGREL
- Colchicine: azithromycin, clarithromycin and erythromycin possibly increase risk of COLCHICINE toxicity—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- Corticosteroids: erythromycin possibly inhibits metabolism of CORTICOSTEROIDS; erythromycin inhibits the metabolism of METHYLPPREDNISOLONE; clarithromycin possibly increases plasma concentration of METHYLPPREDNISOLONE
- Cyclosporin: macrolides possibly increase plasma concentration of cyclosporin
- Dapagliflozin: clarithromycin possibly increases plasma concentration of dapagliflozin
- Dapoxetine: macrolides possibly increase plasma concentration of dapoxetine
- Dapagliflozin: clarithromycin possibly increases plasma concentration of dapagliflozin
- Darbepoetin: macrolides increase plasma concentration of darbepoetin
- Daclatasvir; plasma concentration of daclatasvir increased; plasma concentration of daclatasvir reduced by
- Dabigatran; plasma concentration of dabigatran increased by
- Darbepoetin: macrolides increase plasma concentration of darbepoetin
- Dapoxetine: macrolides increase plasma concentration of dapoxetine
- Dapagliflozin: macrolides increase plasma concentration of dapagliflozin
- Dapagliflozin: clarithromycin increases plasma concentration of dapagliflozin
Macrolides
- Lipid-regulating Drugs (continued)
  - increased risk of myopathy when erythromycin given with
    - ATORVASTATIN; erythromycin increases plasma concentration of
    - ROSUVASTATIN; erythromycin reduces plasma concentration of
  - increased risk of myopathy when
  - clarithromycin or erythromycin given with
    - SIMVASTATIN (avoid concomitant use); separating administration from
    - azithromycin by 12 hours advised by manufacturer of
    - LOMITAPIDE; avoidance of clarithromycin and erythromycin
    - advised by manufacturer of
    - LOMITAPIDE (plasma concentration of lomitapide possibly increased)
  - Mirabegron: when given with clarithromycin avoid or reduce
dose of MIRABEGRON in hepatic or renal impairment—see
  - Mirabegron, p. 671
  - Oestrogens—erythromycin increases plasma concentration of
    - ESTRADIOL
  - Parasympathomimetics: erythromycin increases plasma concentration of
    - GALANTAMINE
  - Pentamidine isetionate: increased risk of ventricular
    - arrhythmias when parenteral erythromycin given with
    - PENTAMIDINE ISETIONATE
  - Progestogens: erythromycin increases plasma concentration of
    - DIENOGEST
  - Ranolazine: clarithromycin possibly increases plasma
    - concentration of
    - RANOLAZINE—manufacturer of ranolazine
    - advises avoid concomitant use
  - Sildenafil: clarithromycin increases plasma concentration of
    - SILDENAFIL—consider reducing initial dose of sildenafil
      for erectile dysfunction or reduce sildenafil dose frequency to
      once daily for pulmonary hypertension; erythromycin
      increases plasma concentration of
    - SILDENAFIL—reduce initial
dose of sildenafil for erectile dysfunction or reduce sildenafil
dose frequency to twice daily for pulmonary hypertension
  - Sirolimus: clarithromycin increases plasma concentration of
    - SIROLIMUS—avoid concomitant use; plasma concentration of
      both drugs increased when erythromycin given with
    - SIROLIMUS
  - Tacrolimus: clarithromycin and erythromycin increase plasma
    - concentration of
    - TACROLIMUS
  - Tadalafil: clarithromycin increases plasma concentration of
    - TADALAFIL
  - Theophylline: clarithromycin possibly increase plasma
    - concentration of THEOPHYLLINE; erythromycin increases
      plasma concentration of
    - THEOPHYLLINE (also theophylline
      may reduce absorption of oral erythromycin)
  - Ticagrelor: clarithromycin possibly increases plasma
    - concentration of
    - TICAGRELOR—manufacturer of ticagrelor
    - advises avoid concomitant use; erythromycin possibly
      increases plasma concentration of
    - TICAGRELOR
  - Ulcer-healing Drugs: plasma concentration of erythromycin
    increased by
    - CIMETIDINE (increased risk of toxicity, including
      deafness); plasma concentration of both drugs increased when
    - clarithromycin given with
      - OMEPRAZOLE
  - Ulipristal: avoidance of clarithromycin advised by
    - manufacturer of low-dose ULIPRISTAL; erythromycin increases
      plasma concentration of
    - ULIPRISTAL (consider reducing initial dose of
      vardenafil); erythromycin increases plasma concentration of
    - ULIPRISTAL (reduce dose of vardenafil)

Macrolides
- Macrolides (continued)
  - Macrolides: manufacturer of bosutinib advises avoid or consider reducing
dose of bosutinib; clarithromycin and erythromycin possibly increase plasma
  - concentration of
    - CABOZANTINIB; clarithromycin possibly increases plasma concentration of
    - EVEROLIMUS (consider reducing the dose of everolimus
      consult everolimus product literature); clarithromycin and
    - erythromycin advise avoid concomitant use; avoidance of
    - clarithromycin and erythromycin advised by manufacturer of
    - DASATINIB (plasma concentration of dasatinib possibly increased); erythromycin increases plasma concentration of
    - LORATADINE; clarithromycin possibly increases plasma concentration of
    - LORATADINE; clarithromycin possibly increases plasma concentration of
      - LEUKOTRIENE RECEPTOR ANTAGONISTS:
      - Lenalidomide: clarithromycin possibly increases plasma concentration of
      - LENALIDOMIDE (increased risk of toxicity)
      - Leukotriene Receptor Antagonists: erythromycin reduces plasma concentration of
        - ZAFIRILUKAST
      - Lipid-regulating Drugs: clarithromycin increases plasma concentration of
        - ATORVASTATIN and PRAVASTATIN; possible
Mannitol (continued)  
- Ciclosporin: possible increased risk of nephrotoxicity when mannitol given with CICLOSPORIN

MAOIs  
- NOTE: For interactions of reversible MAO-A inhibitors (RIMAs) see Moclobemide, and for interactions of MAO-B inhibitors see Rasagiline and Selegiline; the antibacterial Linezolid is a reversible, non-selective MAO inhibitor  
- ACE inhibitors: MAOIs possibly enhance hypotensive effect of ACE INHIBITORS  
- Adrenergic Neurone Blockers: enhanced hypotensive effect when MAOIs given with ADRENERGIC NEURONE BLOCKERS  
  - Alcohol: MAOIs interact with tyramine found in some beverages containing ALCOHOL and some dealkoholised beverages (hypertensive crisis)—if no tyramine, enhanced hypotensive effect  
  - Alpha2-adrenoceptor Stimulants: avoidance of MAOIs advised by manufacturer of APRACLONIDINE and BRIMONIDINE  
  - Alpha-blockers: avoidance of MAOIs advised by manufacturer of INDORAMIN; enhanced hypotensive effect when MAOIs given with ALPHA-BLOCKERS  
  - Analgesics: possible increased serotonergic effects when MAOIs given with FENTANYL; CNS excitation or depression (hypertension or hypotension) when MAOIs given with • PETHIDINE—avoid concomitant use and for 2 weeks after stopping MAOIs; possible increased serotonergic effects and increased risk of convulsions when MAOIs given with • TRAMADOL—some manufacturers advise avoid concomitant use and for 2 weeks after stopping MAOIs; avoidance of MAOIs advised by manufacturer of • OPIOID ANALGESICS—some manufacturers advise avoid concomitant use and for 2 weeks after stopping MAOIs  
  - Angiotensin-II Receptor Antagonists: MAOIs possibly enhance hypotensive effect of ANGIOTENSIN-II RECEPTOR ANTAGONISTS  
  - Antidepressants: increased risk of hypertension and CNS excitation when MAOIs given with • REBOXETINE (MAOIs should not be started until 1 week after stopping reboxetine, avoid reboxetine for 2 weeks after stopping MAOIs); after stopping MAOIs do not start • CITOLOPRAM, • ESCITALOPRAM, • FLUOXAMINE, • PAROXETINE or • SERTRALINE for 2 weeks, also MAOIs should not be started until at least 1 week after stopping citalopram, escitalopram, fluvoxamine, paroxetine or sertraline; after stopping MAOIs do not start • FLUOXETINE for 2 weeks, also MAOIs should not be started until at least 5 weeks after stopping fluoxetine; after stopping MAOIs do not start • DUOXETINE for 2 weeks, also MAOIs should not be started until at least 5 days after stopping duloxetine; enhanced CNS effects and toxicity when MAOIs given with • VENLAFAXINE (venlafaxine should not be started until 2 weeks after stopping MAOIs, avoid MAOIs for 1 week after stopping venlafaxine); increased risk of hypertension and CNS excitation when MAOIs given with other • MAOIs (avoid for at least 2 weeks after stopping previous MAOIs and then start at a reduced dose); after stopping MAOIs do not start • MOXOLBEMIDE for at least 1 week; MAOIs increase CNS effects of • SSRIS (risk of serious toxicity); after stopping MAOIs do not start • MIRTAZAPINE for 2 weeks, also MAOIs should not be started until at least 2 weeks after stopping mirtazapine; after stopping MAOIs do not start • TRICYCLIC-RELATED ANTIDEPRESSANTS for 2 weeks, also MAOIs should not be started until at least 1–2 weeks after stopping tricyclic-related antidepressants; increased risk of hypertension and CNS excitation when MAOIs given with • TRICYCLICS, tricyclics should not be started until 2 weeks after stopping MAOIs (3 weeks if starting clomipramine or imipramine), also MAOIs should not be started for at least 1–2 weeks after stopping tricyclics (3 weeks in the case of clomipramine or imipramine)  
  - Antidiabetics: MAOIs possibly enhance hypoglycaemic effect of ANTIDIABETICS; MAOIs enhance hypoglycaemic effect of INSULIN, METFORMIN and SULFONYLUREAS  
  - Antiepileptics: MAOIs possibly antagonise anticonvulsant effect of ANTIPELITICS (convulsive threshold lowered);  

MAOIs  
- Antiepileptics (continued)  
  - avoidance for 2 weeks after stopping MAOIs advised by manufacturer of • CARBAMAZEPINE, also antagonism of anticonvulsant effect  
  - Antihistamines: avoidance of MAOIs advised by manufacturer of HYDROXYZINE; avoidance of promethazine for 2 weeks after stopping MAOIs advised by manufacturer of PROMETHAZINE; increased antimuscarinic and sedative effects when MAOIs given with ANTIHISTAMINES  
  - Antimalarias: avoidance of antidepressants advised by manufacturer of • ARTEMETHER WITH LUMEFANTRINE and • ARTEMIMOL WITH PIPERAQUINE  
  - Antimuscarinics: increased risk of antimuscarinic side–effects when MAOIs given with ANTIMUSCARINICS  
  - Antipsychotics: CNS effects of MAOIs possibly increased by • CLOZAPINE  
  - Anxiolytics and Hypnotics: avoidance of MAOIs advised by manufacturer of BUSPIRONE; manufacturer of tranylcypromine advises avoid • BUSPIRONE for 14 days after stopping tranylcypromine  
  - Beta-blockers: enhanced hypotensive effect when MAOIs given with BETA-BLOCKERS  
  - Bupropion: avoidance of bupropion for 2 weeks after stopping MAOIs advised by manufacturer of • BUPROPION  
  - Calcium-channel Blockers: enhanced hypotensive effect when MAOIs given with CALCIUM-CHANNEL BLOCKERS  
  - Clonidine: enhanced hypotensive effect when MAOIs given with CLONIDINE  
  - Dopamine: increased risk of serotonergic effects when MAOIs given with • DAPoxetine (MAOIs should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping MAOIs)  
  - Diazoxide: enhanced hypotensive effect when MAOIs given with DIAZoxide  
  - Diuretics: enhanced hypotensive effect when MAOIs given with DIURETICS  
  - Dopaminergics: risk of hypertensive crisis when MAOIs given with • CO-BENELDOPA, • CO-CARELDOPA or • LEVODOPA, avoid co-beneldopa, co-careldopa or levodopa for at least 2 weeks after stopping MAOIs; avoid concomitant use of non-selective MAOIs with • ENTACAPONE; risk of hypertensive crisis when MAOIs given with • RASAGILINE, avoid MAOIs for at least 2 weeks after stopping rasagiline; enhanced hypotensive effect when MAOIs given with • SELEGILINE—manufacturer of selegiline advises avoid concomitant use; avoid concomitant use of MAOIs with • TOLCAPONE  
  - Doxapram: MAOIs enhance effects of DOXAPRAM  
  - Histamine: avoidance of MAOIs advised by manufacturer of • HISTAMINE  
  - HT1-receptor Agonists: risk of CNS toxicity when MAOIs given with • RIZATRIPTAN or • SUMATRIPTAN (avoid rizatRIPTAN or sumatriptan for 2 weeks after MAOIs); risk of CNS toxicity when MAOIs given with • ZOMITRIPTAN (reduce dose of zolmitriptan)  
  - Methyldopa: avoidance of MAOIs advised by manufacturer of • METHYLDOPA  
  - Moxonidine: enhanced hypotensive effect when MAOIs given with MOXONIDINE  
  - Muscle Relaxants: phenelzine enhances effects of • SUXAMETHONIUM  
  - Nicorandil: enhanced hypotensive effect when MAOIs given with NIcorANDIIL  
  - Nitrates: enhanced hypotensive effect when MAOIs given with NITRATES  
  - Pholcodine: avoidance of pholcodine for 2 weeks after stopping MAOIs advised by manufacturer of PHOLCODINE  
  - Sympathomimetics: risk of hypertensive crisis when MAOIs given with • ADRENALINE (EPINEPHRINE), • DOBUTAMINE, • DOPAMINE, • NORADRENALINE (norepinephrine) or • XYLOMETAZOLINE; risk of hypertensive crisis when MAOIs given with • DEXAMETASONE, • EPHEDRINE, • ISOMETHEPTINE,
MAOIs
- Symptomatics (continued)
  - **LISDEXAMFETAMINE**, **METARAMINOL**, **METHYLPHENIDATE**, **PHENYLEPHRINE** or **PSEUDOEPHEDRINE**, avoid dexamfetamine, ephedrine, isometheptene, lisdeexamfetamine, metaraminol, methylphenidate, phenylephrine or pseudoephedrine for at least 2 weeks after stopping MAOIs; risk of hypertensive crisis when MAOIs given with **OXMETAZOLINE**, some manufacturers advise avoid oxometazoline for at least 2 weeks after stopping MAOIs
  - **TETRABENAZINE** risk of CNS toxicity when MAOIs given with **TETRABENAZINE** (avoid tetrabenazine for 2 weeks after MAOIs)
  - Vasodilator Antihypertensives: enhanced hypotensive effect when MAOIs given with **HYDRAZINE**, **MINOXIDIL** or **SODIUM NITROPRUSSIDE**

MAOIs, reversible see Moclobemide

Maraviroc
- Antibacterials: plasma concentration of maraviroc possibly reduced by **CLARITHROMYCIN** and **TELITHROMYCIN** (consider reducing dose of maraviroc); plasma concentration of maraviroc reduced by **RIFAMPICIN**—consider increasing dose of maraviroc
- Antidepressants: plasma concentration of maraviroc possibly reduced by **ST JOHN’S WORT**—avoid concomitant use
- Antifungals: plasma concentration of maraviroc increased by **KETOCONAZOLE** (consider reducing dose of maraviroc)
- Antivirals: plasma concentration of maraviroc increased by **AZAZANAVIR, BOCEPREVIR, DARUNAVIR, INDINAVIR, LOPINAVIR, SAQUINAVIR and TELAPREVIR** (consider reducing dose of maraviroc); plasma concentration of maraviroc possibly reduced by **EFAVIRENZ**—consider increasing dose of maraviroc; plasma concentration of maraviroc possibly reduced by **STRAVIRINE**, maraviroc reduces plasma concentration of **FOSAMPRENAVIR**—avoid concomitant use; plasma concentration of maraviroc increased by **RITONAVIR**
- Cobicistat: plasma concentration of maraviroc possibly increased by **Cobicistat** (reduce dose of maraviroc)
- Orlistat: absorption of maraviroc possibly reduced by **ORLISTAT**

Mebendazole
- Ulcer-healing Drugs: metabolism of mebendazole possibly inhibited by **CIMETIDINE** (increased plasma concentration)

Medroxyprogesterone see Progestogens

Mefenamic Acid see NSAIDs

Mefloquine (continued)
- **Atomoxetine**: increased risk of ventricular arrhythmias when mefloquine given with **ATOMOXETINE**
- Beta-blockers: increased risk of bradycardia when mefloquine given with Beta-blockers
- Calcium-channel Blockers: possible increased risk of bradycardia when mefloquine given with **CALCIUM-CHANNEL BLOCKERS**
- Cardiac Glycosides: possible increased risk of bradycardia when mefloquine given with **DIGOXIN**
- Cytotoxics: possible increased risk of bradycardia when mefloquine given with **CRIZOTINIB**
- Histamine: avoidance of antimalarials advised by manufacturer of **HISTAMINE**
- Ibradine: increased risk of ventricular arrhythmias when mefloquine given with **IBRADINE**
- Vaccines: antimalarials inactivate **ORAL TYPHOID VACCINE**—see under Typhoid Vaccine in BNF

Megestrol see Progestogens

Melatonin see Anxiolytics and Hypnotics

Meloxicam see NSAIDs

Melphalan
- Antibacterials: increased risk of melphalan toxicity when given with **NALIDIXIC ACID**
- Antipsychotics: avoid concomitant use of cytoxotics with **CLOZAPINE** (increased risk of agranulocytosis)
- Cardiac Glycosides: melphalan possibly reduces absorption of **DIGOXIN tablets**
- Ciclosporin: increased risk of nephrotoxicity when melphalan given with **CICLOSPORIN**
- Memantine: increased risk of CNS toxicity when memantine given with **CICLOSPORIN**
- Memantine possibly enhances effects of **WARFARIN**
- Antimuscarinics: memantine possibly enhances effects of **ANTIMUSCARINICS**
- Antipsychotics: memantine possibly reduces effects of **ANTIPSYCHOTICS**
- Dopaminergics: memantine possibly enhances effects of **DOPAMINERGICS and SELEGILINE**; increased risk of CNS toxicity when memantine given with **CLOZAPINE** (manufacturer of memantine advises avoid concomitant use)
- Muscle Relaxants: memantine possibly modifies effects of **BACLOfen and DANTROLENE**

Meningococcal Vaccines see Vaccines

Mepacrine
- Antimalarials: mepacrine increases plasma concentration of **PRIMAQUINE** (increased risk of toxicity)

Meprobamate see Anxiolytics and Hypnotics

Meptazinol see Opioid Analgesics

Mercaptopurine
- Allopurinol: enhanced effects and increased toxicity of mercaptopurine when given with **ALLOPURINOL** (reduce dose of mercaptopurine to one quarter of usual dose)
- Antibacterials: increased risk of haematological toxicity when mercaptopurine given with **SULFAMETHOXAZOLE** (as cotrimoxazole); increased risk of haematological toxicity when mercaptopurine given with **TRIMETHOPRIM** (also with cotrimoxazole)
- Anticoagulants: mercaptopurine possibly reduces anticoagulant effect of **COUMARINS**
- Antipsychotics: avoid concomitant use of cytoxotics with **CLOZAPINE** (increased risk of agranulocytosis)
- Dairy Products: plasma concentration of mercaptopurine possibly reduced by **DAIRY PRODUCTS**—manufacturer of mercaptopurine advises give at least 1 hour before or 2 hours after dairy products
- Febuxostat: avoidance of mercaptopurine advised by manufacturer of **FEBUXOSTAT**
Methotrexate
- Antiepileptics: carbamazepine reduces plasma concentration of methotrexate.
- Iron Salts: increased risk of hyperbilirubinaemia when methotrexate given with iron salts.
- Cimetidine: increased anticoagulant effect when methotrexate given with cimetidine.
- Oral Anticoagulants: increased anticoagulant effect when methotrexate given with oral anticoagulants.
- Antiplatelets: increased risk of bleeding when methotrexate given with antiplatelets.
- Antidiabetics (gliclazide): increased risk of hypoglycaemia when methotrexate given with gliclazide.
- ACE Inhibitors: increased risk of hypotension when methyldopa given with ACE inhibitors.
- Adrenergic Neurone Blockers: increased hypotensive effect when methyldopa given with adrenergic neurone blockers.

Methyldopa (continued)
- Alcohol: enhanced hypotensive effect when methyldopa given with alcohol.
- Aldesleukin: enhanced hypotensive effect when methyldopa given with aldesleukin.
- Alpha-blockers: enhanced hypotensive effect when methyldopa given with alpha-blockers.
- Anaeasthetics, General: enhanced hypotensive effect when methyldopa given with general anaesthetic.
- Analgesics: hypotensive effect of methyldopa antagonised by NSAIDs.
- Angiotensin II Receptor Antagonists: enhanced hypotensive effect when methyldopa given with angiotensin II receptor antagonists.
- Antidepressants: manufacturer of methyldopa advises avoid concomitant use with MAOIs.
- Antipsychotics: enhanced hypotensive effect when methyldopa given with antipsychotics.
- Antiepileptics: enhanced hypotensive effect when methyldopa given with antiepileptics.
- Beta-blockers: enhanced hypotensive effect when methyldopa given with beta-blockers.
- Calcium-channel Blockers: enhanced hypotensive effect when methyldopa given with calcium-channel blockers.
- Clonidine: enhanced hypotensive effect when methyldopa given with clonidine.
- Corticosteroids: hypotensive effect of methyldopa antagonised by corticosteroids.
- Diazoxide: enhanced hypotensive effect when methyldopa given with diazoxide.
- Diuretics: enhanced hypotensive effect when methyldopa given with diuretics.
- Dopaminergics: methyldopa antagonises antiparkinsonian effect of dopaminergics, increased risk of extrapyramidal side-effects when methyldopa given with amantadine.
- Enhanced hypotensive effect when methyldopa given with beta-blockers.
- Calcium-channel Blockers: enhanced hypotensive effect when methyldopa given with calcium-channel blockers.
- Clonidine: enhanced hypotensive effect when methyldopa given with clonidine.
- Corticosteroids: hypotensive effect of methyldopa antagonised by corticosteroids.
- Diazoxide: enhanced hypotensive effect when methyldopa given with diazoxide.
- Diuretics: enhanced hypotensive effect when methyldopa given with diuretics.
- Dopaminergics: methyldopa antagonises antiparkinsonian effect of dopaminergics, increased risk of extrapyramidal side-effects when methyldopa given with amantadine.
- Enhanced hypotensive effect when methyldopa given with beta-blockers.
- Calcium-channel Blockers: enhanced hypotensive effect when methyldopa given with calcium-channel blockers.
- Clonidine: enhanced hypotensive effect when methyldopa given with clonidine.
- Corticosteroids: hypotensive effect of methyldopa antagonised by corticosteroids.
- Diazoxide: enhanced hypotensive effect when methyldopa given with diazoxide.
- Diuretics: enhanced hypotensive effect when methyldopa given with diuretics.
- Dopaminergics: methyldopa antagonises antiparkinsonian effect of dopaminergics, increased risk of extrapyramidal side-effects when methyldopa given with amantadine.
- Enhanced hypotensive effect when methyldopa given with beta-blockers.
- Calcium-channel Blockers: enhanced hypotensive effect when methyldopa given with calcium-channel blockers.
- Clonidine: enhanced hypotensive effect when methyldopa given with clonidine.
- Corticosteroids: hypotensive effect of methyldopa antagonised by corticosteroids.
- Diazoxide: enhanced hypotensive effect when methyldopa given with diazoxide.
- Diuretics: enhanced hypotensive effect when methyldopa given with diuretics.
- Dopaminergics: methyldopa antagonises antiparkinsonian effect of dopaminergics, increased risk of extrapyramidal side-effects when methyldopa given with amantadine.
- Enhanced hypotensive effect when methyldopa given with beta-blockers.
- Calcium-channel Blockers: enhanced hypotensive effect when methyldopa given with calcium-channel blockers.
- Clonidine: enhanced hypotensive effect when methyldopa given with clonidine.
- Corticosteroids: hypotensive effect of methyldopa antagonised by corticosteroids.
- Diazoxide: enhanced hypotensive effect when methyldopa given with diazoxide.
- Diuretics: enhanced hypotensive effect when methyldopa given with diuretics.
- Dopaminergics: methyldopa antagonises antiparkinsonian effect of dopaminergics, increased risk of extrapyramidal side-effects when methyldopa given with amantadine.
- Enhanced hypotensive effect when methyldopa given with beta-blockers.
- Calcium-channel Blockers: enhanced hypotensive effect when methyldopa given with calcium-channel blockers.
- Clonidine: enhanced hypotensive effect when methyldopa given with clonidine.
- Corticosteroids: hypotensive effect of methyldopa antagonised by corticosteroids.
- Diazoxide: enhanced hypotensive effect when methyldopa given with diazoxide.
- Diuretics: enhanced hypotensive effect when methyldopa given with diuretics.
- Dopaminergics: methyldopa antagonises antiparkinsonian effect of dopaminergics, increased risk of extrapyramidal side-effects when methyldopa given with amantadine.
- Enhanced hypotensive effect when methyldopa given with beta-blockers.
- Calcium-channel Blockers: enhanced hypotensive effect when methyldopa given with calcium-channel blockers.
- Clonidine: enhanced hypotensive effect when methyldopa given with clonidine.
- Corticosteroids: hypotensive effect of methyldopa antagonised by corticosteroids.
- Diazoxide: enhanced hypotensive effect when methyldopa given with diazoxide.
- Diuretics: enhanced hypotensive effect when methyldopa given with diuretics.
- Dopaminergics: methyldopa antagonises antiparkinsonian effect of dopaminergics, increased risk of extrapyramidal side-effects when methyldopa given with amantadine.
- Enhanced hypotensive effect when methyldopa given with beta-blockers.
- Calcium-channel Blockers: enhanced hypotensive effect when methyldopa given with calcium-channel blockers.
- Clonidine: enhanced hypotensive effect when methyldopa given with clonidine.
- Corticosteroids: hypotensive effect of methyldopa antagonised by corticosteroids.
- Diazoxide: enhanced hypotensive effect when methyldopa given with diazoxide.
Interactions

Methyldionium
- Antioxidants: possible dose of methyldionium and observe patient for up to 4 hours after administration
- Bupropion: possible risk of CNS toxicity when methyldionium given with bupropion—avoid concomitant use (if avoidance not possible, use lowest possible dose of methyldionium and observe patient for up to 4 hours after administration)

Metoclopramide
- Alcohol: metoclopramide possibly increases absorption of alcohol
- Anaesthetics, General: metoclopramide enhances effects of thiopental
- Analgesics: metoclopramide increases rate of absorption of aspirin (increased effect); effects of metoclopramide on gastro-intestinal activity antagonised by opioid analgesics; metoclopramide increases rate of absorption of paracetamol
- Antiarrhythmics: metoclopramide reduces plasma concentration of fosfomycin
- Antidepressants: CNS toxicity reported when metoclopramide given with SSRIs
- Antimuscarinics: effects of metoclopramide on gastro-intestinal activity antagonised by antimuscarinics
- Antipsychotics: increased risk of extrapyramidal side-effects when metoclopramide given with antipsychotics
- Atovaquone: metoclopramide reduces plasma concentration of atovaquone—avoid concomitant use
- Cisoprin: metoclopramide increases plasma concentration of cisoprin
- Dopaminergics: metoclopramide antagonises hypoprolactinaemic effects of bromocriptine and cabergoline; metoclopramide antagonises antiparkinsonian effect of pergolide; avoidance of metoclopramide advised by manufacturer of ropinirole and rotigotine (antagonism of effect)
- Muscle Relaxants: metoclopramide enhances effects of suxamethonium
- Tetrabenazine: increased risk of extrapyramidal side-effects when metoclopramide given with tetrabenazine

Metolazone
- See Diuretics

Metoprolol
- See Beta-blockers

Metronidazole
- Note Interactions do not apply to topical metronidazole preparations
- Alcohol: disulfiram-like reaction when metronidazole given with alcohol
- Anticoagulants: metronidazole enhances anticoagulant effect of coumarins
- Antiepileptics: metronidazole possibly inhibits metabolism of fosphenytoin and phenytoin (increased plasma concentration); metabolism of metronidazole accelerated by phenobarbital and primidone (reduced effect)
- Cytotoxics: metronidazole increases plasma concentration of
  - busulfan (increased risk of toxicity); metronidazole inhibits metabolism of capetitabine, fluoroouracil and tegafur (increased toxicity)
- Disulfiram: psychotic reaction reported when metronidazole given with disulfiram
- Lithium: metronidazole increases risk of lithium toxicity
- Mycophenolate: metronidazole possibly reduces bioavailability of mycopHENolate
- Ulcer-healing Drugs: metabolism of metronidazole inhibited by cimetidine (increased plasma concentration)
- Vaccines: antibacterials inactivate oral typhoid vaccine—see under Typhoid Vaccine in BNF

Mianserin
- See Antidepressants, Tricyclic (related)

Micafungin
- Antifungals: micafungin possibly increases plasma concentration of amphotericin; micafungin increases plasma concentration of itraconazole (consider reducing dose of itraconazole)
- Calcium-channel Blockers: micafungin increases plasma concentration of nifedipine

Micafungin (continued)
- Ciclosporin: micafungin possibly increases plasma concentration of ciclosporin
- Sirolimus: micafungin increases plasma concentration of sirolimus

Miconazole
- See Antifungals, Imidazoles

Midazolam
- See Anxiolytics and Hypnotics

Mifamurtide
- Analgesics: manufacturer of mifamurtide advises avoid concomitant use with high doses of NSAIDs
- Ciclosporin: manufacturer of mifamurtide advises avoid concomitant use with ciclosporin
- Corticosteroids: manufacturer of mifamurtide advises avoid concomitant use with corticosteroids
- Tacrolimus: manufacturer of mifamurtide advises avoid concomitant use with tacrolimus

Mifepristone
- Corticosteroids: mifepristone may reduce effect of corticosteroids (including inhaled corticosteroids) for 3–4 days

Milrinone
- See Phosphodiesterase Inhibitors

Minoxidine
- See Vasodilator Antihypertensives

Mirabegron
- Antibacterials: avoid or reduce dose of mirabegron in hepatic or renal impairment when given with clarithromycin—see Mirabegron, p. 671
- Antifungals: avoid or reduce dose of mirabegron in hepatic or renal impairment when given with itraconazole and ketoconazole—see Mirabegron, p. 671
- Antivirals: avoid or reduce dose of mirabegron in hepatic or renal impairment when given with ritonavir—see Mirabegron, p. 671
- Beta-blockers: mirabegron increases plasma concentration of metoprolol
- Cardiac Glycosides: mirabegron increases plasma concentration of digoxin—reduce initial dose of digoxin

Mirtazapine
- Alcohol: increased sedative effect when mirtazapine given with alcohol
- Analgesics: possible increased serotonergic effects when mirtazapine given with tramadol
- Anticoagulants: mirtazapine enhances anticoagulant effect of warfarin
- Antidepressants: possible increased serotonergic effects when mirtazapine given with fluoxetine, fluvoxamine or venlafaxine; mirtazapine should not be started until 2 weeks after stopping MAOIs, also MAOIs should not be started until at least 2 weeks after stopping mirtazapine; after stopping mirtazapine do not start moclobemide for at least 1 week
- Antiepileptics: plasma concentration of mirtazapine reduced by carbamazepine, fosphenytoin and phenytoin
- Antifungals: plasma concentration of mirtazapine increased by ketoconazole
- Antimalarials: avoidance of antidepressants advised by manufacturer of arteether with lumefantrine and artemether with lumefantrine
- Antidepressants: possible increased risk of convulsions when antidepressants given with atomoxetine
- Clonidine: mirtazapine possibly antagonises hypotensive effect of clonidine
- Methylthionium: possible risk of CNS toxicity when mirtazapine given with methylthionium—avoid concomitant use (if avoidance not possible, use lowest possible dose of methylthionium and observe patient for up to 4 hours after administration)
- Ulcer-healing Drugs: plasma concentration of mirtazapine increased by cimetidine

Mitomycin
- Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)
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Mitotane
- Anticoagulants: mitotane possibly reduces anticoagulant effect of
  - COUMARINS
- Antipsychotics: avoid concomitant use of cytotoxics with
  - CLOzapine (increased risk of agranulocytosis)
- Diuretics: manufacturer of mitotane advises avoid concomitant use of SPIRONOLACTONE (antagonism of effect)

Mitoxantrone
- Antipsychotics: avoid concomitant use of cytotoxics with
  - CLOzapine (increased risk of agranulocytosis)
- Ciclosporin: excretion of mitoxantrone reduced by CICLOSPORIN (increased plasma concentration)

Mivacurium see Muscle Relaxants

Mizolastine see Antihistamines

MMR Vaccine see Vaccines

Moclobemide
- Analgesics: possible CNS excitation or depression (hypertension or hypotension) when moclobemide given with
  - DEXTROMETHORPHAN or PETHIDINE—avoid concomitant use; possible CNS excitation or depression (hypertension or hypotension) when moclobemide given with OPIOD ANALGESICS—manufacturer of moclobemide advises consider reducing dose of opioid analgesics
- Antidepressants: moclobemide should not be started for at least 1 week after stopping MAOIS, SSRi-RELATED ANTIDEPRESSANTS, FLUOXETINE, FLUVAXMINE, MIRTAZAPINE, PAROXETINE, SERTRALINE, TRICYCLIC-RELATED ANTIDEPRESSANTS or TRICYCLICS; increased risk of CNS toxicity when moclobemide given with ESCITALOPRAM, preferably avoid concomitant use; moclobemide should not be started until 5 weeks after stopping FLUOXETINE; possible increased serotonergic effects when moclobemide given with
  - DULOXETINE
- Antimalarials: avoidance of antidepressants advised by manufacturer of ARTEMETHER WITH LUMEFANTRINE and ARTEMISOL WITH PIPERAQUINE
- Atomoxetine: possible increased risk of convulsions when antidepressants given with ATOMOXETINE
- Bupropion: avoidance of moclobemide advised by manufacturer of BUPROPION
- Diazoxide: enhanced hypotensive effect when moclobemide given with
  - MEXITIL
- Dopaminergics: increased risk of side-effects when moclobemide given with CO-BENELDOPA, CO-CARELDOPA or LEVODOPA; caution with moclobemide advised by manufacturer of ENTACAPONE; avoid concomitant use of moclobemide with
  - SELEGILINE
- SfH, receptor Agonists: risk of CNS toxicity when moclobemide given with RIZATRIPTAN or SUMATRIPTAN (avoid rizatriptan or sumatriptan for 2 weeks after moclobemide); risk of CNS toxicity when moclobemide given with ZOLMITRIPTAN (reduce dose of zolmitriptan)
- Sympathomimetics: risk of hypertensive crisis when moclobemide given with SYMPATHOMIMETICS
- Uterus—uterine contraction: increased by CYMELODINE (halve dose of moclobemide)

Modafinil
- Antiepileptics: modafinil possibly increases plasma concentration of FOSPHENYTOIN and PHENYTOIN
- Ciclosporin: modafinil reduces plasma concentration of CICLOSPORIN
- Ciclosporin: modafinil reduces plasma concentration of BOsUTINIB—manufacturer of bosutinib advises avoid concomitant use
- Oestrogens: modafinil accelerates metabolism of OESTROGENS (reduced contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF)

Moxepril see ACE Inhibitors

Mometasone see Corticosteroids

MonoBactams see Aztreonam

Monoclonal antibodies see individual drugs

Montelukast see Leukotriene Receptor Antagonists

Morphine see Opioid Analgesics

Moxifloxacin see Quinolones

Moxisylyte
- ACE Inhibitors: enhanced hypotensive effect when moxisylyte given with ACE INHIBITORS
- Alpha-blockers: possible severe postural hypotension when moxisylyte given with ALPHA-BLOCKERS
- Antidepressants: increased risk of agranulocytosis when moxisylyte given with MAOIS
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when moxisylyte given with ANGIOTENSIN-II RECEPTOR ANTAGONISTS
- Beta-blockers: possible severe postural hypotension when moxisylyte given with BETA-BLOCKERS
- Calcium-channel Blockers: enhanced hypotensive effect when moxisylyte given with CALCIUM-CHANNEL BLOCKERS
- Corticosteroids: enhanced hypotensive effect of moxisylyte antagonised by CORTICOSTEROIDS
- Diazoxide: enhanced hypotensive effect when moxisylyte given with DIAZOXIDE
- Diuretics: enhanced hypotensive effect when moxisylyte given with DIURETICS
- Methyldopa: enhanced hypotensive effect when moxisylyte given with METHYLDOPA
- Moxonidine: enhanced hypotensive effect when moxisylyte given with MOXONIDINE
- Nitrate: enhanced hypotensive effect when moxisylyte given with NITRATES
- Vasodilators: enhanced hypotensive effect when moxisylyte given with HYDRAZINE, MINOXIDIL or SODIUM NITROPRUSSIDE

Moxonidine
- ACE Inhibitors: enhanced hypotensive effect when moxonidine given with ACE INHIBITORS
- Adrenergic Neurone Blockers: enhanced hypotensive effect when moxonidine given with ADRENERGIC NEURONE BLOCKERS
- Alcohol: enhanced hypotensive effect when moxonidine given with ALCOHOL
- Aidesleukin: enhanced hypotensive effect when moxonidine given with AIDESLEUKIN
- Alpha-blockers: enhanced hypotensive effect when moxonidine given with ALPHA-BLOCKERS
- Anaesthetics, General: enhanced hypotensive effect when moxonidine given with GENERAL ANAESTHETICS
- Analgesics: hypotensive effect of moxonidine antagonised by NSAIDS
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when moxonidine given with ANGIOTENSIN-II RECEPTOR ANTAGONISTS
- Antidepressants: enhanced hypotensive effect when moxonidine given with MAOIS; hypotensive effect of moxonidine possibly antagonised by TRICYCLICS (manufacturer of moxonidine advises avoid concomitant use)
- Antipsychotics: enhanced hypotensive effect when moxonidine given with PHENOTHIAZINES
- Anxiolytics and Hypnotics: enhanced hypotensive effect when moxonidine given with ANXIOLYTICS AND HYPNOTICS; sedative effects possibly increased when moxonidine given with BENZODIAZEPINES
- Beta-blockers: enhanced hypotensive effect when moxonidine given with BETA-BLOCKERS
- Calcium-channel Blockers: enhanced hypotensive effect when moxonidine given with CALCIUM-CHANNEL BLOCKERS
- Clonidine: enhanced hypotensive effect when moxonidine given with CLONIDINE
- Corticosteroids: enhanced hypotensive effect of moxonidine antagonised by CORTICOSTEROIDS
- Diazoxide: enhanced hypotensive effect when moxonidine given with DIAZOXIDE
- Diuretics: enhanced hypotensive effect when moxonidine given with DIURETICS
- Dopaminergics: enhanced hypotensive effect when moxonidine given with CO-BENELDOPA, CO-CARELDOPA or LEVODOPA
- Methyldopa: enhanced hypotensive effect when moxonidine given with METHYLDOPA
- Moxisylyte: enhanced hypotensive effect when moxonidine given with MOXISYLYTE
Appendix 1 Interactions

Moxonidine (continued)

Muscle Relaxants: enhanced hypotensive effect when moxonidine given with BACLOFEN or TIZANIDINE
Nitrites: enhanced hypotensive effect when moxonidine given with NITRATES
Oestrogens: hypotensive effect of moxonidine antagonised by OESTROGENS
Prostaglandins: enhanced hypotensive effect when moxonidine given with ALPROSTADIL
Vasodilator Antihypertensives: enhanced hypotensive effect when moxonidine given with HYDRAZINE, MINOXIDIL or SODIUM NITROPRUSSIDE

Muscle Relaxants

ACE Inhibitors: enhanced hypotensive effect when baclofen or tizanidine given with ACE INHIBITORS
Adrenergic Neurone Blockers: enhanced hypotensive effect when baclofen or tizanidine given with ADRENERGIC NEURONE BLOCKERS
Alcohol: increased sedative effect when baclofen, methohexital or tizanidine given with ALCOHOL
Alpha-blockers: enhanced hypotensive effect when baclofen or tizanidine given with ALPHA-BLOCKERS
● Anaesthetics, General: effects of atracurium enhanced by KETAMINE; increased risk of myocardial depression and bradycardia when suxamethonium given with PROPFOFOL; effects of non-depolarising muscle relaxants and suxamethonium enhanced by VOLATILE LIQUID GENERAL ANAESTHETICS
● Analgesics: excretion of baclofen possibly reduced by NSAIDS; (increased risk of toxicity) excretion of baclofen reduced by IBUPROFEN (increased risk of toxicity); increased sedative effect when baclofen given with FENTANYL or MORPHINE
● Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when baclofen or tizanidine given with ANGIOTENSIN-II RECEPTOR ANTAGONISTS
● Anti-arrhythmics: neuromuscular blockade enhanced and prolonged when suxamethonium given with LIDOCAINE
● Antibacterials: effects of non-depolarising muscle relaxants and suxamethonium enhanced by PIPERACILLIN; plasma concentration of tizanidine possibly increased by NORFLOXACIN (increased risk of toxicity)—avoid concomitant use; plasma concentration of tizanidine possibly increased by RIFAMPICIN; effects of non-depolarising muscle relaxants and suxamethonium enhanced by AMINOGLYCOSIDES; effects of non-depolarising muscle relaxants and suxamethonium enhanced by CLINDAMYCIN; plasma concentration of tizanidine possibly increased by POLYMYXIN; effects of suxamethonium enhanced by VANCOMYCIN
● Antidepressants: plasma concentration of tizanidine increased by FLUVORAMINE (increased risk of toxicity)—avoid concomitant use; effects of suxamethonium enhanced by PHENELZINE; muscle relaxant effect of baclofen enhanced by TRICYCLICS
● Antiepileptics: muscle relaxant effect of non-depolarising muscle relaxants antagonised by CARBAMAZEPINE (accelerated recovery from neuromuscular blockade); effects of non-depolarising muscle relaxants reduced by long-term use of FOSPHENYTOIN and PHENYTOIN (but effects of non-depolarising muscle relaxants might be increased by acute use of fosphenytoin and phenytoin)
● Antimalarials: effects of suxamethonium possibly enhanced by QUININE
● Antipsychotics: effects of suxamethonium possibly enhanced by PROMAZINE
● Anxiolytics and Hypnotics: increased sedative effect when baclofen or tizanidine given with ANXIOLYTICS and HYPNOTICS
● Beta-blockers: enhanced hypotensive effect when baclofen given with BETA-BLOCKERS; possible enhanced hypotensive effect and bradycardia when tizanidine given with BETA-BLOCKERS; effects of muscle relaxants enhanced by PROPRANOLOL
● Calcium-channel Blockers: enhanced hypotensive effect when baclofen or tizanidine given with CALCIUM-CHANNEL BLOCKERS; effects of non-depolarising muscle relaxants possibly enhanced by CALCIUM-CHANNEL BLOCKERS; possible increased risk of ventricular arrhythmias when intravenous dantrolene given with DILTIAZEM—manufacturer of diltiazem advises avoid concomitant use; effects of non-depolarising muscle relaxants and suxamethonium enhanced by VERAPAMIL; avoidance of intravenous dantrolene advised by manufacturer of VERAPAMIL
● Cardiac Glycosides: possible increased risk of bradycardia when tizanidine given with CARDIAC GLYCOSIDES; risk of ventricular arrhythmias when suxamethonium given with CARDIAC GLYCOSIDES
● Clonidine: enhanced hypotensive effect when baclofen or tizanidine given with CLONIDINE
● Corticosteroids: effects of pancuronium and vecuronium possibly antagonised by CORTICOSTEROIDS
● Cytoxicities: effects of suxamethonium enhanced by CYCLOPHOSPHAMIDE and THIOPETA
● Deferasirox: avoidance of tizanidine advised by manufacturer of DEFERASIROX
● Diazoxide: enhanced hypotensive effect when baclofen or tizanidine given with DIAZOXIDE
● Diuretics: enhanced hypotensive effect when baclofen or tizanidine given with DIURETICS
● Dopaminergics: possible agitation, confusion and hallucinations when baclofen given with CO-BENEDOLPA, CO-CARDELPOPA or LEVODOPA
● Lithium: effects of muscle relaxants enhanced by LITHIUM; baclofen possibly aggravates hyperkinesia caused by LITHIUM
● Magnesium (parenteral): effects of non-depolarising muscle relaxants and suxamethonium enhanced by PARENTERAL MAGNESIUM
● Memantine: effects of baclofen and dantrolene possibly modified by MEMANTINE
● Methylxyp: enhanced hypotensive effect when baclofen or tizanidine given with METHYLPAPA
● Metoclopramide: effects of suxamethonium enhanced by METOCLOPRAMIDE
● Moxonidine: enhanced hypotensive effect when baclofen or tizanidine given with MOXONIDINE
● Nitrites: enhanced hypotensive effect when baclofen or tizanidine given with NITRATES
● Oestrogens: plasma concentration of tizanidine possibly increased by OESTROGENS (increased risk of toxicity)
● Parasympathomimetics: effects of non-depolarising muscle relaxants possibly antagonised by DONEPEZIL; effects of suxamethonium possibly enhanced by DONEPEZIL; effects of suxamethonium enhanced by GALANTAMINE, NEOSTIGMINE, PYRIDOSTIGMINE and RIVASTIGMINE; effects of non-depolarising muscle relaxants antagonised by NEOSTIGMINE, PYRIDOSTIGMINE and RIVASTIGMINE
● Progestogens: plasma concentration of tizanidine possibly increased by PROGESTOGENS (increased risk of toxicity)
● Symptomimetics, Beta2: effects of suxamethonium enhanced by BAMBUTEROL
● Vasodilator Antihypertensives: enhanced hypotensive effect when baclofen or tizanidine given with HYDRAZINE; enhanced hypotensive effect when baclofen or tizanidine given with MINOXIDIL; enhanced hypotensive effect when baclofen or tizanidine given with SODIUM NITROPRUSSIDE

Muscle Relaxants, depolarising

See Muscle Relaxants

Muscle Relaxants, non-depolarising

See Muscle Relaxants

Mycophenolate

Antacids: absorption of mycophenolate reduced by ANTACIDS
● Antibacterials: bioavailability of mycophenolate possibly reduced by METRONIDAZOLE and NORFLOXACIN; plasma concentration of mycophenolate possibly reduced by CO-AMOXICLAV; plasma concentration of active metabolite of mycophenolate reduced by Rifampicin
● Antivirals: mycophenolate increases plasma concentration of ACICLOVIR and VALACICLOVIR, also plasma concentration of inactive metabolite of mycophenolate increased; mycophenolate possibly increases plasma concentration of...
Mycophenolate

Antivirals (continued)

**GANCICLOVIR** and **VALGANCICLOVIR**, also plasma concentration of inactive metabolite of mycophenolate possibly increased

- **Colestilan**: manufacturer of colestilan advises give mycophenolate at least 1 hour before or 5 hours after **COLESTILAN**
- **Iron Salts**: absorption of mycophenolate reduced by oral **IRON SALTS**
- **Lipid-regulating Drugs**: absorption of mycophenolate reduced by **COLESTYRAMINE**
- **Sevelamer**: plasma concentration of mycophenolate possibly reduced by **SEVELAMER**

**Nabumetone** see NSAIDs

**Nadolol** see Beta-blockers

**Nalidixic Acid** see **Aminoglycosides**

**Naloxone** see Quinolones

**Naltrexone**

- Analgesics: manufacturer of naloxone advises avoid concomitant use with **OPIOID ANALGESICS**

**Nandrolone** see Anabolic Steroids

**Naproxen** see NSAIDs

**Naratriptan** see **SHT-receptor Agonists (under HT)**

**Natalizumab**

- Antipsychotics: avoid concomitant use of cytoxotics with **CLOzapine** (increased risk of agranulocytosis)
- **Vaccines**: risk of generalised infections when monoclonal antibodies given with live **VACCINES**—avoid concomitant use

**Nateglinide** see Antidiabetics

**Nebivolol** see Beta-blockers

**Nefopam**

- Antidepressants: manufacturer of nefopam advises avoid concomitant use with **MAOIs**; side-effects possibly increased when nefopam given with **TRICYCLICS**
- Antimuscarinics: increased risk of antimuscarinic side-effects when nefopam given with **ANTIMUSCARINICS**

**Neomycin** see Aminoglycosides

**Neostigmine** see Parasympathomimetics

**Nevirapine**

- Analgesics: nevirapine possibly reduces plasma concentration of METHADONE
- **Antibacterials**: nevirapine reduces plasma concentration of **CLARITHROMYCIN** (but concentration of an active metabolite increased), also plasma concentration of nevirapine increased; nevirapine possibly increases plasma concentration of **RIFABUTIN**; plasma concentration of nevirapine reduced by **RIFAMPICIN**—avoid concomitant use
- **Anticoagulants**: nevirapine may enhance or reduce anticoagulant effect of **WARFARIN**
- **Antidepressants**: plasma concentration of nevirapine reduced by **ST JOHN’S WORT**—avoid concomitant use
- Antiepileptics: plasma concentration of nevirapine reduced by **CARRABAMAZEPINE**
- Antifungals: nevirapine reduces plasma concentration of **KETOCONAZOLE**—avoid concomitant use; plasma concentration of nevirapine reduced by **FLUCONAZOLE**; nevirapine possibly reduces plasma concentration of **CASPOFUNGIN** and **ITRACONAZOLE**—consider increasing dose of caspofungin and itraconazole
- Antipsychotics: nevirapine possibly reduces plasma concentration of **ARIPIPRAZOLE** (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature)
- Antivirals: nevirapine possibly reduces plasma concentration of **ATAZANAVIR** and **ETRAVIRINE**—avoid concomitant use; manufacturer of nevirapine advises avoid concomitant use with **BOCEPREVIR** and **RILPIVIRINE**; avoidance of nevirapine advised by manufacturer of **DACLATASVIR** (plasma concentration of daclatasvir possibly reduced); nevirapine possibly reduces the plasma concentration of **DOLUTEGRAVIR** (see under Dolutegravir, p. 557); nevirapine reduces plasma concentration of **EFAVIRENZ**—avoid concomitant use; avoidance of nevirapine advised by manufacturer of **ELVITEGRAVIR**; nevirapine possibly reduces plasma concentration of **FOSAMPRENAVIR**—avoid unboosted fosamprenavir; nevirapine reduces plasma concentration of **INDINAVIR**; nevirapine possibly reduces plasma concentration of **LOPINAVIR** and **TELAPREVIR**—consider increasing dose of lopinavir and telaprevir; nevirapine possibly reduces plasma concentration of **SIMEPREVIR**—manufacturer of simeprevir advises avoid concomitant use; increased risk of granulocytopenia when nevirapine given with **ZIDOVUDINE**
- Colestipol: manufacturer of nevirapine advises avoid concomitant use with **COLESTIPOL**
- Oestrogens: nevirapine accelerates metabolism of **OESTROGENS** (reduced contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see **Contraceptive Interactions in BNF**)
- Oralstat: absorption of nevirapine possibly reduced by **ORLISTAT**
- Progestogens: nevirapine accelerates metabolism of **PROGESTOGENS** (reduced contraceptive effect with combined oral contraceptives, progestogen-only oral contraceptives, contraceptive patches, vaginal rings, etonogestrel-releasing implant, and emergency hormonal contraception—see **Contraceptive Interactions in BNF**)

**Nicardipine** see Calcium-channel Blockers

**Niconorandil**

- Alcohol: hypotensive effect of nicorandil possibly enhanced by **ALCOHOL**
- Antidepressants: enhanced hypotensive effect when nicorandil given with **MAOIs**; hypotensive effect of nicorandil possibly enhanced by **TRICYCLICS**
- **Avanafil**: hypotensive effect of nicorandil significantly enhanced by **AVANafil** (avoid concomitant use)
- Sildenafil: hypotensive effect of nicorandil significantly enhanced by **SILDENAFIL** (avoid concomitant use)
- **Tadalafil**: hypotensive effect of nicorandil significantly enhanced by **TADALAFIL** (avoid concomitant use)
- **Vardenafil**: possible increased hypotensive effect when nicorandil given with **VARDENAFIL**—avoid concomitant use
- Vasodilator Antihypertensives: possible enhanced hypotensive effect when nicorandil given with **HYDRALAZINE, MINOXIDIL, or SODIUM NITROPRUSSIODE**

**Nicotine**

- Anti-arrhythmics: nicotine possibly enhances effects of **ADRENOSINE**

**Nicotinic Acid**

- **Lipid-regulating Drugs**: increased risk of myopathy when nicotinic acid given with **STATINS** (applies to lipid regulating doses of nicotinic acid)

**Nifedipine** see Calcium-channel Blockers

**Nilotinib**

- Antibacterials: manufacturer of nilotinib advises avoid concomitant use with **CLARITHROMYCIN** and **TELITHROMYCIN**; plasma concentration of nilotinib reduced by **RIFAMPICIN**—avoid concomitant use
- **Antifungals**: plasma concentration of nilotinib increased by **KETOCONAZOLE**—avoid concomitant use; manufacturer of nilotinib advises avoid concomitant use with **ITRACONAZOLE** and **VORICONAZOLE**
- Antipsychotics: avoid concomitant use of cytoxotics with **CLOzapine** (Increased risk of agranulocytosis)
- **Antivirals**: avoidance of nilotinib advised by manufacturer of **BOCEPREVIR**; plasma concentration of nilotinib possibly increased by **RITONAVIR**—manufacturer of nilotinib advises avoid concomitant use
- **Anxiolytics and Hypnotics**: nilotinib increases plasma concentration of **MILODILAM**
- **Grapefruit Juice**: manufacturer of nilotinib advises avoid concomitant use with **GRAPEFRUIT JUICE**
- **Lipid-regulating Drugs**: separating administration from nilotinib by 12 hours advised by manufacturer of **LOMITAPIDE**

**Nintedanib** see Calcium-channel Blockers

**Norethandrolone**

- Antibacterials: plasma concentration of norethandrolone reduced by **RIFAMPICIN**—avoid concomitant use
- Antifungals: plasma concentration of norethandrolone increased by **KETOCONAZOLE**

**Naproxen**

- Antivirals (continued)

**Nevirapine**

- Antivirals (continued)

**Naproxen**

- Antivirals (continued)

**Nevirapine**

- Antivirals (continued)
Interactions | Appendix 1

**Nitrazepam** see Anxiolytics and Hypnotics

**Nitrofurantoin**
- Antacids: absorption of nitrofurantoin reduced by ORAL MAGNESIUM SALTS (as magnesium trilisylcate)
- Antibacterials: nitrofurantoin possibly antagonises effects of NALIDIXIC ACID
- Sulfipyrazone: excretion of nitrofurantoin reduced by SULFONYLUREAS (increased risk of toxicity)
- Vaccines: antibacterials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF

**Nitromidazoles** see Metronidazole and Tinidazole

**Nitrous Oxide** see Anaesthetics, General

**Nitrate Antagonists**
- Analgesics: enhanced hypotensive effect when nitrates given with ACETAMINOPHEN
- Antiarrhythmics: enhanced hypotensive effect when nitrates given with AMIODARONE
- Antiarrhythmics: enhanced hypotensive effect when nitrates given with DIGITALIS
- Asthma: enhanced hypotensive effect when nitrates given with beta-blockers
- Asthma: enhanced hypotensive effect when nitrates given with beta-blockers
- Caoids: enhanced hypotensive effect when nitrates given with clofibrate
- Calcium-channel blockers: enhanced hypotensive effect when nitrates given with calcium-channel blockers
- Clonidine: enhanced hypotensive effect when nitrates given with clonidine
- Corticosteroids: enhanced hypotensive effect of nitrates antagonised by corticosteroids
- Diazoxide: enhanced hypotensive effect when nitrates given with diazoxide
- Diuretics: enhanced hypotensive effect when nitrates given with diuretics
- Dopamine: enhanced hypotensive effect when nitrates given with dopamine
- Methyldopa: enhanced hypotensive effect when nitrates given with methyldopa
- Moxisylyte: enhanced hypotensive effect when nitrates given with moxisylyte
- Moxonidine: enhanced hypotensive effect when nitrates given with moxonidine
- Muscle relaxants: enhanced hypotensive effect when nitrates given with baclofen or tizanidine
- Oestrogens: enhanced hypotensive effect of nitrates antagonised by oestrogens
- Prostaglandins: enhanced hypotensive effect when nitrates given with alprostadil
- Riociguat: possible enhanced hypotensive effect when nitrates given with riociguat
- Sildenafil: hypotensive effect of nitrates significantly enhanced by sildenafil
- Tadalafil: enhanced hypotensive effect of nitrates significantly enhanced by tadalafil
- Vardenafil: possible increased hypotensive effect when nitrates given with vardenafil
- Vasodilator Antihypertensives: enhanced hypotensive effect when nitrates given with hydralazine, minoxidil or sodium nitroprusside

**Nitrates**
- ACE Inhibitors: enhanced hypotensive effect when nitrates given with ACE INHIBITORS
- ADRENERGIC NEURONE BLOCKERS: enhanced hypotensive effect when nitrates given with ADRENERGIC NEURONE BLOCKERS
- Alcohol: enhanced hypotensive effect when nitrates given with alcohol
- Aldesleukin: enhanced hypotensive effect when nitrates given with aldesleukin
- Alpha-blockers: enhanced hypotensive effect when nitrates given with alpha-blockers
- Anaesthetics, General: enhanced hypotensive effect when nitrates given with general anaesthetics
- Analgesics: hypotensive effect of nitrates antagonised by NSAIDS
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when nitrates given with angiotensin-II receptor antagonists
- Antiarrhythmics: effects of sublingual tablets of nitrates reduced by failure to dissolve under tongue owing to dry mouth
- Anticoagulants: infusion of glyceryl trinitrate reduces anticoagulant effect of heparin
- Antidepressants: enhanced hypotensive effect when nitrates given with MAOIS; effects of sublingual tablets of nitrates possibly reduced by tricyclic-related antidepressants
- Antimuscarinics: effects of sublingual tablets of nitrates possibly reduced by antimuscarinics
- Antipsychotics: enhanced hypotensive effect when nitrates given with phenothiazines
- Anxiety and Hypnotics: enhanced hypotensive effect when nitrates given with anxiolytics and hypnotics
- Avanafil: hypotensive effect of nitrates significantly enhanced by avanafil (avoid concomitant use)
- Beta-blockers: enhanced hypotensive effect when nitrates given with beta-blockers
- Calcium-channel blockers: enhanced hypotensive effect when nitrates given with calcium-channel blockers
- Clonidine: enhanced hypotensive effect when nitrates given with clonidine
- Corticosteroids: enhanced hypotensive effect of nitrates antagonised by corticosteroids
- Diazoxide: enhanced hypotensive effect when nitrates given with diazoxide
- Diuretics: enhanced hypotensive effect when nitrates given with diuretics
- Dopamine: enhanced hypotensive effect when nitrates given with dopamine
- Methyldopa: enhanced hypotensive effect when nitrates given with methyldopa
- Moxisylyte: enhanced hypotensive effect when nitrates given with moxisylyte
- Moxonidine: enhanced hypotensive effect when nitrates given with moxonidine
- Muscle relaxants: enhanced hypotensive effect when nitrates given with baclofen or tizanidine
- Oestrogens: enhanced hypotensive effect of nitrates antagonised by oestrogens
- Prostaglandins: enhanced hypotensive effect when nitrates given with alprostadil
- Riociguat: possible enhanced hypotensive effect when nitrates given with riociguat
- Sildenafil: hypotensive effect of nitrates significantly enhanced by sildenafil
- Tadalafil: enhanced hypotensive effect of nitrates significantly enhanced by tadalafil
- Vardenafil: possible increased hypotensive effect when nitrates given with vardenafil
- Vasodilator Antihypertensives: enhanced hypotensive effect when nitrates given with hydralazine, minoxidil or sodium nitroprusside

**Nitroimidazoles** see Metronidazole and Tinidazole

**Nitrous Oxide** see Anaesthetics, General

**Nizatidine** see Histamine H2-antagonists

**Nobilegestromin** see Progestogens

**Noradrenaline (norepinephrine)** see Sympathomimetics

**Norfenephrine** note norfenephrine interactions as for noradrenaline, see under sympathomimetics

**Norfloxacin** see Quinolones

**Noroxicin** see Progestogens

**Norgestrel** see Progestogens

**Normal Immunoglobulin** see Immunoglobulins

**Nortriptyline** see Antidepressants, Tricyclic

**NSAIDs**
- **NOTE**: see also aspirin. Interactions do not generally apply to topical NSAIDs
- ACE inhibitors: increased risk of renal impairment when NSAIDs given with ACE inhibitors, also hypotensive effect antagonised
- Adrenergic Neurone Blockers: NSAIDs antagonise hypotensive effect of adrenergic neurone blockers
- Allikiren: NSAIDs possibly antagonise hypotensive effect of allikiren
- Alpha-blockers: NSAIDs antagonise hypotensive effect of alpha-blockers
- Analgesics: avoid concomitant use of NSAIDs with NSAI or aspirin (increased side-effects); avoid concomitant use of NSAIDs with ketorolac (increased side-effects and haemorrhage); ibuprofen possibly reduces antiplatelet effect of aspirin
- Angiotensin-II Receptor Antagonists: increased risk of renal impairment when NSAIDs given with angiotensin-II receptor antagonists, also hypotensive effect antagonised
- Antacids: absorption of acetaminophen possibly reduced by antacids
- Antibacterials: indomethacin possibly increases plasma concentration of amikacin and gentamicin in neonates; plasma concentration of cefoxitin, diclofenac and etoricoxib reduced by rifampicin; possible increased risk of convulsions when NSAIDs given with quinolones
- Anticoagulants: increased risk of haemorrhage when intravenous diclofenac given with anticoagulants (avoid concomitant use, including low-dose heparins); increased risk of haemorrhage when ketorolac given with anticoagulants (avoid concomitant use, including low-dose heparins); NSAIDs possibly enhance anticoagulant effect of coumarins and phenindione; possible increased risk of bleeding when NSAIDs given with dabigatran or heparins
- Antidepressants: increased risk of bleeding when NSAIDs given with SSRIs or venlafaxine
- Antidiabetics: NSAIDs possibly enhance effects of sulfonylureas
- Antiepileptics: acetaminophen possibly reduces excretion of fosphenytoin and phenytoin (increased risk of toxicity)
- Antifungals: plasma concentration of parecoxib increased by fluconazole (reduce dose of parecoxib); plasma concentration of cefoxitin increased by fluconazole (halve dose of cefoxitin); plasma concentration of flurbiprofen and ibuprofen increased by fluconazole; plasma concentration of diclofenac and ibuprofen increased by voriconazole
- Antipsychotics: possible severe drowsiness when acetaminophen or indomethacin given with haloperidol
### Appendix 1 Interactions

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<td><strong>NSAIDs</strong> (continued)</td>
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<tr>
<td>- Antivirals: plasma concentration of piroxicam increased by</td>
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<td>- Ritonavir (risk of toxicity)—avoid concomitant use; plasma concentration of NSAI<em>DS possibly increased by Ritonavir; increased risk of haematological toxicity when NSAI</em>DS given with Zidovudine</td>
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<tr>
<td>- Beta-blockers: NSAI*DS antagonise hypnotic effect of Beta-blockers</td>
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<tr>
<td>- Calcium-channel Blockers: NSAI*DS antagonise hypnotic effect of Calcium-channel blockers</td>
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<tr>
<td>- Cardiac Glycosides: NSAI*DS possibly increase plasma concentration of Cardiac glycosides, also possible exacerbation of heart failure and reduction of renal function</td>
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<tr>
<td>- Ciclosporin: increased risk of nephrotoxicity when NSAI*DS given with Ciclosporin; plasma concentration of ciclofenac increased by Ciclosporin (halve dose of ciclofenac)</td>
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<tr>
<td>- Clonidine: NSAI*DS antagonise hypnotic effect of Clonidine</td>
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<tr>
<td>- Clopidogrel: increased risk of bleeding when NSAI*DS given with Clopidogrel</td>
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<tr>
<td>- Corticosteroids: increased risk of gastro-intestinal bleeding and ulceration when NSAI*DS given with Corticosteroids</td>
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<tr>
<td>- Cytoxotics: NSAI<em>DS probably reduce excretion of Methotrexate (increased risk of toxicity); di clofenac, ibuprofen, indomethacin, ketoprofen, meloxicam and naproxen reduce excretion of Methotrexate (increased risk of toxicity); NSAI</em>DS possibly reduce renal excretion of Pemetermin—consult product literature; increased risk of bleeding when NSAI<em>DS given with Erol tinib; avoidance of mefenamic acid advised by manufacturer of Regorafenib; Diclofenac enhances effects of Iloprost (increased risk of toxicity); Diazoxide: NSAI</em>DS antagonise hypnotic effect of Diazoxide</td>
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<tr>
<td>- Dimethyl sulfoxide: avoid concomitant use of sulindac with</td>
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<tr>
<td>- Diuretics: risk of nephrotoxicity of NSAI<em>DS increased by Diuretics, also antagonism of diuretic effect; indomethacin and ketorolac antagonise effects of Diuretics; excretion of acetaminophen possibly increased by Fluconazole; NSAI</em>DS possibly antagonise diuretic effect of Potassium Canrenoate; occasional reports of reduced renal function when indomethacin given with Triam terene—avoid concomitant use; possible increased risk of hyperkalaemia when NSAI*DS given with Potassium-Sparing Diuretics and Aldosterone Antagonists; increased risk of hyperkalaemia when indomethacin given with Potassium-Sparing Diuretics and Aldosterone Antagonists</td>
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<tr>
<td>- Iloprost: increased risk of bleeding when NSAI*DS given with Iloprost</td>
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<tr>
<td>- Lipid-regulating Drugs: excretion of meloxicam increased by Colestyramine</td>
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<td>- Lithium: NSAI*DS reduce excretion of Lithium (increased risk of toxicity); ketorolac reduces excretion of Lithium (increased risk of toxicity)—avoid concomitant use</td>
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<td>- Methyl dopa: NSAI*DS antagonise hypnotic effect of Methyl dopa</td>
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<tr>
<td>- Mifamurtide: avoidance of high doses of NSAI*DS advised by manufacturer of Mifamurtide</td>
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<td>- Moxonidine: NSAI*DS antagonise hypnotic effect of Moxonidine</td>
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<tr>
<td>- Muscle Relaxants: ibuprofen reduces excretion of Baclofen (increased risk of toxicity); NSAI*DS possibly reduce excretion of Baclofen (increased risk of toxicity)</td>
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<tr>
<td>- Nitrates: NSAI*DS antagonise hypnotic effect of Nitrates</td>
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<tr>
<td>- Oestrogens: etoricoxib increases plasma concentration of Ethinylestradiol</td>
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<tr>
<td>- Pencillamine: possible increased risk of nephrotoxicity when NSAI*DS given with Pencillamine</td>
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<tr>
<td>- Pentoxifylline: possible increased risk of bleeding when NSAI*DS given with Pentoxifylline; increased risk of bleeding when ketorolac given with Pentoxifylline (avoid concomitant use)</td>
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<tr>
<td>- Prasugrel: possible increased risk of bleeding when NSAI*DS given with Prasugrel</td>
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<tr>
<td>- Tacrolimus: possible increased risk of nephrotoxicity when NSAI*DS given with Tacrolimus; increased risk of nephrotoxicity when ibuprofen given with Tacrolimus</td>
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<tr>
<td><strong>NSAIDs</strong> (continued)</td>
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<tr>
<td>- Vasodilator Antihypertensives: NSAI*DS antagonise hypnotic effect of Hydralazine, Minoxidil and Sodium Nitroprusside</td>
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<td>- Obinutuzumab</td>
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<tr>
<td>- Antipsychotics: avoid concomitant use of cytoxotics with Clozapine (increased risk of agranulocytosis)</td>
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<tr>
<td>- Vaccines: risk of generalised infections when monoclonal antibodies given with live Vaccines—avoid concomitant use</td>
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<td>- Octreotide</td>
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<tr>
<td>- Antibiotics: octreotide possibly reduces requirements for Antibiotics</td>
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<td>- Ciclosporin: octreotide reduces plasma concentration of Ciclosporin</td>
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<tr>
<td>- Dapompinergics: octreotide increases plasma concentration of Bromocriptine</td>
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<tr>
<td>- Ulcer-healing Drugs: octreotide possibly delays absorption of Cimetidine</td>
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<td>- Oestrogens</td>
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<td>- ACE Inhibitors: oestrogens antagonise hypnotic effect of ACE Inhibitors</td>
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<tr>
<td>- Adrenergic Neurone Blockers: oestrogens antagonise hypnotic effect of Adrenergic Neurone Blockers</td>
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<tr>
<td>- Alpha-blockers: oestrogens antagonise hypnotic effect of Alpha-blockers</td>
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<tr>
<td>- Aminophylline: oestrogens increase plasma concentration of Aminophylline (consider reducing dose of aminophylline)</td>
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<tr>
<td>- Analgesics: plasma concentration of ethinylestradiol increased by Etoricoxib</td>
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<tr>
<td>- Angiotensin-II Receptor Antagonists: oestrogens antagonise hypnotic effect of Angiotensin-II Receptor Antagonists</td>
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<tr>
<td>- Antibacterials: plasma concentration of estradiol increased by Erythromycin; metabolism of oestrogens accelerated by Rifamycins (reduced contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF)</td>
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<tr>
<td>- Anticoagulants: oestrogens may enhance or reduce anticoagulant effect of Coumarins; oestrogens antagonise anticoagulant effect of Phenindione</td>
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<tr>
<td>- Antidepressants: contraceptive effect of oestrogens reduced by St John’s wort (avoid concomitant use); oestrogens antagonise antidepressant effect of Tricyclics (but side-effects of tricyclics possibly increased due to increased plasma concentration)</td>
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<tr>
<td>- Antibiotics: oestrogens antagonise hyperoxygenic effect of Antibiotics</td>
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<tr>
<td>- Antiepileptics: metabolism of oestrogens accelerated by Carbamazepine, Eslicarbazepine, Fosphenytoin, Oxcarbazepine, Pheno barbital, Phenytoin, Primidone, Rufinamide and Topiramate (reduced contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF); oestrogens reduce plasma concentration of Lamotrigine—consider increasing dose of lamotrigine; ethinylestradiol possibly reduces plasma concentration of Sodium Valproate and Valproic Acid</td>
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<tr>
<td>- Antiinflamas: oestrogens increase plasma concentration of Voriconazole; anecdotal reports of contraceptive failure and menstrual irregularities when oestrogens given with Griseofulvin; anecdotal reports of contraceptive failure when oestrogens given with Midazolam; occasional reports of breakthrough bleeding when oestrogens (used for contraception) given with Terbinafine</td>
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<tr>
<td>- Antivirals: plasma concentration of ethinylestradiol increased by Atazanavir; metabolism of oestrogens accelerated by Nevirapine and Ritonavir (reduced contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF); plasma concentration of ethinylestradiol possibly reduced by Clozapine—manufacturer of telaprevir advises additional contraceptive precautions</td>
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<tr>
<td>- Anxiolytics and Hypnotics: oestrogens possibly increase plasma concentration of Chlor Diazepoxide, Diazepam and Nitrazepam; oestrogens possibly reduce plasma concentration of Lorazepam, Oxazepam and Temazepam; oestrogens increase plasma concentration of Melatonin</td>
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Interactions

**Appendix 1**

**Oestrogens** (continued)

- Aprepitant: possible contraceptive failure of hormonal contraceptives involving oestrogens when given with β-blockers; oestrogens antagonise hypotensive effect of β-blockers
- Bosentan: possible contraceptive failure of hormonal contraceptives containing oestrogens when given with bosentan (alternative contraception recommended)
- Calcium-channel blockers: oestrogens antagonise hypotensive effect of calcium-channel blockers
- Ciclosporin: oestrogens possibly increase plasma concentration of ciclosporin
- Clonidine: oestrogens antagonise hypotensive effect of clonidine
- Cobicistat: metabolism of oestrogens accelerated by Cobicistat (reduced contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF)
- Corticosteroids: oral contraceptives containing oestrogens increase plasma concentration of corticosteroids
- Cytotoxics: possible reduction in contraceptive effect of oestrogens advised by manufacturer of CRIZOTINIB and vemurafenib; possible reduced contraceptive effect of hormonal contraceptives containing oestrogens advised by manufacturer of dabrafenib (alternative contraception recommended)
- Diuretics: oestrogens antagonise diuretic effect of diuretics
- Dopaminergics: oestrogens increase plasma concentration of dopaminergics
- Fosaprepitant: possible contraceptive failure of hormonal contraceptives containing oestrogens advised by manufacturer of aprepitant
- Lipid-regulating Drugs: absorption of ethinylestradiol reduced by colesvelam; plasma concentration of ethinylestradiol increased by atorvastatin and rosuvastatin; separating administration from oestrogens by 12 hours advised by manufacturer of lomitapide
- Methyl dopa: oestrogens antagonise hypotensive effect of methyl dopa
- Modafinil: metabolism of oestrogens accelerated by modafinil (reduced contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF)
- Moxonidine: oestrogens antagonise hypotensive effect of moxonidine
- Muscle Relaxants: oestrogens possibly increase plasma concentration of tizanidine (increased risk of toxicity)
- Nitrates: oestrogens antagonise hypotensive effect of nitrates
- Somatropin: oestrogens (when used as oral replacement therapy) may increase dose requirements of somatropin
- Tacrolimus: ethinylestradiol possibly increases plasma concentration of tacrolimus
- Teriflunomide: plasma concentration of ethinylestradiol increased by teriflunomide
- Theophylline: oestrogens increase plasma concentration of theophylline (consider reducing dose of theophylline)
- Thyroid Hormones: oestrogens may increase requirements for thyroid hormones in hypothyroidism
- Vasodilators: oestrogens antagonise hypotensive effect of hydralazine, minoxidil and sodium nitroprusside

**Oestrogens, conjugated** see Oestrogens

**Ofatumumab**

- Antipsychotics: avoid concomitant use of cytoxics with ofatumumab
- Clozapine (increased risk of agranulocytosis)
- Vaccines: risk of generalised infections when monoclonal antibodies given with live vaccines—avoid concomitant use

**Ofoxacin** see Quinolones

**Olanzapine** see Antipsychotics

**Olmesartan** see Angiotensin-II Receptor Antagonists

**Olodaterol** see Sympathomimetics, Beta2

**Omeprazole** see Proton Pump Inhibitors

**Ondansetron** see 5HT-3 Receptor Antagonists (under HT)

**Opioid Analgesics**

- Alcohol: enhanced hypotensive and sedative effects when opioid analgesics given with alcohol
- Anaesthetics, General: fentanyl inhibits metabolism of etomidate, (consider reducing dose of etomidate); opioid analgesics possibly enhance effects of intravenous general anaesthetics and volatile liquid general anaesthetics
- Analgesics: avoidance of buprenorphine advised by manufacturer of fentanyl; manufacturer of fentanyl advises avoid concomitant use with pentazocine
- Antibacterials: plasma concentration of fentanyl possibly increased by clarithromycin; plasma concentration of allantoin increased by erythromycin; metabolism of allantoin, codeine, fentanyl, methadone and morphine accelerated by rifampicin (reduced effect); metabolism of oxycodone possibly accelerated by rifampicin; increased risk of ventricular arrhythmias when methadone given with delamanid; manufacturer of pethidine advises avoid concomitant use with isoniazid; metabolism of oxycodone inhibited by telithromycin; possible increased risk of ventricular arrhythmias when methadone given with telithromycin
- Anticoagulants: tramadol enhances anticoagulant effect of coumarins
- Antidepressants: plasma concentration of methadone possibly increased by fluoxetine, fluvoxamine, paroxetine and sertraline; possible increased serotoninergic effects when pethidine or tramadol given with duloxetine; possible increased serotoninergic effects when tramadol given with mirtazapine or venlafaxine; possible CNS excitation or depression (hypertension or hypotension) when opioid analgesics given with MAOIs—some manufacturers advise avoid concomitant use and for 2 weeks after stopping MAOIs; possible increased serotoninergic effects and increased risk of convulsions when tramadol given with MAOIs—some manufacturers advise avoid concomitant use and for 2 weeks after stopping MAOIs; CNS excitation or depression (hypertension or hypotension) when pethidine given with MAOIs—avoid concomitant use and for 2 weeks after stopping MAOIs; possible increased serotoninergic effects when fentanyl given with MAOIs, SSRI-RELATED ANTIDEPRESSANTS OR SSRIS; possible CNS excitation or depression (hypertension or hypotension) when opioid analgesics given with moclobemide—moclobemide advises consider reducing dose of opioid analgesics; possible CNS excitation or depression (hypertension or hypotension) when dexamethorphan or pethidine given with moclobemide—avoid concomitant use; increased risk of CNS toxicity when tramadol given with SSRIS or tricyclics; plasma concentration of methadone possibly reduced by St John’s Wort; sedative effects possibly increased when opioid analgesics given with tricyclics
- Antiepileptics: effects of tramadol reduced by carbamazepine; plasma concentration of methadone reduced by carbamazepine, phenobarbital and primidone; metabolism of fentanyl possibly accelerated by carbamazepine, fosphenytoin and phenytoin (reduced effect); dextropropoxyphene enhances effects of carbamazepine; metabolism of methadone accelerated by fosphenytoin and phenytoin (reduced effect and risk of withdrawal effects); possible increased risk of pethidine toxicity when given with fosphenytoin and phenytoin; morphine increases bioavailability of gabapentin
- Antifungals: metabolism of buprenorphine inhibited by ketoconazole (reduce dose of buprenorphine); possible increased risk of ventricular arrhythmias when methadone given with ketoconazole—manufacturer of ketoconazole advises avoid concomitant use; plasma concentration of oxycodone increased by itraconazole and ketoconazole and voriconazole; metabolism of allantoin inhibited by fluconazole (risk of prolonged or delayed respiratory depression); plasma concentration of methadone increased by fluconazole; metabolism of allantoin possibly inhibited by itraconazole; plasma concentration of methadone...
Opioid Analgesics
- Antifungals (continued) possibly increased by:itraconazole (increased risk of ventricular arrhythmias); plasma concentration of alfentanil and methadone increased by:voriconazole (consider reduced dose of alfentanil and methadone); plasma concentration of fentanyl possibly increased by:triazoles
- Antihistamines: sedative effects possibly increased when opioid analgesics given with:sedating antihistamines
- Antimicrobials: avoidance of methadone advised by manufacturer of:artemisinil with piperaquine (possible risk of ventricular arrhythmias)
- Antimuscarinics: possibility increased risk of antimuscarinic side-effects when codeine given with:antimuscarinics
- Antidepressants: enhanced hypotensive and sedative effects when opioid analgesics given with:antipsychotics; increased risk of ventricular arrhythmias when methadone given with:antipsychotics that prolong the QT interval; increased risk of convulsions when tramadol given with:antipsychotics; increased risk of ventricular arrhythmias when methadone given with:amisulpride—avoid concomitant use
- Antivirals: plasma concentration of methadone possibly reduced by:abacavir, nevirapine and rifampirine; plasma concentration of methadone possibly affected by:boceprevir; possible increased risk of prolonged sedation and respiratory depression when buprenorphine given with:boceprevir; methadone possibly reduces plasma concentration of:didanosine; plasma concentration of methadone reduced by:efavirenz, fosamprenavir and ritonavir; plasma concentration of buprenorphine possibly increased by:ritonavir; plasma concentration of alfentanil and fentanyl increased by:ritonavir; plasma concentration of pethidine reduced by:ritonavir, but plasma concentration of toxic pethidine metabolite increased (avoid concomitant use); plasma concentration of morphine possibly reduced by:ritonavir; plasma concentration of dextropropoxyphene increased by:ritonavir (risk of toxicity)—avoid concomitant use; increased risk of ventricular arrhythmias when alfentanil, fentanyl or methadone given with:saqunivarin—avoid concomitant use; caution with methadone advised by manufacturer of:telaprevir (risk of ventricular arrhythmias); buprenorphine possibly reduces plasma concentration of:tipranavir; methadone possibly increases plasma concentration of:zidovudine
- Antiepileptics: increased sedative effect when opioid analgesics given with:anxiolytics and hypnotics; fentanyl possibly inhibits metabolism of:miazolam
- Atomoxetine: increased risk of ventricular arrhythmias when methadone given with:atomoxetine; possible increased risk of convulsions when tramadol given with:atomoxetine
- Beta-blockers: morphine possibly increases plasma concentration of:esmolol
- Calcium-channel Blockers: metabolism of alfentanil inhibited by:diltiazem (risk of prolonged or delayed respiratory depression)
- Cytoxotics: possible increased risk of ventricular arrhythmias when methadone given with:busuliniib; caution with alfentanil and fentanyl advised by manufacturer of:crizotinib; possible increased risk of ventricular arrhythmias when methadone given with:vandetanib—avoid concomitant use
- Dapoxetine: possible increased risk of sexualerogenic effects when tramadol given with:dapoxetine (manufacturer of dapoxetine advises tramadol should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping tramadol)
- Dopaminedon: opioid analgesics antagoing effects of:domperidone on gastrointestinal activity
- Dopaminergics: avoid concomitant use of dextromethorphan with:rassagline; risk of CNS toxicity when pethidine given with:rassagline (avoid pethidine for 2 weeks after rasagline); avoidance of opioid analgesics advised by manufacturer of:selegiline; hyperpyrexia and CNS toxicity reported when pethidine given with:selegiline (avoid concomitant use)

Opioid Analgesics (continued)
- Hormone Antagonists: plasma concentration of dextromethorphan increased by:abiraterone
- SH2-receptor Antagonists: effects of tramadol possibly antagonised by:ondansetron
- Memantine: increased risk of CNS toxicity when dextromethorphan given with:memantine (manufacturer of memantine advises avoid concomitant use)
- Metoclopramide: opioid analgesics antagonise effects of:metoclopramide on gastrointestinal activity
- Muscle Relaxants: increased sedative effect when fentanyl or morphine given with:baclofen
- Nalmefene: avoidance of opioid analgesics advised by manufacturer of:nalmefene
- Sodium Oxylate: opioid analgesics enhance effects of:sodium oxybate (avoid concomitant use)
- Ulcer-healing Drugs: metabolism of opioid analgesics inhibited by: CIMETIDINE (increased plasma concentration)

Oritavancin
- Anticoagulants: oritavancin possibly increases plasma concentration of:warfarin
- Vaccines: antibiotics inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF

Orlistat
- Anti-arrhythmics: orlistat possibly reduces plasma concentration of:amiodarone
- Anticoagulants: manufacturer of orlistat recommends monitoring anticoagulant effect of:coumarins
- Antidietetics: manufacturer of orlistat advises avoid concomitant use with:acarbose
- Antiparkinsonism: increased risk of convulsions when orlistat given with:antiepileptics
- Antivirals: orlistat possibly reduces absorption of:abacavir, atazanavir, darunavir, didanosine, efavirenz, elvitegravir, emtricitabine, enfuvirtide, etravirine, fosamprenavir, indinavir, lamivudine, lopinavir, maraviroc, nevirapine, raltegravir, rifampirine, ritonavir, saquinavir, stavudine, tenofovir, tipranavir and:ZIDOVUDINE
- Ciclosporin: orlistat possibly reduces absorption of:ciclosporin
- Thyroid Hormones: possible increased risk of hypothyroidism when orlistat given with:levothyroxine

Orphenadrine see Antimuscarinics Oxaliplatin see Platinum Compounds Oxandrolone see Anabolic Steroids Oxazepam see Anxiolytics and Hypnotics

Oxcarbazepine
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by:MAOIs and:TRICYCLIC-RELATED ANTIDEPRESSANTS (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by:SSRIs and:TRICYCLICS (convulsive threshold lowered)
- Antiepileptics: oxcarbazepine sometimes reduces plasma concentration of:carbamazepine (but concentration of an active metabolite of carbamazepine may be increased), also plasma concentration of an active metabolite of oxcarbazepine often reduced; avoidance of oxcarbazepine advised by manufacturer of:eslicarbazepine; oxcarbazepine increases plasma concentration of:fosphenytoin, phenobarbital, phenytoin and primidone, also plasma concentration of an active metabolite of oxcarbazepine reduced; oxcarbazepine reduces plasma concentration of:perampanel (see under Perampanel, p. 398); plasma concentration of an active metabolite of oxcarbazepine sometimes reduced by:sodium valproate and valproic acid
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by:mefloquine
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by:antipsychotics (convulsive threshold lowered)
- Antivirals: oxcarbazepine possibly reduces plasma concentration of:daclatasvir and:simeprevir—manufacturer of daclatasvir and simeprevir advises avoid concomitant use; avoidance of oxcarbazepine advised by
Oxcarbazepine
- Antivirals (continued)
  manufacturer of Dolutegravir and Sofosbuvir; avoidance of
  oxcarbazepine advised by manufacturer of Ribavirine
  (plasma concentration of ribavirine possibly reduced)
- Ciclosporin: oxcarbazepine possibly reduces plasma
  concentration of Ciclosporin
- Clopidogrel: oxcarbazepine possibly reduces antiplatelet effect
  of Clopidogrel
- Cytotoxics: oxcarbazepine reduces plasma concentration of
  Imatinib—avoid concomitant use
- Oestrogens: oxcarbazepine accelerates metabolism of
  Oestrogens (reduced contraceptive effect with combined
  oral contraceptives, contraceptive patches, and vaginal
  rings—see Contraceptive Interactions in BNF)
- Orlisat: possible increased risk of convulsions when
  antiepileptics given with Orlisat
- Progestogens: oxcarbazepine accelerates metabolism of
  Progestogens (reduced contraceptive effect with combined
  oral contraceptives, progestogen-only oral contraceptives,
  contraceptive patches, vaginal rings, etonogestrel-releasing
  implant, and emergency hormonal contraception—see
  Contraceptive Interactions in BNF)
Oxeprenolol see Beta-blockers
Oxybutynin see Antimuscarinics
Oxycodone see Opioid Analgesics
Oxymetazoline see Sympathomimetics
Oxytetracycline see Tetracyclines
Oxytocin
- Anaesthetics, General: oxytocin effect possibly reduced, also
  enhanced hypotensive effect and risk of arrhythmias when
  oxytocin given with Volatile Liquid General Anaesthetics
- Prostaglandins: uterotonic effect of oxytocin potentiated by
  Prostaglandins
- Sympathomimetics: risk of hypertension when oxytocin given
  with Vasoconstrictor Sympathomimetics (due to enhanced
  vasopressor effect)
Paclitaxel
- Antipsychotics: avoid concomitant use of cytotoxics with
  clozapine (increased risk of agranulocytosis)
- Antivirals: plasma concentration of paclitaxel increased by
  Ritonavir
- Cytotoxics: increased risk of neutropenia when paclitaxel
  given with Lapatinib
Paliperidone see Antipsychotics
Pamidronate Disodium see Bisphosphonates
Pancreatin
- Antidiabetics: pancreatin antagonises hypoglycaemic effect of
  Acarbose
Pancuronium see Muscle Relaxants
Panitumumab
- Antipsychotics: avoid concomitant use of cytotoxics with
  clozapine (increased risk of agranulocytosis)
- Vaccines: risk of generalised infections when monoclonal
  antibodies given with live Vaccines—avoid concomitant use
Pantoprazole see Proton Pump Inhibitors
Papaveretum see Opioid Analgesics
Paracetamol
- Anticoagulants: prolonged regular use of paracetamol possibly
  enhances anticoagulant effect of Coumarins
- Antidiabetics: absorption of paracetamol possibly reduced when
  given 1 to 4 hours after Lixisenatide
- Antiepileptics: metabolism of paracetamol possibly accelerated by
  Carbamazepine, fosphenytoin, phenobarbital, phenytoin
  and Primidone (also isolated reports of hepatotoxicity)
- Antifungals: avoidance of paracetamol advised by
  manufacturer of Ketoconazole
- Cytotoxics: paracetamol possibly inhibits metabolism of
  Intravenous Busulfan (manufacturer of Intravenous busulfan
  advises caution within 72 hours of paracetamol); caution
  with paracetamol advised by manufacturer of Imatinib
- Lipid-regulating Drugs: absorption of paracetamol reduced by
  Colestyramine
- Metoclopramide: rate of absorption of paracetamol increased by
  Metoclopramide
Paraldehyde
- Alcohol: increased sedative effect when paraldehyde given with
  Alcohol
- Disulfiram: risk of toxicity when paraldehyde given with
  Disulfiram
Parasympathomimetics
- Anti-arrhythmics: effects of neostigmine and pyridostigmine
  possibly antagonised by Propafenone
- Antibacterials: plasma concentration of galantamine increased
  by erythromycin; effects of neostigmine and pyridostigmine
  antagonised by AMINOLACTONES; effects of neostigmine
  and pyridostigmine antagonised by clindamycin; effects of
  neostigmine and pyridostigmine antagonised by
  PolyMyxins
- Antidepressants: plasma concentration of galantamine
  increased by Paroxetine
- Antifungals: plasma concentration of galantamine increased by
  Ketoconazole
- Antimalarias: effects of neostigmine and pyridostigmine may
  be diminished because of potential for Chloroquine to
  increase symptoms of myasthenia gravis; effects of
  neostigmine and pyridostigmine may be diminished because of
  potential for Hydroxychloroquine to increase symptoms of
  myasthenia gravis
- Antimuscarinics: effects of parasympathomimetics antagonised
  by Antimuscarinics
- Beta-blockers: increased risk of arrhythmias when picoephine
  given with Beta-blockers; effects of neostigmine and
  pyridostigmine antagonised by Propafenone
- Cytotoxics: possible increased risk of bradycardia when
  picoephine given with Crizotinib
- Lithium: effects of neostigmine antagonised by Lithium
- Muscle Relaxants: donepezil possibly enhances effects of
  Succinimides; galantamine, neostigmine, pyridostigmine and
  rivastigmine enhance effects of Succinimides; neostigmine,
  pyridostigmine and rivastigmine antagonise effects of
  NON-DEPOLARISING MUSCLE RELAXANTS; donepezil
  possibly antagonises effects of NON-DEPOLARISING MUSCLE
  RELAXANTS
Perazocin see NSAIDs
Paricalcitol see Vitamins
Paroxetine see Antidepressants, SSRI
Pasireotide
- Antidiabetics: pasireotide possibly reduces requirements for
  Antidiabetics.
- Antifungals: avoidance of pasireotide advised by manufacturer of
  Ketoconazole
- Antimuscarinics: possible increased risk of bradycardia when
  pasireotide given with Ipratropium or Oxbutynin
- Beta-blockers: possible increased risk of bradycardia when
  pasireotide given with Carvedilol, Metoprolol, Propranolol
  or Sotalol
- Calcium-channel Blockers: possible increased risk of
  bradycardia when pasireotide given with Diltiazem or
  Verapamil
- Ciclosporin: pasireotide possibly reduces plasma concentration of
  Ciclosporin
Pazopanib
- Antibacterials: plasma concentration of pazopanib possibly
  increased by Clarithromycin and Telithromycin (reduce
dose of pazopanib); plasma concentration of pazopanib possibly
  reduced by Rifampicin
- Antifungals: plasma concentration of pazopanib increased by
  Ketoconazole (reduce dose of pazopanib); plasma
  concentration of pazopanib possibly increased by
  Itraconazole and Voriconazole (reduce dose of pazopanib)
- Antipsychotics: avoid concomitant use of cytotoxics with
  Clozapine (increased risk of agranulocytosis)
- Antivirals: plasma concentration of pazopanib possibly
  increased by Atazanavir, Indinavir and Ritonavir
  (reduce dose of pazopanib); avoidance of pazopanib
  advised by manufacturer of Boceprevir; increased risk of
  ventricular arrhythmias when pazopanib given with
  Saquinavir—avoid concomitant use
Pazopanib (continued)  
▶ Cytotoxics: plasma concentration of pazopanib increased by  
  • LAPATINIB  
  • Grapefruit Juice: manufacturer of pazopanib advises avoid concomitant use with  
  • GRAPEFRUIT JUICE  
  • Lipid-regulating Drugs: separating administration from pazopanib by 12 hours advised by manufacturer of  
  • LOMITAPIDE  
  • Ulcer-healing Drugs: absorption of pazopanib possibly reduced by  
  • HISTAMINE H2-ANTAGONISTS—manufacturer of pazopanib advises give at least 2 hours before or 10 hours after  
  • histamine H2-antagonists; absorption of pazopanib possibly reduced by  
  • PROTON PUMP INHIBITORS—manufacturer of pazopanib advises give at the same time as proton pump inhibitors  

Pegfilgrastim  
▶ Cytotoxics: neutropenia possibly exacerbated when pegfilgrastim given with  
  • CAPECITABINE, FLUOROURACIL or  
  • TEGAFUR  

Pegloticase Alfa see Interferons

Penicillamine  
▶ Analgesics: renal excretion of penicillamine possibly reduced by  
  • NSAIDS and ASPIRIN—consult product literature  
  • Antimalarials: antifolate effect of penicillamine increased by  
  • SULFINPYRAZONE  
  • Antipsychotics: avoid concomitant use of penicillamines with  
  • LIOTHERAPY  
  • Antidyspepsics: absorption of penicillamine reduced by  
  • TACAMIDINE  
  • Antipsychotics: avoid concomitant use of penicillamines with  
  • CITALOPRAM (increased risk of agranulocytosis)  

Penicillin  
▶ Analgesics: possible increased risk of nephrotoxicity when penicillin given with  
  • NSAIDS  
  • Antidepressants: absorption of penicillin reduced by  
  • ANTACIDS  
  • Antipsychotics: avoid concomitant use of penicillamines with  
  • CITALOPRAM (increased risk of agranulocytosis)  
  • Cardiac Glycosides: penicillin possibly reduces plasma concentration of  
  • DIGOXIN  
  • Iron Salts: absorption of penicillin reduced by  
  • ORAL IRON SALTS  
  • Sodium Aurothiomalate: manufacturer of penicillamine advises avoid concomitant use with  
  • SODIUM AUROTHIOMALATE (increased risk of toxicity)  
  • Zinc: penicillamine reduces absorption of  
  • ZINC, also absorption of penicillamine reduced by zinc  

Penicillins  
▶ Allopurinol: increased risk of rash when allopurinol, ampicillin or  
  • co-amoxiclav given with  
  • ANTACIDS  
  • Antibacterials: absorption of phenoxymethylpenicillin reduced by  
  • NEOMYCIN; effects of penicillins possibly antagonised by  
  • TETRACYCLINES  
  • Anticoagulants: an interaction between broad-spectrum penicillins and  
  • CUMINARINS and  
  • PHENIDINONE has not been demonstrated in studies, but common experience in anticoagulant clinics is that INR can be altered  
  • Antiepileptics: manufacturer of pivmecillinam advises avoid concomitant use with  
  • SODIUM VALPROATE and  
  • VALPROIC ACID  
  • Cytotoxics: penicillin reduces excretion of  
  • METHOTREXATE (increased risk of toxicity)  
  • Muscle Relaxants: piperacillin enhances effects of  
  • NON-DEPOLARISING MUSCLE RELAXANTS and  
  • SUXAMETHONIUM  
  • Mycophenolate: co-amoxiclav possibly reduces plasma concentration of  
  • MYCOPHENOLATE  
  • Sulfinpyrazone: excretion of penicillins reduced by  
  • SULFINPYRAZONE  
  • Vaccines: antibacterials inactivate  
  • ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF  

Penicillamine Isotenate  
▶ Anti-arrhythmics: increased risk of ventricular arrhythmias when penicillamine isetionate given with  
  • AMIODARONE—avoid concomitant use; possible increased risk of ventricular arrhythmias when penicillamine isetionate given with  
  • DISOPRIMIDE  
  • Antibacterials: increased risk of ventricular arrhythmias when penicillamine isetionate given with  
  • ERYTHROMYCIN; increased risk of ventricular arrhythmias when penicillamine isetionate given with  
  • MOXIPRAZACIN—

Pentamidine Isetenate  
▶ Anticholinergic: increased risk of ventricular arrhythmias when pentamidine isetenate given with  
  • AINSAMANID; possible increased risk of ventricular arrhythmias when pentamidine isetenate given with  
  • TETRACYCLES  
  ■ Antidepressants: avoidance of pentamidine isetenate advised by manufacturer of  
  • CITALOPRAM and  
  • ESCITALOPRAM (risk of ventricular arrhythmias); limited risk of ventricular arrhythmias when penicillamine isetionate given with  
  • DISOPRIMIDE  
  ▶ Antifungals: possible increased risk of nephrotoxicity when  
  • PENICILLAMINE or  
  • PENTAMINIDINE isetionate given with  
  • AMPHOTERICIN B  
  ▶ Antimalarials: avoidance of pentamidine isetenate advised by manufacturer of  
  • ARTENIMOL WITH PIPERAQUINE (possible risk of ventricular arrhythmias)  
  ▶ Antipsychotics: increased risk of ventricular arrhythmias when penicillamine isetionate given with  
  • AMISULPRIDE or  
  • DROPERIDOL; avoid concomitant use; increased risk of ventricular arrhythmias when penicillamine isetionate given with  
  • PHENOTHIAZINES  
  ▶ Antivirals: increased risk of hypocalcaemia when  
  • AINAMIDANID isetionate given with  
  • FOSCARIN; increased risk of ventricular arrhythmias when penicillamine isetionate given with  
  • SAQUINAVIR—avoid concomitant use  
  ▶ Cytotoxics: possible increased risk of ventricular arrhythmias when pentamidine isetenate given with  
  • VANETANID—avoid concomitant use  
  ▶ Ibuprofen: increased risk of ventricular arrhythmias when pentamidine isetenate given with  
  • IBUPROFEN  

Penkacin  see Opioid Analgesics

Pentazocine  
▶ Antipsychotics: avoid concomitant use of cyctoxics with  
  • CITALOPRAM (increased risk of agranulocytosis)  
  ▶ Cytotoxics: increased toxicity when pentazocine given with  
  • CYCLOPHOSPHAMIDE—avoid concomitant use; increased pulmonary toxicity when pentazocine given with  
  • FLUDARABINE (unacceptably high incidence of fatalities)  

Pentoxifylline  
▶ Aminophylline: pentoxifylline increases plasma concentration of  
  • AINAMIDANID  
  ▶ Analgesics: possible increased risk of bleeding when  
  • PENICILLAMINE given with  
  • NSAIDS; increased risk of bleeding  
  • KETOROLAC (avoid concomitant use)  
  ▶ Theophylline: pentoxifylline increases plasma concentration of  
  • THEOPHYLLINE  

Perampanel  
▶ Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by  
  • MAOIS and  
  • TRICYCLIC-RELATED ANTIDEPRESSANTS (convulsive threshold lowered);  
  • Anticonvulsant effect of antiepileptics antagonised by  
  • SSNIS and  
  • TRICYCLICS (convulsive threshold lowered)  
  ▶ Antiepileptics: plasma concentration of perampanel reduced by  
  • CARBAMAZEPINE,  
  • FOSPHENTOIN,  
  • OXCARBAZEPINE and  
  • PHENYTOIN (see under Perampanel, p. 398); plasma concentration of perampanel reduced by  
  • TOPIRAMATE  
  ▶ Antifungals: plasma concentration of perampanel increased by  
  • KETOCONAZOLE  
  ▶ Antimalarials: anticonvulsant effect of antiepileptics antagonised by  
  • MELOQUINE  
  ▶ Antipsychotics: anticonvulsant effect of antiepileptics antagonised by  
  • ANTIPSYCHOTICS (convulsive threshold lowered)  
  ▶ Anxiolytics and Hypnotics: perampanel reduces plasma concentration of  
  • MIDAZOLAM  
  ▶ Orlistat: possible increased risk of convulsions when  
  • PENTAMINIDINE isetionate given with  
  • ORLISTAT  
  ▶ Progestogens: perampanel accelerates metabolism of  
  • PROGESTGENS (reduced contraceptive effect with combined oral contraceptives, progestogen-only oral contraceptives, contraceptive patches, vaginal rings, etonogestrel-releasing implant, and emergency hormonal contraception—see Contraceptive Interactions in BNF)  

PROTEINS
Phenindione

- Antipsychotics: effects of phenindione antagonised by
  - **ANTIPSYCHOTICS**
  - Memantine: effects of dopaminergics possibly enhanced by MEMANTINE
  - Methyldopa: antiparkinsonian effect of dopaminergics antagonised by METHYLDOPA
  - Metoclopramide: antiparkinsonian effect of dopaminergics antagonised by METOCLOPRAMIDE

Percyazine

- see Antipsychotics
- Perindopril: see ACE Inhibitors
- Perphenazine: see Antipsychotics

Pertuzumab

- Antipsychotics: avoid concomitant use of cytotoxics with
  - **CLOZAPINE** (increased risk of agranulocytosis)
- Vaccines: risk of generalised infections when monoclonal antibodies given with live **VACCINES**—avoid concomitant use

Pethidine

- see Opioid Analgesics

Phenelzine

- see MAOIs

Phenindione

**Note:** Change in patient’s clinical condition particularly associated with liver disease, intercurrent illness, or drug administration, necessitates more frequent testing. Major changes in diet (especially involving salads and vegetables) and in alcohol consumption may also affect anticoagulant control.

- **Alcohol:** anticoagulant control with phenindione may be affected by major changes in consumption of **ALCOHOL**
- **Anabolic Steroids:** anticoagulant effect of phenindione enhanced by **ANABOLIC STEROIDS**
- **Analgesics:** anticoagulant effect of phenindione possibly enhanced by **NSAIDS**; increased risk of haemorrhage when anticoagulants given with **intravenous DICLOFENAC** (avoid concomitant use, including low-dose heparins); increased risk of haemorrhage when anticoagulants given with **METOMOLAC** (avoid concomitant use, including low-dose heparins); increased risk of bleeding when phenindione given with **ASPIRIN** (due to antiplatelet effect)
- **Anti-arrhythmics:** metabolism of phenindione inhibited by
  - **AMIODARONE** (enhanced anticoagulant effect); anticoagulant effect of phenindione possibly enhanced by **DROKEDARONE**
- **Antibacterials:** experience in anticoagulant clinics suggests that **INR** possibly altered when phenindione is given with **NEOMYCIN** (given for local action on gut); anticoagulant effect of phenindione possibly enhanced by **LEVOLOXACIN** and **TRETACYCLINES**; an interaction between phenindione and broad-spectrum **PENICILLINS** has not been demonstrated in studies, but common experience in anticoagulant clinics is that **INR** can be altered; metabolism of phenindione possibly inhibited by **SULFONAMIDES**
- **Anticonvulsants:** increased risk of haemorrhage when other anticoagulants given with **APIXABAN**, **DARIGATAN** and **RIVAROXABAN** (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)
- **Antivirals:** anticoagulant effect of phenindone possibly enhanced by **RITONAVIR**
- **Clopidogrel:** anticoagulant effect of phenindone enhanced due to antiplatelet action of **CLOPIDOGREL**
- **Corticosteroids:** anticoagulant effect of phenindone may be enhanced or reduced by **CORTICOSTEROIDS**
- **Cytotoxics:** avoidance of phenindione advised by manufacturer of **IBUTINIB**
- **Dipyridamole:** anticoagulant effect of phenindone enhanced due to antiplatelet action of **DIPYRIDAMOLE**
- **Enteral Foods:** anticoagulant effect of phenindone antagonised by vitamin K (present in some **ENTERAL FEEDS**)**
- **Hloprost:** increased risk of bleeding when phenindone given with **HLOPROST**
- **Lipid-regulating Drugs:** anticoagulant effect of phenindone may be enhanced or reduced by **COLESTYRAMINE**; anticoagulant effect of phenindone possibly enhanced by **ROSUVASTATIN**; anticoagulant effect of phenindone enhanced by **FIBRATES**

**Phenindione (continued)**

- **Oestrogens:** anticoagulant effect of phenindone antagonised by **OESTROGENS**
- **Prasugrel:** possible increased risk of bleeding when phenindione given with **PRAUGREL**
- **Progestogens:** anticoagulant effect of phenindone antagonised by **PROGESTOGENS**
- **Testolactone:** anticoagulant effect of phenindone enhanced by **TESTOLACTONE**
- **Testosterone:** anticoagulant effect of phenindone enhanced by **TESTOSTERONE**
- **Thyroid Hormones:** anticoagulant effect of phenindone enhanced by **THYROID HORMONES**
- **Vitamins:** anticoagulant effect of phenindone antagonised by **VITAMIN K**

**Phenobarbital**

- **Alcohol:** increased sedative effect when phenobarbital given with **ALCOHOL**
- **Aminophylline:** phenobarbital accelerates metabolism of **AMINOPHYLLINE** (reduced effect)
- **Analgesics:** phenobarbital reduces plasma concentration of **METADOLE** and **FABADOLANET**—consider increasing albenzadole and praziquantel dose when given for systemic infections
- **Antiepileptics:** metabolism of phenobarbital accelerated by **DIPHTYRAMIDE** (reduced plasma concentration); phenobarbital possibly reduces plasma concentration of **DROKEDARONE**—avoid concomitant use; phenobarbital possibly accelerates metabolism of **PROPANE**
- **Antibacterials:** phenobarbital accelerates metabolism of **DISOPYRAMIDE** (reduced plasma concentration); phenobarbital possibly reduces plasma concentration of **RIFAMPICIN**; phenobarbital accelerates metabolism of **DOXYCYCLINE** (reduced plasma concentration); phenobarbital possibly accelerates metabolism of **CHLORAPHEXATIC** (reduced plasma concentration); phenobarbital reduces plasma concentration of **TELITHROMYCIN** (avoid during and for 2 weeks after phenobarbital)
- **Anticoagulants:** phenobarbital possibly reduces plasma concentration of **APIXABAN**; phenobarbital accelerates metabolism of **COUMARINS** (reduced anticoagulant effect); phenobarbital possibly reduces plasma concentration of **RIVAROXABAN**—manufacturer of rivaroxaban advises monitor for signs of thrombosis
- **Antidepressants:** phenobarbital reduces plasma concentration of **REDOBOTINE**; phenobarbital reduces plasma concentration of **PAROXETINE**; phenobarbital accelerates metabolism of **MIANDERON** (reduced plasma concentration); anticonvulsant effect of antiepileptics possibly antagonised by **MAOIS** and **TRICYCLIC-RELATED ANTIDEPRESSANTS** (convulsive threshold lowered); anticonvulsant effect of antiepileptic antagonised by **SSRIS** and **TRICYCLICS** (convulsive threshold lowered); plasma concentration of phenobarbital possibly reduced by **ST JOHN’S WORT**—avoid concomitant use; phenobarbital possibly accelerates metabolism of **TRICYCLICS** (reduced plasma concentration)
- **Antiepileptics:** plasma concentration of phenobarbital possibly increased by **CARBAMAZEPINE**; phenobarbital possibly reduces plasma concentration of **ETHOSUXIMIDE**, **RUFINAMIDE** and **TOPRAMES**; plasma concentration of phenobarbital often increased by **PHOSPHETON** and **PHNETOIN**, plasma concentration of fosphenytoin and phenytoin often reduced but may be increased; phenobarbital reduces plasma concentration of **LAMOTRIPINE**, **TAPIAGINE** and **ZONISAMIDE**; plasma concentration of phenobarbital increased by **OXYCARBAPINE**; also plasma concentration of an active metabolite of oxcarbapene reduced and broad-spectrum of phenobarbital increased by **SODIUM VALPROATE** and **VALPROIC ACID** (also plasma concentration of sodium valproate and valproic acid reduced); plasma concentration of phenobarbital increased by **STRIPENAL**
- **Antifungals:** phenobarbital possibly reduces plasma concentration of **ITRAVONAZOLE** and **POSACZANOME**.
Phenobarbital

- Antifungals (continued)
  - Phenobarbital possibly reduces plasma concentration of voriconazole—avoid concomitant use; phenobarbital reduces absorption of griseofulvin (reduced effect).
  - Antimicrobials: avoidance of phenobarbital advised by manufacturer of arteminol with piperaquine; anticonvulsant effect of antiepileptics antagonised by mefloquine.
  - Antipsychotics: anticonvulsant effect of antiepileptics antagonised by antipsychotics (convulsive threshold lowered); phenobarbital accelerates metabolism of haloperidol (reduced plasma concentration); plasma concentration of both drugs reduced when phenobarbital given with chlorpromazine; phenobarbital possibly reduces plasma concentration of aripiprazole (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature); phenobarbital possibly reduces plasma concentration of clozapine; phenobarbital possibly reduces plasma concentration of lurasidone—avoid concomitant use.
  - Antibiotics: phenobarbital possibly reduces plasma concentration of abacavir, darunavir, fosamprenavir, indinavir, lopinavir and saquinavir; avoidance of phenobarbital advised by manufacturer of boceprevir and rilpivirine (plasma concentration of boceprevir and rilpivirine possibly reduced); phenobarbital possibly reduces plasma concentration of daclatasvir and simprevir—manufacturer of daclatasvir and simprevir advises avoid concomitant use; avoidance of phenobarbital advised by manufacturer of dolasetron, etravirine, fos fosfubuvir and telaprevir.
  - Anxiolytics and Hypnotics: increased sedative effect when phenobarbital given with anxiolytics and hypnotics; phenobarbital often reduces plasma concentration of clonazepam.
  - Aprepitant: phenobarbital possibly reduces plasma concentration of aprepitant.
  - Avanafil: phenobarbital possibly reduces plasma concentration of avanafil—manufacturer of avanafil advises avoid concomitant use.
  - Beta-blockers: phenobarbital possibly reduces plasma concentration of propranolol.
  - Caffeine citrate: effects of phenobarbital possibly antagonised by caffeine citrate.
  - Calcium-channel Blockers: phenobarbital probably reduces effects of calcium-channel blockers; avoidance of phenobarbital advised by manufacturer of isradipine; avoidance of phenobarbital advised by manufacturer of nimodipine (plasma concentration of nimodipine reduced).
  - Cannabinoids: phenobarbital possibly reduces plasma concentration of cannabis extract—manufacturer of cannabis extract advises avoid concomitant use.
  - Ciclosporin: phenobarbital accelerates metabolism of ciclosporin (reduced plasma concentration).
  - Ciclosporin: phenobarbital possibly reduces plasma concentration of ciclosporin—manufacturer of ciclosporin advises avoid concomitant use.
  - Corticosteroids: phenobarbital accelerates metabolism of corticosteroids (reduced effect).
  - Cytotoxic: phenobarbital possibly decreases plasma concentration of axitinib (increase dose of axitinib—consult axitinib product literature); phenobarbital possibly reduces plasma concentration of bortezomib, bosutinib, crizotinib and ponatinib—manufacturer of bortezomib, bosutinib, crizotinib and ponatinib advises avoid concomitant use; phenobarbital possibly reduces plasma concentration of cabozantinib—avoid concomitant use; avoidance of phenobarbital advised by manufacturer of cabazitaxel, dabrafenib and gefitinib; avoidance of phenobarbital advised by manufacturer of dabrafenib and vemurafenib (plasma concentration of dasatinib and vandetanib possibly reduced); phenobarbital possibly reduces plasma concentration of etoposide; phenobarbital reduces plasma concentration of irinotecan and its active metabolite; manufacturer of procarbazine advises possible increased risk of hypersensitivity reactions when phenobarbital given with procarbazine.
  - Diuretics: phenobarbital reduces plasma concentration of eplerenone—avoid concomitant use; increased risk of osteomalacia when phenobarbital given with carbonic anhydrase inhibitors.
  - Fosaprepitant: phenobarbital possibly reduces plasma concentration of fosaprepitant.
  - Hormone Antagonists: phenobarbital possibly reduces plasma concentration of abiraterone—manufacturer of abiraterone advises avoid concomitant use; phenobarbital accelerates metabolism of toremifene (reduced plasma concentration).
  - Ivermectin: phenobarbital possibly reduces plasma concentration of ivermectin.
  - Leukotriene Receptor Antagonists: phenobarbital reduces plasma concentration of montelukast.
  - Oestrogens: phenobarbital accelerates metabolism of oestrogens (reduced contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF).
  - Orlastat: possible increased risk of convulsions when antiepileptics given with orlistat.
  - Progestogens: phenobarbital accelerates metabolism of progestogens (reduced contraceptive effect with combined oral contraceptives, progestogen-only oral contraceptives, contraceptive patches, vaginal rings, eutogestrel-releasing implant, and emergency hormonal contraception—see Contraceptive Interactions in BNF).
  - Roflumilast: phenobarbital possibly inhibits effects of roflumilast (manufacturer of roflumilast advises avoid concomitant use).
  - Sodium Oxybate: avoidance of phenobarbital advised by manufacturer of sodium oxybate.
  - Sympathomimetics: plasma concentration of phenobarbital possibly increased by methylphenidate.
  - Tacrolimus: phenobarbital reduces plasma concentration of tacrolimus.
  - Theophylline: phenobarbital accelerates metabolism of theophylline (reduced effect).
  - Thyroid Hormones: phenobarbital accelerates metabolism of thyroid hormones (may increase requirements for thyroid hormones in hypothyroidism).
  - Ticagrelor: phenobarbital possibly reduces plasma concentration of ticagrelor.
  - Ulipristal: avoidance of phenobarbital advised by manufacturer of ulipristal (contraceptive effect of ulipristal possibly reduced).
  - Vitamins: phenobarbital possibly increases requirements for alfalcalfirol, calcitriol, colcabliciferol, dihydroxachysteryl, ergocalciferol, paricalcitol or vitamin D.

Phenothiazines see Antipsychotics.
Phenobarbital (continued)

- Cytotoxics (continued)
  - Diuretics: phenobarbital reduces plasma concentration of eplerenone—avoid concomitant use; increased risk of osteomalacia when phenobarbital given with carbonic anhydrase inhibitors.
  - Fosaprepitant: phenobarbital possibly reduces plasma concentration of fosaprepitant.
  - Hormone Antagonists: phenobarbital possibly reduces plasma concentration of abiraterone—manufacturer of abiraterone advises avoid concomitant use; phenobarbital accelerates metabolism of toremifene (reduced plasma concentration).
  - Ivermectin: phenobarbital possibly reduces plasma concentration of ivermectin.
  - Leukotriene Receptor Antagonists: phenobarbital reduces plasma concentration of montelukast.
  - Oestrogens: phenobarbital accelerates metabolism of oestrogens (reduced contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF).
  - Orlastat: possible increased risk of convulsions when antiepileptics given with orlistat.
  - Progestogens: phenobarbital accelerates metabolism of progestogens (reduced contraceptive effect with combined oral contraceptives, progestogen-only oral contraceptives, contraceptive patches, vaginal rings, eutogestrel-releasing implant, and emergency hormonal contraception—see Contraceptive Interactions in BNF).
  - Roflumilast: phenobarbital possibly inhibits effects of roflumilast (manufacturer of roflumilast advises avoid concomitant use).
  - Sodium Oxybate: avoidance of phenobarbital advised by manufacturer of sodium oxybate.
  - Sympathomimetics: plasma concentration of phenobarbital possibly increased by methylphenidate.
  - Tacrolimus: phenobarbital reduces plasma concentration of tacrolimus.
  - Theophylline: phenobarbital accelerates metabolism of theophylline (reduced effect).
  - Thyroid Hormones: phenobarbital accelerates metabolism of thyroid hormones (may increase requirements for thyroid hormones in hypothyroidism).
  - Ticagrelor: phenobarbital possibly reduces plasma concentration of ticagrelor.
  - Ulipristal: avoidance of phenobarbital advised by manufacturer of ulipristal (contraceptive effect of ulipristal possibly reduced).
  - Vitamins: phenobarbital possibly increases requirements for alfalcalfirol, calcitriol, colcabliciferol, dihydroxachysteryl, ergocalciferol, paricalcitol or vitamin D.

Phenothiazines see Antipsychotics.
Phenobarbital (continued)

- Alcohol: plasma concentration of phenytoin possibly reduced by chronic heavy consumption of alcohol.
- Aminophylline: plasma concentration of both drugs reduced when phenytoin given with aminophylline.
- Analgesics: excretion of phenytoin possibly reduced by acetaminophen (increased risk of toxicity); phenytoin possibly accelerates metabolism of fentanyl (reduced effect); phenytoin accelerates metabolism of methadone (reduced effect and risk of withdrawal effects); phenytoin possibly increases risk of pethidine toxicity; effects of phenytoin enhanced by aspirin; phenytoin possibly accelerates...
Phenytoin

- Analgesics (continued)
  - metabolism of PARACETAMOL (also isolated reports of hepatotoxicity)

- Antacids: absorption of phenytoin reduced by ANTACIDS

- Antidepressants: phenytoin reduces plasma concentration of ALBENDAZOLE and PRAZIQUANTEL—consider increasing albendazole and praziquantel dose when given for systemic infections; plasma concentration of phenytoin possibly increased by LIVESOL

- Anti-arrhythmics: metabolism of phenytoin inhibited by AMIODARONE (increased plasma concentration); phenytoin reduces plasma concentration of DOPSYPARIDE; phenytoin possibly reduces plasma concentration of DRONEDARONE—avoid concomitant use

- Antibacterials: metabolism of phenytoin inhibited by CLARITHROMYCIN (increased plasma concentration); metabolism of phenytoin possibly inhibited by METRONIDAZOLE (increased plasma concentration); plasma concentration of phenytoin increased or decreased by CIPROFLOXACIN; phenytoin accelerates metabolism of DOXYCYCLINE (reduced plasma concentration); phenytoin possibly reduces plasma concentration of BEDAQUILINE—manufacturer of bedaquiline advises avoid concomitant use; plasma concentration of phenytoin increased by CHLORAMPHENICOL (increased risk of toxicity); metabolism of phenytoin possibly inhibited by ISONIAZID (increased risk of toxicity); metabolism of phenytoin accelerated by RIFAMYCINS (reduced plasma concentration); plasma concentration of phenytoin possibly increased by SULFONAMIDES; phenytoin reduces plasma concentration of TELITHROMYCIN (avoid during and for 2 weeks after phenytoin); plasma concentration of phenytoin increased by TRIMETHOPRIM (also increased antifolate effect)

- Anticonvulsants: phenytoin possibly reduces plasma concentration of APIXABAN; phenytoin accelerates metabolism of COUMARINS (possibility of reduced anticoagulant effect, but enhancement also reported); phenytoin possibly reduces plasma concentration of DARIGATAN—manufacturer of dabigatran advises avoid concomitant use; phenytoin possibly reduces plasma concentration of RIVAROXABAN—manufacturer of rivaroxaban advises monitor for signs of thrombosis

- Antidepressants: plasma concentration of phenytoin increased by BUPROPION and FLUOXETINE; plasma concentration of MIANSERIN, MIRTAZAPINE and PAROXETINE; plasma concentration of phenytoin possibly increased by SERTRALINE, also increased antifolate effect; plasma concentration of phenytoin possibly increased by TRICYCLIC-RELATED ANTIDEPRESSANTS (convasive threshold lowered); anticonvulsant effect of antiepileptics possibly antagonised by MAOIS and a TRICYCLIC-RELATED ANTIDEPRESSANTS (convasive threshold lowered); anticonvulsant effect of antiepileptics antagonised by SSRIS and TRICYCLICS (convasive threshold lowered); plasma concentration of phenytoin possibly reduced by ST JOHN’S WORT—avoid concomitant use; phenytoin possibly reduces plasma concentration of TRICYCLICS

- Antidiabetics: plasma concentration of phenytoin transiently increased by TOLBUTAMIDE (possibility of toxicity)

- Antiepileptics: plasma concentration of both drugs often reduced when phenytoin given with CARBAMAZEPINE, also plasma concentration of phenytoin may be increased; phenytoin reduces plasma concentration of ESLICARBAPZEPINE, also plasma concentration of phenytoin possibly increased; plasma concentration of phenytoin possibly increased by ETHOSUXIMIDE, also plasma concentration of ethosuximide possibly reduced; phenytoin reduces plasma concentration of LAMOTRIGINE, TIAGABINE and Zonisamide; plasma concentration of phenytoin increased by OXCARBZEPINE, also plasma concentration of an active metabolite of oxcarbazepine reduced; phenytoin reduces plasma concentration of PERAMAPANEL (see under Perampanel, p. 398); phenytoin often increases plasma concentration of PHENOBARBITAL and PRIMIDONE, plasma concentration of phenytoin often reduced but may be increased; phenytoin possibly reduces plasma concentration of RETIGABINE;

Phenytoin

- Antiepileptics (continued)
  - phenytoin possibly reduces plasma concentration of RUFINAMIDE, also plasma concentration of phenytoin possibly increased; plasma concentration of phenytoin increased or possibly reduced when given with SODIUM VALPROATE and VALPROIC ACID, also plasma concentration of sodium valproate and valproic acid reduced; plasma concentration of phenytoin increased by STRIPENTOL; plasma concentration of phenytoin increased by TOPiramate (also plasma concentration of topiramate reduced); plasma concentration of phenytoin reduced by VIGABATRIN

- Antifungals: phenytoin reduces plasma concentration of KETOCONAZOLE and POSACONAZOLE; anticonvulsant effect of phenytoin enhanced by MICONAZOLE (plasma concentration of phenytoin increased by FLUCONAZOLE (consider reducing dose of phenytoin); phenytoin reduces plasma concentration of ITRACONAZOLE—avoid concomitant use; plasma concentration of phenytoin increased by VORICONAZOLE, also phenytoin reduces plasma concentration of voriconazole (increase dose of voriconazole and also monitor for phenytoin toxicity); phenytoin possibly reduces plasma concentration of CASPOFUNGIN—consider increasing dose of caspofungin

- Antimalarias: avoidance of phenytoin advised by manufacturer of ARTENIOL WITH PIPERAQUINE; anticonvulsant effect of antiepileptics antagonised by MELLOQUINE; anticonvulsant effect of phenytoin antagonised by PYRIMETHAMINE, also increased antifolate effect

- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by ANTI PSYCHOTICS (convasive threshold lowered); phenytoin possibly reduces plasma concentration of HALOPERIDOL; plasma concentration of phenytoin possibly increased or decreased by CHLORPROMAZINE; phenytoin possibly reduces plasma concentration of AMIPO PRAZOLE (avoid concomitant use or consider increasing the dose of aripiprazole—consult aripiprazole product literature); phenytoin accelerates metabolism of CLOzapINE and QUETiapINE (reduced plasma concentration); phenytoin possibly reduces plasma concentration of Lurasidone—avoid concomitant use

- Antivirals: phenytoin possibly reduces plasma concentration of ABACAVIR, DARUNAVIR, LOPINAVIR and SAQUINAVIR; avoidance of phenytoin recommended

- Antibacterials: plasma concentration of phenytoin possibly inhibited by APREPITANT and RILPIVIRINE (plasma concentration of boceprevir and rilpivirine possibly reduced); phenytoin possibly reduces plasma concentration of DA LCATASIV and SIMEPREVIR—manufacturer of daclatasvir and simeprevir advises avoid concomitant use; avoidance of phenytoin advised by manufacturer of DOLUTEGRAVIR, ELVITEGRAVIR, ETARVIRINE, SOFOSBUVIR and TELAPREVI; phenytoin possibly reduces plasma concentration of INDINAVIR, also plasma concentration of phenytoin possibly increased; phenytoin possibly reduces plasma concentration of RITONAVIR, also plasma concentration of phenytoin possibly affected; plasma concentration of phenytoin increased or decreased by ZIDOVUDINE

- Anxiolytics and Hypnotics: phenytoin often reduces plasma concentration of CLONAZEPAM; plasma concentration of phenytoin increased or decreased by DIAZEPAM; plasma concentration of phenytoin possibly increased or decreased by BENZODIAZEPINES

- Aprepitant: phenytoin possibly reduces plasma concentration of APREPI TANT

- Bupropion: phenytoin reduces plasma concentration of BUPROPION

- Caffeine citrate: phenytoin reduces plasma concentration of CAFFEINE CITRATE

- Calcium-channel Blockers: phenytoin reduces effects of FELODIPINE and VERAPAMIL; avoidance of phenytoin advised by manufacturer of ISRADIPINE; avoidance of phenytoin advised by manufacturer of NIMODIPINE (plasma concentration of nimodipine possibly reduced); plasma
Phenytoin (continued)

▶ Lithium: neurotoxicity may occur when phenytoin given with LITHIUM without increased plasma concentration of lithium
▶ Macitentan: avoidance of phenytoin advised by manufacturer of MACITENTAN
▶ Modafinil: plasma concentration of phenytoin possibly increased by MODAFINIL
▶ Muscle Relaxants: long-term use of phenytoin reduces effects of NON-DEPOLARISING MUSCLE RELAXANTS (but acute use of phenytoin might increase effects of non-depolarising muscle relaxants)
▶ Oestrogens: phenytoin accelerates metabolism of OESTROGENS (reduced contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF)
▶ Oral: possible increased risk of convulsions when antiepileptics given with ORLISTAT
▶ Progestogens: phenytoin accelerates metabolism of PROGESTOGENS (reduced contraceptive effect with combined oral contraceptives, progestogen-only oral contraceptives, contraceptive patches, vaginal rings, etonogestrel-releasing implant, and emergency hormonal contraception—see Contraceptive Interactions in BNF)
▶ Rosuvastatin: phenytoin possibly inhibits effects of ROFLUMILAST (manufacturer of roflumilast advises avoid concomitant use)
▶ Sulfonpyrazone: plasma concentration of phenytoin increased by SULFONPYRAZONE
▶ Symphathomimetics: plasma concentration of phenytoin increased by METHYLPHENIDATE
▶ Tacrolimus: phenytoin reduces plasma concentration of TACROLIMUS, also plasma concentration of phenytoin possibly increased
▶ Theophylline: plasma concentration of both drugs reduced when phenytoin given with THEOPHYLLINE
▶ Thyroid Hormones: phenytoin accelerates metabolism of THYROID HORMONES (may increase requirements in hypothyroidism), also plasma concentration of phenytoin possibly increased
▶ Tibolone: phenytoin accelerates metabolism of TIBOLONE
▶ Ticagrelor: phenytoin possibly reduces plasma concentration of TICAGRELOR
▶ Ulcer-healing Drugs: metabolism of phenytoin inhibited by Cimetidine (increased plasma concentration); effects of phenytoin enhanced by ISOMEPRAZOLE; effects of phenytoin possibly enhanced by OMEPRAZOLE; absorption of phenytoin reduced by SUCRALFATE
▶ Ulipristal: avoidance of phenytoin advised by manufacturer of ULIPRISTAL (contraceptive effect of ulipristal possibly reduced)
▶ Vaccines: effects of phenytoin enhanced by INFLUENZA VACCINE
▶ Vitamins: phenytoin possibly increases requirements for ALFACALCIDOL, CALCITRIOL, COLCACLIFEROL, DIHYDROTACHYSTEROL, ERGOCLIFEROL, PARICALCITOL or VITAMIN D

Phenolamine
▶ Antidepressants: manufacturer of phenoxyamine advises avoid for 2 weeks after stopping MAOIs

Phosphodiesterase Type 3 Inhibitors
▶ Angrenide: avoidance of enoximone and milrinone advised by manufacturer of ANGRELIDE

Pilocarpine see Parasympathomimetics

Pimozone see Antipsychotics

Pindolol see Beta-blockers

Pioglitazone see Antidiabetics

Piperacillin see Piperacillin

Piperazine see Artesin, Arthritis with Piperaquine

Pipitone see Antipsychotics

Pirfenidone
▶ Antibacterials: plasma concentration of pirfenidone increased by CIPROFLOXACIN—see under Pirfenidone, p. 260
▶ Antidepressants: plasma concentration of pirfenidone increased by FLUVOXAMINE—manufacturer of pirfenidone advises avoid concomitant use
▶ Grapefruit Juice: manufacturer of pirfenidone advises avoid concomitant use with GRAPEFRUIT JUICE
Piroxicam see NSAIDs
Pimecrolimus see Pimecrolimus
Pipamperone
- Antipsychotics: avoid concomitant use of cytoxotics with CLOZAPINE (increased risk of agranulocytosis)
- Vaccines: risk of generalised infections when pipamperone given with live VACCINES—avoid concomitant use

Pizotifen
- Adrenergic Neurone Blockers: pizotifen antagonises hypotensive effect of ADRENERGIC NEURONE BLOCKERS

Platinum Compounds
- Aldesleukin: avoidance of cisplatin advised by manufacturer of ALDESLLEUKIN
- Antibacterials: increased risk of nephrotoxicity and possibly of ototoxicity when platinum compounds given with AMINOGlicosIDES or POLYMXYINS; increased risk of nephrotoxicity and ototoxicity when platinum compounds given with CAPREOMYCIN; increased risk of nephrotoxicity and possibly of ototoxicity when cisplatin given with VANCOMYCIN
- Antiepileptics: cisplatin possibly reduces plasma concentration of CICLOSPORIN and PHENTYON
- Antipsychotics: avoid concomitant use of cytoxotics with CLOZAPINE (increased risk of agranulocytosis)
- Anticoagulants: plasma concentration of ponatinib possibly reduced by INHANIVAR, RITONAVIR and SAQUINAVIR—consider reducing initial dose of ponatinib (see under Ponatinib, p. 814)
- Antifungals: plasma concentration of ponatinib increased by KETOCONAZOLE; plasma concentration of ponatinib possibly increased by ITRACONAZOLE and VORICONAZOLE—consider reducing initial dose of ponatinib (see under Ponatinib, p. 814)
- Antivirals: plasma concentration of ponatinib possibly increased by INDINAVIR, RITONAVIR and SAQUINAVIR—consider reducing initial dose of ponatinib (see under Ponatinib, p. 814)
- Grapefruit juice: plasma concentration of ponatinib possibly increased by GRAPFRUIT JUICE

Pneumococcal Vaccine see Vaccines
Polymyxins
- Antibacterials: increased risk of nephrotoxicity when colistimethate sodium or polymyxins given with AMINOGLicosIDES; increased risk of nephrotoxicity when colistimethate sodium or polymyxins given with CAPREOMYCIN; increased risk of nephrotoxicity when polymyxins given with VANCOMYCIN; increased risk of nephrotoxicity and ototoxicity when colistimethate sodium given with VANCOMYCIN
- Antifungals: increased risk of nephrotoxicity when polymyxins given with AMPHOTERICIN
- Ciclosporin: increased risk of nephrotoxicity when polymyxins given with CICLOSPORIN
- Cytotoxics: increased risk of nephrotoxicity and possibly of ototoxicity when polymyxins given with PLATINUM COMPOUNDS
- Diuretics: increased risk of ototoxicity when polymyxins given with LOOP DIURETICS
- Muscle Relaxants: polymyxins enhance effects of NON-DEPOLARISING MUSCLE RELAXANTS and SUXAMETHONIUM
- Parasympathomimetics: polymyxins antagonise effects of NEOSTIGMINE and PYRIDOSTIGMINE
- Vaccines: antibacterials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF

Potassium Bicarbonate see Potassium Salts
Potassium Chloride see Potassium Salts
Potassium Citrate see Potassium Salts
Potassium Salts
- NOTE Includes salt substitutes
- ACE Inhibitors: increased risk of severe hyperkalaemia when potassium salts given with ACE INHIBITORS
- Aloxilren: increased risk of hyperkalaemia when potassium salts given with ALOXILREN
- Angiotensin-II Receptor Antagonists: increased risk of hyperkalaemia when potassium salts given with ANGIOTENSIN-II RECEPTOR ANTAGONISTS
- Antibacterials: avoid concomitant use of potassium citrate with METHENAMINE
- Ciclosporin: increased risk of hyperkalaemia when potassium salts given with CICLOSPORIN
- Diuretics: increased risk of hyperkalaemia when potassium salts given with POTASSIUM-SPARING DIURETICS AND ALDOSTERONE ANTAGONISTS
- Tacrolimus: increased risk of hyperkalaemia when potassium salts given with TACROLIMUS
- Ulcer-healing Drugs: avoidance of potassium citrate advised by manufacturer of SUCRALFATE

Pramipexole
- Antipsychotics: manufacturer of pramipexole advises avoid concomitant use of ANTIPSYCHOTICS (antagonism of effect)
- Memantine: effects of dopaminergics possibly enhanced by MEMANTINE
- Methylodopa: antiparkinsonian effect of dopaminergics antagonised by METHYLODOA
- Ulcer-healing Drugs: excretion of pramipexole reduced by CIMETIDINE (increased plasma concentration)

Prazosin
- Analgesics: possible increased risk of bleeding when prasugrel given with NSAIDS
- Anticoagulants: possible increased risk of bleeding when prasugrel given with COUMARINS or PHENINDIONE
- Clopogrel: possible increased risk of bleeding when prasugrel given with CLOPIDOGREL

Pravastatin see Statins
Praziquantel
- Antibacterials: plasma concentration of praziquantel reduced by rifampicin
- Antiepileptics: plasma concentration of praziquantel reduced by carbamazepine, fosphenytoin, phenobarbital, phenytoin and primidone—consider increasing praziquantel dose when given for systemic infections
- Antifungals: plasma concentration of praziquantel increased by KETOCONAZOLE
Praziquantel (continued)
- Antimalarials: plasma concentration of praziquantel reduced by
  - CHLOROQUINE—consider increasing praziquantel dose when given for systemic infections
- Corticosteroids: plasma concentration of praziquantel possibly reduced by continuous use of DEXAMETHASONE
- Grapefruit Juice: plasma concentration of praziquantel increased by GRAPEFRUIT JUICE
- Ulcer-healing Drugs: plasma concentration of praziquantel increased by Cimetidine

Prazosin see Alpha-blockers
Prednisolone see Corticosteroids
Prednisone see Corticosteroids
Pregabalin
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by MAOIs and TRICYCLIC-RELATED ANTIDEPRESSANTS (convulsive threshold lowered);
- Anticholinergics: anticonvulsant effect of antiepileptics antagonised by ATROPINE
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by ANTIHYPERGLYCEMIC DRUGS
- Antiepileptics: plasma concentration of primidone possibly reduced by SSRIs and TRICYCLICS (convulsive threshold lowered);
- Antihistamines: plasma concentration of primidone possibly reduced by ST JOHN’S WORT—avoid concomitant use; primidone possibly accelerates metabolism of TRICYCLICS (convulsive threshold lowered);
- Antiepileptics: plasma concentration of primidone possibly increased by CARBARbamazepine; primidone possibly reduces plasma concentration of ETHOSUXIMIDE, RUFINAMIDE and TOPIRAMATE; plasma concentration of primidone often increased by FOSPHENytoin and PHENytoin, plasma concentration of fosphenytoin and phenytoin often reduced but may be increased; primidone reduces plasma concentration of LAMOTRIGINE, TIAGABINE and ZONISAMIDE; plasma concentration of primidone increased by oxicABAZEPINE, also plasma concentration of an active metabolite of oxcABAZEPINE reduced; plasma concentration of primidone increased by SAPROFEN; primidone possibly reduces plasma concentration of LAMOTRIGINE.
- Antiepileptics: plasma concentration of primidone possibly increased by trICARAZOLE and POSACOAzoLE—avoid concomitant use; primidone reduces absorption of GISeOFULVIn (reduced effect)
- Antimalarials: avoidance of primidone advised by manufacturer of ARTEMether with LUMEFANTRINE
- Histamine: avoidance of antimalarials advised by manufacturer of NIFEDIPINE
- Mepacrine: plasma concentration of primaquine increased by PRIMAQUINE; avoidance of antimalarials advised by manufacturer of PLASMA.
- Vaccines: antimalarials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF

Primidone
- Alcohol: increased sedative effect when primidone given with ALCOHOL.
- Aminophylline: primidone accelerates metabolism of AMINOPHYLLINE (reduced effect).
- Analgesics: primidone reduces plasma concentration of METHADONE; primidone possibly accelerates metabolism of PARACETAMOL (also isolated reports of hepatotoxicity).
- Antihistamines: primidone reduces plasma concentration of ALBENDAZOLE and PRAZIQUANTEL—consider increasing albendazole and praziquantel dose when given for systemic infections.
- Antihistamines: primidone accelerates metabolism of DISOPYRAMIDE (reduced plasma concentration); primidone possibly reduces plasma concentration of DRONEDARONE—avoid concomitant use; primidone possibly accelerates metabolism of PROPafenONE.
- Antihistamines: primidone accelerates metabolism of METRONIDAZOLE (reduced effect); primidone possibly reduces plasma concentration of Rifampicin; primidone accelerates metabolism of DOXYCYCLINE (reduced plasma concentration); primidone possibly accelerates metabolism of CHLORAMPHENICOL (reduced plasma concentration); primidone reduces plasma concentration of APIXABAN; primidone accelerates metabolism of COUMARINS (reduced anticoagulant effect); primidone possibly reduces plasma concentration of Rivaroxaban; primidone accelerates metabolism of APOTHEKIRIN; primidone accelerates plasma concentration of REBOXETINE; primidone reduces plasma concentration of PAROXETINE; primidone accelerates metabolism of MANSERIN (reduced plasma concentration);
- Antidepressants: primidone possibly reduces plasma concentration of reBOXETINE; primidone reduces plasma concentration of parOXETINE; primidone accelerates metabolism of mANSERIN (reduced plasma concentration);
- Antipsychotics: primidone possibly reduces plasma concentration of LURASIDONE—avoid concomitant use.
- Antivirals: primidone possibly reduces plasma concentration of ABACAVIR, DURANAVIR, FOSSAPRENAVIR, INIDINAVIR, LOpinavIR and SAQUINAVIR; avoidance of primidone advised by manufacturer of BOCERVIR and SIMEPREVIR (plasma concentration of boceprevir and rilpivirine possibly reduced); primidone possibly reduces plasma concentration of DACLATASVIR and SIMEPREVIR—manufacturer of daclatasvir and simeprevir advises avoid concomitant use; avoidance of primidone advised by manufacturer of DULTEGRAVIR, ELVITEGRAVIR, ETVIRINE, SOFOSBUVIR and TELAPREVIR.
- Anxiolytics and Hypnotics: increased sedative effect when primidone given with ANXIOLYTICS AND HYPNOTICS; primidone often reduces plasma concentration of CLONAZEPAM.
- Antipsychotics: primidone possibly reduces plasma concentration of FLUPERCHANT.

Primodone (continued)
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by MAOIs and TRICYCLIC-RELATED ANTIDEPRESSANTS (convulsive threshold lowered);
- Anticholinergics: anticonvulsant effect of antiepileptics antagonised by ATROPINE
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by ANTIHYPERGLYCEMIC DRUGS
- Antiepileptics: plasma concentration of primidone possibly reduced by SSRIs and TRICYCLICS (convulsive threshold lowered);
- Antihistamines: plasma concentration of primidone possibly reduced by ST JOHN’S WORT—avoid concomitant use; primidone possibly accelerates metabolism of TRICYCLICS (convulsive threshold lowered);
- Antiepileptics: plasma concentration of primidone possibly increased by CARBARbamazepine; primidone possibly reduces plasma concentration of ETHOSUXIMIDE, RUFINAMIDE and TOPIRAMATE; plasma concentration of primidone often increased by FOSPHENytoin and PHENytoin, plasma concentration of fosphenytoin and phenytoin often reduced but may be increased; primidone reduces plasma concentration of LAMOTRIGINE, TIAGABINE and ZONISAMIDE; plasma concentration of primidone increased by oxicABAZEPINE, also plasma concentration of an active metabolite of oxcABAZEPINE reduced; plasma concentration of primidone increased by SAPROFEN; primidone possibly reduces plasma concentration of LAMOTRIGINE.
- Antiepileptics: plasma concentration of primidone possibly increased by trICARAZOLE and POSACOAzoLE—avoid concomitant use; primidone reduces absorption of GISeOFULVIn (reduced effect)
- Antimalarials: avoidance of primidone advised by manufacturer of ARTEMether with LUMEFANTRINE
- Histamine: avoidance of antimalarials advised by manufacturer of NIFEDIPINE
- Mepacrine: plasma concentration of primaquine increased by PRIMAQUINE; avoidance of antimalarials advised by manufacturer of PLASMA.
- Vaccines: antimalarials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF

Pregabalin
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by MAOIs and TRICYCLIC-RELATED ANTIDEPRESSANTS (convulsive threshold lowered);
- Anticonvulsants: anticonvulsant effect of antiepileptics antagonised by SSRIS and TRICYCLICS (convulsive threshold lowered);
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by ST JOHN’S WORT—avoid concomitant use; primidone possibly accelerates metabolism of TRICYCLICS (convulsive threshold lowered);
- Antiepileptics: plasma concentration of primidone possibly increased by CARBARbamazepine; primidone possibly reduces plasma concentration of ETHOSUXIMIDE, RUFINAMIDE and TOPIRAMATE; plasma concentration of primidone often increased by FOSPHENytoin and PHENytoin, plasma concentration of fosphenytoin and phenytoin often reduced but may be increased; primidone reduces plasma concentration of LAMOTRIGINE, TIAGABINE and ZONISAMIDE; plasma concentration of primidone increased by oxicABAZEPINE, also plasma concentration of an active metabolite of oxcABAZEPINE reduced; plasma concentration of primidone increased by SAPROFEN; primidone possibly reduces plasma concentration of LAMOTRIGINE.
- Antiepileptics: plasma concentration of primidone possibly increased by trICARAZOLE and POSACOAzoLE—avoid concomitant use; primidone reduces absorption of GISeOFULVIn (reduced effect)
- Antimalarials: avoidance of primidone advised by manufacturer of ARTEMether with LUMEFANTRINE
- Histamine: avoidance of antimalarials advised by manufacturer of NIFEDIPINE
- Mepacrine: plasma concentration of primaquine increased by PRIMAQUINE; avoidance of antimalarials advised by manufacturer of PLASMA.
- Vaccines: antimalarials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF
Primidone (continued)
- Cobicistat: primidone reduces plasma concentration of cobicistat - manufacturer of cobicistat advises avoid concomitant use
- Corticosteroids: primidone accelerates metabolism of corticosteroids (reduced effect)
- Cytotoxics: primidone possibly decreases plasma concentration of cytotoxics (increase dose of cytotoxics — consult cytotoxics product literature); primidone possibly reduces plasma concentration of bortezomib, bosutinib, crizotinib and ponatinib — manufacturer of bortezomib, bosutinib, crizotinib and ponatinib advises avoid concomitant use; primidone possibly reduces plasma concentration of carboxysteroids (reduced effect)
- Diuretics: primidone reduces plasma concentration of diuretics; primidone reduces plasma concentration of irinotecan and its active metabolite; manufacturer of procarbazine advises possible increased risk of hypersensitivity reactions when primidone given with procarbazine
- Folic acid: primidone reduces plasma concentration of folic acid; primidone reduces plasma concentration of etoposide in association with irinotecan and its active metabolite; increased risk of osteomalacia when primidone given with folic acid
- IVacaftor: primidone possibly reduces plasma concentration of ivacaftor — manufacturer of ivacaftor advises avoid concomitant use
- Leukotriene receptor antagonists: primidone reduces plasma concentration of leukotriene receptor antagonists
- Hormone antagonists: primidone possibly reduces plasma concentration of hormone antagonists — manufacturer of abiraterone advises avoid concomitant use; primidone accelerates metabolism of toremifene — reduced plasma concentration
- Progestogens: primidone possibly reduces plasma concentration of progestogens — manufacturer of abiraterone advises avoid concomitant use; primidone accelerates metabolism of progestogens — reduced plasma concentration
- Vincristine: primidone reduces plasma concentration of vincristine
- Etosposes: primidone reduces plasma concentration of etosposes - manufacturer of abiraterone advises avoid concomitant use
- Progestogens: primidone possibly reduces plasma concentration of progestogens — manufacturer of abiraterone advises avoid concomitant use; primidone accelerates metabolism of progestogens — reduced plasma concentration
- Roflumilast: primidone possibly inhibits effects of roflumilast — manufacturer of roflumilast advises avoid concomitant use
- Sodium Oxybate: avoidance of primidone advised by manufacturer of sodium oxybate
- Sympathomimetics: plasma concentration of primidone possibly increased by methylphenidate
- Tacrolimus: primidone reduces plasma concentration of tacrolimus
- Theophylline: primidone accelerates metabolism of theophylline (reduced effect)
- Thyroid Hormones: primidone accelerates metabolism of thyroid hormones (may increase requirements for thyroid hormones in hypothyroidism)
- Ticagrelor: primidone possibly reduces plasma concentration of ticagrelor
- Ulipristal: avoidance of primidone advised by manufacturer of ulipristal — (contraceptive effect of ulipristal possibly reduced)

Primidone (continued)
- Vitamins: primidone possibly increases requirements for alfacalcidol, calcitriol, colecalciferol, dihydrotachysterol, ergocalciferol, paricalcitol or vitamin D

Procarbazine
- Alcohol: disulfiram-like reaction when procarbazine given with alcohol
- Antiepileptics: manufacturer of procarbazine advises possible increased risk of hypersensitivity reactions when given with carbamazepine, fosphenytoin, phenobarbital, phenytoin and primidone
- Antipsychotics: avoidance of concomitant use of cytoprotects with clozapine (increased risk of agranulocytosis)
- Cardiac Glycosides: procarbazine possibly reduces absorption of digoxin tablets

Prochlorperazine
- see Antipsychotics

Procyclidine
- see Antimuscarinics

Progesterone
- see Progestogens

Progestogens
- Antibacterials: plasma concentration of dienogest increased by erythromycin — metabolism of progestogens accelerated by rifamycins (reduced contraceptive effect with combined oral contraceptives, progestogen-only oral contraceptives, contraceptive patches, vaginal rings, etonogestrel-releasing implant, and emergency hormonal contraception — see Contraceptive Interactions in BNF)
- Anticoagulants: progestogens may enhance or reduce anticoagulant effect of coumarins; progestogens antagonise anticoagulant effect of phenindione
- Antidepressants: contraceptive effects of progestogens reduced by st john’s wort (avoid concomitant use)
- Antidiabetics: progestogens antagonise hypoglycaemic effect of antidiabetics
- Antiepileptics: metabolism of progestogens accelerated by carbamazepine, edicatecarbazepine, fosphenytoin, oxcarbazepine, perampanel, phenobarbital, phenytoin, primidone, Rufinamide and topiramate (reduced contraceptive effect with combined oral contraceptives, progestogen-only oral contraceptives, contraceptive patches, vaginal rings, etonogestrel-releasing implant, and emergency hormonal contraception — see Contraceptive Interactions in BNF); desogestrel possibly increases plasma concentration of lamotrigine
- Antifungals: progestogens possibly increase plasma concentration of voriconazole; anecdotal reports of contraceptive failure and menstrual irregularities when progestogens given with griseofulvin; occasional reports of breakthrough bleeding when progestogens (used for contraception) given with terbinafin
- Antivirals: plasma concentration of norethisterone increased by atazanavir; plasma concentration of drospirenone increased by boceprevir (increased risk of toxicity); contraceptive effect of progestogens possibly reduced by efavirenz; plasma concentration of norgestimate increased by elvitegravir; metabolism of progestogens accelerated by nevirapine (reduced contraceptive effect with combined oral contraceptives, progestogen-only oral contraceptives, contraceptive patches, vaginal rings, etonogestrel-releasing implant, and emergency hormonal contraception — see Contraceptive Interactions in BNF)
- Anxiety and Hypnotics: progestogens possibly increase plasma concentration of chlor Diazepoxide, diazepam and nitrazepam; progestogens possibly reduce plasma concentration of lorazepam, oxazepam and temazepam
- Aprepitant: possible contraceptive failure of hormonal contraceptives containing progestogens when given with aprepitant (alternative contraception recommended)
- Bosentan: possible contraceptive failure of hormonal contraceptives containing progestogens when given with bosentan (alternative contraception recommended)
- Ciclosporin: progestogens possibly increase plasma concentration of ciclosporin
- Cobicistat: plasma concentration of norgestimate increased by cobicistat
Propafenone
- Antivirals (continued)
  - Propafenone advised by manufacturer of TELAPREVIR (risk of ventricular arrhythmias)
- Beta-blockers; increased myocardial depression when anti-arrhythmics given with BETA-BLOCKERS; propafenone increases plasma concentration of METOPROLOL and PROPRANOLOL
- Cardiac Glycosides: propafenone increases plasma concentration of DIGOXIN (halve dose of digoxin)
- Cisopropin: propafenone possibly increases plasma concentration of CICLOSPORIN
- Parasympathomimetics: propafenone possibly antagonises effects of NEOSTIGMINE and PYRIDOSTIGMINE
- Theophylline: propafenone increases plasma concentration of THEOPHYLLINE
- Ulcer-healing Drugs: plasma concentration of propafenone increased by CIMETIDINE

Propantheline see Antimuscarinics
Propiverine see Antimuscarinics
Propropofol see Anaesthetics, General
Propranolol see Beta-blockers

Prostaglandins
- ACE Inhibitors: enhanced hypotensive effect when alprostadil given with ACE INHIBITORS
- Adrenergic Neurone Blockers: enhanced hypotensive effect when alprostadil given with ADRENERGIC NEURONE BLOCKERS
- Alpha-blockers: enhanced hypotensive effect when alprostadil given with ALPHA-BLOCKERS
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when alprostadil given with ANGIOTENSIN-II RECEPTOR ANTAGONISTS
- Beta-blockers: enhanced hypotensive effect when alprostadil given with BETA-BLOCKERS
- Calcium-channel Blockers: enhanced hypotensive effect when alprostadil given with CALCIUM-CHANNEL BLOCKERS
- Clonidine: enhanced hypotensive effect when alprostadil given with CLONIDINE
- Diazoxide: enhanced hypotensive effect when alprostadil given with DIAZOXIDE
- Diuretics: enhanced hypotensive effect when alprostadil given with DIURETICS
- Methyldopa: enhanced hypotensive effect when alprostadil given with METHYLDOPA
- Moxonidine: enhanced hypotensive effect when alprostadil given with MOXONIDINE
- Nitrates: enhanced hypotensive effect when alprostadil given with NITRATES
- Oxytocin: prostanoids potentiate uterorecific effect of OXYTOCIN
- Vasodilator Antihypertensives: enhanced hypotensive effect when alprostadil given with HYDRAZALINE, MINOXIDIL or SODIUM NITROPRUSSIDE

Protein Kinase Inhibitors see individual drugs

Proton Pump Inhibitors
- Antacids: absorption of lansoprazole possibly reduced by ANTACIDS
- Antibacterials: plasma concentration of both drugs increased when omeprazole given with CLARITHROMYCIN
- Anticagulants: pantoprazole might enhance the anticoagulant effect of COUMARINS; esomeprazole and omeprazole possibly enhance anticoagulant effect of COUMARINS
- Antidepressants: omeprazole increases plasma concentration of ESCITALOPRAM; plasma concentration of lansoprazole possibly increased by FLUVOXAMINE; plasma concentration of omeprazole possibly reduced by ST JOHN’S WORT
- Antiepileptics: omeprazole possibly enhances effects of FOSPHENYToin and PHYTON; esomeprazole enhances effects of FOSPHENYTin and PHYTON
- Antifungals: proton pump inhibitors reduce absorption of ITRACONAZOLE and KETOCONAZOLE; esomeprazole reduces plasma concentration of POSaconazole—manufacturer of posaconazole suspension advises avoid concomitant use; lansoprazole, omeprazole, pantoprazole and rabeprazole
Pyrazinamide

Antifungals (continued)
possibly reduce plasma concentration of Pyrazinamide—manufacturer of posaconazole suspension advises avoid concomitant use; plasma concentration of fosfomycin possibly increased by voriconazole; plasma concentration of omeprazole increased by voriconazole (consider reducing dose of omeprazole)

Antipsychotics: omeprazole possibly reduces plasma concentration of clozapine

Antivirals: proton pump inhibitors reduce plasma concentration of azithromycin—avoid or adjust dose of both drugs (consult product literature); omeprazole increases plasma concentration of raltegravir; avoidance of esomeprazole, lansoprazole, pantoprazole and rabeprazole advised by manufacturer of rilpivirine (plasma concentration of rilpivirine possibly reduced); omeprazole reduces plasma concentration of rilpivirine—avoid concomitant use; esomeprazole, lansoprazole, pantoprazole and rabeprazole possibly increase plasma concentration of cobicistat—manufacturer of cobicistat advises avoid concomitant use; omeprazole increases plasma concentration of saquinavir—manufacturer of saquinavir advises avoid concomitant use; plasma concentration of esomeprazole and omeprazole reduced by tiprofanesi.

Anxiolytics and Hypnotics: esomeprazole and omeprazole possibly inhibit metabolism of diazepam (increased plasma concentration)

Cardiac Glycosides: proton pump inhibitors possibly slightly increase plasma concentration of digoxin

Ciclosporin: omeprazole possibly affects plasma concentration of ciclosporin

Clotazol: omeprazole increases plasma concentration of clotazol (see under Clotazol, p. 206)

Clopidogrel: esomeprazole and omeprazole reduce antplatelet effect of clopidogrel; lansoprazole, pantoprazole and rabeprazole possibly reduce antplatelet effect of clopidogrel

Cytotoxics: proton pump inhibitors possibly reduce excretion of methotrexate (increased risk of toxicity); lansoprazole reduces plasma concentration of bosutinib; avoidance of proton pump inhibitors advised by manufacturer of dabrafenib (plasma concentration of dabrafenib possibly reduced); avoidance of esomeprazole, lansoprazole, pantoprazole and rabeprazole advised by manufacturer of erlotinib; omeprazole reduces plasma concentration of erlotinib—manufacturer of erlotinib advises avoid concomitant use; proton pump inhibitors possibly reduce absorption of lapatinib; proton pump inhibitors possibly reduce absorption of pazopanib

Tacrolimus: omeprazole possibly increases plasma concentration of tacrolimus

Ulcer-healing Drugs: absorption of lansoprazole possibly reduced by sucralfate

Pseudoephedrine see Sympathomimetics

Pyrazinamide

Sulfispyrazone: pyrazinamide antagonises effects of sulfispyrazone

Vaccines: antimalarials inactivate oral typhoid vaccine—see under Typhoid Vaccine in BNF

Pyridostigmine see Parasympathomimetics

Pyridoxine see Vitamins

Pyrimethamine

Antibacterials: increased antifolate effect when pyrimethamine given with sulfonamides or trimethoprim

Antiepileptics: pyrimethamine antagonises anticonvulsant effect of fosphenytoin and phenytoin, also increased antifolate effect

Antimalarials: avoidance of antimalarials advised by manufacturer of artemether with lumefantrine; increased antifolate effect when pyrimethamine given with proguanil

Antivirals: increased antifolate effect when pyrimethamine given with zidovudine

Pyrimethamine (continued)

Cytotoxics: pyrimethamine increases antifolate effect of methotrexate and pemtrexed

Histamine: avoidance of antimalarials advised by manufacturer of histamine

Vaccines: antimalarials inactivate oral typhoid vaccine—see under Typhoid Vaccine in BNF

Quetiapine see Antipsychotics

Quinidine

Antibacterials: increased risk of ventricular arrhythmias when quinidine given with amiodarone—avoid concomitant use; quinidine increases plasma concentration of flecainide

Antibacterials: increased risk of ventricular arrhythmias when quinidine given with moxifloxacin—avoid concomitant use

Antimalarials: increased risk of ventricular arrhythmias when quinidine given with quinine increased by antiplatelet agents; plasma concentration of quinine increased by cimetidine; increased risk of ventricular arrhythmias when quinine given with warfarin

Antidepressants: possible increased risk of ventricular arrhythmias when quinine given with citalopram or escitalopram—avoid concomitant use

Antimalarials: avoidance of antimalarials advised by manufacturer of artemether with lumefantrine; increased risk of ventricular arrhythmias when quinine given with quinine or moxifloxacin, norfloxacin and ofloxacin reduced by ritonavir

Anticoagulants: plasma concentration of both drugs increased when quinine given with warfarin

Antplatelet agents: increased risk of ventricular arrhythmias when quinine given with quinine or moxifloxacin, norfloxacin and ofloxacin reduced by ritonavir

Antipsychotics: increased risk of ventricular arrhythmias when quinidine given with erlotinib or pazopanib—avoid concomitant use; possible increased risk of ventricular arrhythmias when quinidine given with haloperidol—avoid concomitant use; possible increased risk of ventricular arrhythmias when quinidine given with quinidine or moxifloxacin, norfloxacin and ofloxacin reduced by ritonavir

Cardiac Glycosides: quinidine increases plasma concentration of digoxin

Dopaminergics: quinidine increases plasma concentration of amantadine

Histamine: avoidance of antimalarials advised by manufacturer of histamine

Muscle Relaxants: quinidine possibly enhances effects of succinylcholine

Ulcer-healing Drugs: metabolism of quinidine inhibited by cimetidine (increased plasma concentration)

Vaccines: antimalarials inactivate oral typhoid vaccine—see under Typhoid Vaccine in BNF

Quinolones

Aminoglycosides: possible increased risk of convulsions when quinolones given with amikacin; ciprofloxacin and norfloxacin increase plasma concentration of amikacin

Analgesics: possible increased risk of convulsions when quinolones given with nonsteroidal antiinflammatory agents

Antacids: absorption of ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin and ofloxacin reduced by antacids

Anti-arrhythmics: increased risk of ventricular arrhythmias when levofloxacin or moxifloxacin given with amiodarone—avoid concomitant use; increased risk of ventricular arrhythmias when moxifloxacin given with disopyramide—avoid concomitant use

Antibacterials: increased risk of ventricular arrhythmias when moxifloxacin given with parenteral erythromycin—avoid concomitant use; ciprofloxacin possibly increases plasma concentration of moxifloxacin
Quinolones
- Antibacterials (continued)
  concentration of **BEDAQUILINE**—avoid concomitant use if ciprofloxacin given for more than 14 days; avoidance of moxifloxacin advised by manufacturer of **BEDAQUILINE**;
  increased risk of ventricular arrhythmias when moxifloxacin given with **DELAMANID**; effects of nalidixic acid possibly antagonised by **NITROFURANTOIN**; possible increased risk of ventricular arrhythmias when moxifloxacin given with **TELITHROMYCIN**.
- Anticoagulants: nalidixic acid, norfloxacin and ofloxacin enhance anticoagulant effect of **COUMARINS**; ciprofloxacin and levofloxacin possibly enhance anticoagulant effect of **COUMARINS**; levofloxacin possibly enhances anticoagulant effect of **PHENINDIONE**.
- Antidepressants: avoidance of moxifloxacin advised by manufacturer of **CITALOPRAM** and **ESCITALOPRAM** (risk of ventricular arrhythmias); ciprofloxacin inhibits metabolism of **DULOXETINE**—avoid concomitant use; avoidance of moxifloxacin advised by manufacturer of **AGOMELATINE**; increased risk of ventricular arrhythmias when moxifloxacin given with **TRICYCLES**—avoid concomitant use.
- Antihistamines: increased risk of ventricular arrhythmias when moxifloxacin given with **MILOZUSTINE**—avoid concomitant use.
- Antimalarials: avoidance of quinolones advised by manufacturer of **ARTEMETHER WITH LUMEFANTRINE**; avoidance of moxifloxacin advised by manufacturer of **ARTEMISOL WITH PIDAPERINE** (possible risk of ventricular arrhythmias); increased risk of ventricular arrhythmias when moxifloxacin given with **CHLOROQUINE**.
- Anti-psychotics: ciprofloxacin increases plasma concentration of **FOSPHENYTOIN** and **PHENOTHIAZINES**.
- Antihypertensives: avoidance of quinolones advised by manufacturer of **ARTEMETHER WITH LUMEFANTRINE**; avoidance of moxifloxacin advised by manufacturer of **AGOMELATINE**; increased risk of ventricular arrhythmias when moxifloxacin given with **TRICYCLES**—avoid concomitant use.
- Antidiabetics: norfloxacin possibly enhances effects of **GLIBENCLAMIDE**.
- Antiepileptics: ciprofloxacin increases or decreases plasma concentration of **FOSPHENYTOIN** and **PHENOTHIAZINES**.
- Antipsychotics: increased risk of ventricular arrhythmias when moxifloxacin given with **BENPERIDOL**—manufacturer of benperidol advises avoid concomitant use; increased risk of ventricular arrhythmias when moxifloxacin given with **DROPERIDOL**.
- Antidepressants: increased risk of ventricular arrhythmias when moxifloxacin given with **MELANOSTINE**—avoid concomitant use.
- Antidepressants: increased risk of ventricular arrhythmias when moxifloxacin given with **THERAPY**—avoid concomitant use.
- Anticoagulants: avoidance of moxifloxacin advised by manufacturer of **CITALOPRAM** and **ESCITALOPRAM** (risk of ventricular arrhythmias); ciprofloxacin inhibits metabolism of **DULOXETINE**—avoid concomitant use; avoidance of moxifloxacin advised by manufacturer of **AGOMELATINE**; increased risk of ventricular arrhythmias when moxifloxacin given with **TRICYCLES**—avoid concomitant use.
- Antihistamines: increased risk of ventricular arrhythmias when moxifloxacin given with **MILOZUSTINE**—avoid concomitant use.
- Antimalarials: avoidance of quinolones advised by manufacturer of **ARTEMETHER WITH LUMEFANTRINE**; avoidance of moxifloxacin advised by manufacturer of **ARTEMISOL WITH PIDAPERINE** (possible risk of ventricular arrhythmias); increased risk of ventricular arrhythmias when moxifloxacin given with **CHLOROQUINE**.
- Anti-psychotics: ciprofloxacin increases plasma concentration of **FOSPHENYTOIN** and **PHENOTHIAZINES**.
- Antihypertensives: avoidance of quinolones advised by manufacturer of **ARTEMETHER WITH LUMEFANTRINE**; avoidance of moxifloxacin advised by manufacturer of **AGOMELATINE**; increased risk of ventricular arrhythmias when moxifloxacin given with **TRICYCLES**—avoid concomitant use.
- Antidiabetics: norfloxacin possibly enhances effects of **GLIBENCLAMIDE**.
- Antiepileptics: ciprofloxacin increases plasma concentration of **FOSPHENYTOIN** and **PHENOTHIAZINES**.
- Antipsychotics: ciprofloxacin increases plasma concentration of **FOSPHENYTOIN** and **PHENOTHIAZINES**.
Ranolazine (continued)

- Antifungals: plasma concentration of ranolazine possibly increased by
  - FLUCONAZOLE—avoid concomitant use; plasma concentration of ranolazine increased by
- Beta-blockers: manufacturer of ranolazine advises avoid concomitant use with
  - SOTALOL
- Calcium-channel Blockers: plasma concentration of ranolazine increased by
  - DILTIAZEM and VERAPAMIL (consider reducing dose of ranolazine)
- Cardiac Glycosides: ranolazine increases plasma concentration of
  - DIGOXIN
- Ciclosporin: plasma concentration of both drugs may increase when ranolazine given with
  - CICLOSPORIN
- Grapefruit juice: plasma concentration of ranolazine possibly increased by
  - GRAPEFRUIT JUICE—manufacturer of ranolazine advises avoid concomitant use
- Lipid-regulating Drugs: ranolazine increases plasma concentration of
  - SIMVASTATIN (see under Simvastatin, p. 181); separating administration from ranolazine by 12 hours advised by manufacturer of LOMITAPIDE
- Tacrolimus: ranolazine increases plasma concentration of
  - TACROLIMUS

Rasagiline

- Note Rasagiline is a MAO-B inhibitor
- Analgesics: avoid concomitant use of rasagline with
  - DEXTROMETHORPHAN; risk of CNS toxicity when rasagline given with
  - Pethidine (avoid pethidine for 2 weeks after rasagline)
- Antifungals: plasma concentration of rasagline increased by
  - CIPROFLOXACIN
- Antidepressants: after stopping rasagline do not start
  - FLUOXETINE for 2 weeks, also rasagline should not be started until at least 5 weeks after stopping fluoxetine; after stopping rasagline do not start
- FLUVAXAMINE for 2 weeks; risk of hypertensive crisis when rasagline given with
- MEFLOQUINE, avoid MAOIs for at least 2 weeks after stopping rasagline; increased risk of CNS toxicity when rasagline given with
  - SSRI S or TRICYCLICS
- Dopaminergics: plasma concentration of rasagline possibly reduced by
  - MEMANTINE
- Methyldopa: antiparkinsonian effect of dopaminergics antagonised by
  - METHYLDOPA
- Sympathomimetics: avoid concomitant use of rasagline with
  - SYMPATHOMIMETICS

Reboxetine

- Antibacterials: manufacturer of reboxetine advises avoid concomitant use with
  - MACROLIDES
- Antidepressants: manufacturer of reboxetine advises avoid concomitant use with
  - FLUVAXAMINE; increased risk of hypertension and CNS excitation when reboxetine given with
  - MAOIS (MAOIs should not be started until 1 week after stopping reboxetine, avoid reboxetine for 2 weeks after stopping MAOIs)
- Antiepileptics: plasma concentration of reboxetine possibly reduced by
  - CARBAMAZEPINE, PHENOBARBITAL and PRIMIDONE
- Antifungals: manufacturer of reboxetine advises avoid concomitant use with
  - IMIDAZOLES and TRIAZOLES

Reboxetine (continued)

- Antimalarials: avoidance of antidepressants advised by
  - ARTEMETER WITH LUMEFANTRINE and
  - ARTEMETOMOLL WITH PIPERAZINE
- Atorvastatin: possible increased risk of convulsions when
  - antidepressants given with
- Atorvastatin: possible increased risk of hypokalaemia when reboxetine given with
  - LOOP DIURETICS and THIAZIDES AND RELATED DIURETICS
- Ergot Alkaloids: possible risk of hypertension when reboxetine given with
  - ERGOTAMINE

Regorafenib

- Analgesics: manufacturer of regorafenib advises avoid concomitant use with
  - MEFENAMIC ACID
- Antibacterials: plasma concentration of regorafenib reduced by
  - RIFAMPIN—manufacturer of regorafenib advises avoid concomitant use
- Anticoagulants: increased risk of bleeding when regorafenib given with
  - WARFARIN
- Antifungals: plasma concentration of regorafenib increased by
  - KETOCONAZOLE—avoid concomitant use
- Antipsychotics: avoid concomitant use of cytotoxics with
  - CLOzapine (increased risk of agranulocytosis)
  - Cytotoxics: regorafenib increases plasma concentration of
  - IRINOTECAN

Remifentanil see Opioid Analgesics

Regapride see Antidiabetics

Retigabine

- Alcohol: increased risk of blunted vision when retigabine given with
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by
  - MAOIs and TRICYCLIC-RELATED ANTIDEPRESSANTS (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by
  - SSRI S and TRICYCLICS (convulsive threshold lowered)
- Antiepileptics: plasma concentration of retigabine possibly reduced by
  - CARBAMAZEPINE, FOSPHENYTOIN and PHENYTOIN
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by
  - MELOQUINE
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by
  - ANTIPSYCHOTICS (convulsive threshold lowered)
- Orlistat: possible increased risk of convulsions when antiepileptics given with
  - ORLISTAT

Retinoids

- Alcohol: etretinate formed from acitretin in presence of
  - ALCOHOL (increased risk of teratogenicity in women of child-bearing potential)
- Antibacterials: possible increased risk of benign intracranial hypertension when retinoids given with
  - TETRACYCLINES (avoid concomitant use)
- Anticoagulants: acitretin possibly reduces anticoagulant effect of
  - COUMARINS
- Antiepileptics: isoretinoin possibly reduces plasma concentration of
  - CARBAMAZEPINE
- Antifungals: plasma concentration of alitretinoin increased by
  - KETOCONAZOLE; possible increased risk of tretinoin toxicity when given with
  - FLUCONAZOLE, KETOCONAZOLE and
  - VORICONAZOLE
- Cytotoxics: acitretin increases plasma concentration of
  - METHOTREXATE (also increased risk of hepatotoxicity)—avoid concomitant use
- Lipid-regulating Drugs: alitretinoin reduces plasma concentration of
  - SIMVASTATIN
- Vitamins: risk of hypervitaminosis A when retinoids given with
  - VITAMIN A—avoid concomitant use

Ribavirin

- Antivirals: effects of ribavirin possibly reduced by
  - ABACAVIR; increased risk of side-effects when ribavirin given with
  - DIDANOINES—avoid concomitant use; increased risk of toxicity when ribavirin given with
  - STAVUDINE; increased risk of anaemia when ribavirin given with
  - ZIDOVUDINE—avoid concomitant use
- Azathioprine: ribavirin possibly enhances myelosuppressive effects of
  - AZATHIOPRINE
Rifabutin see Rifamycins
Rifampicin see Rifamycins

Rifamycins

NOTE Interactions do not apply to rifaximin

ACE inhibitors: rifampicin reduces plasma concentration of active metabolite of IMIDAPRIL (reduced antihypertensive effect)

> Aliskiren: rifampicin reduces plasma concentration of ALISKIREN

> Ambisentan: rifampicin possibly increases plasma concentration of AMBISENTAN

> Aminophylline: rifampicin accelerates metabolism of AMINOPHYLLINE (reduced plasma concentration)

> Analgesics: rifampicin reduces plasma concentration of CELECOXIB, DICLOFENAC and ETORICOXIB; rifampicin accelerates metabolism of METHADONE and MORPHINE (reduced effect); rifampicin possibly accelerates metabolism of OXYCODONE

> Angiotensin-II Receptor Antagonists: rifampicin reduces plasma concentration of LOSARTAN and its active metabolite

> Antacids: rifampicin reduces plasma concentration of RANITIDINE

> Anthelmintics: rifampicin accelerates metabolism of PRAZIQANTEL—avoid concomitant use; rifampicin possibly accelerates metabolism of PROPafenONE (reduced effect)

> Antibacterials: increased risk of side-effects including neutropenia when rifabutin given with AZITHROMYCIN; rifampicin reduces plasma concentration of clarithromycin and DOXOPHENE; plasma concentration of rifabutin reduced by CLARITHROMYCIN—increased risk of toxicity—reduce rifabutin dose); rifampicin possibly reduces plasma concentration of TINIDAZOLE and TRIMEITHROM; rifampicin reduces plasma concentration of DOXYCYCLINE—consider increasing dose of doxycycline; rifampicin possibly reduces plasma concentration of BEDAQUILINE—manufacturer of bedaquiline advises avoid concomitant use; rifampicin reduces plasma concentration of BEDAQUILINE—manufacturer of bedaquiline advises avoid concomitant use; rifampicin accelerates metabolism of aripiprazole and its active metabolite of aripiprazole (avoid concomitant use; rifampicin possibly increases plasma concentration of ARIMIPRONE and its active metabolite (increase dose of arimiprone; consult aripiprazole product literature); rifampicin possibly reduces plasma concentration of clozapine; rifampicin reduces plasma concentration of URBANSIDE—avoid concomitant use; rifampicin possibly reduces plasma concentration of ABACAVIR; plasma concentration of rifabutin increased by ATAZANAVIR, DURANAVIR, FOSAMPRENAVIR and ELVITEGRAVIR—manufacturer of elvitegravir and simprevir advises avoid concomitant use; rifampicin possibly reduces plasma concentration of EFVIRENZE—increase dose of efavirenz; plasma concentration of rifabutin reduced by EFVIRENZE—increase dose of rifabutin; avoidance of rifampicin advised by manufacturer of rilpivirine (see under RILPIVIRINE)
Interactions Appendix 1

Cytotoxics:
- Cobicistat:
- Ciclosporin:
- Cardiac Glycosides:
- ▶ Simprevir—manufacturer of simprevir advises avoid concomitant use; avoidance of rifabutin advised by manufacturer of sofosbuvir and telaprevir; rifampicin possibly reduces plasma concentration of tigapan—avoid concomitant use
- Anxiolytics and Hypnotics: rifampicin accelerates metabolism of benzodiazepines (reduced plasma concentration); rifampicin possibly accelerates metabolism of buspirone; rifampicin significantly reduces plasma concentration of zoleifolol (reduced plasma concentration and reduced effect); rifampicin significantly reduces plasma concentration of zopiclone—aprepitant: rifampicin reduces plasma concentration of aprepitant
- Ato伐酮 (also known as atovaquone): avoidance of concomitant rifabutin advised by manufacturer of atovaquone (plasma concentration of both drugs reduced); rifampicin reduces plasma concentration of atovaquone (and concentration of rifampicin increased—avoid concomitant use
- Avanafil: rifampicin possibly reduces plasma concentration of avanafil—manufacturer of avanafil advises avoid concomitant use
- Betablockers: rifampicin accelerates metabolism of bisoprolol and propranolol (plasma concentration significantly reduced); rifampicin reduces plasma concentration of carvedilol, celiprolol and metoprolol; rifampicin possibly reduces plasma concentration of oral timolol
- Bosentan: rifampicin reduces plasma concentration of bosentan—avoid concomitant use
- Calcium-channel blockers: rifampicin possibly reduces plasma concentration of felodipine; rifampicin possibly accelerates metabolism of isradipine and nicardipine (possibly significantly reduced plasma concentration); rifampicin accelerates metabolism of diltiazem, nifedipine, nimodipine and verapamil (plasma concentration significantly reduced)
- Cannabin Extract: rifampicin reduces plasma concentration of cannabis extract—manufacturer of cannabis extract advises avoid concomitant use
- Cardiac Glycosides: rifampicin possibly reduces plasma concentration of digoxin
- Ciclosporin: rifampicin accelerates metabolism of ciclosporin (reduced plasma concentration)
- Cobicistat: rifabutin reduces plasma concentration of cobicistat—adjust dose—consult product literature; rifampicin possibly reduces plasma concentration of cobicistat—manufacturer of cobicistat advises avoid concomitant use
- Corticosteroids: rifamycins accelerate metabolism of corticosteroids (reduced effect)
- Cytotoxics: rifampicin possibly reduces effects of brentuximab vedotin; rifampicin reduces plasma concentration of afatinib, paxilortinib, sorafenib and trabectedin; rifabutin possibly decreases plasma concentration of axitinib (increase dose of axitinib—consult axitinib product literature); rifampicin decreases plasma concentration of axitinib (increase dose of axitinib—consult axitinib product literature)
- DASATINIB (reduced plasma concentration—avoid concomitant use; avoidance of rifampicin advised by manufacturer of dasatinib—lapatinib and vemurafenib—rifampicin accelerates metabolism of dasatinib (reduced plasma concentration); rifampicin reduces plasma concentration of everolimus (avoid concomitant use or consider increasing the dose of everolimus—consult everolimus product literature); avoidance of rifabutin advised by manufacturer of cabazitaxel, lapatinib and vemurafenib; rifampicin possibly reduces plasma concentration of eribulin and pazopanib; rifampicin reduces plasma concentration of active metabolite of temsirolimus—avoid concomitant use; rifampicin possibly reduces plasma concentration of vinflunine—manufacturer of vinflunine advises avoid concomitant use; avoidance of rifampicin advised by manufacturer of vismodegib (plasma concentration of vismodegib possibly reduced)
- Deferasirox: rifampicin reduces plasma concentration of deferasirox
- Diuretics: rifampicin reduces plasma concentration of eplerenone—avoid concomitant use
- Fosaprepitant: rifampicin reduces plasma concentration of fosaprepitant
- Hormone Antagonists: rifabutin possibly reduces plasma concentration of abiraterone—manufacturer of abiraterone advises avoid concomitant use; rifampicin reduces plasma concentration of abiraterone—manufacturer of abiraterone advises avoid concomitant use; avoidance of rifampicin advised by manufacturer of enzalutamide; rifampicin reduces plasma concentration of exemestane; rifampicin accelerates metabolism of tamoxifen (reduced plasma concentration)
- SHT-receptor Antagonists: rifampicin accelerates metabolism of ondansetron (reduced effect)
- Ivacafort: rifabutin possibly reduces plasma concentration of ivacaftor—manufacturer of ivacaftor advises avoid concomitant use; rifampicin reduces plasma concentration of ivacaftor—manufacturer of ivacaftor advises avoid concomitant use
- Leflunomide: rifampicin possibly increases plasma concentration of active metabolite of leflunomide
- Lipid-regulating Drugs: rifampicin possibly reduces plasma concentration of atorvastatin—manufacturer of atorvastatin—manufacturer of atorvastatin—manufacturer of atorvastatin—manufacturer of atorvastatin (plasma concentration of atorvastatin possibly reduced—manufacturer of atorvastatin advises avoid concomitant use)
- Gefitinib and lapatinib—rifampicin reduces plasma concentration of gefitinib and lapatinib—rifampicin reduces plasma concentration of gefitinib and lapatinib—rifampicin reduces plasma concentration of gefitinib and lapatinib—rifampicin reduces plasma concentration of gefitinib and lapatinib—rifampicin reduces plasma concentration of gefitinib and lapatinib (also known as erlotinib and sunitinib)
- Ranolazine: rifampicin reduces plasma concentration of ranolazine—manufacturer of ranolazine advises avoid concomitant use
- Roflumilast: rifampicin inhibits effects of roflumilast (manufacturer of roflumilast advises avoid concomitant use)
- Sirolimus: rifabutin and rifampicin reduce plasma concentration of sirolimus—avoid concomitant use
Rilpivirine

- Rifamycins: rifapentine possibly reduces plasma concentration of TACROLIMUS; rifampicin reduces plasma concentration of
  - TACROLIMUS
  - Tadalafil; rifampicin reduces plasma concentration of
    - TADALAFIL—manufacturer of tadalafil advises avoid concomitant use
  - Teriflunomide: rifampicin reduces plasma concentration of
    - TERIFLUNOMIDE
  - Thiabendazole: rifampicin accelerates metabolism of THEOPHYLLINE (reduced plasma concentration)
  - Thyroid Hormones: rifampicin accelerates metabolism of LEVOTHYROXINE (may increase requirements for levothyroxine in hypothyroidism)
  - Tizanidine: rifampicin accelerates metabolism of TIBOLONE (reduced plasma concentration)
  - Ticagrelor: rifampicin reduces plasma concentration of
    - TICAGRELOR
  - Tolvaptan: rifampicin reduces plasma concentration of
    - TOLVAPTAN
  - Ulcer-healing Drugs: rifampicin accelerates metabolism of
    - Cimetidine (reduced plasma concentration)
  - Ulipristal: avoidance of rifampicin advised by manufacturer of
    - ULPRISTRAL (contraceptive effect of ulipristal possibly reduced)
  - Vaccines: antibacterials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF

Rilpirivine

- Analgesics: rilpirivine possibly reduces plasma concentration of METHADONE
  - Antacids: manufacturer of rifampicin advises give ANTACIDS 2 hours before or 4 hours after rilpirivine
  - Antibacterials: manufacturer of rifampicin advises avoid concomitant use with
    - CLARITHROMYCIN and ERYTHROMYCIN (plasma concentration of rifpirivine possibly increased); plasma concentration of rifpirivine decreased by
    - RIFABUTIN (increase dose of rifpirivine—consult rifpirivine product literature); plasma concentration of rifpirivine reduced by
    - RIFAMPICIN—avoid concomitant use
    - Anticoagulants: rifpirivine possibly increases plasma concentration of DABIGATRAN
  - Antidepressants: manufacturer of rifpirivine advises avoid concomitant use with
    - ST JOHN’S WORT (plasma concentration of rifpirivine possibly reduced)
    - Antiepileptics: manufacturer of rifpirivine advises avoid concomitant use with
      - CARBAMAZEPINE, FOSPHENTOIN, OXCARBAZEPINE, PHENOBARBITAL, PHENYTOIN and PRIMIDONE (plasma concentration of rifpirivine possibly reduced)
    - Antivirals: manufacturer of rifpirivine advises avoid concomitant use with
      - DIDANOSINE 2 hours before or 4 hours after rifpirivine; avoidance of rifpirivine advised by manufacturer of NEVIRAPINE
    - Calcium Salts: manufacturer of rifpirivine advises give CALCIUM SALTS 2 hours before or 4 hours after rifpirivine
    - Corticosteroids: manufacturer of rifpirivine advises avoid concomitant use with
      - DEXAMETHASONE (except when given as a single dose)
    - Orlistat: absorption of rifpirivine possibly reduced by
    - Orlistat
  - Ulcer-healing Drugs: manufacturer of rifpirivine advises avoid concomitant use with
    - ESOMEPRAZOLE, LANSOPRAZOLE, PANTOPRAZOLE and RABEPRAZOLE (plasma concentration of rifpirivine possibly reduced); plasma concentration of rifpirivine reduced by
      - OMEPRAZOLE—avoid concomitant use; manufacturer of rifpirivine advises avoid HISTAMINE H2-ANTAGONISTS for 12 hours before or 4 hours after rifpirivine—consult product literature

Riociguat

- Antacids: absorption of riociguat reduced by
    - ANTACIDS (give at least 2 hours before or 1 hour after riociguat)
  - Antifungals: manufacturer of riociguat advises avoid concomitant use with
    - ITRACONAZOLE, KETOCONAZOLE and VORICONAZOLE
  - Antivirals: manufacturer of riociguat advises avoid concomitant use with RITONAVIR

Riociguat (continued)

- Analgesics: riociguat possibly reduces plasma concentration of
  - ALFENTANIL
  - Aminophylline: riociguat accelerates metabolism of
    - AMINOPHYLLINE (reduced plasma concentration)
  - Analgesics: riociguat possibly increases plasma concentration of
    - NSAIDS and BUPRENORPHINE; riociguat increases plasma concentration of
      - DEXTROPROPOXYPHENE and PIROXICAM (risk of toxicity)—avoid concomitant use; riociguat increases plasma concentration of
        - ALFENTANIL and FENTANYL; riociguat reduces plasma concentration of METHADONE; riociguat possibly reduces plasma concentration of
          - MORPHINE; riociguat reduces plasma concentration of
            - PETHIDINE, but increases plasma concentration of toxic metabolite of pethidine (avoid concomitant use)
  - Anthelmintics: riociguat possibly reduces plasma concentration of active metabolite of
    - ALBENDAZOLE—consider increasing albendazole dose when given for systemic infections
  - Anti-arrhythmics: riociguat increases plasma concentration of
    - AMIODARONE and PROPAFENONE (increased risk of ventricular arrhythmias—avoid concomitant use); riociguat possibly increases plasma concentration of
      - DISOPYRAMIDE (increased risk of toxicity); avoidance of riociguat advised by manufacturer of
        - DRONEDARONE; riociguat possibly increases plasma concentration of
          - FLECAINIDE (increased risk of ventricular arrhythmias—avoid concomitant use)
  - Antibacterials: riociguat possibly increases plasma concentration of
    - AZITHROMYCIN and ERYTHROMYCIN; riociguat increases plasma concentration of
      - CLARITHROMYCIN (reduce dose of clarithromycin in renal impairment); riociguat increases plasma concentration of
        - RIFABUTIN (increased risk of toxicity—reduce rifabutin dose); plasma concentration of riociguat reduced by
          - RIFAMPICIN; riociguat possibly increases plasma concentration of BEDAULUNILE—avoid concomitant use if riociguat given for more than 14 days; riociguat increases plasma concentration of
            - DELAMANIDE; plasma concentration of both drugs increased when riociguat given with
              - FUSIDIC ACID—avoid concomitant use; avoidance of concomitant ritonavir in severe renal and hepatic impairment advised by manufacturer of
                - TELITHROMYCIN
  - Anticoagulants: ritonavir may enhance or reduce anticoagulant effect of
    - WARFARIN; avoidance of ritonavir advised by manufacturer of
      - APIXABAN; rifampicin possibly enhances anticoagulant effect of
        - QUINARINS and PHENINDIONE; ritonavir increases plasma concentration of
          - RIVAROXABAN—avoid concomitant use
  - Antidepressants: ritonavir possibly reduces plasma concentration of
    - PAROXETINE; ritonavir increases plasma concentration of
      - Trazodone (increased risk of toxicity); ritonavir possibly increases plasma concentration of
        - SSRISS and TRICYCLICS; plasma concentration of ritonavir reduced by
          - ST JOHN’S WORT—avoid concomitant use
  - Antidiabetics: riociguat possibly increases plasma concentration of
    - TOBUTAMIDE
  - Antiepileptics: riociguat possibly increases plasma concentration of
    - CARBAMAZEPINE; plasma concentration of ritonavir possibly reduced by
      - FOSPHENTOIN and PHENYTOIN, also plasma concentration of fosphenytoin and phenytoin possibly affected; ritonavir possibly reduces plasma
Ritonavir

- Antiepileptics (continued)
  - concentration of LAMOTRIGINE, SODIUM VALPROATE and VALPROIC ACID
  - Antifungal: ritonavir increases plasma concentration of KETOCONAZOLE (reduce dose of ketoconazole); plasma concentration of ritonavir increased by FLUCONAZOLE; combination of ritonavir with KETOCONAZOLE may increase plasma concentration of either drug (or both); ritonavir reduces plasma concentration of VORICONAZOLE—avoid concomitant use
  - Antihistamines: ritonavir possibly increases plasma concentration of NON-SEDATING ANTIHISTAMINES
  - Antimalarials: caution with ritonavir advised by manufacturer of ARTEMETHER WITH LUMECANTRINE; plasma concentration of ritonavir possibly reduced by METHOLOQUINE; ritonavir increases plasma concentration of QUININE (increased risk of toxicity)
  - Antimycosins: avoidance of ritonavir advised by manufacturer of DARIFENACIN and TOLERTODINE; manufacturer of fosoterodine advises dose reduction when ritonavir given with FOSTERODINE—consult fosoterodine product literature; ritonavir possibly increases plasma concentration of SOLIFENACIN—see under Solifenacin, p. 670
  - Antipsychotics: ritonavir possibly increases plasma concentration of ANTI PSYCHOTICS; ritonavir possibly increases plasma concentration of ARIPIPRAZOLE (reduce dose of aripiprazole—consult aripiprazole product literature); manufacturer of ritonavir advises avoid concomitant use with CLOZAPINE (increased risk of toxicity); ritonavir possibly increases plasma concentration of LURASIDONE—avoid concomitant use; ritonavir reduces plasma concentration of OLANZAPINE—consider increasing dose of olanzapine; ritonavir increases plasma concentration of FINOELOZIDE (increased risk of ventricular arrhythmias—avoid concomitant use); ritonavir possibly increases plasma concentration of GLEPREDON—manufacturer of gelt普惠in advises avoid concomitant use; ritonavir possibly reduces plasma concentration of QUETIAPINE—manufacturer of quetiapine advises avoid concomitant use
  - Antivirals: plasma concentration of both drugs reduced when ritonavir given with RIBAVIRIN; manufacturer of ritonavir advises ritonavir and DIDANOINE should be taken 2.5 hours apart; ritonavir increases the toxicity of EFAVIRENZ, monitor liver function tests—manufacturer of ATRIPHLA advises avoid concomitant use with high-dose ritonavir; ritonavir increases plasma concentration of INDINAVIR, MARAVIROC and SULINDAC; ritonavir increases plasma concentration of SIMPREVIR—manufacturer of simprevir advises avoid concomitant use; ritonavir possibly reduces plasma concentration of TELAPREVIN
  - Anxiolytics and Hypnotics: ritonavir possibly increases plasma concentration of ANXIOLYTICS AND HYPNOTICS; ritonavir possibly increases plasma concentration of ALPROZAMOL, DIAZAPAM, FLURAZEPAM and ZOLPIDEM (risk of extreme sedation and respiratory depression—avoid concomitant use); ritonavir possibly increases plasma concentration of MIDAZOLAM (risk of prolonged sedation—avoid concomitant use of oral midazolam); ritonavir increases plasma concentration of BUSPIONINE (increased risk of toxicity)
  - Aprepitant: ritonavir possibly increases plasma concentration of APERPITANT
  - Atorvastatin: ritonavir possibly reduces plasma concentration of ATOVASTATIN—manufacturer of atovaquone advises avoid concomitant use
  - Avanafil: ritonavir significantly increases plasma concentration of AVANAFIL—avoid concomitant use
  - Bosentan: ritonavir increases plasma concentration of BOSENTAN (consider reducing dose of bosentan)
  - Bupropion: ritonavir reduces plasma concentration of BUPROPION
  - Calcium-channel blockers: ritonavir possibly increases plasma concentration of CALCIUM-CHANNEL BLOCKERS; avoidance of ritonavir advised by manufacturer of LERCANIDIPINE
  - Cardiac Glycosides: ritonavir possibly increases plasma concentration of DIGOXIN
  - Ciclosporin: ritonavir possibly increases plasma concentration of CYCLOSPORIN
  - Ciclosporin (continued)
    - Cilostazol: ritonavir possibly increases plasma concentration of CILOSTAZOL (see under Cilostazol, p. 206)
    - Colchicine: ritonavir possibly increases risk of COCHICINE toxicity—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
    - Corticosteroids: ritonavir possibly increases plasma concentration of CORTICOSTEROIDS—increased risk of adrenal suppression; ritonavir possibly increases plasma concentration of BUDESONIDE (including inhaled, intranasal, and rectal budesonide)—increased risk of adrenal suppression; ritonavir increases plasma concentration of inhaled and intranasal FLUTICASONE—increased risk of adrenal suppression
    - Cytostatics: ritonavir increases the plasma concentration of AFINITIN—manufacturer of afinitin advises separating administration of ritonavir by 6 to 12 hours; ritonavir possibly increases plasma concentration of AXITINIB (reduce dose of axitinib—consult axitinib product literature); ritonavir possibly increases plasma concentration of BOSONITIN and CABAZITAXEL—manufacturer of bosutinib and cabazitaxel advises avoid or consider reducing dose of bosutinib and cabazitaxel; ritonavir possibly increases plasma concentration of CABOZANTINIB and VIBLASTINE; ritonavir possibly increases plasma concentration of CRIZOTINIB, EVEROLIMUS, NILOTINIB and VINFLUNINE—manufacturer of crizotinib, everolimus, nilotinib and vinflunine advises avoid concomitant use; avoidance of ritonavir advised by manufacturer of DASATINIB (plasma clearance of dasatinib possibly increased); ritonavir possibly increases the plasma concentration of IBRUTINIB—reduce dose of ibrutinib (see under Ibrutinib, p. 809); avoidance of ritonavir advised by manufacturer of LAPITINIB; ritonavir possibly increases plasma concentration of PIAZAPANIB (reduce dose of pazopanib); ritonavir possibly increases plasma concentration of PONITINIB—consider reducing initial dose of ponatinib (see under Ponatinib, p. 814); manufacturer of ruxolitinib advises dose reduction when ritonavir given with RUXOLITINIB—consult ruxolitinib product literature; ritonavir possibly increases plasma concentration of DOCETAXEL—manufacturer of docetaxel advises avoid concomitant use or consider reducing docetaxel dose; ritonavir increases plasma concentration of PACITAXEL
    - Dapoxetine: avoidance of ritonavir advised by manufacturer of DAPOXETINE (increased risk of toxicity)
    - Diuretics: ritonavir increases plasma concentration of EPLERENEONE—avoid concomitant use
    - Domperidone: possible increased risk of ventricular arrhythmias when ritonavir given with DOMPERIDONE—avoid concomitant use
    - Ergot Alkaloids: increased risk of ergotism when ritonavir given with ERGOTEMINE or ERGOTAMINE—avoid concomitant use
    - Fosaprepitant: ritonavir possibly increases plasma concentration of FOSAPREPTANT
    - 5HT1-receptor Agonists: ritonavir increases plasma concentration of ELETRIPITAN (risk of toxicity)—avoid concomitant use
    - Ibprofene: ritonavir possibly increases plasma concentration of IBRUPANIB—avoid concomitant use
    - Lipid-regulating Drugs: possible increased risk of myopathy when ritonavir given with ATORVASTATIN; possible increased risk of myopathy when ritonavir given with ROSUVASTATIN—manufacturer of rosuvastatin advises avoid concomitant use; increased risk of myopathy when ritonavir given with SIMVASTATIN (avoid concomitant use); avoidance of ritonavir advised by manufacturer of LOMITAPIDE (plasma concentration of lomitapide possibly increased)
    - Mirabegron: when given with ritonavir advise to reduce dose of MIRABEGRON in hepatic or renal impairment—see Mirabegron, p. 671
    - Oestrogens: ritonavir accelerates metabolism of OESTROGENS (reduced contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF)
Ritonavir (continued)
- Orlistat: absorption of ritonavir possibly reduced by • ORLISTAT
- Ranolazine: ritonavir possibly increases plasma concentration of • RANOLAZINE—manufacturer of ranolazine advises avoid concomitant use
- Riociguat: avoidance of ritonavir advised by manufacturer of • RIOCIGUAT
- Sildenafil: ritonavir significantly increases plasma concentration of • SILDENAFIL—avoid concomitant use
- Symptomatics: ritonavir possibly increases plasma concentration of • DEXAMETHASONE
- Symptomimetics, Beta₂: manufacturer of ritonavir advises avoid concomitant use with • SALMETEROL
- Tacrolimus: ritonavir possibly increases plasma concentration of • TACROLUSM
- Tadalafil: ritonavir increases plasma concentration of • TADALAFIL—manufacturer of tadalafil advises avoid concomitant use
- Theophylline: ritonavir accelerates metabolism of • THEOPHYLINE (reduced plasma concentration)
- Ticagrelor: ritonavir possibly increases plasma concentration of • TICAGRELOR—manufacturer of ticagrelor advises avoid concomitant use
- Ulipristal: avoidance of ritonavir advised by manufacturer of • ULIPRISTAL (contraceptive effect of ulipristal possibly reduced)
- Vardenafil: ritonavir increases plasma concentration of • VARDENAFIL—avoid concomitant use

Rituximab
- Antipsychotics: avoid concomitant use of cytoxics with • CLOZAPINE (increased risk of agranulocytosis)
- Vaccines: risk of generalised infections when monoclonal antibodies given with live • VACCINES—avoid concomitant use

Rivaroxaban
- Analgesics: increased risk of haemorrhage when anticoagulants given with intravenous • DICLOFENAC (avoid concomitant use, including low-dose heparins); increased risk of haemorrhage when anticoagulants given with • KETOROLAC (avoid concomitant use, including low-dose heparins)
- Anti-arrhythmics: manufacturer of rivaroxaban advises avoid concomitant use with • DRONERADONE
- Antibacterials: plasma concentration of rivaroxaban reduced by • RIFAMPICIN—manufacturer of rivaroxaban advises monitor for signs of thrombosis
- Anticoagulants: increased risk of haemorrhage when rivaroxaban given with other • ANTI-HAEMORRHAGIC (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency); increased risk of haemorrhage when other anticoagulants given with • APIXABAN and • DABIGATRAN (avoid concomitant use except when switching with other anticoagulants or using heparin to maintain catheter patency)
- Antidepressants: plasma concentration of rivaroxaban possibly reduced by • ST JOHN'S WORT—manufacturer of rivaroxaban advises monitor for signs of thrombosis
- Antiepileptics: plasma concentration of rivaroxaban possibly reduced by • CARBAMAZEPINE, • PHENYTOIN, • PHENO- BARBITAL, • PHENYTOIN and • PRIMIDONE—manufacturer of rivaroxaban advises monitor for signs of thrombosis
- Antifungals: plasma concentration of rivaroxaban increased by • KETOCONAZOLE—avoid concomitant use; manufacturer of rivaroxaban advises avoid concomitant use with • ITRACONAZOLE, • POSA CONAZOLE and • VORICONAZOLE
- Antivirals: manufacturer of rivaroxaban advises avoid concomitant use with • ATAZANAVIR, • DARUNAVIR, • FOSAMPRENAVIR, • INIDINAVIR, • SQUINAVIR and • TIRPARAVIR; manufacturers advise avoid concomitant use of rivaroxaban with • LOPINAVIR; plasma concentration of rivaroxaban increased by • RITONAVIR—avoid concomitant use
- Cobicistat: anticoagulant effect of rivaroxaban possibly enhanced by • COBICISTAT—avoid concomitant use

Rivastigmine see Parasympathomimetics

Rizatriptan see 5HT₁-receptor Agonists (under HT)

Rocuronium see Muscle Relaxants

Roflumilast
- Aminophylline: manufacturer of roflumilast advises avoid concomitant use with • AMINOPHYLLINE
- Antibacterials: effects of roflumilast inhibited by • RIFAMPICIN (manufacturer of roflumilast advises avoid concomitant use)
- Antidepressants: metabolism of roflumilast inhibited by • FLUVOXAMINE
- Antiepileptics: effects of roflumilast possibly inhibited by • CARBAMAZEPINE, • PHENYTOIN, • PHENO- BARBITAL, • PHENYTOIN and • PRIMIDONE (manufacturer of roflumilast advises avoid concomitant use)
- Theophylline: manufacturer of roflumilast advises avoid concomitant use with • THEOPHYLINE
- Ulcer-healing Drugs: metabolism of roflumilast inhibited by • CIMETIDINE

Ropinirole
- Antibacterials: metabolism of ropinirole inhibited by • CIPROFLOXACIN (increased plasma concentration)
- Antipsychotics: manufacturer of ropinirole advises avoid concomitant use of • ANTI-PSYCHOTICS (antagonism of effect)
- Memantine: effects of dopaminergics possibly enhanced by • MEMANTINE
- Methyldopa: antiparkinsonian effect of dopaminergics antagonised by • METHYLDOPA
- Metoclopramide: manufacturer of ropinirole advises avoid concomitant use of • METOCLOPRAMIDE (antagonism of effect)
- Oestrogens: plasma concentration of ropinirole increased by • OESTROGENS

Rosuvastatin see Statins

Rotavirus Vaccine see Vaccines

Rotigotine
- Antipsychotics: manufacturer of rotigotine advises avoid concomitant use of • ANTI-PSYCHOTICS (antagonism of effect)
- Memantine: effects of dopaminergics possibly enhanced by • MEMANTINE
- Methyldopa: antiparkinsonian effect of dopaminergics antagonised by • METHYLDOPA
- Metoclopramide: manufacturer of rotigotine advises avoid concomitant use of • METOCLOPRAMIDE (antagonism of effect)

Rufinamide
- Antidepressants: anticonvulsant effect of anti-epileptics possibly antagonised by • MAOIs and • TRICYCLIC-RELATED ANTIDEPRESSANTS (convulsive threshold lowered); anticonvulsant effect of anti-epileptics antagonised by • SSRIS and • TRICYCLICS (convulsive threshold lowered)
- Antiepileptics: plasma concentration of both drugs possibly reduced when rufinamide given with • CARBAMAZEPINE; plasma concentration of rufinamide possibly reduced by • FOSPHENYTOIN and • PHENYTOIN, also plasma concentration of fosphenytoin and phenytoin possibly increased; plasma concentration of rufinamide possibly reduced by • PHENO- BARBITAL and • PRIMIDONE; plasma concentration of rufinamide possibly increased by • SODIUM VALPROATE and • VALPROIC ACID (reduce dose of rufinamide)
- Antimalarials: anticonvulsant effect of anti-epileptics antagonised by • MFLOQUINE
- Antipsychotics: anticonvulsant effect of anti-epileptics antagonised by • ANTI-PSYCHOTICS (convulsive threshold lowered)
- Oestrogens: rufinamide accelerates metabolism of • OESTROGENS (reduced contraceptive effect with combined oral contraceptives, contraceptive patches, and vaginal rings—see Contraceptive Interactions in BNF)
- Orlistat: possible increased risk of convulsions when antiepileptics given with • ORLISTAT
- Progestogens: rufinamide accelerates metabolism of • PROGESTOGENS (reduced contraceptive effect with combined oral contraceptives, progestogen-only oral contraceptives,
Interactions

Appendix 1 Interactions

St John’s Wort

Appendix 1

Antivirals:

Antifungals:

Antidepressants:

Anticoagulants:

Analgesics:

Antipsychotics:

Progestogens

Rufinamide

Concentration of rufinamide reduces plasma concentration of ruxolitinib.

St John’s Wort reduces plasma concentration of tadalafil.

St John’s Wort

Antivirals: manufacturer of ruxolitinib advises dose reduction when ruxolitinib given with aminophylline.

Interactions

St John’s Wort

SOFOSBUVIR

LOPINAVIR

TACROLIMUS

MACITENTAN

APREPIANT

SERUM

FOSPHENYTOIN

THELITOMYCIN

PLASMA COUMARINS

THERAPY

DOPED

ALLOSTEROGRAPHS

FRIDAMIRIN

DABIGATRAN

ATACIN

COUMARINS

STEROIDS

DAPOXETINE

MACITENTAN

PHENOBARBITAL

PHLOTOPHILES

PLASMA

PLASMA

PLASMA

PLASMA

PLASMA

PLASMA

PLASMA
St John’s Wort (continued)
- Theophylline: St John’s wort possibly reduces plasma concentration of THEOPHYLLINE.
- Ulcer-healing Drugs: St John’s wort possibly reduces plasma concentration of OMEPRAZOLE.
- Ultrasound: Avoidance of St John’s wort advised by manufacturer of ULIPRISTAL.

Salbutamol see Sympathomimetics, Beta2.
Salmeterol see Sympathomimetics, Beta2.

Saquinavir
- Analgesics: increased risk of ventricular arrhythmias when saquinavir given with - ALFENTANIL, - FENTANYL or
- METHADONE—avoid concomitant use
- Anti-arrhythmics: increased risk of ventricular arrhythmias when saquinavir given with - AMIODARONE, - DISOPRIMIDE, - DRONEDARONE, - FLECAINIDE, - LIDOCAIN or
- PROPafenone—avoid concomitant use
- Antibacterials: plasma concentration of both drugs possibly increased when saquinavir given with - CLARITHROMYCIN (increased risk of ventricular arrhythmias); increased risk of ventricular arrhythmias when saquinavir given with - DAPSONE, - ERTHROMYCIN or - MOXIFLAXACIN—avoid concomitant use; saquinavir increases plasma concentration of - RIFABUTIN (also plasma concentration of saquinavir reduced)—reduce rifabutin dose; plasma concentration of saquinavir significantly reduced by - RIFAMPICIN, also risk of hepatotoxicity—avoid concomitant use; increased risk of ventricular arrhythmias when saquinavir given with - DELAMINIC; plasma concentration of both drugs may increase when saquinavir given with - FUSIDIC ACID; avoidance of saquinavir advised by manufacturer of - TELITHROMYCIN (risk of ventricular arrhythmias)
- Anti-coagulants: saquinavir possibly enhances anticoagulant effect of WARFARIN; avoidance of saquinavir advised by manufacturer of - APLIKABAN and RIVAROBAKAN.
- Antidepressants: increased risk of ventricular arrhythmias when saquinavir given with - TRAZODONE or - TRICYCLICS—avoid concomitant use; plasma concentration of saquinavir reduced by ST JOHN’S WORT—avoid concomitant use
- Antiepileptics: plasma concentration of saquinavir possibly reduced by CARBAMAZEPINE, FOSHENONYNOIN, - PHENOBARBITAL, - PHENETYLL and - PRIMIDONE
- Antifungals: plasma concentration of saquinavir increased by - KETOCONAZOLE—manufacturer of ketoconazole advises avoid concomitant use; plasma concentration of saquinavir possibly increased by - IMIDAZOLE and - TRIAZOLE.
- Antihistamines: increased risk of ventricular arrhythmias when saquinavir given with - MIZOLASTINE—avoid concomitant use
- PONATINIB—avoid concomitant use; caution with saquinavir given with - ARTEMETHER with LUMEFANTRINE; avoidance of saquinavir advised by manufacturer of - ARTENIMOL with PIPERAQUIN (possible risk of ventricular arrhythmias); increased risk of ventricular arrhythmias when saquinavir given with - CLOZAPINE, - HALOPERIDOL or - PHENOTHIAZINES—avoid concomitant use; saquinavir possibly increases plasma concentration of - ARIPPIRAZOLE (reduce dose of ariprazole—consult ariprazole product literature); saquinavir possibly increases plasma concentration of - LURASIDONE—avoid concomitant use; saquinavir possibly increases plasma concentration of - PIMOZIDE (increased risk of ventricular arrhythmias—avoid concomitant use); saquinavir possibly increases plasma concentration of - QUETIPARINE—manufacturer of quetiapine advises avoid concomitant use
- Antivirals: increased risk of ventricular arrhythmias when saquinavir given with - AZATANAVIR or - LOPINAVIR—avoid concomitant use; saquinavir reduces plasma concentration of DARUNAVIR; plasma concentration of saquinavir significantly reduced by EFAVIRENZ; plasma concentration of saquinavir increased by INDINAVIR and - RITONAVIR; saquinavir increases plasma concentration of - MARAVIRIOCO (consider reducing dose of maraviroc); plasma concentration of saquinavir reduced by - TIPRANAVIR
- Anxiolytics and Hypnotics: saquinavir increases plasma concentration of - MIDAZOLAM (risk of prolonged sedation—avoid concomitant use of oral midazolam)
- Avasuflatin: saquinavir possibly increases plasma concentration of - AVANAFIL—manufacturer of avanafil advises avoid concomitant use
- Beta-blockers: increased risk of ventricular arrhythmias when saquinavir given with - SOTALOL—avoid concomitant use
- Ciclosporin: plasma concentration of both drugs increases when saquinavir given with - CICLOSPORIN
- Corticosteroids: plasma concentration of saquinavir possibly reduced by DEXAMETHASONE
- Cytoxics: saquinavir possibly increases the plasma concentration of - AFINATIN—manufacturer of afinatin advises separating administration of saquinavir by 6 to 12 hours; saquinavir possibly increases plasma concentration of - AXITINIB (reduce dose of axitinib—consult axitinib product literature); saquinavir possibly increases the plasma concentration of - BOSUTINIB and - CABAZITAXEL—manufacturer of bosutinib and cabazitaxel advises avoid or consider reducing dose of bosutinib and cabazitaxel; saquinavir possibly increases plasma concentration of ORALZOLE; - CRIZOTINIB and - EVEROLUSM—manufacturer of crizotinib and everolimus advises avoid concomitant use; saquinavir possibly increases the plasma concentration of - IBRUTINIB—reduce dose of ibrutinib (see under Ibrutinib, p. 809); avoidance of saquinavir advised by manufacturer of - LAPATINIB; increased risk of ventricular arrhythmias when saquinavir given with - PAZOPANIB—avoid concomitant use; saquinavir possibly increases plasma concentration of - DOCETAXEL—manufacturer of docetaxel advises avoid concomitant use or consider reducing docetaxel dose
- Dapoxetine: avoidance of saquinavir advised by manufacturer of - DAPOXETINE (increased risk of toxicity)
- Diclofenac: saquinavir increases plasma concentration of - EPLERENONE (reduce dose of eplerenone)
- Domperidone: possibly increased risk of ventricular arrhythmias when saquinavir given with - DOMPERIDONE—avoid concomitant use
- Ergot Alkaloids: increased risk of ergotism when saquinavir given with - ERGOTAMINE—avoid concomitant use
- Lipid-regulating Drugs: possibly increased risk of myopathy when saquinavir given with - ATORVASTATIN; possible increased risk of myopathy when saquinavir given with - ROSUVASTATIN—manufacturer of rosvastatin advises avoid concomitant use; increased risk of myopathy when saquinavir given with - SIMVASTATIN (avoid concomitant use); avoidance of saquinavir advised by manufacturer of - LOMITAPIDE (plasma concentration of lomitapide possibly increased)
- Orlistat: absorption of saquinavir possibly reduced by - ORLISTAT
- Pentamidine: isetionate: increased risk of ventricular arrhythmias when saquinavir given with - PENTAMIDINE ISETIONATE—avoid concomitant use
- Ranolazine: saquinavir possibly increases plasma concentration of - RANOLAZINE—manufacturer of ranolazine advises avoid concomitant use
- Sildenafil: saquinavir increases risk of ventricular arrhythmias when saquinavir given with - SILDENAFIL—avoid concomitant use
- Tacrolimus: saquinavir increases plasma concentration of - TACROLIMUS (consider reducing dose of tacrolimus)
- Tadalafil: saquinavir increases risk of ventricular arrhythmias when saquinavir given with - TADALAFIL—avoid concomitant use

Appendix 1 Interactions
Saxagliptin see Antidiabetics

Selegiline

NOTE Selegiline is a MAO-B inhibitor

— Analgesics: hyperpyrexia and CNS toxicity reported when selegiline given with • PETHIDINE (avoid concomitant use); manufacturer of selegiline advises avoid concomitant use with OPIOID ANALGESICS

— Antidepressants: manufacturer of selegiline advises avoid concomitant use with CITALOPRAM and ESCITALOPRAM; increased risk of hypertension and CNS excitation when selegiline given with • FLUOXETINE (selegiline should not be started until 5 weeks after stopping fluoxetine, avoid fluoxetine for 2 weeks after stopping selegiline); increased risk of hypertension and CNS excitation when selegiline given with • SERTRALINE or • VENLAFAXINE (selegiline should not be started until 1 week after stopping fluvoxamine, sertraline or venlafaxine, avoid fluvoxamine, sertraline or venlafaxine for 2 weeks after stopping selegiline); increased risk of hypertension and CNS excitation when selegiline given with • METHYLDOPA; • PROGRESTGENS — manufacturer of selegiline advises avoid concomitant use; avoid concomitant use of selegiline with • MOCLOBEMIDE; CNS toxicity reported when selegiline given with • TRICYCLICS

— Dopaminergics: selegiline enhances effects and increases toxicity of • CO-BENELDOPA, CO-CARELDOPA or LEVODOPA (reduce dose of co–benelodopa, co-careldopa or levodopa; max. dose of 10 mg selegline advised by manufacturer of ENTACAPONE if used concomitantly

— SHT-receptor Agonists: manufacturer of selegiline advises avoid concomitant use with • SHT, AGONISTS

— Sympathomimetics: effects of dopaminergics and selegiline possibly enhanced by • MEMANTINE

— Methyldopa: antiparkinsonian effect of dopaminergics antagonised by • METHYLDOPA

— Oestrogens: plasma concentration of selegline increased by • OESPROGOST — manufacturer of selegline advises avoid concomitant use

— Progestogens: plasma concentration of selegline increased by • PROGRESTGENS — manufacturer of selegline advises avoid concomitant use

— Sympathomimetits: manufacturer of selegline advises avoid concomitant use with • SYMPATHOMIMETICS; risk of hypertensive crisis when selegline given with • DOPAMINE

Selenium

— Eltrombopag: selenium possibly reduces absorption of ELTROMBOPAG (give at least 4 hours apart)

— Vitamins: absorption of selenium possibly reduced by • ASCORBIC ACID (give at least 4 hours apart)

Sertraline see Antidepressants, SSRI

Sevelamer

— Antibacterials: sevelamer reduces bioavailability of • CIPOFLOXAXIN

— Ciclosporin: sevelamer possibly reduces plasma concentration of • CICLOSPORIN

— Mycophenolate: sevelamer possibly reduces plasma concentration of • MYCOPHENOLATE

— Tacrolimus: sevelamer possibly reduces plasma concentration of • TACROLIMUS

— Thyroid Hormones: sevelamer possibly reduces absorption of • LEVOTHYROXINE

Sildenafil

— Alpha-blockers: enhanced hypotensive effect when sildenafil given with • ALPHA-BLOCKERS (avoid alpha-blockers for 4 hours after sildenafil)—when patient is stable on the alpha blocker initiate sildenafil at the lowest possible dose

— Anti-arrhythmics: avoidance of sildenafil advised by manufacturer of DISOFYPYRAMIDE (risk of ventricular arrhythmias)

— Antibacterials: plasma concentration of sildenafil increased by • CLARITHROMYCIN — consider reducing initial dose of sildenafil for erectile dysfunction or reduce sildenafil dose frequency to once daily for pulmonary hypertension; plasma concentration of sildenafil increased by • ERYTHROMYCIN — reduce initial dose of sildenafil for erectile dysfunction or reduce sildenafil dose frequency to twice daily for pulmonary hypertension; plasma concentration of sildenafil possibly increased by • TELITHROMYCIN — consider reducing initial dose of sildenafil for erectile dysfunction or reduce sildenafil dose frequency to once daily for pulmonary hypertension

— Antifungals: plasma concentration of sildenafil increased by • KETOCONAZOLE — reduce initial dose of sildenafil for erectile dysfunction and avoid sildenafil for pulmonary hypertension; plasma concentration of sildenafil increased by • ITRACONAZOLE — reduce initial dose of sildenafil

— Antivirals: side-effects of sildenafil possibly increased by • ATAZANAVIR; plasma concentration of sildenafil reduced by • ETRAVIRINE; plasma concentration of sildenafil possibly increased by • FOSAMPRENARVIR; plasma concentration of sildenafil increased by • INDINAVIR — reduce initial dose of sildenafil; plasma concentration of sildenafil significantly increased by • Ritonavir — avoid concomitant use; increased risk of ventricular arrhythmias when sildenafil given with • SORAFENIB — avoid concomitant use; avoidance of sildenafil advised by manufacturer of • TELAPREIVIR; avoidance of sildenafil for pulmonary arterial hypertension advised by manufacturer of • TIPRANAVIR

— Bosentan: plasma concentration of sildenafil reduced by • BOSENTAN, also plasma concentration of bosentan increased

— Calcium-channel Blockers: enhanced hypotensive effect when sildenafil given with • AMLODIPINE

— Cobicistat: plasma concentration of sildenafil possibly increased by • Cobicistat — manufacturer of cobicistat advises avoid concomitant use of sildenafil for pulmonary arterial hypertension or reduce dose of sildenafil for erectile dysfunction — consult cobicistat product literature

— Cytoxotics: avoidance of sildenafil for pulmonary arterial hypertension advised by manufacturer of • IDEALISIB

— Dapoxetine: avoidance of sildenafil advised by manufacturer of • DAPoxetine

— Grapefruit Juice: plasma concentration of sildenafil possibly increased by • Grapefruit Juice

— Nicorandil: sildenafil significantly enhances hypotensive effect of • NICORANDIL (avoid concomitant use)

— Nitrates: sildenafil significantly enhances hypotensive effect of • NITRATES (avoid concomitant use)

— Riociguat: enhanced hypotensive effect when sildenafil given with • Riociguat — avoid concomitant use

— Ulcer-healing Drugs: plasma concentration of sildenafil increased by • SEVLEMAFIX — consider reducing dose of sildenafil for erectile dysfunction

Silodosin

— Antibacterials: sevelamer reduces bioavailability of • CIPOFLOXAXIN

— Ciclosporin: sevelamer possibly reduces plasma concentration of • CICLOSPORIN

— Mycophenolate: sevelamer possibly reduces plasma concentration of • MYCOPHENOLATE

— Tacrolimus: sevelamer possibly reduces plasma concentration of • TACROLIMUS

— Thyroid Hormones: sevelamer possibly reduces absorption of • LEVOTHYROXINE

Sevelamer (continued)

— Vitamins: sevelamer reduces absorption of • CALCITRIOL (give at least 1 hour before or 3 hours after sevelamer)

Sevoflurane see Anaesthetics, General

Simeprevir

— Alpha-blocking antibodies given with live VACCINES; risk of generalised infections when monoclonal antibodies given with live VACCINES — avoid concomitant use

— Antibacterials: plasma concentration of simeprevir possibly increased by • CLARITHROMYCIN and • TELITHROMYCIN —
Sirolimus (continued)

> Ciclosporin: plasma concentration of sirolimus increased by CYCLOSPORIN

> Cytoxics: caution with sirolimus advised by manufacturer of CYCLOSPORIN

> Grapefruit Juice: plasma concentration of sirolimus increased by GRAPEFRUIT JUICE—avoid concomitant use

Sitaiglipin see Antidiabetics

Smallpox Vaccine see Vaccines

Sodium Aurothiomolate

> ACE Inhibitors: flushing and hypotension reported when sodium aurothiomolate given with ACE INHIBITORS

> Penicillamine: avoidance of sodium aurothiomolate advised by manufacturer of PENICILLAMINE (increased risk of toxicity)

Sodium Benzoate

> Antiepileptics: effects of sodium benzoate possibly reduced by SODIUM VALPROATE and VALPROIC ACID

> Antipsychotics: effects of sodium benzoate possibly reduced by HALOPERIDOL

Sodium Bicarbonate see Antacids

Sodium Citrate

> Antibacterials: avoid concomitant use of sodium citrate with METHENAMINE

Sodium Nitroprusside see Vasodilator Antihypertensives

Sodium Oxybate

> Analgesics: effects of sodium oxybate enhanced by OPIOID ANALGESICS (avoid concomitant use)

> Antidepressants: increased risk of side-effects when sodium oxybate given with TRICYCLICS

> Antiepileptics: manufacturer of sodium oxybate advises avoid concomitant use with PHENOBARBITAL and PRIMIDONE; plasma concentration of sodium oxybate increased by SODIUM VALPROATE and VALPROIC ACID (see under Sodium Oxybate, p. 425)

> Antipsychotics: effects of sodium oxybate possibly enhanced by ANTIPSYCHOTICS

> Anxiolytics and Hypnotics: effects of sodium oxybate enhanced by ANTIPSYCHOTICS

Sodium Phenylbutyrate

> Antiepileptics: effects of sodium phenylbutyrate possibly reduced by SODIUM VALPROATE and VALPROIC ACID

> Antipsychotics: effects of sodium phenylbutyrate possibly reduced by HALOPERIDOL

> Corticosteroids: effects of sodium phenylbutyrate possibly reduced by CORTICOSTEROIDS

Sodium Stibogluconate

> Antifungals: possible increased risk of arrhythmias when sodium stibogluconate given before AMPHOTERICIN—manufacturer of sodium stibogluconate advises giving 14 days apart

Sodium Valproate

> Analgesics: effects of sodium valproate enhanced by ASPIRIN

> Antidepressants: increased risk of side-effects; sodium valproate increases or possibly enhances ANTIPSYCHOTICS

> Anticonvulsant effect of antiepileptics possibly antagonised by MAOIs and TRICYCLIC-RELATED ANTIDEPRESSANTS (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by SSRIS and TRICYCLICS (convulsive threshold lowered)

> Antiepileptics: plasma concentration of sodium valproate reduced by CARBAMAZEPINE, also plasma concentration of active metabolite of carbamazepine increased; sodium valproate possibly increases plasma concentration of ETHOSUXIMIDE; sodium valproate increases or possibly
Interactions
Sorafenib (continued)
• Antipsychotics: avoid concomitant use of cytoxics with
  • CLOZAPINE (increased risk of agranulocytosis)
• Antivirals: avoidance of sorafenib advised by manufacturer of
  • BOCEPREVIR
  • Cytototics: sorafenib increases plasma concentration of
    • DOCEtaxEL and DOXOribUrin; sorafenib possibly increases
      plasma concentration of IRINOteCAn
  • SpironOlaCTone see Diuretics
Statins
• Antacids: absorption of rosuvastatin reduced by ANTACIDS
  • Anti-arrhythmics: increased risk of myopathy when simvastatin
    given with • AMIODARONE (see under Simvastatin, p. 181);
    plasma concentration of rosuvastatin increased by
    • DRONERADONE—adjust dose of rosuvastatin (consult product
      literature); increased risk of myopathy when simvastatin
      given with • DRONERADONE; plasma concentration of
      atorvastatin possibly increased by DRONERADONE
• Antibacterials: plasma concentration of atorvastatin and
  pravastatin increased by • PHENYTOIN; increased risk of
  myopathy when simvastatin given with • CLARITHRMYCIN,
  • ERYTHROMYCIN or • TELITHRMYCIN (avoid concomitant use);
  plasma concentration of rosuvastatin reduced by
  • ERYTHROMYCIN; possible increased risk of myopathy when
    atorvastatin given with • ERYTHROMYCIN; plasma concentration
    of pravastatin increased by • ERYTHROMYCIN; plasma
    concentration of atorvastatin and simvastatin possibly
    reduced by • RIFAMPICIN; metabolism of fluvastatin accelerated
    by • RIFAMPICIN (reduced effect); increased risk of myopathy
    when statins given with • CLOBAZAM; possibly increased risk
    of myopathy when myopathy present at start of treatment
    with • TELITHRMYCIN
• Anticoagulants: atorvastatin may transiently reduce
  anticoagulant effect of WARfarin; rosuvastatin possibly
  enhances anticoagulant effect of • COUMARINS and
  • PHENINDION; simvastatin can enhance the anticoagulant
    effect of COUMARINS; fluvastatin enhances anticoagulant
    effect of • COUMARINS
  • Antidepressants: plasma concentration of simvastatin reduced
    by ST JOHN’S WORT
  • Antidiabetic: fluvastatin possibly increases plasma
    concentration of • GLIBENCLAMIDE
• Antiepileptics: plasma concentration of simvastatin reduced by
  • CARBAMAZEPINE and • ESICARBZEPINE—consider increasing
    dose of simvastatin; plasma concentration of rosuvastatin
    reduced by • ESICARBZEPINE; combination of fluvastatin with
    • FOSPHEnyTOIN or PHENYTOIN may increase plasma
    concentration of either drug (or both)
• Antifungals: possible increased risk of myopathy when
  atorvastatin given with • KETOCONAZOLE—manufacturer of
  ketoconazole advises avoid concomitant use; increased risk
  of myopathy when simvastatin given with • ITRACNAZOLE,
  • KETOCONAZOLE or • POSACONAZOLE (avoid concomitant use);
    possible increased risk of myopathy when simvastatin given with
    • FLUCONAZOLE or • MICNAZOLE; possible increased risk
    of myopathy when atorvastatin given with • FLUCONAZOLE or
    • IMIDAZOLES; plasma concentration of fluvastatin increased by
    • FLUCONAZOLE—possible increased risk of myopathy; plasma
    concentration of rosuvastatin increased by • ITRACNAZOLE—
    adjust dose of rosuvastatin (consult product literature); increased
    risk of myopathy when atorvastatin given with • ITRACNAZOLE,
    • POSACONAZOLE or • VORICONAZOLE;
    increased risk of myopathy when simvastatin given with • VORICONAZOLE
• Antivirals: possible increased risk of myopathy when
  atorvastatin or pravastatin given with • ATAZANAVIR; plasma
  concentration of rosuvastatin increased by • ATAZANAVIR,
  • DARUNAVIR, • LOPINAVIR and • TIPRANAVIR—adjust dose
    of rosuvastatin (consult product literature); increased risk
    of myopathy when simvastatin given with • ATAZANAVIR,
Statins
- Lipid-regulating Drugs (continued)
  - when simvastatin given with • CIPROFIBRATE (see under Simvastatin, p. 181); when given with statins reduce maximum dose of FENOIBRATE—see under Fenofibrate, p. 172; increased risk of myopathy when atorvastatin, fluvastatin or pravastatin given with • GEMFIBROZIL (preferably avoid concomitant use); increased risk of myopathy when simvastatin given with • GEMFIBROZIL (avoid concomitant use); plasma concentration of rosuvastatin increased by • EZEtimibe—adjust dose of rosuvastatin (consult product literature); increased risk of myopathy when statins given with • FIBRATES; increased risk of myopathy when rosuvastatin given with • FIBRATES (see under Rosuvastatin, p. 180); plasma concentration of simvastatin increased by • Lomitapide—manufacturer of lomitapide advises reduce dose of atorvastatin by half or separate administration by 12 hours; increased risk of myopathy when statins given with • NICOTINIC ACID (applies to lipid regulating doses of nicotinic acid)

- Antivirals (continued)
  - • INDINAVIR, • RITONAVIR or • SAQUINAVIR (avoid concomitant use); plasma concentration of pravastatin increased by • BOCEPREVIR; plasma concentration of atorvastatin increased by • DASLAMIDE; increased risk of myopathy when atorvastatin given with • DASLAMIDE, • ROSUVASTATIN; plasma concentration of atorvastatin possibly reduced by • FOSAMPRENAVIR (see under Atorvastatin, p. 179); plasma concentration of atorvastatin possibly reduced by • Efavirenz; plasma concentration of atorvastatin possibly reduced by • ETRAVIRINE; possible increased risk of myopathy when rosuvastatin given with • FOSAMPRENAVIR, • INDINAVIR, • RITONAVIR or • SAQUINAVIR—manufacturer of rosuvastatin advises avoid concomitant use; possible increased risk of myopathy when simvastatin given with • FOSAMPRENAVIR or • LOPINAVIR—avoid concomitant use; plasma concentration of atorvastatin, rosuvastatin and simvastatin increased by • SIMEPRENAVIR (consider reducing dose of atorvastatin, rosuvastatin and simvastatin); avoidance of atorvastatin advised by manufacturer of • TELAPREVIR; plasma concentration of simvastatin possibly increased by • TIPRANAVIR—avoid concomitant use; increased risk of myopathy when atorvastatin given with • TIPRANAVIR (see under Atorvastatin, p. 179)

- Antidepressants and Hypnotics: atorvastatin possibly increases plasma concentration of • MIDAZOLAM—Bosentan: plasma concentration of simvastatin reduced by • BOSEANTAN

- Calcium-channel Blockers: possible increased risk of myopathy when simvastatin given with • AMLODIPINE or • DILTIAZEM (see under Simvastatin, p. 181); plasma concentration of atorvastatin increased by • DILTIAZEM—possible increased risk of myopathy; increased risk of myopathy when simvastatin given with • VERAPAMIL (see under Simvastatin, p. 181); atorvastatin increases plasma concentration of • VERAPAMIL, also possible increased risk of myopathy (consider reducing dose of atorvastatin)

- Cardiac Glycosides: atorvastatin possibly increases plasma concentration of • DIGOXIN

- Cytotoxic: increased risk of myopathy when rosuvastatin or simvastatin given with • CICLOSPORIN (avoid concomitant use); increased risk of myopathy when atorvastatin given with • CICLOSPORIN (see under Atorvastatin, p. 179); increased risk of myopathy when fluvastatin or pravastatin given with • CICLOSPORIN; • COPIDOGREL: plasma concentration of rosuvastatin increased by • COPIDOGREL—adjust dose of rosuvastatin (consult product literature)

- Cobicistat: plasma concentration of atorvastatin possibly increased by • COBICISTAT—manufacturer of cobicistat advises reduce dose of atorvastatin; avoidance of simvastatin advised by manufacturer of • COBICISTAT

- Colchicine: possible increased risk of myopathy when statins given with • COLCHICINE

- Cytoxics: plasma concentration of simvastatin possibly increased by • DASLAMIDE; avoidance of simvastatin advised by manufacturer of • IDEALISIB; plasma concentration of simvastatin increased by • IMATINIB

- Etilomabopag: plasma concentration of rosuvastatin increased by • EILTROMBOPAG—adjust dose of rosuvastatin (consult product literature)

- Grapefruit Juice: plasma concentration of atorvastatin possibly increased by • GRAPEFRUIT JUICE; plasma concentration of simvastatin increased by • GRAPEFRUIT JUICE—avoid concomitant use

- Hormone Antagonists: possible increased risk of myopathy when simvastatin given with • DANAZOL—avoid concomitant use

- Lipid-regulating Drugs: possible increased risk of myopathy when simvastatin given with • BEZAFIBRATE (see under Simvastatin, p. 181); possible increased risk of myopathy
Sulfonamides (continued)
- Anticoagulants: sulfonamides enhance anticoagulant effect of
- COUMARINS; sulfonamides possibly inhibit metabolism of PHENINDIONE
- Antidiabetics: sulfonamides rarely enhance the effects of SULfonylureAS
- Antiepileptics: sulfonamides possibly increase plasma concentration of PHOSPHENYTOIN and PHENYTOIN
- Antimarials: increased antifolate effect when sulfonamides given with PYRIMETHAMINE
- Antipsychotics: avoid concomitant use of sulfonamides with
- CLOZAPINE (increased risk of agranulocytosis)
- Azathioprine: increased risk of haematological toxicity when sulfamethoxazole (as co-trimoxazole) given with
- AZATHIOPRINE
- Ciclosporin: increased risk of nephrotoxicity when sulfonamides given with • CICLOSPORIN; sulfadiazine possibly reduces plasma concentration of • CICLOSPORIN
- Cytotoxics: increased risk of haematological toxicity when sulfamethoxazole (as co-trimoxazole) given with
- MERCAPTOPURINE or • METHOTREXATE; sulfonamides increase risk of METHOTREXATE toxicity
- Potassium Aminobenzoate: effects of sulfonamides inhibited by
POTASSIUM AMINOBENZOATE
- Vaccines: antibacterials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF

SulfonilureAes see Antidiabetics
Sulindac see NSAIDs
Sulpiride see Antipsychotics
Sumatriptan see 5HT1-receptor Agonists (under HT)
Sunitinib
- Antibacterials: metabolism of sunitinib accelerated by RIFAMPICIN (reduced plasma concentration)
- Antifungals: metabolism of sunitinib inhibited by KETOCONAZOLE (increased plasma concentration)
- Antipsychotics: avoid concomitant use of cytotoxics with • CLOZAPINE (increased risk of agranulocytosis)
- Antivirals: avoidance of sunitinib advised by manufacturer of • BOCEPREVIR

Suxamethonium see Muscle Relaxants

Sympathomimetics
- Adrenergic Neurone Blockers: ephedrine, isometheptene, metaraminol, methylenphedinit, noradrenaline (norepinephrine), oxymetazoline, phenylephrine, pseudoephedrine and xylometazoline antagonise hypertensive effect of • ADRENERGIC NEURONE BLOCKERS; dexamethasamine and lisdexametase antagonise hypertensive effect of • GUANETHIDINE; increased risk of hypertension when adrenaline (epinephrine) given with • GUANETHIDINE
- Alcohol: effects of methylphenidate possibly enhanced by ALCOHOL
- Alpha-adrenoceptor Stimulants: avoidance of sympathomimetics advised by manufacturer of APRACLONIDINE
- Alpha-blockers: avoid concomitant use of adrenaline (epinephrine) or dopamine with VOLAZOLINE
- Aminophylline: avoidance of ephedrine in children advised by manufacturer of AMINOPHYLLINE
- Anaesthetics, General: avoidance of sympathomimetics advised by manufacturer of • ISOFLURANE (risk of ventricular arrhythmias); increased risk of arrhythmias when adrenaline (epinephrine) or noradrenaline (norepinephrine) given with • VOLATILE LIQUID GENERAL ANAESTHETICS;
- Antacids: absorption of pseudoephedrine possibly increased by ALUMINIUM HYDROXIDE
- Antipsychotics: methylphenidate possibly enhances anticoagulant effect of • COUMARIN
- Antidepressants: risk of hypertensive crisis when adrenaline (epinephrine), dobutamine, dopamine, noradrenaline (norepinephrine) or xylometazoline given with • MAOI; risk of hypertensive crisis when dexamethasamine, ephedrine, isometheptene, lisdexametase, metaraminol,
**Sympathomimetics**
- Antidepressants (continued): methylphenidate, phenylephrine or pseudoephedrine given with MAOIs, avoid dexamfetamine, ephedrine, isometheptene, lisdamphetamine, metaraminol, methylphenidate, phenylephrine or pseudoephedrine for at least 2 weeks after stopping MAOIs; risk of hypertensive crisis when oxymetazoline given with MAOIs, some manufacturers advise avoiding oxymetazoline for at least 2 weeks when stopping MAOIs; risk of hypertensive crisis when sympathomimetics given with moclobemide; methylphenidate possibly inhibits metabolism of SSRIs and tricyclics; increased risk of hypertension and arrhythmias when adrenaline (epinephrine) given with tricyclics (but local anaesthetics with adrenaline appear to be safe); increased risk of hypertension and arrhythmias when noradrenaline (norepinephrine) or phenylephrine given with tricyclics.
- Antipsychotics: methylphenidate increases plasma concentration of osphenytoin and phenytoin; methylphenidate possibly increases plasma concentration of phenoxybarbital and primidone.
- Antipyschotics: hypertensive effect of sympathomimetics antagonised by antipsychotics; effects of lisdamphetamine possibly reduced by chlorpromazine; dexamfetamine possibly antagonises antipsychotic effects of chlorpromazine; methylphenidate possibly increases side-effects of risperidone.
- Antivirals: plasma concentration of dexamfetamine possibly increased by ritonavir.
- Beta-blockers: increased risk of severe hypertension and bradycardia when adrenaline (epinephrine) given with non-cardioselective beta-blockers, also response to adrenaline (epinephrine) may be reduced; increased risk of severe hypertension and bradycardia when dobutamine given with non-cardioselective beta-blockers; possible increased risk of severe hypertension and bradycardia when noradrenaline (norepinephrine) given with non-cardioselective beta-blockers.
- Anticoagulants: possible risk of hypertension when adrenaline (epinephrine) or phenylephrine given with clonidine; serious adverse events reported with concomitant use of methylphenidate and clonidine (causality not established).
- Corticosteroids: ephedrine accelerates metabolism of dexamethasone.
- Dopaminergics: risk of toxicity when isometheptene given with bromocriptine; effects of adrenaline (epinephrine), dobutamine, dopamine and noradrenaline (norepinephrine) possibly enhanced by entacapone, avoid concomitant use of sympathomimetics with rasagiline; avoidance of sympathomimetics advised by manufacturer of selegiline; risk of hypertensive crisis when dopamine given with selegiline.
- Selegiline: dopamine, increased risk of hypertension when sympathomimetics given with doxapram.
- Ergot Alkaloids: increased risk of ergotism when sympathomimetics given with ergotamine.
- Oxytocin: risk of hypertension when vasoconstrictor sympathomimetics given with oxytocin (due to enhanced vasopressor effect).
- Sympathomimetics: effects of adrenaline (epinephrine) possibly enhanced by dopexamine; dopexamine possibly enhances effects of noradrenaline (norepinephrine).
- Theophylline: avoidance of ephedrine in children advised by manufacturer of theophylline.
- Ulcer-healing Drugs: metabolism of dobutamine possibly inhibited by cimetidine.

**Sympathomimetics, Beta₂**
- Antivirals (continued): salmeterol advised by manufacturer of telaprevir (risk of ventricular arrhythmias).
- Atomoxetine: increased risk of cardiovascular side-effects when parenteral salbutamol given with atomoxetine.
- Cardiac Glycosides: salbutamol possibly reduces plasma concentration of digoxin.
- Cocistat: avoidance of salbutamol advised by manufacturer of cocistat.
- Corticosteroids: increased risk of hypokalaemia when high doses of beta₂; sympathomimetics given with corticosteroids.
- Cytotoxics: avoidance of salbutamol advised by manufacturer of idelalisib.
- Diuretics: increased risk of hypokalaemia when high doses of beta₂; sympathomimetics given with acetazolamide, loop diuretics or thiazides and related diuretics.
- Methyldopa: acute hypotension reported when infusion of salbutamol given with methyldopa.
- Muscle Relaxants: bantemur bolus enhances effects of suxamethonium.
- Theophylline: increased risk of hypokalaemia when high doses of beta₂; sympathomimetics given with theophylline.

**Tacrolimus**
- Note: Interactions do not generally apply to tacrolimus used topically; risk of facial flushing and skin irritation with topical tacrolimus on consumption of alcohol.
- Analgesics: possible increased risk of nephrotoxicity when tacrolimus given with nsaids; increased risk of nephrotoxicity when tacrolimus given with ibuprofen.
- Angiotensin-II Receptor Antagonists: increased risk of hyperkalaemia when tacrolimus given with angiotensin-II receptor antagonists.
- Anti-arrhythmics: caution with tacrolimus advised by manufacturer of ibotenic acid.
- Antibacterials: plasma concentration of tacrolimus increased by clarithromycin and erythromycin; plasma concentration of tacrolimus possibly reduced by rifabutin; plasma concentration of tacrolimus reduced by rifampicin; increased risk of nephrotoxicity when tacrolimus given with am influences.
- Anticoagulants: tacrolimus possibly increases plasma concentration of dabigatran—manufacturer of dabigatran advises avoid concomitant use.
- Antidepressants: plasma concentration of tacrolimus reduced by st john’s wort—avoid concomitant use.
- Antiepileptics: plasma concentration of tacrolimus reduced by fosphenytoin and phenytoin; plasma concentration of tacrolimus increased by phenobarbital and primidone.
- Antifungals: plasma concentration of tacrolimus increased by fluconazole, itraconazole, ketoconazole, posaconazole and voriconazole (consider reducing dose of tacrolimus); plasma concentration of tacrolimus possibly increased by miconazole oral gel; increased risk of nephrotoxicity when tacrolimus given with amphotericin; plasma concentration of tacrolimus reduced by caspofungin.
- Antipsychotics: avoidance of tacrolimus advised by manufacturer of droperidol (risk of ventricular arrhythmias).
- Antivirals: possible increased risk of nephrotoxicity when tacrolimus given with aciclovir, ganciclovir, valaciclovir or valganciclovir; plasma concentration of tacrolimus possibly increased by telaprevir and ritonavir; plasma concentration of tacrolimus increased by boceprevir (reduce dose of tacrolimus); plasma concentration of tacrolimus possibly affected by efavirenz; plasma concentration of tacrolimus increased by fosamprenavir, plasma concentration of tacrolimus increased by saquinavir (consider reducing dose of tacrolimus); plasma...
Tacrolimus
- Antivirals (continued) concentration of both drugs increased when tacrolimus given with TELAPREVIr (reduce dose of tacrolimus)
- Calcium-channel Blockers: plasma concentration of tacrolimus possibly increased by FELODIPINE and VERAPAMIL; plasma concentration of tacrolimus increased by DILTAZEM, NICARDIPINE and NIFEDIPINE
- Ciclosporin: tacrolimus increases plasma concentration of CICLOSPORIN (increased risk of nephrotoxicity)—avoid concomitant use
- Colestilan: manufacturer of colestilan advises give tacrolimus at least 1 hour before or 3 hours after COLESTILAN
- Cytoxics: tacrolimus possibly increases plasma concentration of CYCLOSPORIN (increased risk of nephrotoxicity)—avoid concomitant use
- DEXRAZOXANE: increased risk of immunosuppression with tacrolimus advised by manufacturer of DEXRAZOXANE
- Diuretics: increased risk of hyperkalaemia when tacrolimus given with POTASSIUM-SPARING DIURETICS and ALDOSTERONE ANTAGONISTS
- Grapefruit Juice: plasma concentration of tacrolimus increased by GRAPEFRUIT JUICE
- Hormone Antagonists: plasma concentration of tacrolimus possibly increased by DANOZOL
- Lipid-regulating Drugs: separating administration from tacrolimus by 12 hours advised by manufacturer of LOMITAPIDE
- Mifamurtide: avoidance of tacrolimus advised by manufacturer of MIFAMURTIDE
- Oestradiols: plasma concentration of tacrolimus possibly increased by ETHINYLESTRADIOL
- Potassium Salts: increased risk of hyperkalaemia when tacrolimus given with POTASSIUM SALTS
- Ranolazine: plasma concentration of tacrolimus increased by RANOLAZINE
- Sevelamer: plasma concentration of tacrolimus possibly reduced by SEVELAMER
- Ulcer-healing Drugs: plasma concentration of tacrolimus possibly increased by OMEPRAZOLE

Tadalafil
- Alpha-blockers: enhanced hypotensive effect when tadalafil given with DOXAZOSIN—manufacturer of tadalafil advises avoid concomitant use; enhanced hypotensive effect when tadalafil given with ALPHA-BLOCKERS—when patient is stable on the alpha blocker initiate tadalafil at the lowest possible dose
- Anti-arrhythmics: avoidance of tadalafil advised by manufacturer of DISOPYRAMIDE (risk of ventricular arrhythmias)
- Antibacterials: plasma concentration of tadalafil possibly increased by CLARITHROMYCIN and ERYTHROMYCIN; plasma concentration of tadalafil reduced by RIFAMPICIN—manufacturer of tadalafil advises avoid concomitant use
- Antifungals: tadalafil concentration is increased by KETOCONAZOLE—avoid concomitant use of tadalafil for pulmonary hypertension; plasma concentration of tadalafil possibly increased by ITRACONAZOLE
- Antivirals: plasma concentration of tadalafil possibly increased by FOSAMPRENAVIR and INDAVIR; plasma concentration of tadalafil increased by RITONAVIR—manufacturer of tadalafil advises avoid concomitant use; increased risk of ventricular arrhythmias when tadalafil given with SACHINAVIR—avoid concomitant use; avoidance of high doses of tadalafil advised by manufacturer of TELAPREVIr consult product literature
- Bosentan: plasma concentration of tadalafil reduced by BOSENTAN
- Cobastic: plasma concentration of tadalafil possibly increased by COBICASTM—manufacturer of cobastic advises reduce dose of tadalafil (consult cobastic product literature)
- Dapoxetine: avoidance of tadalafil advised by manufacturer of DAPOXETINE

Tadalafil (continued)
- Grapefruit Juice: plasma concentration of tadalafil possibly increased by GRAPEFRUIT JUICE
- Nicorandil: tadalafil significantly enhances hypotensive effect of NICORANDIL (avoid concomitant use)
- Nitrates: tadalafil significantly enhances hypotensive effect of NITRIC OXIDE (avoid concomitant use)
- NITRATES (avoid concomitant use)
- Riociguat: possible enhanced hypotensive effect when tadalafil given with RIOCIGUAT—avoid concomitant use

Tamoxifen
- Antibacterials: metabolism of tamoxifen accelerated by RIFAMPICIN (reduced plasma concentration)
- Antiocoagulants: tamoxifen enhances anticoagulant effect of COUMARINS
- Antidepressants: metabolism of tamoxifen to active metabolite possibly inhibited by FLUOXETINE and PAROXETINE (avoid concomitant use)
- Antipsychotics: avoidance of tamoxifen advised by manufacturer of DROPERIDOL (risk of ventricular arrhythmias)
- Bupropion: metabolism of tamoxifen to active metabolite possibly inhibited by BUPROPION (avoid concomitant use)
- Cinacalcet: metabolism of tamoxifen to active metabolite possibly inhibited by CINACALCEt (avoid concomitant use)

Tamulosin see Alpha-blockers

Tapentadol see Opioid Analgesics

Taxanes see Cabazitaxel, Docetaxel, and Paclitaxel

Tegafur
- Antibacterials: metabolism of tegafur inhibited by METRONIDAZOLE (increased toxicity)
- Anticoagulants: tegafur enhances anticoagulant effect of COUMARINS
- Anti-epileptics: tegafur possibly inhibits metabolism of FOSPHENYTOIN and PHENYTOIN (increased risk of toxicity)
- Antipsychotics: avoid concomitant use of cytoxotics with CLOzapine (increased risk of agranulocytosis)
- Filgrastim: neutropenia possibly exacerbated when tegafur given with FILGRASTIM
- Folates: toxicity of tegafur increased by FOLIC ACID—avoid concomitant use
- Lipogfilgrastim: neutropenia possibly exacerbated when tegafur given with LIPGfilGRASTIM
- Pegfilgrastim: neutropenia possibly exacerbated when tegafur given with PEGFILGRASTIM
- Ulcer-healing Drugs: metabolism of tegafur inhibited by CIMETIDINE (increased plasma concentration)

Teicoplanin
- Vaccines: antibacterials inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF

Telaprevir
- Alpha-blockers: manufacturer of telaprevir advises avoid concomitant use with ALFuzosIN
- Analgesics: manufacturer of telaprevir advises caution with METHADONE (risk of ventricular arrhythmias)
- Anti-arrhythmics: manufacturer of telaprevir advises avoid concomitant use with AMIODARONE and DISOPYRAMIDE (risk of ventricular arrhythmias); manufacturer of telaprevir advises caution with intravenous LIDOCAINE
- Antibacterials: plasma concentration of both drugs possibly increased when telaprevir given with CLARITHROMYCIN, ERYTHROMYCIN and TELITHROMYCIN (increased risk of ventricular arrhythmias); manufacturer of telaprevir advises caution with INDAVIR; concentration of Cimetidine (increased plasma concentration)

Tezepelumab see Antibacterials

Teriflunomide see Immune Modulating Drugs

Tocilizumab see Antipsychotics, Biologic Anti-rheumatic Drugs and JAK Inhibitors

Tolfenamic Acid see Nonsteroidal Anti-inflammatory Drugs
Telaprevir (continued)

- Anti-diabetics: telaprevir increases plasma concentration of METFORMIN (consider reducing dose of metformin)
- Antiepileptics: manufacturer of telaprevir advises avoid concomitant use with CARBAMAZEPINE, FOSPHENYTOIN, PHYTONTOIN and SIRMIDONE
- Antifungals: plasma concentration of both drugs possibly increased when telaprevir given with KETOCONAZOLE (increased risk of ventricular arrhythmias)—reduce dose of ketcocazole; telaprevir possibly increases plasma concentration of ITRACONAZOLE; telaprevir possibly increases plasma concentration of POSACONAZOLE (increased risk of ventricular arrhythmias); telaprevir possibly affects plasma concentration of VORICONAZOLE (possible increased risk of ventricular arrhythmias)
- Antipsychotics: telaprevir possibly increases plasma concentration of LEVOSIDONE—avoid concomitant use; manufacturer of telaprevir advises avoid concomitant use with PIMOZIDE; telaprevir possibly increases plasma concentration of QUETIAPINE—manufacturer of quetiapine advises avoid concomitant use
- Antivirals: telaprevir possibly reduced by DASLATASVIR—manufacturer of daslatasvir (see under Daslatasvir, p. 544); avoid concomitant use of telaprevir with DARUNAVIR; plasma concentration of telaprevir reduced by EFAVIRENZ—increase dose of telaprevir; manufacturers advise avoid concomitant use of telaprevir with OSAPRANAVIR and LOPINAVIR; telaprevir increases plasma concentration of MARAVIROC (consider reducing dose of maraviroc); plasma concentration of telaprevir possibly reduced by NEVIRAPINE—consider increasing dose of telaprevir; plasma concentration of telaprevir possibly reduced by BOSENTAN, also plasma concentration of bosentan possibly increased
- Calcium-channel Blockers: telaprevir increases plasma concentration of AMLODIPINE (consider reducing dose of amlodipine); manufacturer of telaprevir advises caution with DILTIAZEM, FELODIPINE, NICARDIPINE, NIFEDIPINE and VERAPAMIL
- Cardiac Glycosides: telaprevir increases plasma concentration of DIGOXIN
- Ciclosporin: plasma concentration of both drugs increased when telaprevir given with CILOSPORIN (reduce dose of ciclosporin)
- Cislozal: telaprevir possibly increases plasma concentration of CILOSTAZOL (see under Cilostazol, p. 206)
- Colchicine: telaprevir possibly increases risk of COLCHICINE toxicity—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
- Corticosteroids: telaprevir possibly increases plasma concentration of INHALED and INTRanasal Budesonide and FLUTicasone; plasma concentration of telaprevir possibly reduced by DXEMETHASONE
- Cytotoxics: telaprevir possibly increases the plasma concentration of BOSUTINIB—manufacturer of bosutinib advises avoid or consider reducing dose of bosutinib; manufacturer of ruxolitinib advises dose reduction when telaprevir given with RUXOLITINIB—consult ruxolitinib product literature
- Dapemidine: possible increased risk of ventricular arrhythmias when telaprevir given with DAPERMIDINE—avoid concomitant use
- Ergot Alkaloids: manufacturer of telaprevir advises avoid concomitant use with ERGOT ALKALOIDS

Telaprevir (continued)

- Lipid-regulating Drugs: manufacturer of telaprevir advises avoid concomitant use with ATORVASTATIN; manufacturers advise avoid concomitant use of telaprevir with SIMVASTATIN; avoidance of telaprevir advised by manufacturer of LOMITAPIDE (plasma concentration of lomitapide possibly increased)
- Nitrates: telaprevir possibly reduces plasma concentration of ETHYNLESTRADIOL—manufacturer of telaprevir advises additional contraceptive precautions
- Sildenafil: manufacturer of telaprevir advises avoid concomitant use with SILDENAFIL
- Sirolimus: plasma concentration of both drugs increased when telaprevir given with SIROLIMUS (reduce dose of sirolimus)
- Sympathomimetics, Beta; manufacturer of telaprevir advises avoid concomitant use with SALMETEROL (risk of ventricular arrhythmias)
- Tacrolimus: plasma concentration of both drugs increased when telaprevir given with TACROLIMUS (reduce dose of tacrolimus)
- Tadalafil: manufacturer of telaprevir advises avoid concomitant use with high doses of TADALAFIL—consult product literature
- Vardenafil: manufacturer of telaprevir advises avoid concomitant use with VARDENAFIL

Telavancin

- Vaccines: antibiotics inactivate ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF

Telbivudine

- Interferons: increased risk of peripheral neuropathy when telbivudine given with INTERFERON ALFA and PEGINTERFERON ALFA

Telithromycin

- Analgesics: possible increased risk of ventricular arrhythmias when telithromycin given with METADONE; telithromycin inhibits the metabolism of OXYCODONE
- Anti-arrhythmics: possible increased risk of ventricular arrhythmias when telithromycin given with AMIODARONE and DISOPRYRAMIDE; increased risk of ventricular arrhythmias when telithromycin given with DRONEDARONE—avoid concomitant use
- Antibacterials: possible increased risk of ventricular arrhythmias when telithromycin given with MOXIFLOXACIN; plasma concentration of telithromycin reduced by BIMFAMIC (avoid during and for 2 weeks after rifampicin)
- Anticoagulants: avoidance of telithromycin advised by manufacturer of APIXABAN
- Antidepressants: possible increased risk of ventricular arrhythmias when telithromycin given with CITLORPAM and TRICYCLICS; plasma concentration of telithromycin reduced by ST JOHN’S WORT (avoid during and for 2 weeks after St John’s wort)
- Antiepileptics: plasma concentration of telithromycin reduced by CARBAMAZEPINE, FOSPHENYTOIN, PHENOBARBITAL, PHENTYTOIN and PRIMIDONE (avoid during and for 2 weeks after carbamazepine, fosphenytoin, phenobarbital, phenytoin and primidone)
- Antifungals: plasma concentration of telithromycin increased by KETOCONAZOLE—avoid in severe renal and hepatic impairment
- Immunomodulators: manufacturer of fesoterodine advises dose reduction when telithromycin given with FESOTERODINE—consult fesoterodine product literature
- Antipsychotics: possible increased risk of ventricular arrhythmias when telithromycin given with CHLORPROMAZINE; telithromycin possibly increases plasma concentration of LURASIDONE—avoid concomitant use; increased risk of ventricular arrhythmias when telithromycin given with PIMOZIDE—avoid concomitant use; telithromycin possibly increases plasma concentration of QUETIAPINE
- Antivirals: manufacturer of telithromycin advises avoid concomitant use with ATAZANAVIR, POSACONAZOLE, RITONAVIR and TIPRANAVIR in severe renal and hepatic impairment; telithromycin possibly increases the plasma concentration of DACLATASVIR—reduce
Telithromycin

- Antivirals (continued)
  - dose of daclatasvir (see under Daclatasvir, p. 544); telithromycin possibly increases plasma concentration of
  - MARAVIROC (consider reducing dose of maraviroc); manufacturer of telithromycin advises avoid concomitant use with
    - SAQUINAVIR (risk of ventricular arrhythmias); telithromycin possibly increases plasma concentration of
  - SIMPEPREVIR—manufacturer of simprevir advises avoid concomitant use; plasma concentration of both drugs possibly increased when telithromycin given with
  - TELAPREVIR (increased risk of ventricular arrhythmias)
  - Anxiolytics and Hypnotics: telithromycin inhibits metabolism of
  - MIDAZOLAM (increased plasma concentration with increased sedation)
  - Aprepitant: telithromycin possibly increases plasma concentration of
  - Aprepitant
  - AVANAFIL: telithromycin possibly increases plasma concentration of
    - AVANAFIL—manufacturer of avanafil advises avoid concomitant use
  - Calcium-channel blockers: telithromycin possibly inhibits metabolism of
    - CICLOSPORIN—telithromycin possibly increases plasma concentration of
  - Colchicine: telithromycin possibly increases risk of
    - COLCHICINE toxicity—suspend or reduce dose of colchicine (avoid concomitant use in hepatic or renal impairment)
  - Cytotoxics: telithromycin possibly increases plasma concentration of
    - AXITINIB (reduce dose of axitinib—consult axitinib product literature); telithromycin possibly increases the plasma concentration of
    - BOSUTINIB and
    - CABAZITAXEL—manufacturer of bostutinib and cabazitaxel advises avoid or consider reducing dose of bostutinib and cabazitaxel; telithromycin possibly increases plasma concentration of
    - CRIZOTINIB and
    - EVEROLINUS—manufacturer of crizotinib and everolimus advises avoid concomitant use; avoidance of telithromycin advised by manufacturer of
    - LARATINIB and
    - NILOTINIB; telithromycin possibly increases plasma concentration of
    - PAZOPANIB (reduce dose of pazopanib); telithromycin possibly increases plasma concentration of
    - PONATINIB—consider reducing initial dose of ponatinib (see under Ponatinib, p. 814); manufacturer of ruxolitinib advises dose reduction when telithromycin given with
    - RUXOLITINIB—consult ruxolitinib product literature; telithromycin possibly increases plasma concentration of
    - DOCETAXEL—manufacturer of docetaxel advises avoid concomitant use or consider reducing docetaxel dose
  - Dapoxetine: avoidance of telithromycin advised by manufacturer of
    - DAPOXETINE (increased risk of toxicity)
  - Diuretics: telithromycin increases plasma concentration of
    - EPLERENONE—avoid concomitant use
  - Ergot alkaloids: increased risk of ergotism when telithromycin given with
    - ERGOTAMINE—avoid concomitant use
  - Fosaprepitant: telithromycin possibly increases plasma concentration of
  - IVACAFOR (see under Ivacaftor, p. 257)
  - Lipid-regulating Drugs: increased risk of myopathy when telithromycin given with
    - ATORVASTATIN or
    - SIMVASTATIN (avoid concomitant use); possible increased risk of myopathy when telithromycin given with
    - PRAVASTATIN; avoidance of telithromycin advised by manufacturer of
    - LOMITAPIDE (plasma concentration of lomitapide possibly increased)

Telithromycin (continued)

- Pentamidine isetionate: possible increased risk of ventricular arrhythmias when telithromycin given with
  - PENTAMIDINE ISETIONATE
- Ranolazine: telithromycin possibly increases plasma concentration of
  - RANOLAZINE—manufacturer of ranolazine advises avoid concomitant use
- Sildenafil: telithromycin possibly increases plasma concentration of
  - SILDENAFIL—consider reducing initial dose of sildenafil for erectile dysfunction or reduce sildenafil dose frequency to once daily for pulmonary hypertension
- Sirolimus: telithromycin increases plasma concentration of
  - SIROLIMUS—avoid concomitant use
- Tacrolimus: telithromycin possibly increases plasma concentration of
  - TACROLIMUS
- Ulipristal: avoidance of telithromycin advised by manufacturer of
  - ULIPRISTAL
- Vaccines: antibacterials inactivate
  - ORAL TYPHOID VACCINE—see under Typhoid Vaccine in BNF
- Temsirolimus
  - NOTE
  - The main active metabolite of temsirolimus is sirolimus—see also interactions of sirolimus and consult product literature
  - Antibacterials: plasma concentration of active metabolite of temsirolimus reduced by
    - RIFAMPICIN—avoid concomitant use
  - Antifungals: plasma concentration of active metabolite of temsirolimus increased by
    - KETOCONAZOLE—avoid concomitant use; manufacturer of temsirolimus advises avoid concomitant use with
    - ITRACONAZOLE (plasma concentration of temsirolimus possibly increased)
  - Antipsychotics: avoid concomitant use of cytotoxics with
    - CLOzapine (increased risk of agranulocytosis)

Tenafavir

- Antivirals: manufacturer of tenafavir advises avoid concomitant use with ADEOFAVIR; tenafavir reduces plasma concentration of
  - ATAZANAVIR, also plasma concentration of tenafavir possibly increased; tenafavir increases plasma concentration of
  - DIDANOxINE (increased risk of toxicity)—avoid concomitant use; plasma concentration of tenafavir increased by
  - LOPINAVIR and TELAPREVIR
  - Orlistat: absorption of tenafavir possibly reduced by
    - ORLISTAT

Tenoxicam see NSAIDs

Terazosin see Alpha-blockers

Terbinafine

- Antibacterials: plasma concentration of terbinafine reduced by
  - RIFAMPICIN
- Antidepressants: terbinafine possibly increases plasma concentration of
  - PAROXETINE and TRICYCLICS
- Antifungals: terbinafine increases plasma concentration of
  - FLUCONAZOLE
- Ciclosporin: terbinafine possibly reduces plasma concentration of
  - CICLOSPORIN
- Oestrogens: occasional reports of breakthrough bleeding when terbinafine given with
  - OESTROGENS (when used for contraception)
- Progestogens: occasional reports of breakthrough bleeding when terbinafine given with
  - PROGESTGENS (when used for contraception)
- Ulcer-healing Drugs: plasma concentration of terbinafine increased by
  - CIMETIDINE

Terbutaline see Sympathomimetics, Beta2
Teriflunomide
▶ Antibacterials: teriflunomide increases plasma concentration of cefaclor; plasma concentration of teriflunomide reduced by rifampicin.
▶ Antidiabetics: teriflunomide increases plasma concentration of repaglinide.
▶ Lipid-regulating Drugs: the effect of teriflunomide is significantly decreased by colestyramine (enhanced elimination)—avoid unless drug elimination desired; teriflunomide increases plasma concentration of • rosuvastatin (consider reducing dose of rosuvastatin).
▶ Oestrogens: teriflunomide increases plasma concentration of ethinylestradiol.
▶ Progestogens: teriflunomide increases plasma concentration of levonorgestrel.
▶ Vaccines: risk of generalised infections when teriflunomide given with live • vaccines—avoid concomitant use.

Testolactone
▶ Anticoagulants: testolactone enhances anticoagulant effect of • coumarins and ▶ phenindione.
▶ Antidepressants: testolactone enhances anticoagulant effect of • coumarins and ▶ phenindione.
▶ Antidiabetics: testolactone possibly enhances hypoglycaemic effect of antidiabetics.

Tetabenazine
▶ Antidepressants: risk of CNS toxicity when tetabenazine given with • MAOIs (avoid tetabenazine for 2 weeks after MAOIs).
▶ Antipsychotics: increased risk of extrapyramidal side-effects when tetabenazine given with antipsychotics.
▶ Dopaminergics: increased risk of extrapyramidal side-effects when tetabenazine given with amantadine.
▶ Metoclopramide: increased risk of extrapyramidal side-effects when tetabenazine given with metoclopramide.

Tetracosactide
▶ See Corticosteroids.

Tetracyclines
▶ ACE inhibitors: absorption of tetracyclines reduced by quinapril tablets (quinapril tablets contain magnesium carbonate).
▶ Adsorbents: absorption of tetracyclines possibly reduced by kaolin.
▶ Antacids: absorption of tetracyclines reduced by antacids.
▶ Antidiabetics: plasma concentration of doxycycline reduced by rifampicin—consider increasing dose of doxycycline; tetracyclines possibly antagonise effects of penicillins.
▶ Anticoagulants: tetracyclines possibly enhance anticoagulant effect of • coumarins and ▶ phenindione.
▶ Antidiabetics: tetracyclines possibly enhance hypoglycaemic effect of antidiabetics.
▶ Tetraphenylboron: absorption of tetracycline reduced by tetrphenylboron.
▶ Fosphenytoin, phenobarbital, phenytoin and primidone (reduced plasma concentration).
▶ Alovacaine: tetracycline reduces plasma concentration of atovaquone.
▶ Calcium Salts: absorption of tetracycline reduced by calcium salts.
▶ Cytotoxics: doxycycline or tetracycline increase risk of methotrexate toxicity.
▶ Dairy Products: absorption of tetracyclines (except doxycycline and minocycline) reduced by dairy products.
▶ Diuretics: manufacturer of lymecycline advises avoid concomitant use with diuretics.
▶ Ergot Alkaloids: increased risk of ergotism when tetracyclines given with ergotamine.
▶ Iron Salts: absorption of tetracyclines reduced by oral iron salts, also absorption of oral iron salts reduced by tetracyclines.
▶ Lipid-regulating Drugs: absorption of tetracycline possibly reduced by colestipol and colestyramine.
▶ Retinoids: possible increased risk of benign intracranial hypertension when tetracyclines given with ▶ retinoids (avoid concomitant use).

Tetracyclines (continued)
▶ Strontium ranelate: absorption of tetracyclines reduced by strontium ranelate (manufacturer of strontium ranelate advises avoid concomitant use).
▶ Ulcer-healing Drugs: absorption of tetracyclines reduced by sucralfate and tripotassium dicitratabisulfate.
▶ Vaccines: antibacterials inactivate oral typhoid vaccine—see under Typhoid Vaccine in BNF.
▶ Zinc: absorption of tetracyclines reduced by zinc, also absorption of zinc reduced by tetracyclines.

Theophylline
▶ Allopurinol: plasma concentration of theophylline possibly increased by allopurinol.
▶ Anaesthetics: general: increased risk of convulsions when theophylline given with ketamine.
▶ Anti-arrhythmics: theophylline antagonises anti-arrhythmic effect of adenosine—manufacturer of adenosine advises avoid theophylline for 24 hours before adenosine; plasma concentration of theophylline increased by propafenone.
▶ Antibacterials: plasma concentration of theophylline possibly increased by clarithromycin and isoniazid; plasma concentration of theophylline increased by erythromycin; plasma concentration of theophylline increased by ciprofloxacin and norfloxacin; metabolism of theophylline accelerated by rifampicin (reduced plasma concentration); possible increased risk of convulsions when theophylline given with quinolones.
▶ Antidepressants: plasma concentration of theophylline increased by fluvoxamine (concomitant use should usually be avoided, but where not possible halve theophylline dose and monitor plasma-theophylline concentration); plasma concentration of theophylline possibly reduced by ST JOHN’S WORT.
▶ Antiepileptics: metabolism of theophylline accelerated by carbamazepine, phenobarbital and ▶ primidone (reduced effect); plasma concentration of both drugs reduced when theophylline given with fosphenytoin and phenytoin.
▶ Antifungals: plasma concentration of theophylline possibly increased by fluconazole and ketoconazole.
▶ Antivirals: plasma concentration of theophylline possibly increased by aciclovir and valaciclovir; metabolism of theophylline accelerated by ritonavir (reduced plasma concentration).
▶ Anti-arrhythmics and Hypnotics: theophylline possibly reduces effects of benzodiazepines.
▶ Caffeine citrate: avoidance of theophylline advised by manufacturer of caffeine citrate.
▶ Calcium-channel Blockers: plasma concentration of theophylline possibly increased by calcium-channel blockers (enhanced effect); plasma concentration of theophylline increased by diltiazem; plasma concentration of theophylline increased by verapamil (enhanced effect).
▶ Corticosteroids: increased risk of hypokalaemia when theophylline given with corticosteroids.
▶ Cytotoxics: plasma concentration of theophylline possibly increased by methotrexate.
▶ Deferasirox: plasma concentration of theophylline increased by deferasirox (consider reducing dose of theophylline).
▶ Disulfiram: metabolism of theophylline inhibited by disulfiram (increased risk of toxicity).
▶ Diuretics: increased risk of hypokalaemia when theophylline given with acetazolamide, loop diuretics of thiazides and related diuretics.
▶ Doxapram: increased CNS stimulation when theophylline given with doxapram.
▶ Interferons: metabolism of theophylline inhibited by interferon alfa and peginterferon alfa (consider reducing dose of theophylline).
▶ Leukotriene Receptor Antagonists: plasma concentration of theophylline possibly increased by zafirlukast; also plasma concentration of zafirlukast reduced.
▶ Lithium: theophylline increases excretion of lithium (reduced plasma concentration).
▶ Oestrogens: plasma concentration of theophylline increased by oestrogens (consider reducing dose of theophylline).
Appendix 1 Interactions

Thyroid Hormones

Thiabendazole: reduced absorption of levothyroxine possibly reduced by ANTACIDS and ANTICOLICICATIONS.

Cimetidine: increased plasma concentration of levothyroxine possibly reduced by ANTACIDS.

Colestyramine: absorption of levothyroxine possibly reduced by ANTACIDS.

Calcium Salts: increased plasma concentration of levothyroxine possibly reduced by ANTACIDS.

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Calcium Salts: absorption of levothyroxine reduced by ANTACIDS.

Calcium Salts: increased plasma concentration of levothyroxine possibly reduced by ANTACIDS.
Tipranavir
- Analgesics: plasma concentration of tipranavir possibly reduced by BUPRENORPHINE.
- Antacids: absorption of tipranavir reduced by ANTACIDS (give at least 2 hours apart).
- Antidepressants: tipranavir increases plasma concentration of CLARITHROMYCIN (reduce dose of clarithromycin in renal impairment), also plasma concentration of tipranavir increased by clarithromycin; tipranavir increases plasma concentration of RIFABUTIN (reduce dose of rifabutin); plasma concentration of tipranavir possibly reduced by RIFAMPICIN—avoid concomitant use; avoidance of concomitant tipranavir in severe renal and hepatic impairment advised by manufacturer of TELITHROMYCIN.
- Anticoagulants: avoid tipranavir advised by manufacturer of ST JOHN'S WORT—avoid concomitant use.
- Antiepileptics: plasma concentration of tipranavir possibly reduced by CARBAMAZEPINE.
- Antifungals: plasma concentration of tipranavir increased by FLUCONAZOLE.
- Antimalarials: caution with tipranavir advised by manufacturer of ARTEMETHER WITH LUMEFANTRINE; tipranavir possibly increases plasma concentration of QUININE (increased risk of toxicity).
- Antimucosals: avoidance of tipranavir advised by manufacturer of DARIFENACIN.
- Antipsychotics: tipranavir possibly increases plasma concentration of ARIPIPRAZOLE (reduce dose of aripiprazole—consult aripiprazole product literature); tipranavir possibly increases plasma concentration of QUETIAPINE—manufacturer of quetiapine advises avoid concomitant use.
- Antiretrovirals: tipranavir reduces plasma concentration of ABACAVIR, FOSAMPRENAVIR, LOPINAVIR, SAQUINAVIR and ZIDOVUDINE; plasma concentration of tipranavir increased by ATAZANAVIR (also plasma concentration of atazanavir reduced); manufacturer of tipranavir advises avoid concomitant use with BOSONERI and TELAPREVIR; tipranavir reduces plasma concentration of DIDOSINASE—manufacturer of tipranavir advises tipranavir and didanosine capsules should be taken at least 2 hours apart; tipranavir reduces the plasma concentration of DOLTEGRAVIR (see under Dolutegravir, p. 75); tipranavir reduces plasma concentration of ETARVIREN, also plasma concentration of tipranavir increased (avoid concomitant use).
- Beta-blockers: manufacturer of tipranavir advises avoid concomitant use with METOPROLOL for heart failure.
- Benzodiazepine manufacturer of tipranavir advises avoid concomitant use with BOSENAT.
- Cobicistat: plasma concentration of both drugs reduced when tipranavir given with Cobicistat (see under Atorvastatin, p. 179); tipranavir increases plasma concentration of ROSUVASTATIN—adjust dose of rosuvastatin (consult product literature); tipranavir possibly increases plasma concentration of SIMVASTATIN—avoid concomitant use; avoidance of tipranavir advised by manufacturer of LOMITAPIDE (plasma concentration of lomitapide possibly increased).
- Orlistat: absorption of tipranavir possibly reduced by ORLISTAT.
- Ranolazine: tipranavir possibly increases plasma concentration of RANOLAZINE—manufacturer of ranolazine advises avoid concomitant use.
- Sildenafil: manufacturer of tipranavir advises avoid concomitant use of SILDENAFIL for pulmonary arterial hypertension.
- Sympathomimetics, Beta-2: manufacturer of tipranavir advises avoid concomitant use with SALMETEROL.
- Ulcer-healing Drugs: tipranavir reduces plasma concentration of ESOMEPRAZOLE and OMEPRAZOLE.
- Vardenafil: manufacturer of tipranavir advises caution with VARDENAFIL.

Tipranavir (continued)
- Vitamins: increased risk of bleeding when tipranavir given with high doses of VITAMIN E.
- Tirolanib: increased risk of bleeding when tirolanib given with EBOSPOST.
- Tizanidine: see Muscle Relaxants.
- Tobramycin: see Aminoglycosides.
- Tocilizumab: avoid anticonvulsant use of cytotoxics with CARBAMAZEPINE (increased risk of agranulocytosis).
- Vaccines: risk of generalised infections when monoclonal antibodies given with live VACCINES—avoid concomitant use.
- Tolazoline: see Alpha-blockers.
- Tolbutamide: see Antidiabetics.
- Tocapone: avoid anticonvulsant use of tolcapone with MAOIS.
- Memantine: effects of dopaminergics possibly enhanced by MEMANTINE.
- Methyldopa: antiparkinsonian effect of dopaminergics antagonised by METHYLDOPA.
- Tolmentamic Acid: see NSAIDs.
- Tolterodine: see Antimuscarinics.
- Tolvaptan: avoid anticonvulsant use of tolvaptan with MAOIS.
- Memantine: effects of dopaminergics possibly enhanced by MEMANTINE.
- Methyldopa: antiparkinsonian effect of dopaminergics antagonised by METHYLDOPA.
- Topiramate: avoid anticonvulsant use of topiramate with MAOIS.
- Memantine: effects of dopaminergics possibly enhanced by MEMANTINE.
- Methyldopa: antiparkinsonian effect of dopaminergics antagonised by METHYLDOPA.
- Topiramate: avoid anticonvulsant use of topiramate with MAOIS.
- Memantine: effects of dopaminergics possibly enhanced by MEMANTINE.
- Methyldopa: antiparkinsonian effect of dopaminergics antagonised by METHYLDOPA.

Tipranavir: see Antipsychotics.
- Antipsychotics: avoid concomitant use of cytotoxics with CARBAMAZEPINE (increased risk of agranulocytosis).
- Vaccines: risk of generalised infections when monoclonal antibodies given with live VACCINES—avoid concomitant use.

Tipranavir (continued)
- Vitamins: increased risk of bleeding when tipranavir given with high doses of VITAMIN E.
- Tirolanib: increased risk of bleeding when tirolanib given with EBOSPOST.
- Tizanidine: see Muscle Relaxants.
- Tobramycin: see Aminoglycosides.
- Tocilizumab: avoid anticonvulsant use of cytoxics with CARBAMAZEPINE (increased risk of agranulocytosis).
- Vaccines: risk of generalised infections when monoclonal antibodies given with live VACCINES—avoid concomitant use.
- Tolazoline: see Alpha-blockers.
- Tolbutamide: see Antidiabetics.
- Tocapone: avoid anticonvulsant use of tolcapone with MAOIS.
- Memantine: effects of dopaminergics possibly enhanced by MEMANTINE.
- Methyldopa: antiparkinsonian effect of dopaminergics antagonised by METHYLDOPA.
- Tolmentamic Acid: see NSAIDs.
- Tolterodine: see Antimuscarinics.
- Tolvaptan: avoid anticonvulsant use of tolvaptan with MAOIS.
- Memantine: effects of dopaminergics possibly enhanced by MEMANTINE.
- Methyldopa: antiparkinsonian effect of dopaminergics antagonised by METHYLDOPA.
- Topiramate: avoid anticonvulsant use of topiramate with MAOIS.
- Memantine: effects of dopaminergics possibly enhanced by MEMANTINE.
- Methyldopa: antiparkinsonian effect of dopaminergics antagonised by METHYLDOPA.
- Topiramate: avoid anticonvulsant use of topiramate with MAOIS.
- Memantine: effects of dopaminergics possibly enhanced by MEMANTINE.
- Methyldopa: antiparkinsonian effect of dopaminergics antagonised by METHYLDOPA.
Interactions

Trimethoprim

- Anticoagulants: toremifene possibly increases anticoagulant effect of COUMARINS.
- Antibiotics: metabolism of toremifene possibly accelerated by CARRABAZEPINE (reduced plasma concentration); metabolism of toremifene possibly accelerated by FOSPHENYTIOIN and PHENOTYIN; metabolism of toremifene accelerated by PHENOBARBITAL and PRIMIDONE (reduced plasma concentration).

- Cytotronics: possible increased risk of ventricular arrhythmias when trimethoprim given with VANDETANIB—avoid concomitant use.
- Diuretics: increased risk of hypercalcaemia when toremifene given with THIAZIDES AND RELATED DIURETICS.

Trabectedin

- Alcohol: manufacturer of trabectedin advises avoid concomitant use with ALCOHOL.

- Antivirals: co-trimoxazole increases plasma concentration of AZATHIOPRINE.

- Antihypertensives: co-trimoxazole increases plasma concentration of AZATHIOPRINE.

- Antidepressants: co-trimoxazole increases plasma concentration of AZATHIOPRINE.

- ACE Inhibitors: possible increased risk of hyperkalaemia when trimethoprim given with ACE INHIBITORS.

- Angiotensin-II Receptor Antagonists: possible increased risk of hyperkalaemia when trimethoprim given with ANGIOSTENIN-II RECEPTOR ANTAGONISTS.

- Anti-arrrhythmics: possible increased risk of ventricular arrhythmias when trimethoprim (as co-trimoxazole) given with AMIODARONE—manufacturer of amiodarone advises avoid concomitant use of co-trimoxazole.

- Anticoagulants: trimethoprim possibly enhances anticoagulant effect of COUMARINS.

- Antibacterials: trimethoprim increases plasma concentration of REPAGLINIDE (contraceptive effect of ulipristal possibly reduced).

- Analgesics: trimethoprim possibly enhances anticoagulant effect of COUMARINS.

- Sulfonylureas: trimethoprim increases plasma concentration of PHOSPHENYTIOIN and PHENOTYIN (increased antifolate effect).

- Antimalarials: increased antifolate effect when trimethoprim given with PYRIMETHamine.

- Antituberculars: trimethoprim increases plasma concentration of LAMIVUDINE—avoid concomitant use of high-dose co-trimoxazole.

- Azathioprine: increased risk of haematological toxicity when trimethoprim (also with co-trimoxazole) given with AZATHIOPRINE.

- Cardiac Glycosides: manufacturer of ulipristal advises avoid concomitant use with DIBUGATRAN at least 1.5 hours before or after ulipristal.

- Progestogens: ulipristal possibly reduces contraceptive effect of DIBUGATRAN.

- Ursodeoxycholic Acid: see Bilirubins.

- Antipsychotics: ulipristal possibly reduces contraceptive effect of DIBUGATRAN.

- Vaccines: risk of generalised infections when monoclonal antibodies given with live VACCINES—avoid concomitant use.

- Anti-arrhythmics: possible increased risk of hyperkalaemia when trimethoprim given with EPLERENONE; possible increased risk of hyperkalaemia when trimethoprim given with SPIRONOLACTONE.

- Anticoagulants: toremifene possibly increased anticoagulant effect of WARFARIN.
Vaccines (continued)
  • Anakinra: risk of generalised infections when live vaccines given with • ANAKINRA—avoid concomitant use
  • Antibacterials: oral typhoid vaccine inactivated by ANTI-BACTERIALS—see under Typhoid Vaccine in BNF
  • Antivirals: influenza vaccine possibly enhances anticoagulant effect of WARFARIN
  • Antiepileptics: influenza vaccine enhances effects of FOSPHENYTOIN and PHENYTOIN
  • Antimalarials: oral typhoid vaccine inactivated by ANTIMALARIALS—see under Typhoid Vaccine in BNF
  • Corticosteroids: immune response to vaccines impaired by high doses of • CORTICOSTEROIDS—avoid concomitant use with live vaccines
  • Cytotoxics: risk of generalised infections when live vaccines given with • DOXORUBICIN, • MONOCLONAL ANTIBODIES,
    • PIAXANTRONE or • TRABECTEDIN—avoid concomitant use
  • Dexrazoxane: risk of generalised infections when live vaccines given with • DEXRAZOXANE—avoid concomitant use
  • Etanercept: risk of generalised infections when live vaccines given with • ETANERCEPT—avoid concomitant use
  • Immunoglobulins: impaired immune response to oral poliomyelitis vaccine might occur with • ANTI-D IMMUNOGLOBULINS and • NORMAL IMMUNOGLOBULIN—give oral poliomyelitis vaccine at least 5 weeks before or 3 months after anti-d immunoglobulins and normal immunoglobulin; impaired immune response to BCG vaccine, MMR vaccine, oral typhoid vaccine, rotavirus vaccine, smallpox vaccine, varicella-zoster vaccine and yellow fever vaccine might occur with • ANTI-D IMMUNOGLOBULINS—give BCG vaccine, MMR vaccine, oral typhoid vaccine, rotavirus vaccine, smallpox vaccine, varicella-zoster vaccine and yellow fever vaccine at least 3 weeks before or 3 months after anti-d immunoglobulins; impaired immune response to live influenza vaccine might occur with • ANTI-D IMMUNOGLOBULINS and • NORMAL IMMUNOGLOBULIN—give live influenza vaccine at least 3 weeks before or 3 months after anti-d immunoglobulins and normal immunoglobulin; impaired immune response to BCG vaccine, MMR vaccine, oral typhoid vaccine, rotavirus vaccine, smallpox vaccine, varicella-zoster vaccine and yellow fever vaccine might occur with • NORMAL IMMUNOGLOBULIN—give BCG vaccine, MMR vaccine, oral typhoid vaccine, rotavirus vaccine, smallpox vaccine, varicella-zoster vaccine and yellow fever vaccine at least 3 weeks before or 3 months after normal immunoglobulin
  • Interferons: avoidance of vaccines advised by manufacturer of • INTERFERON GAMMA
  • Leflunomide: risk of generalised infections when live vaccines given with • LEFLUNOMIDE—avoid concomitant use
  • Teriflunomide: risk of generalised infections when live vaccines given with • TERIFLUNOMIDE—avoid concomitant use
  • Theophylline: influenza vaccine possibly increases plasma concentration of • THEOPHYLLINE
  • Valaciclovir
Valaciclovir (continued)
  • Mycophenolate: plasma concentration of inactive metabolite of mycophenolate possibly increased
• Tacrolimus: possible increased risk of nephrotoxicity when valaciclovir given with • TACROLIMUS
Valproic Acid
  • Analgesics: effects of valproic acid enhanced by • ASPIRIN
  • Antibacterials: metabolism of valproic acid possibly inhibited by • ERYTHROMYCIN (increased plasma concentration); avoidance of valproic acid advised by manufacturer of • PIVMECILLINAM; plasma concentration of valproic acid reduced by • CARBAPENEMS—avoid concomitant use
  • Anticoagulants: valproic acid possibly enhances anticoagulant effect of • COUMARINS
  • Antidepressants: anticonvulsant effect of antiiepileptics possibly antagonised by • MAOIS and • TRICYCLIC-RELATED ANTIDEPRESSANTS (convulsive threshold lowered); anticonvulsant effect of antiiepileptics antagonised by • SSRIS and • TRICYCLICS (convulsive threshold lowered)
  • Antiepileptics: plasma concentration of valproic acid reduced by • CARBAMAZEPINE, also plasma concentration of active metabolite of carbamazepine increased; valproic acid possibly increases plasma concentration of • ETHOSUXIMIDE; valproic acid increases or possibly decreases plasma concentration of • FOSPHENYTOIN and • PHENYTOIN, also plasma concentration of valproic acid reduced; valproic acid increases plasma concentration of • LAMOTRIGINE (increased risk of toxicity—reduce lamotrigine dose); valproic acid sometimes reduces plasma concentration of an active metabolite of • OXCARBAZEPINE; valproic acid increases plasma concentration of • PHENOBARBITAL and • PRIMIDONE (also plasma concentration of valproic acid reduced); valproic acid possibly increases plasma concentration of • RUFINAMIDE (reduce dose of rufinamide); hyperammonaemia and CNS toxicity reported when valproic acid given with • TOPIRAMATE
  • Antimalarials: anticonvulsant effect of antiiepileptics antagonised by • MEFLOQUINE
  • Antipsychotics: anticonvulsant effect of antiiepileptics antagonised by • ANTI-PsyCHOTiCS (convulsive threshold lowered); valproic acid possibly increases or decreases plasma concentration of • CLOZAPiNE; increased risk of side-effects including neutropenia when valproic acid given with • OLANZAPiNE
  • Antivirals: plasma concentration of valproic acid possibly reduced by • RITONAViR; valproic acid possibly increases plasma concentration of • ZIDOVUDiNE (increased risk of toxicity)
  • Anxiolytics and Hypnotics: plasma concentration of valproic acid possibly increased by • CLOBAZAM; increased risk of side-effects when valproic acid given with • CLONAZEPAM; valproic acid possibly increases plasma concentration of • DIAZEPAM and • LORAZEPAM
  • Bupropion: valproic acid inhibits the metabolism of • BUPROPiON
  • Cytoxics: valproic acid increases plasma concentration of • TEMOZOLOMiDE
  • Lipid-regulating Drugs: absorption of valproic acid possibly reduced by • COLESTiRAMiNE
  • Oestrogens: plasma concentration of valproic acid possibly reduced by • ETHiNYLESTRADiOL
  • Orlistat: possible increased risk of convulsions when antiepileptics given with • ORLISTAT
  • Sodium Benzoate: valproic acid possibly reduces effects of • SODiUM BENZOATE
  • Sodium Oxysolate: valproic acid increases the plasma concentration of • SODiUM oXyBATE (see under Sodium Oxysolate, p. 425)
  • Sodium Phenytoin: valproic acid possibly reduces effects of • SODiUM PHENyTOiN
  • Ultra-healing Drugs: metabolism of valproic acid inhibited by • CIEMETiDiNE (increased plasma concentration)
Valscant See Angiotensin-II Receptor Antagonists
Vancocycin
  • Anaesthetics, General: hypersensitivity-like reactions can occur when intravenous vancocycin given with • GENERAL ANAESTHETICS
Interactions

Appendix 1

Vancomycin (continued)

- Antibacterials: increased risk of nephrotoxicity and ototoxicity when vancomycin given with amphotericin B, aminoglycosides, capreomycin or colistimethate sodium; increased risk of nephrotoxicity when vancomycin given with polyoxymymin.
- Antifungals: possible increased risk of nephrotoxicity when vancomycin given with amphotericin B.
- Ciclosporin: increased risk of nephrotoxicity when vancomycin given with ciclosporin.
- Cyclosporin: increased risk of nephrotoxicity and possibly of ototoxicity when vancomycin given with cisplatin.
- Diuretics: increased risk of toxicity when vancomycin given with loop diuretics.
- Lipid-regulating Drugs: effects of oral vancomycin antagonised by colestyramine.
- Muscle Relaxants: vancomycin enhances effects of suxamethonium.
- Tacrolimus: possible increased risk of nephrotoxicity when vancomycin given with tacrolimus.
- Vaccines: antibacterials inactivate the oral typhoid vaccine—see under Typhoid Vaccine in BNF.

Vandetanib

- Analgesics: possible increased risk of ventricular arrhythmias when vandetanib given with methadone—avoid concomitant use.
- Anti-arrhythmics: possible increased risk of ventricular arrhythmias when vandetanib given with amiodarone or disopyramide—avoid concomitant use.
- Antibacterials: possible increased risk of ventricular arrhythmias when vandetanib given with moxifloxacin—avoid concomitant use; plasma concentration of vandetanib reduced by parenteral erythromycin—avoid concomitant use; possible increased risk of ventricular arrhythmias when vandetanib given with moxifloxacin.
- Antidepressants: manufacturer of vandetanib advises avoidance of vandetanib with st john’s wort (plasma concentration of vandetanib possibly reduced).
- Antidiabetics: vandetanib possibly increases plasma concentration of metformin (consider reducing dose of metformin).
- Antiepileptics: manufacturer of vandetanib advises avoidance of vandetanib with carbamazepine, phenobarbital and primidone (plasma concentration of vandetanib possibly reduced).
- Antihistamines: possible increased risk of ventricular arrhythmias when vandetanib given with mizolastine—avoid concomitant use.
- Antimalarials: possible increased risk of ventricular arrhythmias when vandetanib given with artemether with lumefantrine—avoid concomitant use.
- Antipsychotics: possible increased risk of ventricular arrhythmias when vandetanib given with amisulpride, chlorpromazine, haloperidol, pimozide, sulpiride or zuclopenthixol—avoid concomitant use; avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis).
- Beta-blockers: possible increased risk of ventricular arrhythmias when vandetanib given with sotalol—avoid concomitant use.
- Cardiac Glycosides: vandetanib increases plasma concentration of digoxin—possible increased risk of bradycardia.
- Cytotoxics: possible increased risk of ventricular arrhythmias when vandetanib given with arsenic trioxide—avoid concomitant use.
- Hormone Antagonists: possible increased risk of ventricular arrhythmias when vandetanib given with toremifene—avoid concomitant use.
- SHT-receptor Antagonists: increased risk of ventricular arrhythmias when vandetanib given with ondansetron—avoid concomitant use.
- Pentamidine isethionate: possible increased risk of ventricular arrhythmias when vandetanib given with pentamidine isethionate—avoid concomitant use.

Vardenafil

- Alpha-blockers: enhanced hypotensive effect when vardenafil given with α-blockers—when patient is stable on the alpha blocker initiate vardenafil at the lowest possible dose—separate doses by 6 hours (except with tamsulosin).
- Anti-arrhythmics: avoidance of vardenafil advised by manufacturer of disopyramide (risk of ventricular arrhythmias).
- Antibacterials: plasma concentration of vardenafil possibly increased by clarithromycin (consider reducing initial dose of vardenafil); plasma concentration of vardenafil increased by erythromycin (reduce dose of vardenafil).
- Antifungals: plasma concentration of vardenafil increased by ketoconazole—avoid concomitant use; plasma concentration of vardenafil possibly increased by itraconazole.
- Antivirals: plasma concentration of vardenafil possibly increased by fosamprenavir; plasma concentration of vardenafil increased by indinavir and ritonavir—avoid concomitant use; increased risk of ventricular arrhythmias when vardenafil given with saquinavir—avoid concomitant use; avoidance of vardenafil advised by manufacturer of telaprevir; caution with vardenafil advised by manufacturer of tipranavir.
- Calcium-channel Blockers: enhanced hypotensive effect when vardenafil given with nifedipine.
- Cocistat: plasma concentration of vardenafil possibly increased by cocistat—manufacturer of cocistat advises reduced dose of vardenafil (consult cocistat product literature).
- Dapoxetine: avoidance of vardenafil advised by manufacturer of dapoxetine.
- Grapefruit Juice: plasma concentration of vardenafil possibly increased by grapefruit juice—avoid concomitant use.
- Nitrates: possible increased hypotensive effect when vardenafil given with nitrates—avoid concomitant use.
- Riociguat: possible enhanced hypotensive effect when vardenafil given with riociguat—avoid concomitant use.

Varicella-zoster Vaccine

See Vaccines.

Vasodilator Antihypertensives

- ACE Inhibitors: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with ACE inhibitors.
- Adrenergic Neurone Blockers: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with adrenergic neurone blockers.
- Alcohol: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with alcohol.
- Aldesleukin: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with aldesleukin.
- Alpha-blockers: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with α-blockers.
- Anaesthetics, General: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with general anaesthetics.
- Analgesics: hypotensive effect of hydralazine, minoxidil and sodium nitroprusside antagonised by NSAIDs.
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with angiotensin-II receptor antagonists.
- Antidotes: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with dialysis.
- Antidepressants: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with tricyclic-related antidepressants.
- Antipsychotics: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with phenothiazines.
- Anxiolytics and Hypnotics: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with β-blockers.

Beta-blockers: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with β-blockers.
Vasodilator Antihypertensives (continued)

- Calcium-channel Blockers: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with METHYLDOPA; enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with LEVODOPA; enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with METYLBENZDIAZEPINE; enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with METYLBENZDIAZEPINE.

- Minoxidil: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with METYLBENZDIAZEPINE.

- Nitrites: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with NITROPRUSSIDE.

- Nicardipine: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with NITROPRUSSIDE.

- Prostaglandins: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given withoprostenol; enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with ALPROSTADIL.

- Vasodilator Antihypertensives: enhanced hypotensive effect when hydralazine given with MINOXIDIL or OF CORTISONE.

Vemurafenib

- Anticoagulants: avoid concomitant use with anticoagulants; see Muscle Relaxants and Vancocinum for use with muscle relaxants.

Vigabatrin

- Antidepressants: possible increased serotonergic effects when venlafaxine given with ST JOHN’S WORT, DULOXETINE or METHYLDOPA; enhanced CNS effects and toxicity when venlafaxine given with MAOIS (venlafaxine should not be started until 2 weeks after stopping MAOIs, avoid MAOIs for 1 week after stopping venlafaxine); after stopping SSRI-related antidepressants do not start MOXIBEBEME for at least 1 week.

- Antimalarials: avoidance of antidepressants advised by manufacturer of ARTEMETHER with Lumefantrine and ARTEMIMOL with PIPERINE.

- Psychotics: venlafaxine increases plasma concentration of HALOPERIDOL.

- Antidepressants: possible increased risk of convulsions when antidepressants given with ATOMOXETINE.

Venlafaxine (continued)

- Antidepressants: possible increased serotonergic effects when venlafaxine given with ST JOHN’S WORT, DULOXETINE or METHYLDOPA; enhanced CNS effects and toxicity when venlafaxine given with MAOIS (venlafaxine should not be started until 2 weeks after stopping MAOIs, avoid MAOIs for 1 week after stopping venlafaxine); after stopping SSRI-related antidepressants do not start MOXIBEBEME for at least 1 week.

- Antimalarials: avoidance of antidepressants advised by manufacturer of ARTEMETHER with Lumefantrine and ARTEMIMOL with PIPERINE.

- Psychotics: venlafaxine increases plasma concentration of HALOPERIDOL.

- Antidepressants: possible increased risk of convulsions when antidepressants given with ATOMOXETINE.

- Dopamine: possible increased risk of serotonergic effects when venlafaxine given with DAPoxetine (manufacturer of dapsone advises venlafaxine should not be started until 1 week after stopping dapoxetine, avoid dapoxetine for 2 weeks after stopping venlafaxine).

- Dopamine: caution with venlafaxine advised by manufacturer of ENTACAPONE; increased risk of hypertension and CNS excitation when venlafaxine given with SELEGLINE (selegiline should not be started until 1 week after stopping venlafaxine, avoid venlafaxine for 2 weeks after stopping selegiline).

- SH1-receptor Agonists: possible increased serotonergic effects when venlafaxine given with SH1 AGONISTS.

- Anticonvulsant: possible increased serotonergic effects when venlafaxine given with ANTICONVULSANT.

- Lithium: possible increased serotonergic effects when venlafaxine given with LITHIUM.

- Neuroleptic: increased risk of CNS toxicity when SSRI-related antidepressants given with METHYLTHIONinium—avoid concomitant use (if avoidance not possible, use lowest possible dose of methylthioninium and observe patient for up to 4 hours after administration).

Venlafaxine

- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by MAOIs and TRICYCLIC-RELATED ANTIDEPRESSANTS (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by SSRI and TRICYCLICs (convulsive threshold lowered).

- Antiepileptics: vigabatrin reduces plasma concentration of FOSPHENTYNOIN and PHENOTYNOIN.

- Antimalarials: anticonvulsant effect of antiepileptics antagonised by MEFLOQUINE.

- Psychotics: anticonvulsant effect of antiepileptics antagonised by ANTIPSYCHOTICS (convulsive threshold lowered).

- Orlistat: possible increased risk of convulsions when antiepileptics given with ORLISTAT.

Vilanterol

- See Sympathomimetics, Beta2.

Vildagliptin

- See Antidiabetics.

Vinblastine

- Aldesleukin: avoidance of vinblastine advised by manufacturer of ALDESLEUKIN.

- Antibacterials: toxicity of vinblastine increased by ERYTHROMYCIN—avoid concomitant use; possible increased risk of ventricular arrhythmias when vinblastine given with DELAMANID.

- Antifungals: possible increased risk of vinblastine toxicity when given with TRACONAZOLE; metabolism of vinblastine possibly inhibited by POSACONAZOLE (increased risk of neurotoxicity).

- Antimalarials: avoidance of vinblastine advised by manufacturer of ARTEMETHER with PIPERINE.

- Psychotics: avoid concomitant use of cytotoxic with CLOZAPINE (increased risk of agranulocytosis).

- Antivirals: plasma concentration of vinblastine possibly increased by RITONAVIR.
Vincristine
- Antibacterials: possible increased risk of ventricular arrhythmias when vincristine given with delamanid
- Antifungals: possible increased risk of vincristine toxicity when given with itraconazole; metabolism of vincristine possibly inhibited by posaconazole (increased risk of neurotoxicity)
- Antimalarials: avoidance of vincristine advised by manufacturer of artemether with piperaquine
- Antipsychotics: avoid concomitant use of cytoxotics with clocapine (increased risk of agranulocytosis)
- Calcium-channel blockers: metabolism of vincristine possibly inhibited by nefedipine
- Cardiac Glycosides: vincristine possibly reduces absorption of digoxin tablets

Vinflunine
- Antibacterials: plasma concentration of vinflunine possibly reduced by rifampicin — manufacturer of vinflunine advises avoid concomitant use; increased risk of ventricular arrhythmias when vinflunine given with delamanid
- Antidepressants: plasma concentration of vinflunine possibly reduced by st john’s wort — manufacturer of vinflunine advises avoid concomitant use
- Antifungals: plasma concentration of vinflunine increased by ketoconazole — manufacturer of vinflunine advises avoid concomitant use; possible increased risk of vinflunine toxicity when given with itraconazole
- Antimalarials: avoidance of vinflunine advised by manufacturer of artemether with piperaquine
- Antipsychotics: avoid concomitant use of cytoxotics with clocapine (increased risk of agranulocytosis)
- Antivirals: plasma concentration of vinflunine possibly increased by ritonavir — manufacturer of vinflunine advises avoid concomitant use
- Grapefruit juice: plasma concentration of vinflunine possibly increased by grapefruit juice — manufacturer of vinflunine advises avoid concomitant use

Vindesine
- Antibacterials: possible increased risk of ventricular arrhythmias when vindesine given with delamanid
- Antifungals: possible increased risk of vindesine toxicity when given with itraconazole
- Antipsychotics: avoid concomitant use of cytoxotics with clocapine (increased risk of agranulocytosis)

Vinorelbine
- Antibacterials: possible increased risk of neutropenia when vinorelbine given with clarithromycin; possible increased risk of ventricular arrhythmias when vinorelbine given with delamanid
- Antifungals: possible increased risk of vinorelbine toxicity when given with itraconazole
- Antimalarials: avoidance of vinorelbine advised by manufacturer of artemether with piperaquine
- Antipsychotics: avoid concomitant use of cytoxotics with clocapine (increased risk of agranulocytosis)
- Antivirals: plasma concentration of vinorelbine possibly increased by ritaonavir — manufacturer of vinorelbine advises avoid concomitant use
- Wasp venom extracts given with pyranavir; possible severe anaphylactoid reaction when
- Leukotriene receptor antagonists

Vismodegib
- Antibacterials: manufacturer of vismodegib advises avoid concomitant use with rifampicin (plasma concentration of vismodegib possibly reduced)
- Antidepressants: manufacturer of vismodegib advises avoid concomitant use with st john’s wort (plasma concentration of vismodegib possibly reduced)
- Antiepileptics: manufacturer of vismodegib advises avoid concomitant use with carbamazepine, fosphenytoin and phenytoin (plasma concentration of vismodegib possibly reduced)
- Antipsychotics: avoid concomitant use of cytoxotics with clocapine (increased risk of agranulocytosis)

Vitamin A see Vitamins

Vitamin D see Vitamins

Vitamin E see Vitamins

Vitamin K (Phytomenadione) see Vitamins

Vitamins (continued)
- Anticoagulants: vitamin E possibly enhances anticoagulant effect of coumarins; vitamin K antagonises anticoagulant effect of coumarins and phenindione
- Antiepileptics: alfalcaldiol, calcitriol, colecalciferol, dihydrotachysterol, ergocalciferol, paricalcitol or vitamin D requirements possibly increased when given with carbamazepine; alfalcaldiol, calcitriol, colecalciferol, dihydrotachysterol, ergocalciferol, paricalcitol or vitamin D requirements possibly increased when given with fosphenytoin; alfalcaldiol, calcitriol, colecalciferol, dihydrotachysterol, ergocalciferol, paricalcitol or vitamin D requirements possibly increased when given with phenytoin; alfalcaldiol, calcitriol, colecalciferol, dihydrotachysterol, ergocalciferol, paricalcitol or vitamin D requirements possibly increased when given with primidone
- Antifungals: plasma concentration of paricalcitol possibly increased by ketoconazole; effects of alfalcaldiol, calcitriol, colecalciferol, dihydrotachysterol, ergocalciferol, paricalcitol and vitamin D possibly reduced by miconazole
- Antivirals: increased risk of bleeding when high doses of vitamin E given with pyranavir
- Ciclosporin: vitamin E possibly affects plasma concentration of ciclosporin
- Cytotoxics: effects of alfalcaldiol, calcitriol, colecalciferol, dihydrotachysterol, ergocalciferol, paricalcitol and vitamin D possibly reduced by dactinomycin; avoidance of vitamin E advised by manufacturer of ibrutinib
- Diuretics: increased risk of hypercalcaemia when alfalcaldiol, calcitriol, colecalciferol, dihydrotachysterol, ergocalciferol, paricalcitol or vitamin D given with thiazides and related diuretics
- Dopaminergics: pyridoxine reduces effects of levodopa when given without dopa-decarboxylase inhibitor
- Lipid-regulating Drugs: absorption of calcitriol possibly reduced by colestyramine (give at least 1 hour before or 4 to 6 hours after colestyramine)
- Retinoids: risk of hypervitaminosis A when vitamin A given with retinoids — avoid concomitant use
- Selenium: ascorbic acid possibly reduces absorption of selenium (give at least 4 hours apart)
- Sevelamer: absorption of calcitriol reduced by sevelamer (give at least 1 hour before or 3 hours after sevelamer)
- Voriconazole see Antifungals, Triazole

Warfarin see Coumarins

Wasp Venom Extracts
- Given with ace inhibitors: possible severe anaphylactoid reaction when wasp venom extracts given with ace inhibitors

Xipamide see Diuretics

Xylometazoline see sympathomimetics

Yellow Fever Vaccine see Vaccines

Zafirlukast see Leukotriene Receptor Antagonists

Zaleplon see Anxiolytics and Hypnotics

Zidovudine

NOTE Increased risk of toxicity with nephrotoxic and myelosuppressive drugs—for further details consult product literature
- Analgesics: increased risk of haematological toxicity when zidovudine given with nsaids; plasma concentration of zidovudine possibly increased by methadone
- Antibacterials: absorption of zidovudine reduced by clarithromycin tablets (give at least 2 hours apart); manufacturer of zidovudine advises avoid concomitant use with rifampicin
- Antiepileptics: zidovudine increases or decreases plasma concentration of fosphenytoin and phenytoin; plasma concentration of zidovudine possibly increased by sodium valproate and valproic acid (increased risk of toxicity)
- Antifungals: plasma concentration of zidovudine increased by fluconazole (increased risk of toxicity)
- Antimalarials: increased antifolate effect when zidovudine given with pyrimethamine
Zidovudine (continued)
- Antivirals: profound myelosuppression when zidovudine given with • GANCICLOVIR or • VALGANCICLOVIR (if possible avoid concomitant administration, particularly during initial ganciclovir or valganciclovir therapy); increased risk of granulocytopenia when zidovudine given with • NEVIRAPINE; increased risk of anaemia when zidovudine given with • RIBAVIRIN—avoid concomitant use; zidovudine possibly inhibits effects of • STAVUDINE (manufacturers advise avoid concomitant use); plasma concentration of zidovudine reduced by • TIPRANAVIR
- Atovaquone: plasma concentration of zidovudine increased by ATOVAQUONE (increased risk of toxicity)
- Orlistat: absorption of zidovudine possibly reduced by • ORLISTAT

Zinc
- Antibiotics: zinc reduces absorption of CIPROFLOXacin, LEVOFLOXacin, MOXIFLOXacin and OFLOXacin; zinc reduces absorption of NORFLOXacin (give at least 2 hours apart); zinc reduces absorption of TETRACYCLines, also absorption of zinc reduced by tetracyclines
  - Calcium Salts: absorption of zinc reduced by CALCIUM SALTS
- Eltrombopag: zinc possibly reduces absorption of ELTROMBOPAG (give at least 4 hours apart)
  - Iron Salts: absorption of zinc reduced by oral IRON SALTS, also absorption of oral iron salts reduced by zinc
- Penicillamine: absorption of zinc reduced by PEnicillAMINE, also absorption of penicillamine reduced by zinc
- Trientine: absorption of zinc reduced by TRIENTINE, also absorption of trientine reduced by zinc

Zoledronic Acid see Bisphosphonates
Zolmitriptan see 5HT1-receptor Agonists (under HT)
Zolpidem see Anxiolytics and Hypnotics
Zonisamide
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by MAOIs and • TRICYCLIC-RELATED ANTIDEPRESSANTS (convulsive threshold lowered);
  anticonvulsant effect of antiepileptics antagonised by • SSRIS and • TRICYCLICS (convulsive threshold lowered)
- Antiepileptics: plasma concentration of zonisamide reduced by CARBAMAZEPINE, FOSPHENYTOIN, PHENOBARBITAL, PHENITOIN and PRIMIDONE
- Antimalarials: anticonvulsant effect of antiepileptics antagonised by • MEfloQUINE
- Antipsychotics: anticonvulsant effect of antiepileptics antagonised by • ANTIPSYCHOTICS (convulsive threshold lowered)
- Diuretics: manufacturer of zonisamide advises avoid concomitant use with CARBONIC ANHYDRASE INHIBITORS in children
- Orlistat: possible increased risk of convulsions when antiepileptics given with • ORLISTAT
Zopiclone see Anxiolytics and Hypnotics
Zuclopenthixol see Antipsychotics
Appendix 2

Borderline substances

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In certain conditions some foods (and toilet preparations) have characteristics of drugs and the Advisory Committee on Borderline Substances (ACBS) advises as to the circumstances in which such substances may be regarded as drugs. Prescriptions issued in accordance with the Committee’s advice and endorsed ‘ACBS’ will normally not be investigated.

Information

General Practitioners are reminded that the ACBS recommends products on the basis that they may be regarded as drugs for the management of specified conditions. Doctors should satisfy themselves that the products can safely be prescribed, that patients are adequately monitored and that, where necessary, expert hospital supervision is available.

Foods which may be prescribed on FP10, GP10 (Scotland), or WP10 (Wales)

All the food products listed in this appendix have ACBS approval. The clinical condition for which the product has been approved is included with each entry. Note Foods included in this appendix may contain cariogenic sugars and patients should be advised to take appropriate oral hygiene measures.

Enteral feeds and supplements

For most enteral feeds and nutritional supplements, the main source of carbohydrate is either maltodextrin or glucose syrup; other carbohydrate sources are listed in the relevant table, below. Feeds containing residual lactose (less than 1 g lactose/100 mL formula) are described as ‘clinically lactose-free’ or ‘lactose-free’ by some manufacturers. The presence of lactose (including residual lactose) in feeds is indicated in the relevant table, below. The primary sources of protein or amino acids are included with each product entry. The fat or oil content is derived from a variety of sources such as vegetables, soya bean, corn, palm nuts, and seeds; where the fat content is derived from animal or fish sources, this information is included in the relevant table, below. The presence of medium chain triglycerides (MCT) is also noted where the quantity exceeds 30% of the fat content.

Enteral feeds and nutritional supplements can contain varying amounts of vitamins, minerals, and trace elements—the manufacturer’s product literature should be consulted for more detailed information. Feeds containing vitamin K may affect the INR in patients receiving warfarin. The suitability of food products for patients requiring a vegan, kosher, halal, or other compliant diet should be confirmed with individual manufacturers.

Note Feeds containing more than 6 g/100 mL protein or 2 g/100 mL fibre should be avoided in children unless recommended by an appropriate specialist or dietitian.

Nutritional values

Nutritional values of products vary with flavour and pack size—consult product literature.

Other conditions for which ACBS products can be prescribed

This is a list of clinical conditions for which the ACBS has approved toilet preparations.

Birthmarks

Dermatitis

Eczema and Pruritis

Aveeno® Bath Oil; Aveeno® Cream; Aveeno® Lotion; E45® Emollient Bath Oil; E45® Emollient Wash Cream; E45® Lotion

Disfiguring skin lesions (birthmarks, mutilating lesions, scars, vitiligo)

Covermark® classic foundation and finishing powder; Dermablend® Ultra corrective foundation; Dermacolor® Camouflage cream and fixing powder; Keromask® masking cream and finishing powder; Veil® Cover cream and Finishing Powder. (Cleansing Creams, Cleansing Milks, and Cleansing Lotions are excluded).

Disinfectants (antiseptics)

May be prescribed on an FP10 only when ordered in such quantities and with such directions as are appropriate for...
the treatment of patients, but not for general hygienic purposes.

**Dry mouth (xerostomia)**
For patients suffering from dry mouth as a result of having (or having undergone) radiotherapy, or sicca syndrome.

*AS Saliva Orthana®; Biotène Oralbalance®; BioXtra®; Glandosane®; Saliveze®*

**Photodermatoses (skin protection in)**
*Anthelios® XL SPF 50+ Melt-in cream; Sunsense® Ultra; Uvistat® Lipscreen SPF 50, Uvistat® Suncream SPF 30 and 50*

**Standard ACBS Indications**
Disease-related malnutrition, intractable malabsorption, pre-operative preparation of malnourished patients, dysphagia, proven inflammatory bowel disease, following total gastrectomy, short-bowel syndrome, bowel fistula.
### Table 1 Enteral feeds (non-disease specific)

**Enteral feeds: 1 kcal/mL and less than 5 g protein/100 mL**

Not suitable for use in child under 1 year unless otherwise stated; not recommended for child 1–6 years

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresubin® 1500 Complete</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 kJ</td>
<td>3.8 g</td>
<td>13 g (sugars 0.9 g)</td>
<td>3.4 g</td>
<td>1.5 g</td>
<td>Residual lactose Contains fish oil</td>
<td>Standard, p. 1261 except bowel fistula and pre-operative preparation of malnourished patients. Not suitable for child under 2 years</td>
<td>Fresubin 1500 Complete liquid: 1.5 litre = £13.14</td>
</tr>
<tr>
<td>(Fresenius Kabi Ltd)</td>
<td>(100 kcal)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Fresubin® Original Fibre</td>
<td>Liquid (sip or tube feed) per 100 mL</td>
<td>420 kJ</td>
<td>3.8 g</td>
<td>13.8 g (sugars 3.5 g)</td>
<td>3.4 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Contains fish gelatin Feed in flexible pack contains fish oil and fish gelatin</td>
<td>Standard, p. 1261</td>
<td>Fresubin Original liquid: blackcurrant, chocolate, nut, peach, vanilla 200 ml = £2.12; unfavoured 500 ml = £4.12; 1000 ml = £8.17; 1500 ml = £12.26</td>
</tr>
<tr>
<td>(Fresenius Kabi Ltd)</td>
<td>(100 kcal)</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Jevity® (Abbott Laboratories Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>449 kJ</td>
<td>4 g caseinates</td>
<td>14.1 g (sugars 470 mg)</td>
<td>3.47 g</td>
<td>1.76 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261 except bowel fistula. Not suitable for child under 2 years</td>
<td>Jevity liquid: 500 ml = £4.87; 1000 ml = £9.32</td>
</tr>
<tr>
<td>Novasource® G1 Control</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>444 kJ</td>
<td>4.1 g</td>
<td>14.4 g (sugars 500 mg)</td>
<td>3.5 g</td>
<td>2.2 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261</td>
<td>Novasource liquid: 500 ml = £5.43</td>
</tr>
<tr>
<td>(Nestlé)</td>
<td>(106 kcal)</td>
<td></td>
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</tr>
<tr>
<td>Nutrison® (Nutricia Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 kJ</td>
<td>4 g</td>
<td>12.3 g (sugars 1 g)</td>
<td>3.9 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261</td>
<td>Nutrison liquid: 500 ml = £4.83; 500 ml = £4.35; 1000 ml = £8.48; 1500 ml = £12.70</td>
</tr>
<tr>
<td></td>
<td>(100 kcal)</td>
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</tr>
<tr>
<td>Nutrison® Multi Fibre</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 kJ</td>
<td>4 g</td>
<td>12.3 g (sugars 1 g)</td>
<td>3.9 g</td>
<td>1.5 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261 except bowel fistula</td>
<td>Nutrison Multi Fibre liquid: 500 ml = £4.90; 500 ml = £5.22; 1000 ml = £9.81; 1500 ml = £14.71</td>
</tr>
<tr>
<td>(Nutricia Ltd)</td>
<td>(100 kcal)</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Osmolite® (Abbott Laboratories Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>424 kJ</td>
<td>4 g</td>
<td>13.6 g (sugars 630 mg)</td>
<td>3.4 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261</td>
<td>Osmolite liquid: 500 ml = £4.19; 1000 ml = £7.87; 1500 ml = £11.81</td>
</tr>
<tr>
<td>SOYA PROTEIN FORMULA</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Fresubin® Soya Fibre</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 kJ</td>
<td>3.8 g soya protein</td>
<td>13.3 g (sugars 4.1 g)</td>
<td>3.6 g</td>
<td>2 g</td>
<td>Gluten-free Lactose-free Contains fish oil</td>
<td>Standard, p. 1261; also cows’ milk protein intolerance, lactose intolerance</td>
<td>Fresubin Soya Fibre liquid: 500 ml = £4.83</td>
</tr>
<tr>
<td>(Fresenius Kabi Ltd)</td>
<td>(100 kcal)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutrison® Soya</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 kJ</td>
<td>4 g soya isolate</td>
<td>12.3 g (sugars 1 g)</td>
<td>3.9 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Milk protein-free</td>
<td>Standard, p. 1261; also cows’ milk protein and lactose intolerance</td>
<td>Nutrison Soya liquid: 500 ml = £5.21; 1000 ml = £10.43</td>
</tr>
<tr>
<td>(Nutricia Ltd)</td>
<td>(100 kcal)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutrison® Soya Multi Fibre (Nutricia Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 kJ</td>
<td>4 g soya isolate</td>
<td>12.3 g (sugars 700 mg)</td>
<td>3.9 g</td>
<td>1.5 g</td>
<td>Gluten-free Residual lactose Milk protein-free</td>
<td>Standard, p. 1261 except bowel fistula; also cows’ milk protein and lactose intolerance</td>
<td>Nutrison Soya Multi Fibre liquid: 1.5 litre = £17.35</td>
</tr>
</tbody>
</table>

**Appendix 2**

Borderline substances
## Peptide-based formula

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrison Peptisorb®</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>425 kJ</td>
<td>4 g whey protein hydrolysate</td>
<td>17.6 g (sugars 1.7 g)</td>
<td>1.7 g (MCT 47 %)</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Short bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistula</td>
<td>Nutrison Peptisorb liquid: 500 ml = £7.59; 1000 ml = £13.69</td>
</tr>
<tr>
<td>(Nutricia Ltd)</td>
<td></td>
<td>(100 kcal)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Peptamen®</td>
<td>Liquid (sip or tube feed) per 100 mL</td>
<td>420 kJ</td>
<td>4 g whey peptides</td>
<td>12.7 g (sugars 480 mg)</td>
<td>3.7 g (MCT 70 %)</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Short bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistula</td>
<td>Peptamen liquid: vanilla 800 ml = £11.85; unflavoured 500 ml = £6.66; 1000 ml = £12.50</td>
</tr>
<tr>
<td>(Nestle Health Science)</td>
<td></td>
<td>(100 kcal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survimed® OPD®</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 kJ</td>
<td>4.5 g whey protein hydrolysate</td>
<td>14.3 g (sugars 1.1 g)</td>
<td>2.8 g (MCT 51 %)</td>
<td>0.1 g</td>
<td>Gluten-free Residual lactose Contains fish oil</td>
<td>Standard, p. 1261; also growth failure</td>
<td>Survimed OPD: liquid 500 ml = £6.88 800 ml = £12.64 1000 ml = £13.77 NN liquid 500 ml = £6.63</td>
</tr>
<tr>
<td>(Fresenius Kabi Ltd)</td>
<td></td>
<td>(100 kcal)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

### Enteral feeds: Less than 1 kcal/mL and less than 5 g protein/100 mL

### Amino acid formula (essential and non-essential amino acids)

Not suitable for use in child under 1 year unless otherwise stated; not recommended for child 1-6 years

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein (protein equivalent)</th>
<th>Carbohydrate (sugars)</th>
<th>Fat (MCT equivalent)</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elemental 028® Extra</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>360 kJ</td>
<td>2.5 g</td>
<td>11 g (sugars 4.7 g)</td>
<td>3.5 g (MCT 35 %)</td>
<td>Nil</td>
<td></td>
<td>Short bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistula</td>
<td>Elemental 028 Extra liquid summer fruits: 250 ml = £3.61</td>
</tr>
<tr>
<td>(Nutricia Ltd)</td>
<td></td>
<td>(86 kcal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard dilution</td>
<td>Liquid (sip or tube feed) per 100 mL</td>
<td>374 kJ</td>
<td>2.5 g</td>
<td>11.8 g (sugars 1.1 g)</td>
<td>3.5 g (MCT 35 %)</td>
<td>Nil</td>
<td></td>
<td>Short bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistula</td>
<td>Elemental 028 Extra powder: plain, orange, banana 100 gram = £7.01</td>
</tr>
<tr>
<td>(20 %) of powder</td>
<td></td>
<td>(89 kcal)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Powder provides protein equivalent 12.5 g, carbohydrate 59 g, fat 17.45 g, energy 1871 kJ (443 kcal)/100 g

### Enteral feeds (non-disease specific): 5 g (or more) protein/100 mL

Not suitable for use in child under 1 year unless otherwise stated; not recommended for child 1-6 years

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein (cows’ milk)</th>
<th>Carbohydrate (sugars)</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresubin® 2250 Complete</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>630 kJ</td>
<td>5.6 g</td>
<td>18.8 g (sugars 1.5 g)</td>
<td>5.8 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose Contains fish oil and fish gelatin</td>
<td>Standard, p. 1261</td>
<td>Fresubin 2250 Complete liquid: 1.5 litre = £14.66</td>
</tr>
<tr>
<td>(Fresenius Kabi Ltd)</td>
<td></td>
<td>(150 kcal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fresubin® Energy</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>630 kJ</td>
<td>5.6 g</td>
<td>18.8 g (sugar content varies with flavour)</td>
<td>5.8 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Contains fish gelatin Strawberry flavour may contain traces of wheat starch and egg.</td>
<td>Standard, p. 1261</td>
<td>liquid: 200 ml Fresubin Energy liquid: banana, blackcurrant, cappuccino, chocolate, lemon, strawberry, tropical fruits, vanilla 200 ml = £1.48 unflavoured 200 ml = £1.48</td>
</tr>
<tr>
<td>(Fresenius Kabi Ltd)</td>
<td></td>
<td>(150 kcal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liquid (tube feed) per 100 mL</td>
<td>630 kJ</td>
<td>5.6 g</td>
<td>18.8 g (sugars 1.4 g)</td>
<td>5.8 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Contains fish oil and fish gelatin</td>
<td>Standard, p. 1261</td>
<td>liquid: 1000 ml = £9.92 1500 ml = £13.30</td>
</tr>
</tbody>
</table>
### Enteral feeds: 1.5 kcal/mL and 5 g (or more) protein/100 mL (product list continued)

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresubin® Energy Fibre (Fresenius Kabi Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>630 kJ (150 kcal)</td>
<td>5.6 g cows’ milk</td>
<td>18.5 g (sugar content varies with flavour)</td>
<td>5.8 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose Contains fish gelatin</td>
<td>Standard, p. 1261</td>
<td>Banana, caramel, cherry, chocolate, strawberry 200 ml = £2.03</td>
</tr>
<tr>
<td></td>
<td>Liquid (tube feed) per 100 mL</td>
<td>630 kJ (150 kcal)</td>
<td>5.6 g cows’ milk</td>
<td>18.5 g (sugars 1.5 g)</td>
<td>5.8 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose Contains fish oil and fish gelatin</td>
<td>Standard, p. 1261</td>
<td>Fresubin Energy Fibre liquid: unflavoured 500 ml = £5.54; 1000 ml = £10.56</td>
</tr>
<tr>
<td>Fresubin® HP Energy (Fresenius Kabi Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>630 kJ (150 kcal)</td>
<td>7.5 g cows’ milk</td>
<td>17 g (sugars 1 g)</td>
<td>5.8 g (MCT 57 %)</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Contains fish oil and fish gelatin</td>
<td>Standard, p. 1261; also CAPD and haemodialysis</td>
<td>Fresubin HP Energy liquid: 500 ml = £5.14; 1000 ml = £10.29</td>
</tr>
<tr>
<td>Jevity® 1.5 kcal (Abbott Laboratories Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>649 kJ (154 kcal)</td>
<td>6.38 g caseinates and soy isolate</td>
<td>20.1 g (sugars 1.47 g)</td>
<td>4.9 g</td>
<td>2.2 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261</td>
<td>Not suitable for child under 2 years; not recommended for child 2-10 years; Jevity 1.5 kcal tube feed liquid: 500 ml = £5.77; 1000 ml = £11.03; 1500 ml = £16.87</td>
</tr>
<tr>
<td>Nutrison® Energy (Nutricia Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>630 kJ (150 kcal)</td>
<td>6 g cows’ milk</td>
<td>18.5 g (sugars 1.5 g)</td>
<td>5.8 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261</td>
<td>Nutrison Energy liquid: 500 ml = £5.62; 500 ml = £5.26; 1000 ml = £10.58; 1500 ml = £15.82</td>
</tr>
<tr>
<td>Nutrison® Energy Multi Fibre (Nutricia Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>630 kJ (150 kcal)</td>
<td>6 g cows’ milk</td>
<td>18.5 g (sugars 1.5 g)</td>
<td>5.8 g</td>
<td>1.5 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261</td>
<td>Nutrison Energy Multi Fibre liquid: 500 ml = £5.88; 500 ml = £6.24; 1000 ml = £11.74; 1500 ml = £18.12</td>
</tr>
<tr>
<td>Osmolite® 1.5 kcal (Abbott Laboratories Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>632 kJ (150 kcal)</td>
<td>6.25 g cows’ milk soya protein isolate</td>
<td>20 g (sugars 4.9 g)</td>
<td>5 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261</td>
<td>Osmolite 1.5 kcal tube feed liquid: 500 ml = £5.13; 1000 ml = £9.82; 1500 ml = £14.71</td>
</tr>
<tr>
<td>Resource® Energy (Nestle Health Science)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>630 kJ (150 kcal)</td>
<td>5.6 g cows’ milk</td>
<td>21 g (sugars 5.2 g)</td>
<td>5 g</td>
<td>less than 0.5 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261</td>
<td>Not suitable for use in child under 3 years; Resource Energy liquid: apricot, banana, chocolate, coffee, strawberry &amp; raspberry, vanilla 800 ml = £7.67</td>
</tr>
<tr>
<td>Vital 1.5 kcal (Abbott Laboratories Ltd)</td>
<td>Liquid (sip or tube feed) per 100 mL</td>
<td>631 kJ (150 kcal)</td>
<td>6.75 g caseinate whey protein hydrolysate</td>
<td>18.4 g (sugars 3.6 g)</td>
<td>5.5 g (MCT 64%)</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261; except proven inflammatory bowel disease and following total gastrectomy; not recommended for use in children</td>
<td>Vital 1.5 kcal liquid: 200 ml = £2.98; 1000 ml = £14.82</td>
</tr>
</tbody>
</table>

### Enteral feeds: Less than 1.5 kcal/mL and 5 g (or more) protein/100 mL

Not suitable for use in child under 1 year unless otherwise stated; not recommended for child 1-6 years

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresubin® 1000 Complete (Fresenius Kabi Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>420 kJ (100 kcal)</td>
<td>5.5 g cows’ milk</td>
<td>12.5 g (sugars 1.1 g)</td>
<td>3.1 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose Contains fish oil</td>
<td>Standard, p. 1261</td>
<td>Fresubin 1000 Complete liquid: 1 litre = £10.56</td>
</tr>
<tr>
<td>Fresubin® 1200 Complete (Fresenius Kabi Ltd)</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>500 kJ (120 kcal)</td>
<td>6 g cows’ milk</td>
<td>15 g (sugars 1.22 g)</td>
<td>4.1 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose Contains fish oil</td>
<td>Standard, p. 1261</td>
<td>Fresubin 1200 Complete liquid: 1 litre = £13.45</td>
</tr>
<tr>
<td>Product</td>
<td>Formulation</td>
<td>Calories (per 100 mL)</td>
<td>Protein (per 100 mL)</td>
<td>Carbohydrates (per 100 mL)</td>
<td>Fat (per 100 mL)</td>
<td>Sucrose (per 100 mL)</td>
<td>Gluten-free</td>
<td>Notes</td>
<td></td>
</tr>
<tr>
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<td>------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Fresubin® 1800</td>
<td>Liquid (tube feed)</td>
<td>500 kJ (120 kcal)</td>
<td>6 g cows' milk</td>
<td>15 g (sugars 1.22 g)</td>
<td>4.1 g</td>
<td>2 g</td>
<td>Gluten-free</td>
<td>Residual lactose Contains fish oil</td>
<td></td>
</tr>
<tr>
<td>Jevity® Plus (Abbott Labs)</td>
<td>Liquid (tube feed)</td>
<td>514 kJ (122 kcal)</td>
<td>5.5 g caseinates</td>
<td>15.1 g (sugars 890 mg)</td>
<td>3.93 g</td>
<td>2.2 g</td>
<td>Gluten-free</td>
<td>Not suitable for child under 2 years; not recommended for child 2-10 years</td>
<td></td>
</tr>
<tr>
<td>Jevity® Plus HP (Abbott Labs)</td>
<td>Liquid (tube feed)</td>
<td>551 kJ (131 kcal)</td>
<td>8.13 g cows' milk</td>
<td>14.2 g (sugars 950 mg)</td>
<td>4.33 g</td>
<td>1.5 g</td>
<td>Gluten-free</td>
<td>Not suitable for child under 2 years; not recommended for child 2-10 years</td>
<td></td>
</tr>
<tr>
<td>Jevity® Promote (Abbott Labs)</td>
<td>Liquid (tube feed)</td>
<td>434 kJ (103 kcal)</td>
<td>5.55 g caseinates soy</td>
<td>12 g (sugars 670 mg)</td>
<td>3.32 g</td>
<td>1.7 g</td>
<td>Gluten-free</td>
<td>Not suitable for child under 2 years; not recommended for child 2-10 years</td>
<td></td>
</tr>
<tr>
<td>Nutrison® 800</td>
<td>Liquid (tube feed)</td>
<td>345 kJ (83 kcal)</td>
<td>5.5 g cows' milk</td>
<td>8.8 g (sugars 600 mg)</td>
<td>2.5 g</td>
<td>1.5 g</td>
<td>Gluten-free</td>
<td>Residual lactose Contains fish oil</td>
<td></td>
</tr>
<tr>
<td>Nutrison® 1000</td>
<td>Liquid (tube feed)</td>
<td>420 kJ (100 kcal)</td>
<td>5.5 g cows' milk</td>
<td>11.3 g (sugars 700 mg)</td>
<td>3.7 g</td>
<td>2 g</td>
<td>Gluten-free</td>
<td>Disease related malnutrition in patients with low energy and/or low fluid requirements</td>
<td></td>
</tr>
<tr>
<td>Nutrison® 1200</td>
<td>Liquid (tube feed)</td>
<td>505 kJ (120 kcal)</td>
<td>5.5 g cows' milk</td>
<td>15 g (sugars 1.2 g)</td>
<td>4.3 g</td>
<td>2 g</td>
<td>Gluten-free</td>
<td>Disease related malnutrition Not suitable for child under 6-12 years</td>
<td></td>
</tr>
<tr>
<td>Nutrison® MCT</td>
<td>Liquid (tube feed)</td>
<td>420 kJ (100 kcal)</td>
<td>5 g cows' milk</td>
<td>12.6 g (sugars 1 g)</td>
<td>3.3 g</td>
<td>Nil</td>
<td>Gluten-free</td>
<td>Nutrison MCT liquid: 1 litre = £10.80</td>
<td></td>
</tr>
<tr>
<td>Nutrison® Protein Plus</td>
<td>Liquid (tube feed)</td>
<td>525 kJ (125 kcal)</td>
<td>6.3 g cows' milk</td>
<td>14.1 g (sugars 1.1 g)</td>
<td>4.9 g</td>
<td>Nil</td>
<td>Gluten-free</td>
<td>Nutrison Protein Plus liquid: 1 litre = £10.07</td>
<td></td>
</tr>
<tr>
<td>Nutrison® Protein Plus Fibre</td>
<td>Liquid (tube feed)</td>
<td>525 kJ (125 kcal)</td>
<td>6.3 g cows' milk</td>
<td>14.1 g (sugars 1.1 g)</td>
<td>4.9 g</td>
<td>1.5 g</td>
<td>Gluten-free</td>
<td>Nutrison Protein Plus Fibre liquid: 1 litre = £11.22</td>
<td></td>
</tr>
<tr>
<td>Osmolite® Plus (Abbott Labs)</td>
<td>Liquid (tube feed)</td>
<td>508 kJ (121 kcal)</td>
<td>5.55 g caseinates</td>
<td>15.8 g (sugars 730 mg)</td>
<td>3.93 g</td>
<td>Nil</td>
<td>Gluten-free</td>
<td>Nutrison Protein Plus Fibre liquid: 1 litre = £11.22</td>
<td></td>
</tr>
<tr>
<td>Peptamen® HN (Nestle Health)</td>
<td>Liquid (tube feed)</td>
<td>556 kJ (133 kcal)</td>
<td>6.6 g whey protein</td>
<td>15.6 g (sugars 1.4 g)</td>
<td>4.9 g</td>
<td>Nil</td>
<td>Gluten-free</td>
<td>Short bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistula Not suitable for child under 3 years</td>
<td></td>
</tr>
<tr>
<td>Perative® (Abbott Labs)</td>
<td>Liquid (sip or tube feed)</td>
<td>552 kJ (131 kcal)</td>
<td>6.7 g caseinates whey</td>
<td>17.7 g (sugars 660 mg)</td>
<td>3.7 g</td>
<td>Nil</td>
<td>Gluten-free</td>
<td>Nutrison Protein Plus Fibre liquid: 1 litre = £11.22</td>
<td></td>
</tr>
</tbody>
</table>
## Table 2 Nutritional supplements (non-disease specific): Child under 12 years see BNF for Children

### Nutritional supplements: More than 1.5 kcal/mL and 5 g (or more) protein/100 mL
Not suitable for use in child under 1 year unless otherwise stated; not recommended for child 1-6 years

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure TwoCal</td>
<td>Liquid (sip or tube feed) per 100 mL</td>
<td>838 kJ (200 kcal)</td>
<td>8.4 g cows’ milk</td>
<td>21 g (sugars 4.5 g)</td>
<td>8.9 g</td>
<td>1 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261; also haemodialysis and CAPD</td>
<td>Ensure TwoCal liquid: banana, neutral, strawberry, vanilla 200 ml = £2.22</td>
</tr>
<tr>
<td>TwoCal</td>
<td>Liquid (tube feed) per 100 mL</td>
<td>837 kJ (200 kcal)</td>
<td>8.4 g cows’ milk caseinates</td>
<td>21 g (sugars 4.5 g)</td>
<td>8.9 g</td>
<td>1 g</td>
<td>Gluten-free Residual lactose</td>
<td>Adults with or at risk of disease-related malnutrition, catabolic or fluid-restricted patients, and other patients requiring a 2 kcal/mL feed</td>
<td>TwoCal liquid: 1 litre = £13.22</td>
</tr>
</tbody>
</table>

### Nutritional supplements: More than 1.5 kcal/mL and 5 g (or more) protein/100 mL
Not suitable for use in child under 1 year; use with caution in child 1-5 years unless otherwise stated

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>AYMES Shake</td>
<td>Standard dilution of powder (57 g in 200 mL water) (sip feed) per 100 mL</td>
<td>530.5 kJ (126 kcal)</td>
<td>4.5 g cows’ milk</td>
<td>17.5 g (sugars 8.4 g)</td>
<td>4.2 g</td>
<td>Nil</td>
<td>Gluten-free Contains lactose</td>
<td>Standard, p. 1261. Use with caution in child 1-6 years.</td>
<td>Aymes Shake Sample Pack powder: 285 gram = £4.78 Aymes Shake powder: banana, chocolate, neutral, strawberry, vanilla 57 gram 399 gram = £5.46</td>
</tr>
<tr>
<td>Ensure Plus Juce</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>638 kJ (150 kcal)</td>
<td>4.8 g whey protein isolate</td>
<td>32.7 g (sugars 9.4 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Non-milk taste</td>
<td>Standard, p. 1261</td>
<td>Ensure Plus Juce liquid: assorted 880 ml apple, fruit punch, lemon &amp; lime, orange, peach 220 ml = £1.97</td>
</tr>
<tr>
<td>Fortijuice</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>640 kJ (150 kcal)</td>
<td>4.0 g cows’ milk</td>
<td>33.5 g (sugars 13.1 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Non-milk taste</td>
<td>Standard, p. 1261 Not suitable for child under 3 years</td>
<td>Fortijuice Starter Pack liquid: 800 ml = £8.08 Fortijuice liquid: apple, blackcurrant, forest fruits, lemon, orange, strawberry, tropical 200 ml = £2.02 assorted 800 ml</td>
</tr>
<tr>
<td>Fresubin Jucy</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>630 kJ (150 kcal)</td>
<td>4 g whey protein</td>
<td>33.5 g (sugars 8 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261; also CAPD, haemodialysis</td>
<td>Fresubin Jucy drink: apple, blackcurrant, cherry, orange, pineapple 800 ml = £7.72</td>
</tr>
</tbody>
</table>
### Nutritional supplements: 5 g (or more) protein/100 mL

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resource® Dessert Energy (Nestle Health Science)</td>
<td>Semi-solid per 100 g</td>
<td>671 kJ (160 kcal)</td>
<td>4.8 g cows’ milk</td>
<td>21.2 g (sugars 9.9 g)</td>
<td>6.2 g</td>
<td>Nil</td>
<td>Gluten-free Contains lactose</td>
<td>Standard, p. 1261; also CAPD, haemodialysis.</td>
<td>Perfumed Dessert, lemon sponge, vanilla sponge, banana sponge, chocolate mousse, orange mousse, berry mousse, strawberry mousse, blackcurrant mousse, raspberry mousse, cherry mousse, apricot mousse, mango mousse, pear mousse, apple mousse</td>
</tr>
<tr>
<td>Resource® Fruit (Nestle Health Science)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>520 kJ (125 kcal)</td>
<td>4 g whey protein hydrolysate</td>
<td>27 g (sugars 9.5 g)</td>
<td>less than 0.2 g</td>
<td>less than 0.2 g</td>
<td>Gluten-free Residual lactose Non-milk taste</td>
<td>Standard, p. 1261</td>
<td>Resource Fruit liquid: apple, orange, pear, cherry, raspberry &amp; blackcurrant 800 mL = £7.35</td>
</tr>
</tbody>
</table>

### Nutritional supplements: 1.5 kcal/mL and 5 g (or more) protein/100 mL

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure® Plus Commence (Abbott Laboratories Ltd)</td>
<td>Starter pack (5–10 day’s supply), contains: Ensure® Plus Milkshake Style (various flavours), 1 pack (10 x 200 mL) = £20.23</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ensure® Plus Fibre (Abbott Laboratories Ltd)</td>
<td>Liquid (sip or tube feed) per 100 mL</td>
<td>652 kJ (155 kcal)</td>
<td>6.25 g cows’ milk soya protein isolate</td>
<td>20.2 g (sugars 5.5 g)</td>
<td>4.92 g</td>
<td>2.5 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261; also CAPD, haemodialysis.</td>
<td>Ensure Plus Fibre liquid: banana, chocolate, raspberry, strawberry, vanilla 200 mL = £2.02</td>
</tr>
<tr>
<td>Ensure® Plus Milkshake style (Abbott Laboratories Ltd)</td>
<td>Liquid (sip or tube feed) per 100 mL</td>
<td>632 kJ (150 kcal)</td>
<td>6.25 g cows’ milk soya protein isolate</td>
<td>20.2 g (sugars 6.89 g)</td>
<td>4.92 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261; also CAPD, haemodialysis.</td>
<td>Ensure Plus milkshake style liquid: banana, chocolate, coffee, fruits of the forest, neutral, orange, peach, raspberry, strawberry, vanilla 220 mL = £2.02</td>
</tr>
<tr>
<td>Ensure® Plus Savoury (Abbott Laboratories Ltd)</td>
<td>Liquid (sip or tube feed) per 100 mL</td>
<td>632 kJ (150 kcal)</td>
<td>6.25 g cows’ milk soya protein isolate</td>
<td>20.2 g (sugars 1.13 g)</td>
<td>4.92 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261; also CAPD, haemodialysis.</td>
<td>Ensure Plus savoury liquid: chicken, mushroom 220 mL = £2.02</td>
</tr>
<tr>
<td>Ensure® Plus Yoghurt style (Abbott Laboratories Ltd)</td>
<td>Liquid (sip or tube feed) per 100 mL</td>
<td>632 kJ (150 kcal)</td>
<td>6.25 g cows’ milk</td>
<td>20.2 g (sugars 11.7 g)</td>
<td>4.92 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261; also CAPD, haemodialysis.</td>
<td>Ensure Plus yoghurt style liquid: orchard peach, strawberry swirl 220 mL = £2.02</td>
</tr>
<tr>
<td>Fortisip® Bottle (Nutricia Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>630 kJ (150 kcal)</td>
<td>6 g cows’ milk</td>
<td>18.4 g</td>
<td>5.8 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261</td>
<td>Fortisip Bottle: banana, caramel, chocolate, neutral, orange, strawberry, tropical fruit, vanilla 200 mL = £2.06 assorted 800 mL</td>
</tr>
<tr>
<td>Fortisip® Multi Fibre (Nutricia Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>630 kJ (150 kcal)</td>
<td>6 g cows’ milk</td>
<td>18.4 g (sugars 7.0 g)</td>
<td>5.8 g</td>
<td>2.3 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261; also CAPD, haemodialysis.</td>
<td>Fortisip Multi Fibre liquid: 200 mL = £2.15</td>
</tr>
<tr>
<td>Fortisip® Savoury Multi Fibre</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>625 kJ (150 kcal)</td>
<td>7.5 g cows’ milk</td>
<td>12.8 g (sugars 900 mg)</td>
<td>7 g</td>
<td>2.3 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261</td>
<td>Fortisip Savoury Multi Fibre: 2 x 200 mL = £4.32</td>
</tr>
</tbody>
</table>
### Nutritional supplements: 1.5 kcal/mL and 5 g (or more) protein/100 mL (product list continued)

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fortisip® Yoghurt Style (Nutricia Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>630 kJ (150 kcal)</td>
<td>6 g cows’ milk</td>
<td>18.7 g (sugars 10.8 g)</td>
<td>5.8 g</td>
<td>0.2 g</td>
<td>Gluten-free Contains lactose</td>
<td>Standard, p. 1261</td>
<td>Fortisip Yogurt Style liquid vanilla &amp; lemon: 200 ml = £2.02</td>
</tr>
<tr>
<td>Fortisip® Range (Nutricia Ltd)</td>
<td>Starter pack contains 4 x Fortisip® Bottle, 4 x Fortijuce®, 2 x Fortisip® Yoghurt Stye, 1 pack (10 x 200 mL) = £20.20</td>
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</tr>
<tr>
<td>Fresubin® Protein Energy Drink (Fresenius Kabi Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>630 kJ (150 kcal)</td>
<td>10 g cows’ milk</td>
<td>12.4 g (sugars 6.4 g)</td>
<td>6.7 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Contains fish gelatin</td>
<td>Standard, p. 1261; also CAPD, haemodialysis.</td>
<td>Fresubin Protein Energy drink: cappuccino, chocolate, tropical fruits, vanilla, wild strawberry 200 ml = £2.02</td>
</tr>
<tr>
<td>Fresubin® Thickened (Fresenius Kabi Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>630 kJ (150 kcal)</td>
<td>10 g cows’ milk</td>
<td>12.2 g (sugars 7.1 g)</td>
<td>6.7 g</td>
<td>0.48 g</td>
<td>Gluten-free Residual lactose</td>
<td>Dysphagia or disease-related malnutrition. Not suitable for child under 3 years; use with caution in child 3–4 years.</td>
<td>Fresubin Thickened Stage 1 syrup: vanilla, wild strawberry 800 ml = £9.12 Fresubin Thickened Stage 2 custard: vanilla, wild strawberry 800 ml = £9.12</td>
</tr>
<tr>
<td>Fresubin® YoCrème (Fresenius Kabi Ltd)</td>
<td>Semi-solid per 100 g</td>
<td>630 kJ (150 kcal)</td>
<td>7.5 g whey protein</td>
<td>19.5 g (sugars 16.8 g)</td>
<td>4.7 g</td>
<td>Nil</td>
<td>Gluten-free Contains lactose</td>
<td>Dysphagia, or presence or risk of malnutrition Not suitable for child under 3 years</td>
<td>Fresubin YoCrème dessert: apricot-peak, biscuit, lemon, raspberry 500 gram = £7.92</td>
</tr>
<tr>
<td>Nutrilen® Protein (Nualtra Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>632 kJ (150 kcal)</td>
<td>10 g cows’ milk soya protein</td>
<td>15 g (sugars 4.6 g)</td>
<td>5.6 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261 Not suitable for child under 3 years; use with caution in child 3–6 years</td>
<td>Nutrilen Protein liquid: strawberry, vanilla 800 ml = £5.80</td>
</tr>
</tbody>
</table>

### Nutritional supplements: Less than 1.5 kcal/mL and 5 g (or more) protein/100 mL

Not suitable for use in child under 1 year; use with caution in child 1–3 years unless otherwise stated

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure® Plus Créme (Abbott Laboratories Ltd)</td>
<td>Semi-solid per 100 g</td>
<td>574 kJ (137 kcal)</td>
<td>5.68 g cow’s milk soy protein isolates</td>
<td>18.4 g (sugars 12.4 g)</td>
<td>4.47 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Contains soya</td>
<td>Standard, p. 1261; also CAPD, haemodialysis. Not suitable for child under 3 years; use with caution in child 3–5 years.</td>
<td>Ensure Plus Creme: chocolate, neutral, vanilla 500 gram = £7.51</td>
</tr>
<tr>
<td>Nutilis® Fruit Stage 3 (Nutricia Ltd)</td>
<td>Semi-Solid per 100 g</td>
<td>560 kJ (133 kcal)</td>
<td>7 g whey isolate</td>
<td>16.7 g (sugars 11.3 g)</td>
<td>4 g</td>
<td>2.6 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261 except bowel fistula; also CAPD, haemodialysis. Not suitable for child under 3 years; use with caution in child 3–5 years.</td>
<td>Nutilis Fruit Stage 3: apple, strawberry 450 gram = £7.08</td>
</tr>
<tr>
<td>Oral Impact® (Nestle Health Science)</td>
<td>Standard dilution of powder (74 g in 250 mL water) (sip feed) per 100 mL</td>
<td>425 kJ (101 kcal)</td>
<td>5.6 g cow’s milk</td>
<td>13.4 g (sugars 7.4 g)</td>
<td>2.8 g</td>
<td>1 g</td>
<td>Residual lactose Contains fish oil</td>
<td>Pre-operative nutritional supplement for malnourished patients or patients at risk of malnourishment Not suitable for child under 3 years; use with caution in child 3–5 years.</td>
<td>Oral Impact oral powder 74g sachets: citrus, coffee, tropical 5 sachet = £16.93</td>
</tr>
</tbody>
</table>
### Nutritional supplements: More than 1.5 kcal/mL and 5 g (or more) protein/100 mL

Not suitable for use in child under 1 year; use with caution in child 1–5 years unless otherwise stated.

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complan® Shake (Nutricia Ltd)</td>
<td>Powder per 57 g</td>
<td>1057 kJ (251 kcal)</td>
<td>8.8 g cows’ milk</td>
<td>35.2 g (sugars 22.7 g)</td>
<td>8.4 g</td>
<td>Trace g</td>
<td>Gluten-free, Contains lactose</td>
<td>Standard, p. 1261</td>
<td>Complan Shake Starter Pack sachets: 5 sachet = £4.79 Complan Shake oral powder 57 g sachets: banana, chocolate, milk, strawberry, vanilla 4 sachet = £3.40</td>
</tr>
<tr>
<td>Powder 57 g reconstituted with 200 mL whole milk provides: protein 15.6 g, carbohydrate 44.5 g, fat 16.4 g, energy 1621 kJ (387 kcal)</td>
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<tr>
<td>Foodlink® Complete (Foodlink (UK) Ltd)</td>
<td>Powder per 100 g</td>
<td>1826 kJ (434 kcal)</td>
<td>21.3 g cows’ milk</td>
<td>56.7 g</td>
<td>13.5 g</td>
<td>Nil</td>
<td>Contains lactose</td>
<td>Standard, p. 1261</td>
<td>Foodlink Complete powder: banana, chocolate, natural, strawberry 450 g = £3.25</td>
</tr>
<tr>
<td>Recommended serving = 4 heaped dessertspoonfuls in 200 mL full cream milk provides: protein 18.9 g, carbohydrate 41.8 g, fat 15.7 g, energy 1605 kJ (383 kcal)</td>
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</tr>
<tr>
<td>Foodlink® Complete with Fibre (Foodlink (UK) Ltd)</td>
<td>Powder per 100 g</td>
<td>1683 kJ (400 kcal)</td>
<td>19.4 g cows’ milk</td>
<td>52.7 g (sugars 27.3 g)</td>
<td>12.4 g</td>
<td>7.2 g</td>
<td>Contains lactose</td>
<td>Standard, p. 1261</td>
<td>Foodlink Complete powder with fibre: vanilla lactose free 450 g = £3.54 vanilla 53 g = £0.67 450 g = £3.25</td>
</tr>
<tr>
<td>Recommended serving = 4 heaped dessertspoonfuls (or the contents of a 63 g sachet) in 200 mL full cream milk provides: protein 19.0 g, carbohydrate 42.7 g, fat 15.8 g, fibre 4.5 g, energy 1624 kJ (388 kcal)</td>
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</tr>
<tr>
<td>Forticreme® Complete (Nutricia Ltd)</td>
<td>Semi-solid per 100 g</td>
<td>675 kJ (160 kcal)</td>
<td>9.5 g cows’ milk</td>
<td>19.2 g (sugars 10.6 g)</td>
<td>5 g</td>
<td>0.1 g</td>
<td>Gluten-free, Residual lactose</td>
<td>Standard, p. 1261; also CAPD, haemodialysis. Not suitable for child under 3 years; use with caution in child 3–5 years.</td>
<td>Forticreme Complete dessert: banana, chocolate, forest fruits, vanilla 500 g = £7.84</td>
</tr>
<tr>
<td>Fortisip® Compact (Nutricia Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>1010 kJ (240 kcal)</td>
<td>9.6 g cows’ milk</td>
<td>29.7 g (sugars 15 g)</td>
<td>9.3 g</td>
<td>Nil</td>
<td>Residual lactose</td>
<td>Standard, p. 1261 Not suitable for child under 3 years; use with caution in child 3–5 years.</td>
<td>Fortisip Compact liquid: apricot, banana, forest fruit, mocha, strawberry, vanilla 500 ml = £8.08 chocolate 500 ml = £8.08</td>
</tr>
<tr>
<td>Fortisip® Compact Fibre (Nutricia Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>1000 kJ (240 kcal)</td>
<td>9.4 g cows’ milk</td>
<td>25.2 g (sugars 13.9 g)</td>
<td>10.4 g</td>
<td>3.6 g</td>
<td>Gluten-free, Residual lactose</td>
<td>Standard, p. 1261 Not suitable for child under 3 years; use with caution in child 3–5 years.</td>
<td>Fortisip Compact Fibre Starter Pack liquid: 500 ml = £8.36 Fortisip Compact Fibre liquid: mocha, strawberry, vanilla 500 ml = £8.36</td>
</tr>
<tr>
<td>Fortisip® Compact Protein (Nutricia Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>1010 kJ (240 kcal)</td>
<td>14.4 g cows’ milk</td>
<td>24.4 g (sugars 13.3 g)</td>
<td>9.4 g</td>
<td>Nil</td>
<td>Gluten-free, Residual lactose</td>
<td>Standard, p. 1261 Not suitable for child under 3 years; use with caution in child 3–5 years.</td>
<td>Fortisip Compact Protein Starter Pack liquid: 500 ml = £8.00 Fortisip Compact Protein liquid: banana, mocha, strawberry, vanilla 500 ml = £8.00</td>
</tr>
<tr>
<td>Fortisip® Extra (Nutricia Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>675 kJ (160 kcal)</td>
<td>10.0 g cows’ milk</td>
<td>18.1 g (sugars 9 g)</td>
<td>5.3 g</td>
<td>Nil</td>
<td>Gluten-free, Contains lactose</td>
<td>Standard, p. 1261 Not suitable for child under 3 years; use with caution in child 3–5 years.</td>
<td>Fortisip Extra Starter Pack liquid: 800 ml = £8.56 Fortisip Extra liquid: chocolate, forest fruits, mocha, strawberry, vanilla 200 ml = £2.14</td>
</tr>
<tr>
<td>Fresubin® 2 kcal Drink (Fresenios Kabi Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>840 kJ (200 kcal)</td>
<td>10.0 g cows’ milk</td>
<td>22.5 g (sugars 5.8 g)</td>
<td>7.8 g</td>
<td>Nil</td>
<td>Gluten-free, Residual lactose</td>
<td>Standard, p. 1261; also CAPD, haemodialysis.</td>
<td>Fresubin 2kcal drink: apricot-peach, cappuccino, fruits of the forest, neutral, toffee, vanilla 200 ml = £1.96</td>
</tr>
<tr>
<td>Product</td>
<td>Formulation</td>
<td>Energy</td>
<td>Protein</td>
<td>Carbohydrate</td>
<td>Fat</td>
<td>Fibre</td>
<td>Special Characteristics</td>
<td>ACBS Indications</td>
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</tr>
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<tr>
<td>Fresubin® 2 kcal Fibre Drink (Fresenius Kabi Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>840 kJ (200 kcal)</td>
<td>10 g cows’ milk</td>
<td>22.5 g (sugars 5.8 g)</td>
<td>7.8 g</td>
<td>1.6 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261; also CAPD, haemodialysis.</td>
<td>Fresubin 2 kcal Fibre drink: apricot, peach, cappuccino, chocolate, lemon, neutral 200 ml = £1.96</td>
</tr>
<tr>
<td>Fresubin® Powder Extra (Fresenius Kabi Ltd)</td>
<td>Powder per 100 g</td>
<td>1764 kJ (420 kcal)</td>
<td>17.5 g cows’ milk whey protein</td>
<td>63 g (sugars 24.7 g)</td>
<td>10.9 g</td>
<td>Nil</td>
<td>Gluten-free Contains lactose</td>
<td>Standard, p. 1261</td>
<td>Fresubin Powder Extra oral powder 62 g sachets: chocolate, neutral, strawberry, vanilla 7 sachet = £5.60</td>
</tr>
<tr>
<td>Nutrilis Complete Stage 1 (Nutricia Ltd)</td>
<td>Liquid (pre-thickened) per 100 mL</td>
<td>1010 kJ (240 kcal)</td>
<td>9.6 g cows’ milk</td>
<td>29.1 g (sugars 5.4 g)</td>
<td>9.3 g</td>
<td>3.2 g</td>
<td>Residual lactose</td>
<td>Standard, p. 1261 Not suitable for child under 3 years.</td>
<td>Nutrilis Complete Stage 1 liquid: strawberry, vanilla 500 ml = £8.84</td>
</tr>
<tr>
<td>Nutrilis Complete Stage 2 (Nutricia Ltd)</td>
<td>Semi-solid per 100 g</td>
<td>1030 kJ (245 kcal)</td>
<td>9.6 g cows’ milk</td>
<td>29.1 g (sugars 11.8 g)</td>
<td>9.4 g</td>
<td>3.2 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261 Not suitable for child under 3 years; use with caution in child 3-6 years.</td>
<td>Nutrilis Complete Stage 2 custard: chocolate, strawberry, vanilla 500 gram = £8.16</td>
</tr>
<tr>
<td>Nutricrem® (Nualtra Ltd)</td>
<td>Semi-solid per 100 g</td>
<td>756 kJ (180 kcal)</td>
<td>10 g cows’ milk soya protein</td>
<td>18.8 g (sugars 9.7 g)</td>
<td>7.2 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261 Not suitable for child under 3 years; use with caution in child 3-6 years.</td>
<td>Nutricrem dessert: strawberry, vanilla 500 gram = £5.60</td>
</tr>
<tr>
<td>Nutriplen® (Nualtra Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>1008 kJ (240 kcal)</td>
<td>9.6 g cows’ milk soya protein</td>
<td>28.8 g (sugars 11.6 g)</td>
<td>9.6 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261 Not suitable for child under 3 years; use with caution in child 3-6 years.</td>
<td>Nutriplen liquid: strawberry, vanilla 500 ml = £5.80</td>
</tr>
<tr>
<td>Renilon® 7.5 (Nutricia Ltd)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>840 kJ (200 kcal)</td>
<td>7.5 g cows’ milk</td>
<td>20 g (sugars 4.8 g)</td>
<td>10 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261 Not suitable for child under 3 years; use with caution in child 3-5 years.</td>
<td>Renilon 7.5 liquid: apricot, caramel 500 ml = £8.48</td>
</tr>
<tr>
<td>Resource® 2.0 Fibre (Nestlé Health Science)</td>
<td>Liquid (sip feed) per 100 mL</td>
<td>836 kJ (200 kcal)</td>
<td>9 g cows’ milk</td>
<td>21.4 g (sugars 5.5 g)</td>
<td>8.7 g</td>
<td>2.5 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261 Not suitable for child under 6 years; use with caution in child 6-10 years.</td>
<td>Resource Fibre 2.0 liquid: apricot, coffee, neutral, strawberry, summer fruit, vanilla 200 ml = £1.88</td>
</tr>
<tr>
<td>Vegenat®-med Balanced Protein (Vegenat)</td>
<td>Powder per 110 g serving</td>
<td>1924 kJ (458 kcal)</td>
<td>18 g cows’ milk</td>
<td>62 g</td>
<td>15.35 g</td>
<td>5.8 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261 except bowel fistula Not suitable for child under 14 years</td>
<td>Vegenat-med balanced protein oral powder sachets: apple, chocolate, honey, orange 1320 gram = £36.26</td>
</tr>
<tr>
<td>Vegenat®-med High Protein (Vegenat)</td>
<td>Powder per 110 g serving</td>
<td>1940 kJ (463 kcal)</td>
<td>23.3 g cows’ milk</td>
<td>57.2 g</td>
<td>15.6 g</td>
<td>6 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 1261 except bowel fistula Not suitable for child under 14 years</td>
<td>Vegenat-med high protein oral powder sachets: curry chicken 1320 gram = £48.95 chicken, fish, ham, lentils, veal 1320 gram = £50.76</td>
</tr>
<tr>
<td>Product</td>
<td>Formulation</td>
<td>Energy</td>
<td>Protein</td>
<td>Carbohydrate</td>
<td>Fat</td>
<td>Fibre</td>
<td>Special Characteristics</td>
<td>ACBS Indications</td>
<td>Presentation &amp; Flavour</td>
</tr>
<tr>
<td>-------------------------------</td>
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<td>----------------------------------------</td>
</tr>
<tr>
<td>Alicalm®</td>
<td>Standard dilution (30%) of powder per 100 mL</td>
<td>567 kJ (135 kcal)</td>
<td>4.5 g caseinate whey</td>
<td>17.4 g (sugars 3.2 g)</td>
<td>5.3 g</td>
<td>Nil</td>
<td>Residual lactose</td>
<td>Crohn's disease Not suitable for child under 1 year; use as nutritional supplement only in children 1-6 years.</td>
<td>Alicalm oral powder: 400 gram = £21.09</td>
</tr>
<tr>
<td>Forticare®</td>
<td>Liquid (sip feed) per 100 mL.</td>
<td>675 kJ (160 kcal)</td>
<td>9 g cows' milk</td>
<td>19.1 g (sugars 13.6 g)</td>
<td>5.3 g</td>
<td>2.1 g</td>
<td>Gluten-free Residual lactose Contains fish oil</td>
<td>Nutritional supplement in patients with lung cancer undergoing chemotherapy, or with pancreatic cancer Not suitable in child under 3 years</td>
<td>Forticare liquid: cappuccino, orange &amp; lemon, peach &amp; ginger 500 ml = £8.76</td>
</tr>
<tr>
<td>Heparon Junior®</td>
<td>Standard dilution (18%) of powder per 100 mL</td>
<td>363 kJ (86 kcal)</td>
<td>2 g cows' milk</td>
<td>11.6 g (sugars 2.9 g)</td>
<td>3.6 g</td>
<td>Nil</td>
<td>Contains lactose Electrolytes/100 mL: Na⁺ 0.56 mmol K⁺ 1.9 mmol Ca²⁺ 2.3 mmol P⁴⁻ 1.6 mmol</td>
<td>Enteral feed or nutritional supplement for children with acute or chronic liver failure</td>
<td>Heparon Junior powder: 400 gram = £21.25</td>
</tr>
<tr>
<td>KetoCal®</td>
<td>Standard dilution (20%) of powder per 100 mL</td>
<td>602 kJ (146 kcal)</td>
<td>3.1 g cows' milk with additional amino acids</td>
<td>600 mg (sugars 120 mg)</td>
<td>14.6 g (LCT 100 %)</td>
<td>Nil</td>
<td>Electrolytes/100 mL: Na⁺ 4.3 mmol K⁺ 4.1 mmol Ca²⁺ 2.15 mmol P⁴⁻ 2.77 mmol</td>
<td>Enteral feed or nutritional supplement as part of ketogenic diet in management of epilepsy resistant to drug therapy, in children over 1 year, only on the advice of secondary care physician with experience of ketogenic diet.</td>
<td>KetoCal 4:1 powder: unflavoured, vanilla 300 gram = £29.91</td>
</tr>
<tr>
<td>KetoCal® 3:1</td>
<td>Standard dilution (9.5%) of powder per 100 mL</td>
<td>276 kJ (66 kcal)</td>
<td>1.5 g</td>
<td>680 mg (sugars 570 mg)</td>
<td>6.4 g</td>
<td>Nil</td>
<td>Electrolytes/100 mL: Na⁺ 1.3 mmol K⁺ 2.4 mmol Ca²⁺ 2 mmol P⁴⁻ 1.7 mmol</td>
<td>Enteral feed or nutritional supplement as part of ketogenic diet in management of drug resistant epilepsy or other conditions for which a ketogenic diet is indicated in children from birth to 6 years; as a nutritional supplement in children over 6 years.</td>
<td>KetoCal 3:1 powder: 300 gram = £28.95</td>
</tr>
<tr>
<td>KetoCal® 4:1 LQ</td>
<td>Liquid (sip or tube feed) per 100 mL.</td>
<td>620 kJ (150 kcal)</td>
<td>3.09 g casein and whey with additional amino acids</td>
<td>610 mg (sugars 230 mg)</td>
<td>14.8 g (LCT 100 %)</td>
<td>1.12 g</td>
<td>Electrolytes/100 mL: Na⁺ 4.9 mmol K⁺ 4.7 mmol Ca²⁺ 2.4 mmol P⁴⁻ 3.1 mmol</td>
<td>Enteral feed or nutritional supplement as part of ketogenic diet in management of drug resistant epilepsy or other conditions for which a ketogenic diet is indicated in children 1-10 years; as a nutritional supplement in children over 10 years.</td>
<td>KetoCal 4:1 LQ liquid: unflavoured, vanilla 200 ml = £4.27</td>
</tr>
<tr>
<td>Product</td>
<td>Formulation</td>
<td>Energy</td>
<td>Protein</td>
<td>Carbohydrate</td>
<td>Fat</td>
<td>Fibre</td>
<td>Special Characteristics</td>
<td>ACSB Indications</td>
<td>Presentation &amp; Flavour</td>
</tr>
<tr>
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</tr>
<tr>
<td>Kindergen®</td>
<td>Standard dilution (20%) of powder per 100 mL</td>
<td>421 kJ (101 kcal)</td>
<td>1.5 g whey protein</td>
<td>11.8 g (sugars 1.2 g)</td>
<td>5.3 g (LCT 93%)</td>
<td>Electrolytes/100 mL: Na⁺ 2 mmol K⁺ 0.6 mmol Ca²⁺ 2.8 mmol P³ 3 mmol</td>
<td>Low Vitamin A</td>
<td>Kindergen powder: 400 gram = £28.52</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Powder provides: protein 7.5 g, carbohydrate 59 g, fat 26.3 g, energy 2104 kJ (504 kcal)/100 g</td>
<td></td>
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</tr>
<tr>
<td>Modulen IBD®</td>
<td>Standard dilution (20%) of powder (sip or tube feed) per 100 mL</td>
<td>420 kJ (100 kcal)</td>
<td>3.6 g casein</td>
<td>11 g (sugars 3.98 g)</td>
<td>4.7 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Crohn's disease active phase, and in remission if malnourished</td>
<td>Modulen IBD powder: 400 gram = £15.06</td>
</tr>
<tr>
<td></td>
<td>Powder provides: protein 16 g, carbohydrate 54 g, fat 23 g, energy 2070 kJ (500 kcal)/100 g</td>
<td></td>
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</tr>
<tr>
<td>Nepro®</td>
<td>Liquid (sip or tube feed) per 100 mL</td>
<td>838 kJ (200 kcal)</td>
<td>7 g cows' milk</td>
<td>20.6 g (sugars 3.26 g)</td>
<td>9.6 g</td>
<td>1.56 g</td>
<td>Gluten-free Residual lactose Electrolytes/100 mL: Na⁺ 3.67 mmol K⁺ 2.72 mmol Ca²⁺ 3.43 mmol P³ 2.23 mmol</td>
<td>Enteral feed or nutritional supplement in patients with chronic renal failure who are on haemodialysis or CAPD, or with cirrhosis, or other conditions requiring a high energy, low fluid, low electrolyte diet. Not suitable for child under 1 year; use with caution in child 1-5 years.</td>
<td>Nepro HP liquid: strawberry 220 ml = £2.98 vanilla 220 ml = £2.98 500 ml = £6.12</td>
</tr>
<tr>
<td></td>
<td>Powder (sip or tube feed when reconstituted) per 100 g</td>
<td>2003 kJ (477 kcal)</td>
<td>4.6 g cows' milk</td>
<td>70.8 g</td>
<td>19.3 g</td>
<td>Nil</td>
<td>Contains lactose Electrolytes/100 g: Na⁺ 1.04 mmol K⁺ 0.13 mmol Ca²⁺ 10.22 mmol P³ 1.06 mmol Contains no vitamin A or vitamin D</td>
<td>Enteral feed or nutritional supplement for adults and children over 1 year with chronic renal failure.</td>
<td>Renamil powder: 10 x 100 gram = £25.40</td>
</tr>
<tr>
<td>Renamil®</td>
<td>Powder per 100 g</td>
<td>1580 kJ (372 kcal)</td>
<td>90 g whey protein</td>
<td>800 mg</td>
<td>1 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Electrolytes/100 g: Na⁺ 2 mmol K⁺ 2 mmol Ca²⁺ 4.99 mmol P³ 4.84 mmol</td>
<td>Nutritional supplement for biochemically proven hypoproteinaemia and patients undergoing dialysis. Not suitable for child under 1 year.</td>
<td>Renapro powder: 600 gram = £69.60</td>
</tr>
<tr>
<td></td>
<td>Powder provides: protein 18 g, energy 316 kJ (74 kcal)/20 g sachet</td>
<td></td>
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</tr>
</tbody>
</table>

**Kindergen powder:** 400 gram = £28.52  
**Modulen IBD powder:** 400 gram = £15.06  
**Nepro HP liquid:** strawberry 220 ml = £2.98 vanilla 220 ml = £2.98 500 ml = £6.12  
**Renamil powder:** 10 x 100 gram = £25.40  
**Renapro powder:** 600 gram = £69.60
### Renastart®

(Vitaflo International Ltd)

<table>
<thead>
<tr>
<th>Standard dilution (20%) of powder per 100 mL</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renastart powder: 400 gram = £26.08</td>
<td>414 kj (99 kcal)</td>
<td>1.5 g cows' milk soya</td>
<td>12.5 g (sugars 1.3 g)</td>
<td>4.8 g</td>
<td>Nil</td>
<td>Contains lactose</td>
<td>Dietary management of renal failure in child from birth to 10 years.</td>
<td>Renastart powder: 400 gram = £26.08</td>
</tr>
</tbody>
</table>

Powder provides: protein 7.5 g, carbohydrate 62.5 g, fat 23.8 g, energy 2071 kj (494 kcal)/100 g

### Respifor®

(Nutricia Ltd)

<table>
<thead>
<tr>
<th>Liquid (sip feed) per 100 mL</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respifor milkshake style liquid: chocolate, strawberry, vanilla 500 ml = £8.32</td>
<td>633 kj (150 kcal)</td>
<td>7.5 g cows' milk</td>
<td>22.5 g (sugars 6.4 g)</td>
<td>3.3 g</td>
<td>Nil</td>
<td>Contains lactose</td>
<td>Nutritional supplement for dietary management of disease-related malnutrition in patients with chronic obstructive pulmonary disease and body-mass index less than 20.</td>
<td>Respifor milkshake style liquid: chocolate, strawberry, vanilla 500 ml = £8.32</td>
</tr>
</tbody>
</table>

### Maxijul®

(Super Soluble, Nutricia Ltd)

<table>
<thead>
<tr>
<th>Powder per 100 g</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maxijul Super Soluble powder: 200 gram = £2.55; 528 gram = £6.36; 2112 gram; 25000 gram = £152.66</td>
<td>1615 kj (380 kcal)</td>
<td>95 g Glucose polymer (sugars 8.6 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Lactose-free</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high or readily available carbohydrate supplement.</td>
<td>Maxijul Super Soluble powder: 200 gram = £2.55; 528 gram = £6.36; 2112 gram; 25000 gram = £152.66</td>
<td>Maxijul Super Soluble powder: 200 gram = £2.55; 528 gram = £6.36; 2112 gram; 25000 gram = £152.66</td>
</tr>
</tbody>
</table>

### Polycal®

(Nutricia Ltd)

<table>
<thead>
<tr>
<th>Liquid per 100 mL</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powder per 100 g</td>
<td>1630 kj (384 kcal)</td>
<td>96 g Maltodextrin (sugars 6 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Lactose-free</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high or readily available carbohydrate supplement.</td>
<td>Polycal liquid: neutral, orange 200 mL = £1.69</td>
<td>Polycal liquid: neutral, orange 200 mL = £1.69</td>
</tr>
</tbody>
</table>

### Table 4 Feed supplements

**High-energy supplements**

Flavoured carbohydrate supplements are not suitable for child under 1 year; liquid supplements should be diluted before use in child under 5 years.

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caloreen® (Nestle Health Science)</td>
<td>Powder per 100 g</td>
<td>1640 kj (390 kcal)</td>
<td>Nil</td>
<td>96 g Maltodextrin</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Lactose-free</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high or readily available carbohydrate supplement.</td>
<td>Caloreen powder: 500 gram = £3.69</td>
</tr>
</tbody>
</table>

| Maxijul® Super Soluble (Nutricia Ltd) | Powder per 100 g | 1615 kj (380 kcal) | Nil | 95 g Glucose polymer (sugars 8.6 g) | Nil | Nil | Gluten-free Lactose-free | Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high or readily available carbohydrate supplement. | Maxijul Super Soluble powder: 200 gram = £2.55; 528 gram = £6.36; 2112 gram; 25000 gram = £152.66 |

| Polycal® (Nutricia Ltd) | Liquid per 100 mL | 1050 kj (247 kcal) | Nil | 61.9 g Maltodextrin (sugars 12.2 g) | Nil | Nil | Gluten-free Lactose-free | Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high or readily available carbohydrate supplement. | Polycal liquid: neutral, orange 200 mL = £1.69 |

| Polycal® (Nutricia Ltd) | Powder per 100 g | 1630 kj (384 kcal) | Nil | 96 g Maltodextrin (sugars 6 g) | Nil | Nil | Gluten-free Lactose-free | Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high or readily available carbohydrate supplement. | Polycal powder: 400 gram = £4.20 |
### High-energy supplements: carbohydrate (product list continued)
Flavoured carbohydrate supplements are not suitable for child under 1 year; liquid supplements should be diluted before use in child under 5 years

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.O.S.® (Vitaflo International Ltd)</td>
<td>Powder per 100 g</td>
<td>1590 kJ (380 kcal)</td>
<td>Nil</td>
<td>95 g (sugars 9 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>S.O.S. products are age-range specific-consult product literature</td>
<td>For use as an emergency regimen in the dietary management of inborn errors of metabolism in adults and children from birth.</td>
<td>S.O.S. 15 oral powder 31g sachets 30 sachet = £10.67; S.O.S. 10 oral powder 21g sachets 30 sachet = £7.23; S.O.S. 20 oral powder 42g sachets 30 sachet = £14.46; S.O.S. 25 oral powder 52g sachets 30 sachet = £17.89</td>
</tr>
</tbody>
</table>

Contents of each sachet should be reconstituted with water to a total volume of 200 mL

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitajoule® (Vitaflo International Ltd)</td>
<td>Powder per 100 g</td>
<td>1590 kJ (380 kcal)</td>
<td>Nil</td>
<td>95 g Dried glucose syrup (sugars 9 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Lactose-free</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high or readily available carbohydrate supplement.</td>
<td>Vitajoule powder: 500 gram = £4.33</td>
</tr>
</tbody>
</table>

### High-energy supplements: fat
Liquid supplements should be diluted before use in child under 5 years

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calogen® (Nutricia Ltd)</td>
<td>Liquid (emulsion) per 100 mL</td>
<td>1850 kJ (450 kcal)</td>
<td>Nil</td>
<td>100 mg</td>
<td>50 g (LCT 100 %)</td>
<td>Nil</td>
<td>Gluten-free Lactose-free</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat (or fat and carbohydrate) supplement.</td>
<td>Calogen emulsion: banana 500 ml = £10.72 neutral, strawberry 200 ml = £4.36 500 ml = £10.72</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresubin® 5 kcal Shot (Fresenius Kabi Ltd)</td>
<td>Liquid (emulsion) per 100 mL</td>
<td>2100 kJ (500 kcal)</td>
<td>Nil</td>
<td>4.0 g (sucrose)</td>
<td>53.8 g</td>
<td>400 mg</td>
<td>Gluten-free Lactose-free</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat (or fat and carbohydrate) supplement. Not suitable for child under 3 years.</td>
<td>Fresubin 5kcal shot drink neutral: 480 ml = £11.08</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquigen® (Nutricia Ltd)</td>
<td>Liquid (emulsion) per 100 mL</td>
<td>1850 kJ (450 kcal)</td>
<td>Nil</td>
<td>Nil</td>
<td>50 g (MCT 97 %) Fractionated coconut oil</td>
<td>Nil</td>
<td>Gluten-free Lactose-free</td>
<td>Steatorrhoea associated with cystic fibrosis of the pancreas, intestinal lymphangiectasia, intestinal surgery, chronic liver disease, liver cirrhosis, other proven malabsorption syndromes, ketogenic diet in epilepsy, and in type 1 lipoproteinaemia Not suitable for child under 1 year</td>
<td>Liquigen emulsion: 250 ml = £9.09</td>
</tr>
</tbody>
</table>
Medium-chain Triglyceride (MCT) Oil (Nutricia Ltd)

<table>
<thead>
<tr>
<th>Liquid per 100 mL</th>
<th>3515 kJ (855 kcal)</th>
<th>Nil</th>
<th>Nil</th>
<th>MCT 100 %</th>
<th>Nil</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FAT AND CARBOHYDRATE</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Product</strong></td>
<td><strong>Formulation</strong></td>
<td><strong>Energy</strong></td>
<td><strong>Protein</strong></td>
<td><strong>Carbohydrate</strong></td>
<td><strong>Fat</strong></td>
</tr>
<tr>
<td>Duocal® Super Soluble (Nutricia Ltd)</td>
<td>Powder per 100 g</td>
<td>2061 kJ (492 kcal)</td>
<td>Nil</td>
<td>72.7 g (sugars 6.5 g)</td>
<td>22.3 g (MCT 35 %)</td>
</tr>
<tr>
<td>Energivit® (Nutricia Ltd)</td>
<td>Standard dilution (15%) of powder per 100 mL</td>
<td>309 kJ (74 kcal)</td>
<td>Nil</td>
<td>10 g (sugars 900 mg)</td>
<td>3.75 g</td>
</tr>
</tbody>
</table>

Powder provides: carbohydrate 66.7 g, fat 25 g, energy 2059 kJ (492 kcal)/100 g

**High-energy supplements: protein**

<table>
<thead>
<tr>
<th><strong>Product</strong></th>
<th><strong>Formulation</strong></th>
<th><strong>Energy</strong></th>
<th><strong>Protein</strong></th>
<th><strong>Carbohydrate</strong></th>
<th><strong>Fat</strong></th>
<th><strong>Fibre</strong></th>
<th><strong>Special Characteristics</strong></th>
<th><strong>ACBS Indications</strong></th>
<th><strong>Presentation &amp; Flavour</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>ProSource® Jelly (Nutrinovo Ltd)</td>
<td>Semi-solid per 100 mL</td>
<td>315 kJ (75 kcal)</td>
<td>16.9 g collagen protein hydrolysate whey protein isolate</td>
<td>Less than 1 g</td>
<td>Nil</td>
<td>Less than 1 g</td>
<td>Gluten-free</td>
<td>Lactose-free</td>
<td>Contains porcine derivatives</td>
</tr>
<tr>
<td>Protifar® (Nutricia Ltd)</td>
<td>Powder per 100 g</td>
<td>1580 kJ (373 kcal)</td>
<td>88.5 g cows' milk</td>
<td>less than 1.5 g</td>
<td>1.6 g</td>
<td>Nil</td>
<td>Gluten-free</td>
<td>Residual lactose Electrolytes/100 mL: Na⁺ 1.3 mmol K⁺ 1.28 mmol Ca²⁺ 33.75 mmol P⁺ 22.58 mmol</td>
<td>Nutritional supplement for use in biochemically proven hypoproteinaemia.</td>
</tr>
</tbody>
</table>

Powder provides: protein 2.2 g per 2.5 scoopful

Nutritional supplement for steatorrhoea associated with cystic fibrosis of the pancreas, intestinal lymphangiectasia, intestinal surgery, chronic liver disease and liver cirrhosis, other proven malabsorption syndromes, ketogenic diet in management of epilepsy, type 1 hyperlipoproteinaemia

MCT oil: 500 ml = £14.41
### High-energy supplements: protein (product list continued)

#### PROTEIN AND CARBOHYDRATE

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialamine® (Nutricia Ltd)</td>
<td>Standard dilution (20%) of powder per 100 mL</td>
<td>264 kJ (62 kcal)</td>
<td>4.3 g protein (essential and non-essential amino acids)</td>
<td>11.2 g (sugars 10.2 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Contains vitamin C</td>
<td>Hypoproteinaemia, chronic renal failure, wound fistula leakage with excessive protein loss, conditions requiring a controlled nitrogen intake, and haemodialysis. Not suitable for child under 6 months.</td>
<td>Dialamine powder: 400 g = £72.09</td>
</tr>
</tbody>
</table>

Powder provides: protein equivalent 25 g, carbohydrate 65 g, vitamin C 125 mg, energy 1530 kJ (360 kcal)/100 g

| ProSource® Liquid (Nutrinovo Ltd) | Liquid per 30 mL | 420 kJ (100 kcal) | 10 g collagen protein whey protein isolate | 15 g (sugars 8 g) | Nil | Nil | Gluten-free Lactose-free May contain porcine derivatives | Biochemically proven hypoproteinaemia Not recommended for child under 3 years. | ProSource liquid 30 ml sachets: citrus berry, lemon, orange creme, original 100 sachet = £97.23 |

| ProSource® Plus (Nutrinovo Ltd) | Liquid per 30 mL | 420 kJ (100 kcal) | 15 g collagen protein whey protein isolate | 11 g (sugars 10 g) | Nil | Nil | Gluten-free Lactose-free May contain porcine derivatives | Hypoproteinaemia Not recommended for child under 3 years | ProSource plus liquid 100 x 30 ml sachets: unflavoured: £140.53 |

#### PROTEIN, FAT, AND CARBOHYDRATE

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
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<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calogen® Extra (Nutricia Ltd)</td>
<td>Liquid per 100 mL</td>
<td>1650 kJ (400 kcal)</td>
<td>5 g cows’ milk</td>
<td>4.5 g (sugars 3.5 g)</td>
<td>40.3 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Contains vitamins and minerals</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 3 years; use with caution in child 3-6 years. May require dilution for child 3-5 years.</td>
<td>Calogen Extra emulsion: neutral, strawberry 200 mL = £4.98</td>
</tr>
</tbody>
</table>

<p>| Calogen® Extra Shots (Nutricia Ltd) | Liquid per 100 mL | 1650 kJ (400 kcal) | 5 g cows’ milk | 4.5 g (sugars 3.5 g) | 40.3 g | Nil | Gluten-free Residual lactose With vitamins and minerals | Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 3 years; use with caution in child 3-6 years. May require dilution for child 3-5 years. | Calogen Extra Shots emulsion: neutral, strawberry 240 mL = £5.75 |</p>
<table>
<thead>
<tr>
<th>Feed supplements</th>
<th>Powder: 85 g reconstituted with 240 mL whole milk provides: protein 11.7 g, carbohydrate 66.8 g, fat 30.4 g, energy 2457 kJ (588 kcal)</th>
</tr>
</thead>
</table>
| Calshake<sup>®</sup> (Fresenius Kabi Ltd) | Powder per 87 g  
1841 kJ (439 kcal)  
4.1 g cows' milk  
56.4 g (sugars 20 g)  
22 g Nil  
Contains lactose Gluten-free  
Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 1 year.  
Calshake powder: chocolate 7 x 90 g sachets = £16.52 banana, neutral, strawberry, vanilla 7 x 87 g sachets = £16.52 |
| Enshake<sup>®</sup> (Abbott Laboratories Ltd) | Powder per 100 g  
1893 kJ (450 kcal)  
8.4 g cows' milk  
69 g (sugars 14.5 g)  
15.6 g Nil  
Residual lactose Contains vitamins and minerals  
Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 1 year; use with caution in child 1-6 years.  
Enshake oral powder 96.5g sachets: banana, chocolate, strawberry, vanilla 6 sachet = £12.93 |
| MCT Procal<sup>®</sup> (Vitaflo International Ltd) | Powder per 100 g  
2742 kJ (657 kcal)  
12.5 g cows' milk  
20.6 g (sugars 3.1 g)  
63.1 g (MCT 99%) Nil  
Contains lactose  
Dietary management of disorders of long-chain fatty acid oxidation, fat malabsorption, and other disorders requiring a low LCT, high MCT supplement. Not suitable for child under 1 year.  
MCT procal oral powder 16g sachets: 30 sachet = £23.51 |
| Pro-Cal<sup>®</sup> (Vitaflo International Ltd) | Powder per 100 g  
2787 kJ (667 kcal)  
13.6 g cows' milk  
28.2 g (sugars 16 g)  
55.5 g Nil  
Contains lactose Gluten-free  
Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 1 year; use with caution in child 1-5 years.  
Pro-Cal powder: 375 gram = £15.66; 510 gram = £14.51; 1500 gram = £29.56; 3000 gram = £69.77; 12500 gram = £210.06 |
| Pro-Cal<sup>®</sup> Shot (Vitaflo International Ltd) | Liquid per 100 mL  
1385 kJ (334 kcal)  
6.7 g cows' milk  
13.2 g (sugars 13.3 g)  
28.2 g Nil  
Contains lactose Gluten-free Contains soya  
Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 3 years.  
Pro-Cal: shot starter pack 240 ml = £4.82 750 ml = £15.05 neutral, strawberry 250 ml = £5.02 720 ml = £14.44 banana 250 ml = £5.02 720 ml = £14.44 |
| Scandishake<sup>®</sup> Mix (Nutricia Ltd) | Powder per 100 g  
2099 kJ (500 kcal)  
4.7 g cows' milk  
65 g (sugars 14.3 g)  
24.7 g Nil  
Gluten-free Contains lactose  
Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 3 years.  
Scandishake Mix oral powder 85g sachets: banana, caramel, chocolate, strawberry, unflavoured, vanilla 6 sachet = £14.46 |
### High-energy supplements: protein (product list continued)

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
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<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitasavoury® (Vitalfo International Ltd)</td>
<td>Powder per 100 g</td>
<td>2562 kJ (619 kcal)</td>
<td>12 g cows’ milk</td>
<td>22.5 g (sugars 1.4 g)</td>
<td>52 g</td>
<td>6.4 g</td>
<td>Contains lactose, Contains soya (chicken flavour)</td>
<td>Disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement. Not suitable for child under 3 years.</td>
<td>Vitasavoury 200 powder: chicken, golden vegetable, leek &amp; potato, mushroom 24 x 33 g = £30.75 Vitasavoury 300 powder: chicken, golden vegetable, leek &amp; potato, mushroom 10 x 50 g = £18.77</td>
</tr>
</tbody>
</table>

### Fibre, vitamin, and mineral supplements

#### High-fibre supplements

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resource® Optifibre® (Nestle Health Science)</td>
<td>Powder per 100 g</td>
<td>323 kJ (76 kcal)</td>
<td>Nil</td>
<td>19 g guar gum partially hydrolysed</td>
<td>Nil</td>
<td>78 g</td>
<td>Gluten-free, Lactose-free</td>
<td>Standard, p. 1261 except dysphagia Not suitable for child under 5 years</td>
<td>Resource Optifibre powder: 160 gram = £6.35; 250 gram = £10.28</td>
</tr>
</tbody>
</table>

#### Vitamin and Mineral supplements

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
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<th>Special Characteristics</th>
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</tr>
</thead>
<tbody>
<tr>
<td>FruitiVits® (Vitalfo International Ltd)</td>
<td>Powder per 100 g</td>
<td>133 kJ (33 kcal)</td>
<td>Nil</td>
<td>8.3 g (sugars 400 mg)</td>
<td>less than 100 mg</td>
<td>3.3 g</td>
<td>Vitamin, mineral, and trace element supplement in children 3–10 years with restrictive therapeutic diets</td>
<td>Sachets: 30 x 6 g = £63.53 orange</td>
<td></td>
</tr>
<tr>
<td>Paediatric Seravit® (Nutricia Ltd)</td>
<td>Powder per 100 g</td>
<td>1275 kJ (300 kcal)</td>
<td>Nil</td>
<td>75 g (sugars 6.75 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Pineapple flavour not suitable for child under 6 months</td>
<td>Vitamin, mineral, and trace element supplement in infants and children with restrictive therapeutic diets. Seravit Paediatric powder: pineapple 200 gram = £18.72 unflavoured 200 gram = £17.58</td>
<td></td>
</tr>
<tr>
<td>Renavit® (Stanningley Pharma Ltd)</td>
<td>Tablet per 450 mg</td>
<td>3.15 kJ (0.75 kcal)</td>
<td>Nil</td>
<td>170 mg</td>
<td>Nil</td>
<td>Nil</td>
<td>Dietary management of water-soluble vitamin deficiency in adults with renal failure on dialysis</td>
<td>Renavit tablets: 100 tablet = £12.50</td>
<td></td>
</tr>
</tbody>
</table>
Feed additives
Special additives for conditions of intolerance

Colief®
- For the relief of symptoms associated with lactose intolerance in infants, provided that lactose intolerance is confirmed by the presence of reducing substances and/or excessive acid in stools, a low concentration of the corresponding disaccharide enzyme on intestinal biopsy or by breath hydrogen test or lactose intolerance test. For dosage and administration details, consult product literature.

Fructose
- (Laevulose) For proven glucose/galactose intolerance

Glucose
- (Dextrose monohydrate) For use as an energy supplement in sucrose-/isomaltase deficiency

VSL#3®
- Nutritional supplement for use under the supervision of a physician, for the maintenance of remission of ileoanal pouchitis induced by antibacterials in adults. For dosage and administration details, consult product literature.

POWDER, containing 8 strains of live, freeze-dried, lactic acid bacteria. Contains traces of soya, gluten, and lactose.

VSL#3® Probiotic Food Supplement oral powder 4.4 g sachets (Ferring Pharmaceuticals Ltd)
10 sachet (ACBS) - NHS indicative price = £14.64 | 30 sachet (ACBS) - NHS indicative price = £41.66

Feed thickeners and pre-thickened drinks

Carobel, Instant®
- For thickening feeds in the treatment of vomiting.

Instant Carobel powder (Cow & Gate Ltd)
155 gram (ACBS) - NHS indicative price = £2.80

Multi-thick®
- For thickening of liquids and foods in dysphagia. Not suitable for children under 1 year except in cases of failure to thrive.

Multi-thick powder (Abbott Laboratories Ltd)
250 gram (ACBS) - NHS indicative price = £4.83

Nutilis® Clear
- For thickening of liquids or foods in dysphagia. Not suitable for children under 3 years.

Nutilis Clear powder (Nutricia Ltd)
175 gram (ACBS) - NHS indicative price = £8.46

Nutilis® Powder
- For thickening of foods in dysphagia. Not suitable for child under 3 years.

Nutilis powder (Nutricia Ltd)
240 gram (ACBS) - NHS indicative price = £6.40 | 300 gram (ACBS) - NHS indicative price = £4.92

Resource® ThickenUp Clear
- For thickening of liquids or foods in dysphagia. Not suitable for children under 3 years.

Resource ThickenUp Clear powder (Nestle Health Science)
24 x 1.2 g sachets (ACBS) - NHS indicative price = £5.28 | 125 gram (ACBS) - NHS indicative price = £8.46

Resource® Thickened Drink
- For dysphagia. Not suitable for children under 1 year.

Resource Thickened Drink custard (Nestle Health Science)
apple, orange 114 ml (ACBS) - NHS indicative price = £0.71

Resource ThickenUp powder (Nestle Health Science)
227 gram (ACBS) - NHS indicative price = £4.55 | 337.5 gram (ACBS) - NHS indicative price = £17.44

Resource® Thickened® Clear
POWDER, maltodextrin, xanthan gum, gluten- and lactose-free, sweetened with fructose. Available in 12 strengths.

Resource Thickened Drink (Ferring Pharmaceuticals Ltd)
consistency (3 consistencies available), see product literature.

Thick and Easy®
- For thickening of foods in dysphagia. Not suitable for children under 1 year except in cases of failure to thrive.

POWDER, modified maize starch

Thick & Easy powder (Fresenius Kabi Ltd)
225 gram (ACBS) - NHS indicative price = £5.06 | 900 gram (ACBS) - NHS indicative price = £31.00 | 4540 gram (ACBS) - NHS indicative price = £84.71

Thicken Aid powder (M & A Pharmachem Ltd)
225 gram (ACBS) - NHS indicative price = £3.71 | 900 gram (ACBS) - NHS indicative price = £22.40

Thixo-D®
- For thickening of foods in dysphagia. Not suitable for children under 1 year except in cases of failure to thrive.

POWDER, modified maize starch, gluten- and lactose-free.

Thixo-D (Sutherland Health Ltd)
Cal-Free powder 50 gram - NHS indicative price = £2.85 powder 375 gram (ACBS) - NHS indicative price = £7.15

Vitaquick®
- For thickening of foods in dysphagia. Not suitable for children under 1 year except in cases of failure to thrive.

POWDER, modified maize starch.

Vitaquick powder (Vitaflo International Ltd)
300 gram (ACBS) - NHS indicative price = £7.05 | 2000 gram (ACBS) - NHS indicative price = £38.92

Flavouring preparations

Flavour Mix®
POWDER

Nestle Nutrition Flavour (Nestle Health Science)
Mix banana, Mix chocolate 60 gram (ACBS) - NHS indicative price = £7.17

FlavourPac®
- For use with Vitaflor’s range of unflavoured protein substitutes for metabolic diseases; not suitable for child under 3 years.

POWDER
**Foods for special diets**

**Gluten-free foods**

**ACBS indications:** established gluten-sensitive enteropathies including steatorrhoea due to gluten sensitivity, coeliac disease, and dermatitis herpetiformis.

**Bread**

- **Gluten-free bread**
  - **Genius gluten free brown bread**
    - 500 gram (ACBS) - NHS indicative price = £5.73
  - **Glutafin gluten free brown bread 456 gram**
    - NHS indicative price = £3.43
  - **Barkat gluten free brown bread**
    - £3.69
  - **Juvela gluten free brown sandwich bread sliced 400 gram**
    - NHS indicative price = £2.77
  - **Genius Gluten Free bread**
    - £3.54
  - **Proceli gluten free brown loaf sliced 400 gram**
    - NHS indicative price = £2.67
  - **Livwell® Loaf**
    - £3.72
  - **Barkat gluten free Select Loaves**
    - £3.98
  - **Juvela gluten free Select Loaves**
    - £3.67
  - **Glutafin gluten free Select Loaves**
    - £3.43
  - **Glutafin gluten free Select fresh Loaves**
    - £3.95
  - **Glutafin gluten free Select seeded Loaves**
    - £3.43
  - **Glutafin gluten free Select white Loaves**
    - £3.72
  - **Juvela® Loaf**
    - £3.45
  - **Livwell gluten free Select Loaves**
    - £3.59
  - **Glutafin gluten free Select Loaves**
    - £3.59

**Wholemeal bread sliced 500 gram (ACBS) - NHS indicative price = £5.98**

**Gluten-free brown rice bread 474 gram (ACBS)**

**Gluten-free brown rice bread 456 gram (ACBS)**

**Glutafin gluten free Select Loaves sliced 600 gram (ACBS) - NHS indicative price = £3.98**

**Gluten-free loaves**

- **Glutafin gluten free loaf sliced**
  - 400 gram (ACBS) - NHS indicative price = £3.85
  - 375 gram (ACBS) - NHS indicative price = £3.59
  - 400 gram (ACBS) - NHS indicative price = £3.17
  - 400 gram (ACBS) - NHS indicative price = £3.17
  - 400 gram (ACBS) - NHS indicative price = £3.17

- **Glutafin gluten free loaf unsliced**
  - 400 gram (ACBS) - NHS indicative price = £3.54

**Glutafin gluten free loaf part baked**

- **Glutafin gluten free Select Loaves**
  - 425 gram (ACBS) - NHS indicative price = £3.98

- **Glutafin gluten free Select Loaves sliced**
  - 400 gram (ACBS) - NHS indicative price = £3.43

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<table>
<thead>
<tr>
<th>Brand</th>
<th>Product Description</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lifestyle® Rolls</strong></td>
<td>Brown bread rolls, high fibre bread rolls, white bread rolls</td>
<td>£2.80</td>
</tr>
<tr>
<td><strong>Livwell® Baguettes, buns and rolls</strong></td>
<td>Toasting bread buns 180 gram (ACBS)</td>
<td>£2.15</td>
</tr>
<tr>
<td><strong>Warburtons® Baguettes and rolls</strong></td>
<td>White rolls 240 gram (ACBS)</td>
<td>£2.25</td>
</tr>
<tr>
<td><strong>Wellfoods® Buns and rolls</strong></td>
<td>Baguettes 150 gram (ACBS)</td>
<td>£2.86</td>
</tr>
<tr>
<td><strong>Wellfoods gluten free</strong></td>
<td>Burger buns 380 gram (ACBS)</td>
<td>£3.95</td>
</tr>
<tr>
<td><strong>Livwell® Flat bread</strong></td>
<td>Tear drop flat bread 180 gram (ACBS)</td>
<td>£3.00</td>
</tr>
<tr>
<td><strong>Cereals</strong></td>
<td>Fibre flakes and oats</td>
<td>£5.00</td>
</tr>
<tr>
<td><strong>Nairns® Porridge</strong></td>
<td>Pure oats 500 gram (ACBS)</td>
<td>£2.78</td>
</tr>
<tr>
<td><strong>Nairn’s gluten free oat porridge</strong></td>
<td>500 gram (ACBS)</td>
<td>£3.05</td>
</tr>
<tr>
<td><strong>Cookies and biscuits</strong></td>
<td>Digestive biscuits, sweet biscuits 150 gram (ACBS)</td>
<td>£2.15</td>
</tr>
<tr>
<td><strong>Glutafin® Cookies</strong></td>
<td>Tea biscuits 150 gram (ACBS)</td>
<td>£2.09</td>
</tr>
<tr>
<td><strong>Glutafin gluten free</strong></td>
<td>Savoury short biscuits 130 gram (ACBS)</td>
<td>£2.80</td>
</tr>
<tr>
<td><strong>Juvela® Biscuits</strong></td>
<td>Shortbread biscuits 100 gram (ACBS)</td>
<td>£1.73</td>
</tr>
<tr>
<td><strong>Juvela gluten free</strong></td>
<td>Sweet biscuits 150 gram (ACBS)</td>
<td>£2.88</td>
</tr>
<tr>
<td><strong>Glutafin® Crackers</strong></td>
<td>Digestive biscuits, tea biscuits 150 gram (ACBS)</td>
<td>£5.05</td>
</tr>
<tr>
<td><strong>Glutafin gluten free</strong></td>
<td>Savoury biscuits 150 gram (ACBS)</td>
<td>£3.82</td>
</tr>
<tr>
<td><strong>Crackers, crispbreads, and breadsticks</strong></td>
<td><strong>Barkat® Crackers</strong></td>
<td>£3.52</td>
</tr>
<tr>
<td><strong>Glutafin Select® Cookies</strong></td>
<td><strong>Glutezyme® Crackers</strong></td>
<td>£6.66</td>
</tr>
<tr>
<td><strong>Glutafin gluten free Select bread mix</strong></td>
<td>(Gluten Free Foods Ltd)</td>
<td>£6.81</td>
</tr>
<tr>
<td><strong>Glutafin gluten free Select fibre bread mix</strong></td>
<td>(Gluten Free Foods Ltd)</td>
<td>£6.98</td>
</tr>
<tr>
<td><strong>Glutafin gluten free Select multipurpose white mix</strong></td>
<td>(Gluten Free Foods Ltd)</td>
<td>£6.66</td>
</tr>
<tr>
<td><strong>Glutafin® Flax mix</strong></td>
<td><strong>Glutafin Select® Flax mix</strong></td>
<td>£6.66</td>
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<td><strong>Glutafin® Tea mix</strong></td>
<td><strong>Glutafin Select® Tea mix</strong></td>
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<td><strong>Glutafin® Pancake mix</strong></td>
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<td><strong>Glutafin® Crepe mix</strong></td>
<td><strong>Glutafin Select® Crepe mix</strong></td>
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Juvela gluten free (Hero UK Ltd)
- fibre mix, harvest mix, mix 500 gram (ACBS) - NHS indicative price = £7.35
- raspberry mix 250 gram (ACBS) - NHS indicative price = £4.95
- flour mix, white bread mix 1000 gram (ACBS) - NHS indicative price = £6.65

Mrs Crimble's® Flour mixes
- GLUTEN-FREE
- £3.53

Mrs Crimble’s gluten free (Stiletto Foods (UK) Ltd)
- bread mix 275 gram (ACBS) - NHS indicative price = £1.09

Orgran® Flour mix
- GLUTEN-FREE

Orgran gluten free (Naturally Good Food Ltd)
- £3.80

Proceli gluten free (Innovative Solutions (UK) Ltd)
- GLUTEN-FREE

Proceli gluten free white plain flour (Ambe Ltd)
- 1000 gram (ACBS) - NHS indicative price = £9.95

Tobia® Flour mix
- GLUTEN-FREE

Tobia Teff gluten free (Tobia Teff UK Ltd)
- £3.53

Tritamyl® Flour mix
- GLUTEN-FREE

Tritamyl gluten free (Gluten Free Foods Ltd)
- brown bread mix 1000 gram (ACBS) - NHS indicative price = £7.10
- flour mix, white bread mix 2000 gram (ACBS) - NHS indicative price = £14.26

Wellfoods® Flour mix
- GLUTEN-FREE

Wellfoods gluten free flour alternative (Wellfoods Ltd)
- 1000 gram (ACBS) - NHS indicative price = £7.65

XANTHAN GUM

Ener-G® Xanthan gum
- GLUTEN-FREE

Ener-G xanthan gum (General Dietary Ltd)
- 170 gram (ACBS) - NHS indicative price = £8.53

Pure® Xanthan gum
- GLUTEN-FREE

Innovative Solutions Pure xanthan gum (Innovative Solutions (UK) Ltd)
- 100 gram (ACBS) - NHS indicative price = £6.85

Pasta

Barkat® Pasta
- GLUTEN-FREE

- macaroni (Gluten Free Foods Ltd)
  - 500 gram (ACBS) - NHS indicative price = £5.88

- spaghetti (Gluten Free Foods Ltd)
  - 500 gram (ACBS) - NHS indicative price = £5.88

- spirals (Gluten Free Foods Ltd)
  - 500 gram (ACBS) - NHS indicative price = £5.88

- tagliatelle (Gluten Free Foods Ltd)
  - 500 gram (ACBS) - NHS indicative price = £5.88

- Barnet gluten free pasta animal shapes (Gluten Free Foods Ltd)
  - 500 gram (ACBS) - NHS indicative price = £5.88

- Barnet gluten free pasta buckwheat (Gluten Free Foods Ltd)
  - penne, spirals 250 gram (ACBS) - NHS indicative price = £2.93

BiAlimenta® Pasta
- GLUTEN-FREE

- BiAlimenta gluten free Pasta (Drossa Ltd)
  - spirals, sagnette 500 gram (ACBS) - NHS indicative price = £3.97

Glutafin® Pasta
- GLUTEN-FREE

Glutafin gluten free pasta (Dr Schar UK Ltd)
- lasagne, tagliatelle nests 250 gram (ACBS) - NHS indicative price = £5.53
- fibre spaghetti 500 gram (ACBS) - NHS indicative price = £5.74
- macaroni, penne, shells, long-cut spaghetti 500 gram (ACBS) - NHS indicative price = £6.73

Juvela® Pasta
- GLUTEN-FREE

Juvela gluten free fibre penne (Hero UK Ltd)
- 500 gram (ACBS) - NHS indicative price = £6.61

Juvela gluten free pasta (Hero UK Ltd)
- tagliatelle 250 gram (ACBS) - NHS indicative price = £3.47
- fusilli, macaroni, spaghetti 500 gram (ACBS) - NHS indicative price = £7.21
- lasagne 250 gram (ACBS) - NHS indicative price = £3.68

Orgran® Pasta
- GLUTEN-FREE

Orgran gluten free pasta brown rice spirals (Naturally Good Food Ltd)
- 250 gram (ACBS) - NHS indicative price = £2.42

Orgran gluten free pasta buckwheat spirals (Naturally Good Food Ltd)
- 250 gram (ACBS) - NHS indicative price = £2.42

Orgran gluten free pasta corn spirals (Naturally Good Food Ltd)
- 250 gram (ACBS) - NHS indicative price = £2.42

Orgran gluten free pasta rice & corn (Naturally Good Food Ltd)
- macaroni, spirals 250 gram (ACBS) - NHS indicative price = £2.42
- lasagne 200 gram (ACBS) - NHS indicative price = £3.13

Orgran gluten free pasta rice & millet spirals (Naturally Good Food Ltd)
- 250 gram (ACBS) - NHS indicative price = £2.42

Rizopia® Pasta
- GLUTEN-FREE

Rizopia gluten free organic brown rice pasta (PGR Health Foods Ltd)
- lasagne 375 gram (ACBS) - NHS indicative price = £2.72

Pizza bases

Barkat®, Pizza crust
- GLUTEN-FREE

Barkat gluten free (Gluten Free Foods Ltd)
- brown rice pizza crust, white rice pizza crust 150 gram (ACBS) - NHS indicative price = £5.00

Glutafin® Pizza base
- GLUTEN-FREE

Glutafin gluten free pizza base (Dr Schar UK Ltd)
- 300 gram (ACBS) - NHS indicative price = £6.56

Juvela® Pizza base
- GLUTEN-FREE

Juvela gluten free pizza base (Hero UK Ltd)
- 360 gram (ACBS) - NHS indicative price = £8.78

Proceli® Pizza base
- GLUTEN-FREE

Proceli gluten free pizza base (Ambe Ltd)
- 250 gram (ACBS) - NHS indicative price = £3.90

Ultra® Pizza base
- GLUTEN-FREE

Wellfoods® Pizza base
- GLUTEN-FREE

Wellfoods gluten free pizza base (Wellfoods Ltd)
- 600 gram (ACBS) - NHS indicative price = £8.95

Juvela gluten free fibre pasta (Hero UK Ltd)
- 500 gram (ACBS) - NHS indicative price = £6.61
Gluten- and wheat-free foods
ACBS indications: established gluten-sensitive enteropathies with coexisting established wheat sensitivity only.

Ener-G® (General Dietary Ltd)
Gluten-free, wheat-free. Rolls, Seattle brown, round (hamburger) 4 x 80 gram (ACBS) - NHS indicative price = £4.08
long (hot dog) 4 x 80 gram (ACBS) - NHS indicative price = £4.08
Pizza base 3 x 124 gram (ACBS) - NHS indicative price = £4.74

Glutafin® (Dr Schar UK Ltd)
Gluten-free, wheat-free. Flour mix, bread, fibre 500 gram (ACBS) - NHS indicative price = £6.66

Heron Foods® (Gluten Free Foods Ltd)
Gluten-free, wheat-free. Flour mix, organic, bread, fibre 500 gram (ACBS) - NHS indicative price = £8.96

Crispbread 150 gram (ACBS) - NHS indicative price = £8.96
PK Foods Aminex low protein (General Dietary Ltd)
Liver failure, requiring a low-protein diet
Discard products within 24 hours once opened.

Low-protein foods
ACBS indications: inherited metabolic disorders, renal or liver failure, requiring a low-protein diet

Bread
Ener-G® Rice bread
LOW PROTEIN
Ener-G low protein rice bread (General Dietary Ltd)
600 gram (ACBS) - NHS indicative price = £5.54

Juvela® Loaf and rolls
LOW PROTEIN
Juvela gluten free loaf sliced (Hero UK Ltd)
400 gram (ACBS) - NHS indicative price = £3.54
Juvela low protein loaf (Hero UK Ltd)
loaf sliced 400 gram (ACBS) - NHS indicative price = £3.64
bread rolls 350 gram (ACBS) - NHS indicative price = £4.52

Loprofin® Bread
LOW-PROTEIN
Loprofin low protein part baked (Nutricia Ltd)
loaf sliced 400 gram (ACBS) - NHS indicative price = £3.91
bread rolls 260 gram (ACBS) - NHS indicative price = £4.12

PK Foods® Loaf
LOW PROTEIN
PK Foods low protein white bread sliced (Gluten Free Foods Ltd)
550 gram (ACBS) - NHS indicative price = £4.75

Cake, biscuits, and snacks
Juvela® cookies
LOW-PROTEIN
Juvela low protein (Hero UK Ltd)
chocolate chip cookies 110 gram (ACBS) - NHS indicative price = £7.62
cinnamon cookies, orange cookies 125 gram (ACBS) - NHS indicative price = £7.62

Loprofin® Wafers
LOW-PROTEIN
Loprofin low protein (Nutricia Ltd)
chocolate cream wafers, vanilla cream wafers 100 gram (ACBS) - NHS indicative price = £2.53
 crackers, herb crackers 150 gram (ACBS) - NHS indicative price = £3.53

PK Foods® Biscuits
LOW-PROTEIN
PK Foods Aminex low protein (Gluten Free Foods Ltd)
biscuits, rusks 200 gram (ACBS) - NHS indicative price = £5.04
cookies 150 gram (ACBS) - NHS indicative price = £5.04
PK Foods low protein (Gluten Free Foods Ltd)
crispbread 75 gram (ACBS) - NHS indicative price = £2.42

chocolate chip cookies, cinnamon cookies, orange cookies
150 gram (ACBS) - NHS indicative price = £5.04
Promin® Cooked and flavoured pasta snax
LOW-PROTEIN
Promin low protein (Firstplay Dietary Foods Ltd)
Snax salt & vinegar 25g sachets, Snax ready salted 25g sachets,
Snax cheese & onion 25g sachets 3 sachet

Taranis® Cake bars
LOW-PROTEIN
Taranis low protein (Firstplay Dietary Foods Ltd)
apricot cake, lemon cake, pear cake 240 gram (ACBS) - NHS indicative price = £6.08

Vita Bite®
Not recommended for any child under 1 year.
LOW PROTEIN. Bar, protein 50 mg (less than 2.5 mg phenylalanine), carbohydrate 15.35 g, fat 8.4 g, energy 572 kJ (137 kcal)/25 g.

VitaBite bar (Vitaflo International Ltd)
175 gram (ACBS) - NHS indicative price = £8.52

Vitaflo Choices® Mini crackers
LOW-PROTEIN
Vitaflo Choices mini crackers (Vitaflo International Ltd)
40 gram (ACBS) - NHS indicative price = £0.84

Cereals
Loprofin® breakfast cereal
LOW-PROTEIN
Loops (Nutricia Ltd)
375 gram (ACBS) - NHS indicative price = £8.12

Loprofin low protein breakfast cereal flakes (Nutricia Ltd)
apple, chocolate, strawberry 375 gram (ACBS) - NHS indicative price = £7.85

Promin® Hot breakfast
LOW-PROTEIN
Promin low protein hot breakfast powder sachets (Firstplay Dietary Foods Ltd)
apple & cinnamon, banana, chocolate 342 gram (ACBS) - NHS indicative price = £8.09
original 336 gram (ACBS) - NHS indicative price = £8.09

Desserts
Loprofin® Powder
LOW-PROTEIN
Loprofin low protein dessert (Nutricia Ltd)
mix chocolate, mix strawberry, mix vanilla 150 gram (ACBS) - NHS indicative price = £4.79

PK Foods® Jelly
LOW-PROTEIN
PK Foods low protein jelly mix dessert (Gluten Free Foods Ltd)
cherry, orange 320 gram (ACBS) - NHS indicative price = £8.03

Promin® Desserts
LOW-PROTEIN
Promin low protein imitation rice pudding (Firstplay Dietary Foods Ltd)
apple, banana, original, strawberry 276 gram (ACBS) - NHS indicative price = £6.33

Flour mixes and egg substitutes
Ener-G® Egg replacer
LOW-PROTEIN
Ener-G low protein egg replacer (General Dietary Ltd)
454 gram (ACBS) - NHS indicative price = £5.11

Fate® Flour mix
LOW PROTEIN
Fate low protein (Fate Special Foods)
all purpose mix, chocolate cake mix, plain cake mix 500 gram (ACBS) - NHS indicative price = £6.97

Juvela® Mix
LOW-PROTEIN
Nutritional supplements for metabolic diseases

Glutaric aciduria (type 1)

GA1 Anamix® Infant

– Nutritional supplement for the dietary management of proven glutaric aciduria (type 1) in children from birth to 3 years. POWDER, protein equivalent (essential and non-essential amino acids except lysine, and low tryptophan) 13.1 g, carbohydrate 49.5 g, fat 23 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 5.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.

GA Gel®

– Nutritional supplement for dietary management of type 1 glutaric aciduria in children 6 months–10 years. GEL, protein equivalent (essential and non-essential amino acids except lysine, and low tryptophan) 10 g, carbohydrate 10.3 g, fat trace, energy 339 kJ (81 kcal)/24 g, with vitamins, minerals, and trace elements.

GA gel oral powder 24g sachets (Vitalfo International Ltd)
30 sachet (ACBS) - NHS indicative price = £210.12

XLYS, Low TRY, Maxamaid®

– Nutritional supplement for the dietary management of type 1 glutaric aciduria. POWDER, protein equivalent (essential and non-essential amino acids except lysine, and low tryptophan) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1311 kJ (327 kcal)/100 g, with vitamins, minerals, and trace elements.

XLYS LOW TRY Maxamaid powder (Nutricia Ltd)
500 gram (ACBS) - NHS indicative price = £96.40

XLYS, TRY Glutaridon®

– Nutritional supplement for the dietary management of type 1 glutaric aciduria in children and adults; requires additional source of vitamins, minerals, and trace elements. POWDER, protein equivalent (essential and non-essential amino acids except lysine and tryptophan) 79 g, carbohydrate 4 g, energy 1411 kJ (332 kcal)/100 g.

XLYS TRY Glutaridon powder (Nutricia Ltd)
500 gram (ACBS) - NHS indicative price = £182.61

Juvela low protein mix (Hero UK Ltd)
500 gram (ACBS) - NHS indicative price = £7.79

Loprofin® Flour mixes and egg substitutes

mix (Nutricia Ltd)
500 gram (ACBS) - NHS indicative price = £8.27

Loprofin low protein cake (Nutricia Ltd)
mix lemon, mix chocolate 500 gram (ACBS) - NHS indicative price = £8.76

Loprofin low protein egg (Nutricia Ltd)
white replace 100 gram (ACBS) - NHS indicative price = £9.79
replacer 500 gram (ACBS) - NHS indicative price = £15.22

PK Foods® Flour mix and egg substitute

PK Foods low protein (Gluten Free Foods Ltd)
egg replace 200 gram (ACBS) - NHS indicative price = £4.08
flour mix 750 gram (ACBS) - NHS indicative price = £10.71

Pasta

Loprofin® Pasta

Loprofin low protein pasta (Nutricia Ltd)
penne, long cut spaghetti 500 gram (ACBS) - NHS indicative price = £8.66
animal shapes 500 gram (ACBS) - NHS indicative price = £8.33
tagliatelle, macaroni elbows 250 gram (ACBS) - NHS indicative price = £4.16
lasagne 250 gram (ACBS) - NHS indicative price = £4.21

Promin® Pasta

Promin Plus low protein pasta (Firstplay Dietary Foods Ltd)
macaroni, flat noodles 500 gram (ACBS) - NHS indicative price = £6.99

Promin low protein imitation rice (Firstplay Dietary Foods Ltd)
500 gram (ACBS) - NHS indicative price = £6.99

Promin low protein lasagne sheets (Firstplay Dietary Foods Ltd)
200 gram (ACBS) - NHS indicative price = £3.03

Promin low protein pasta (Firstplay Dietary Foods Ltd)
alphabets, shells, short cut spaghetti, spirals 500 gram (ACBS) - NHS indicative price = £6.99

Promin low protein tricolour pasta (Firstplay Dietary Foods Ltd)
spirals, alphabets, shells 500 gram (ACBS) - NHS indicative price = £6.99

Pizza bases

Juvela® Pizza base

Juvela low protein pizza base (Hero UK Ltd)
360 gram (ACBS) - NHS indicative price = £8.61

Savoury meals and mixes

Promin® Savoury meals and mixes

pastameal (Firstplay Dietary Foods Ltd)
500 gram (ACBS) - NHS indicative price = £6.99

elbows (Firstplay Dietary Foods Ltd)
500 gram (ACBS) - NHS indicative price = £6.99

macaroni (Firstplay Dietary Foods Ltd)
500 gram (ACBS) - NHS indicative price = £6.99

Promin Plus low protein pasta spirals (Firstplay Dietary Foods Ltd)
500 gram (ACBS) - NHS indicative price = £6.99

Promin low protein X-Pot (Firstplay Dietary Foods Ltd)
all day scramble, beef & tomato, chip shop curry, rogan style curry 240 gram (ACBS) - NHS indicative price = £20.94

Promin low protein burger mix (Firstplay Dietary Foods Ltd)
124 gram (ACBS) - NHS indicative price = £6.36
Glycogen storage disease

Corn flour and corn starch
For glycogen storage disease

Glycosad®
- A nutritional supplement for use in the dietary management of glycogen storage disease and other metabolic conditions where a constant supply of glucose is essential. Not suitable for use in children under 2 years.
- POWDER, protein 200 mg, carbohydrate (maize starch) 47.6 g, fat 100 mg, fibre less than 600 mg, energy 805 kJ (192 kcal)/60 g.
- Glycosade oral powder 60g sachets (Vitafo International Ltd) 50 sachet (ACBS) - NHS indicative price = £110.44

Homocystinuria or hypermethioninaemia

HCU Anamix® Infant
- Nutritional supplement for the dietary management of proven vitamin B6 non-responsive homocystinuria or hypermethioninaemia in children from birth to 5 years.
- POWDER, protein equivalent (essential and non-essential amino acids except methionine) 15.1 g, carbohydrate 49.5 g, fat 23 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.
- HCU Anamix Infant powder (Nutricia Ltd) 400 gram (ACBS) - NHS indicative price = £38.18

HCU Express® 15
- A methionine-free protein substitute for use as a nutritional supplement in patients over 3 years with homocystinuria. LIQUID, protein (essential and non-essential amino acids except methionine) 15 g, carbohydrate 7 g, fat 500 mg, energy 595 kJ (92 kcal)/150 mL, with vitamins, minerals, and trace elements.
- HCU orange cooler 15 liquid (Vitafo International Ltd) 130 mL (ACBS) - NHS indicative price = £11.09

HCU Express® 20
- A methionine-free protein substitute for use as a nutritional supplement in children over 8 years with homocystinuria. POWDER, protein (essential and non-essential amino acids except methionine) 15 g, carbohydrate 5.8 g, fat 30 mg, energy 515 kJ (75.3 kcal)/25 mL, with vitamins, minerals, and trace elements.
- HCU express 20 oral powder 25g sachets (Vitafo International Ltd) 30 sachet (ACBS) - NHS indicative price = £52.30

HCU gel®
- A methionine-free protein substitute for use as a nutritional supplement for the dietary management of children 1-10 years with homocystinuria. POWDER, protein (essential and non-essential amino acids except methionine) 10 g, carbohydrate 10.5 g, fat 20 mg, energy 539 kJ (81 kcal)/24 g with vitamins, minerals, and trace elements.
- HCU gel oral powder 24g sachets (Vitafo International Ltd) 30 sachet (ACBS) - NHS indicative price = £210.07

HCU Lophlex® LQ 20
- Nutritional supplement for the dietary management of homocystinuria in patients over 3 years. LIQUID, protein equivalent (essential and non-essential amino acids except methionine) 20 g, carbohydrate 8.8 g, fat 440 mg, energy 509 kJ (120 kcal)/125 mL, with vitamins, minerals, and trace elements.
- HCU Lophlex LQ 20 liquid (Nutricia Ltd) 125 ml (ACBS) - NHS indicative price = £15.75

HCU LV®
- Nutritional supplement for the dietary management of hypermethioninaemia or vitamin B6 non-responsive homocystinuria in children over 8 years.
- POWDER, protein (essential and non-essential amino acids except methionine) 20 g, carbohydrate 2.5 g, fat 190 mg, energy 390 kJ (92 kcal)/27.8-g sachet, with vitamins, minerals, and trace elements.
- HCU-LV oral powder 27.8g sachets (Nutricia Ltd) tropical, unflavoured 30 sachet (ACBS) - NHS indicative price = £483.90

XMET Homidon®
- Nutritional supplement for the dietary management of hypermethioninaemia or homocystinuria in children and adults.
- POWDER, protein equivalent (essential and non-essential amino acids except methionine) 77 g, carbohydrate 4.5 g, fat nil, energy 1386 kJ (326 kcal)/100 g.
- XMET Homidon powder (Nutricia Ltd) 500 gram (ACBS) - NHS indicative price = £182.61

XMET Maxamaid®
- Nutritional supplement for the dietary management of hypermethioninaemia or homocystinuria in children and adults.
- POWDER, protein equivalent (essential and non-essential amino acids except methionine) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1511 kJ (369 kcal)/100 g, with vitamins, minerals, and trace elements.
- Maxamaid products are generally intended for use in children 1-8 years.
- XMET Maxamaid powder (Nutricia Ltd) 500 gram (ACBS) - NHS indicative price = £96.40

XMET Maxamum®
- Nutritional supplement for the dietary management of hypermethioninaemia or homocystinuria.
- POWDER, protein equivalent (essential and non-essential amino acids except methionine) 39 g, carbohydrate 54 g, fat less than 500 mg, energy 1260 kJ (297 kcal)/100 g, with vitamins, minerals, and trace elements.
- Maxamum products are generally intended for use in children over 8 years.
- XMET Maxamum powder (Nutricia Ltd) 500 gram (ACBS) - NHS indicative price = £154.52

Hyperlysinaemia

HYPER LYS Anamix® Infant
- Nutritional supplement for the dietary management of proven hyperlysinaemia in children from birth to 3 years.
- POWDER, protein equivalent (essential and non-essential amino acids except lysine) 15.1 g, carbohydrate 49.5 g, fat 23 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre less than 500 mg, energy 1260 kJ (297 kcal)/100 g.
- HYPER LYS Anamix Infant powder (Nutricia Ltd) 400 gram (ACBS) - NHS indicative price = £38.18

XLYS Maxamaid®
- Nutritional supplement for the dietary management of hyperlysinaemia.
- POWDER, protein equivalent (essential and non-essential amino acids except lysine) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1511 kJ (369 kcal)/100 g, with vitamins, minerals, and trace elements.
- XLYS Maxamaid powder (Nutricia Ltd) 500 gram (ACBS) - NHS indicative price = £96.40
**Isovaleric acidemia**

**IVA Anamix® Infant**
- Nutritional supplement for the dietary management of proven isovaleric acidemia or other proven disorders of leucine metabolism in children from birth to 3 years.

POWDER, protein equivalent (essential and non-essential amino acids except leucine) 15.1 g, carbohydrate 49.5 g, fat 23 g, fibre 5.5 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.

**IVA Anamix Infant powder** (Nutricia Ltd)
- 400 gram (ACBS) - NHS indicative price = £38.18

**XLEU Faladon®**
- Nutritional supplement for the dietary management of isovaleric acidemia.

POWDER, protein equivalent (essential and non-essential amino acids except leucine) 77 g, carbohydrate 4.5 g, fat nil, energy 1386 kJ (326 kcal)/100 g.

**XLEU Maxamaid®**
- Nutritional supplement for the dietary management of isovaleric acidemia.

POWDER, protein equivalent (essential and non-essential amino acids except leucine) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1311 kJ (309 kcal)/100 g with vitamins, minerals, and trace elements.

**XLEU Maxamaid powder** (Nutricia Ltd)
- 500 gram (ACBS) - NHS indicative price = £96.40

**Maple syrup urine disease**

**MSUD Aid III®**
- Nutritional supplement for the dietary management of maple syrup urine disease and related conditions in children and adults where it is necessary to limit the intake of branched chain amino acids.

POWDER, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 77 g, carbohydrate 4.5 g, fat nil, energy 1386 kJ (326 kcal)/100 g.

**MSUD Aid III powder** (Nutricia Ltd)
- 500 gram (ACBS) - NHS indicative price = £182.61

**MSUD Anamix® Infant**
- Nutritional supplement for the dietary management of proven maple syrup urine disease in children from birth to 3 years.

POWDER, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 15.1 g, carbohydrate 49.5 g, fat 23 g, fibre 5.5 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.

**MSUD Anamix Infant powder** (Nutricia Ltd)
- 400 gram (ACBS) - NHS indicative price = £38.18

**MSUD Anamix® Junior**
- Nutritional supplement for the dietary management of maple syrup urine disease in children 1–10 years.

POWDER, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 8.4 g, carbohydrate 11 g, fat 3.9 g, energy 474 kJ (115 kcal)/29 g sachet, with vitamins, minerals, and trace elements.

**MSUD Anamix Junior oral powder 29g sachets** (Nutricia Ltd)
- 30 sachet (ACBS) - NHS indicative price = £204.00

**MSUD Anamix® Junior LQ**
- Nutritional supplement for the dietary management of maple syrup urine disease in children 1–10 years.

LIQUID, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 10 g, carbohydrate 8.8 g, fat 4.8 g, fibre 310 mg, energy 497 kJ (118 kcal)/125 mL, with vitamins, minerals, and trace elements. Lactose-free.

**MSUD Anamix Junior LQ liquid** (Nutricia Ltd)
- 125 ml (ACBS) - NHS indicative price = £8.85

**MSUD cooler® 15**
- Nutritional supplement for the dietary management of maple syrup urine disease in children over 3 years and adults.

LIQUID, protein equivalent (essential and non-essential amino acids except leucine, isoleucine, and valine) 15 g, carbohydrate 7 g, fat 500 mg, energy 395 kJ (92 kcal)/150 mL pouch, with vitamins, minerals, and trace elements.

**MSUD (Vitalfo International Ltd)**
- orange cooler 15 liquid, red cooler 15 liquid 130 ml (ACBS) - NHS indicative price = £11.09

**MSUD express® 15**
- Nutritional supplement for the dietary management of maple syrup urine disease in children over 8 years and adults.

POWDER, protein equivalent (essential and non-essential amino acids except leucine, isoleucine, and valine) 15 g, carbohydrate 5.8 g, fat less than 100 mg, energy 315 kJ (75 kcal)/25 g, with vitamins, minerals, and trace elements.

**MSUD express 15 oral powder 25g sachets** (Vitalfo International Ltd)
- 30 sachet (ACBS) - NHS indicative price = £326.30

**MSUD express® 20**
- Nutritional supplement for the dietary management of maple syrup urine disease in children over 8 years and adults.

POWDER, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 20 g, carbohydrate 4.7 g, fat less than 100 mg, energy 416 kJ (99 kcal)/24 g, with vitamins, minerals, and trace elements.

**MSUD express 20 oral powder 34g sachets** (Vitalfo International Ltd)
- 30 sachet (ACBS) - NHS indicative price = £421.57

**MSUD Gel®**
- Nutritional supplement for the dietary management of maple syrup urine disease in children 1–10 years.

POWDER, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 10 g, carbohydrate 10.3 g, fat less than 100 mg, energy 539 kJ (81 kcal)/24 g, with vitamins, minerals, and trace elements.

**MSUD gel 24g sachets** (Vitalfo International Ltd)
- 30 sachet (ACBS) - NHS indicative price = £212.54

**MSUD Lophelix® LQ 20**
- Nutritional supplement for the dietary management of maple syrup urine disease in children over 3 years and adults.

LIQUID, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 20 g, carbohydrate 8.8 g, fat less than 500 mg, energy 509 kJ (120 kcal)/125 mL, with vitamins, minerals, and trace elements.

**MSUD Lophelix LQ 20 liquid** (Nutricia Ltd)
- 125 ml (ACBS) - NHS indicative price = £15.75

**MSUD Maxamaid®**
- Nutritional supplement for the dietary management of maple syrup urine disease.

POWDER, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1311 kJ (309 kcal)/100 g, with vitamins, minerals, and trace elements. Maxamaid products are generally intended for use in children 1–8 years.

**MSUD Maxamaid powder** (Nutricia Ltd)
- 500 gram (ACBS) - NHS indicative price = £96.40

**MSUD Maxamum®**
- Nutritional supplement for the dietary management of maple syrup urine disease.

POWDER, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 39 g, carbohydrate 54 g, fat less than 500 mg, energy 1260 kJ (297 kcal)/100 g, with vitamins, minerals, and trace elements. Maxamum products are generally intended for use in children over 8 years.

**MSUD Maxamum powder** (Nutricia Ltd)
- orange, unflavoured 500 gram (ACBS) - NHS indicative price = £154.52
Methylmalonic or propionic acidaemia

**MMA/PA Anamix® Infant**

- Nutritional supplement for the dietary management of proven methylmalonic acidaemia or propionic acidaemia in children from birth to 3 years.
- POWDER, protein equivalent (essential and non-essential amino acids except methionine, threonine, and valine, and low isoleucine) 15.1 g, carbohydrate 49.5 g, fat 25 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.
- **MMA PA Anamix Infant powder** (Nutricia Ltd) 400 gram (ACBS) - NHS indicative price = £38.18
- **XMTVI Asadon®**
- Nutritional supplement for the dietary management of methylmalonic acidaemia or propionic acidaemia in children and adults.
- POWDER, protein equivalent (essential and non-essential amino acids except methionine, threonine, and valine, and low isoleucine) 77 g, carbohydrate 4.5 g, fat nil, energy 1586 kJ (32 kcal)/100 g.
- **XMTVI Asadon powder** (Nutricia Ltd) 200 gram (ACBS) - NHS indicative price = £73.04
- **XMTVI Maxamaid®**
- Nutritional supplement for the dietary management of methylmalonic acidemia or propionic acidemia.
- POWDER, protein equivalent (essential and non-essential amino acids except methionine, threonine, and valine, and low isoleucine) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1311 kJ (309 kcal)/100 g, with vitamins, minerals, and trace elements.
- **XMTVI Maxamaid powder** (Nutricia Ltd) 500 gram (ACBS) - NHS indicative price = £96.40
- **XMTVI Maxamum®**
- Nutritional supplement for the dietary management of methylmalonic acidemia or propionic acidemia.
- POWDER, protein equivalent (essential and non-essential amino acids except methionine, threonine, and valine, and low isoleucine) 39 g, carbohydrate 34 g, fat less than 500 mg, energy 1260 kJ (297 kcal)/100 g, with vitamins, minerals, and trace elements.
- **XMTVI Maxamum powder** (Nutricia Ltd) 500 gram (ACBS) - NHS indicative price = £115.52

Other inborn errors of metabolism

**Cystine50®**

- Nutritional supplement for the dietary management of inborn errors of amino acid metabolism in adults and children from birth.
- POWDER, cystine 500 mg, carbohydrate 3.3 g, fat nil, energy 63 kJ (15 kcal)/4 g
- **DocOmega®**
- Nutritional supplement for the dietary management of inborn errors of metabolism for adults and children from birth.
- POWDER, protein (cows’ milk, soya) 100 mg, carbohydrate 3.2 g, fat 500 mg (of which docosahexaenoic acid 200 mg), fibre nil, energy 74 kJ (18 kcal)/4 g, with minerals
- **DocOmega oral powder 4g sachets** (Vitafllo International Ltd) 30 sachet (ACBS) - NHS indicative price = £38.64
- **EAA® Supplement**
- Nutritional supplement for the dietary management of disorders of protein metabolism including urea cycle disorders. Not suitable for children under 5 years.
- POWDER, protein equivalent (essential amino acids) 5 g, carbohydrate 4 g, fat nil, energy 151 kJ (36 kcal)/12.5 g, with vitamins, minerals, and trace elements.
- **EAA Supplement oral powder 12.5g sachets** (Vitafllo International Ltd) 50 sachet (ACBS) - NHS indicative price = £201.42

**Isoleucine50®**

- Nutritional supplement for use in the dietary management of inborn errors of amino acid metabolism in adults and children from birth.
- POWDER, isoleucine 50 mg, carbohydrate 3.8 g, fat nil, energy 63 kJ (15 kcal)/4 g
- **Isoleucine50 oral powder 4g sachets** (Vitafllo International Ltd) 30 sachet (ACBS) - NHS indicative price = £53.38

**KeyOmega®**

- Nutritional supplement for the dietary management of inborn errors of metabolism.
- POWDER, protein (cows’ milk, soya) 170 mg, carbohydrate 2.8 g, fat 800 mg (of which arachidonic acid 200 mg, docosahexaenoic acid 100 mg), energy 80 kJ (19 kcal)/4 g
- **KeyOmega oral powder 4g sachets** (Vitafllo International Ltd) 30 sachet (ACBS) - NHS indicative price = £59.50

**Leucine100®**

- Nutritional supplement for the dietary management of inborn errors of amino acid metabolism in adults and children from birth.
- POWDER, leucine 100 mg, carbohydrate 3.7 g, fat nil, energy 63 kJ (15 kcal)/4 g
- **Leucine100 oral powder sachets** (Vitafllo International Ltd) 30 sachet (ACBS) - NHS indicative price = £53.38

**Low protein drink**

- Nutritional supplement for the dietary management of inborn errors of amino acid metabolism in adults and children over 1 year.
- POWDER, protein (cows’ milk) 4.5 g (phenylalanine 100 mg), carbohydrate 59.5 g, fat 29.9 g, fibre nil, energy 2194 kJ (528 kcal)/100 g, with vitamins, minerals, and trace elements. Contains lactose.
- **Milupa LP drink** (Nutricia Ltd) 400 gram (ACBS) - NHS indicative price = £9.06

**Phenylalanine50®**

- Nutritional supplement for use in the dietary management of inborn errors of metabolism in adults and children from birth.
- POWDER, phenylalanine 50 mg, carbohydrate 5.8 g, fat nil, energy 65 kJ (15 kcal)/4 g
- **Phenylalanine50 oral powder sachets** (Vitafllo International Ltd) 30 sachet (ACBS) - NHS indicative price = £51.83

**ProZero®**

- A protein-free nutritional supplement for the dietary management of inborn errors of metabolism in children over 6 months and adults.
- LIQUID, carbohydrate 8.1 g (of which sugars 3.5 g), fat 3.8 g, energy 278 kJ (66 kcal)/100 mL. Contains lactose.
- **ProZero liquid** (Vitafllo international Ltd) 250 ml (ACBS) - NHS indicative price = £1.42 | 1000 ml (ACBS) - NHS indicative price = £5.68

**Tyrosine100®**

- Nutritional supplement for the dietary management of inborn errors of amino acid metabolism in adults and children from birth.
- POWDER, tyrosine 1 g, carbohydrate 2.9 g, fat nil, energy 65 kJ (15 kcal)/4-g sachet.
- **Tyrosine100 oral powder 4g sachets** (Vitafllo International Ltd) 30 sachet (ACBS) - NHS indicative price = £4.89

**Valine50®**

- Nutritional supplement for the dietary management of inborn errors of amino acid metabolism in adults and children from birth.
- POWDER, valine 50 mg, carbohydrate 5.8 g, fat nil, energy 65 kJ (15 kcal)/4 g
- **Valine50 oral powder 4g sachets** (Vitafllo International Ltd) 30 sachet (ACBS) - NHS indicative price = £53.38
Phenylketonuria

Add-ins®
- Nutritional supplement for the dietary management of proven phenylketonuria. Not suitable for children under 4 years.
  POWDER, protein equivalent (containing essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate nil, fat 5.1 g, energy 359 kJ (86 kcal)/18.2-g sachet, with vitamins, minerals, and trace elements.

Add Ins oral powder 18.2g sachets (Nutricia Ltd)
60 sachet (ACBS) - NHS indicative price = £368.40

Easyphen®
- Nutritional supplement for the dietary management of proven phenylketonuria. Not suitable for children under 8 years.
  LIQUID, protein equivalent (containing essential and non-essential amino acids except phenylalanine) 6.7 g, carbohydrate 5.1 g, fat 2 g, energy 275 kJ (65 kcal)/100 mL with vitamins, minerals, and trace elements.

Easyphen liquid (Nutricia Ltd)
250 ml (ACBS) - NHS indicative price = £9.47

Lophlex®
- Nutritional supplement for the dietary management of proven phenylketonuria in children over 8 years and adults including pregnant women.
  POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine) 20 g, carbohydrate 2.5 g, fat 60 mg, fibre 220 mg, energy 585 kJ (141 kcal)/27.8-g sachet, with vitamins, minerals, and trace elements.

Lophlex powder 27.8g sachets (Nutricia Ltd)
berry, orange, unflavoured 30 sachet (ACBS) - NHS indicative price = £284.40

Loprofin® PKU Drink
- Nutritional supplement for the dietary management of phenylketonuria in children over 1 year and adults.
  LIQUID, protein (cows’ milk) 400 mg (phenylalanine 10 mg), lactose 9.4 g, fat 2 g, energy 165 kJ (40 kcal)/100 mL.

Loprofin PKU drink (Nutricia Ltd)
200 ml (ACBS) - NHS indicative price = £0.74

Loprofin® Sno-Pro
- Nutritional supplement for the dietary management of phenylketonuria, chronic renal failure and other inborn errors of amino acid metabolism.
  LIQUID, protein (cows’ milk) 220 mg (phenylalanine 12.5 mg), carbohydrate 8 g, fat 5.8 g, energy 273 kJ (65 kcal)/100 mL. Contains lactose.

Loprofin SNO-PRO drink (Nutricia Ltd)
200 ml (ACBS) - NHS indicative price = £1.25

Milupa PKU 2-prima®
- Nutritional supplement for the dietary management of phenylketonuria in children 1-8 years.
  POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine) 60 g, carbohydrate 10 g, fat nil, energy 1190 kJ (280 kcal)/100 g, with vitamins, minerals, and trace elements.

Milupa PKU 2 Prima powder (Nutricia Ltd)
500 gram (ACBS) - NHS indicative price = £153.73

Milupa PKU 2-secunda®
- Nutritional supplement for the dietary management of phenylketonuria in children 9-15 years.
  POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine) 70 g, carbohydrate 6.8 g, fat nil, energy 1306 kJ (307 kcal)/100 g, with vitamins, minerals, and trace elements.

Milupa PKU 2 Secunda powder (Nutricia Ltd)
500 gram (ACBS) - NHS indicative price = £179.34

Milupa PKU 3-advanta®
- Nutritional supplement for the dietary management of phenylketonuria in children over 15 years.
  POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine) 70 g, carbohydrate 4.7 g, fat nil, energy 1270 kJ (299 kcal)/100 g, with vitamins, minerals, and trace elements.

Milupa PKU 3 Advanta powder (Nutricia Ltd)
500 gram (ACBS) - NHS indicative price = £179.34

Phlexy-10® Exchange System
- Nutritional supplement for the dietary management of phenylketonuria.
  CAPSULES, protein equivalent (essential and non-essential amino acids except phenylalanine) 416.5 mg/capsule.

Phlexy-10 500mg capsules (Nutricia Ltd)
200 capsule (ACBS) - NHS indicative price = £42.00

Phlexy-Vits®
- For use as a vitamin and mineral component of restricted therapeutic diets in children over 11 years and adults with phenylketonuria and similar amino acid abnormalities.
  POWDER, vitamins, minerals, and trace elements

Phlexy-Vits (Nutricia Ltd)
powder 210 gram (ACBS) - NHS indicative price = £70.20

Phlexy-Vits® (Nutricia Ltd)
tablets 180 tablet (ACBS) - NHS indicative price = £79.20

PK Aid®
- Nutritional supplement for the dietary management of phenylketonuria in children and adults.
  POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine) 79 g, carbohydrate 4.5 g, fat nil, energy 1420 kJ (334 kcal)/100 g.

PK Aid® powder (Nutricia Ltd)
500 gram (ACBS) - NHS indicative price = £140.37

PKU Anamix® Infant
- Nutritional supplement for the dietary management of proven phenylketonuria in children from birth to 3 years.
  POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine) 15.1 g, carbohydrate 49.5 g, fat 23.5 g, fibre 5.5 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.

PKU Anamix Infant powder (Nutricia Ltd)
400 gram (ACBS) - NHS indicative price = £34.70

PKU Anamix® Junior
- Nutritional supplement for the dietary management of phenylketonuria in children 1–10 years.
  POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine) 8.4 g, carbohydrate 9.9 g, fat 3.9 g, energy 455 kJ (108 kcal)/29-g sachet, with vitamins, minerals, and trace elements.

PKU Anamix Junior powder (Nutricia Ltd)
chocolate, neutral 870 gram (ACBS) - NHS indicative price = £125.90 | 1080 gram (ACBS) - NHS indicative price = £123.90

PKU Anamix® Junior LQ
- Nutritional supplement for the dietary management of phenylketonuria in children 1–10 years.
  LIQUID, protein equivalent (essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate 8.8 g, fat 4.8 g, fibre 310 mg, energy 497 kJ (118 kcal)/125 mL, with vitamins, minerals, and trace elements. Lactose-free.

PKU Anamix Junior LQ liquid (Nutricia Ltd)
berry, orange 125 ml (ACBS) - NHS indicative price = £5.51
Nutritional supplement for the dietary management of phenylketonuria. Not recommended for children under 5 years.

**PKU cooler**
- Nutritional supplement for the dietary management of phenylketonuria. Not recommended for children under 5 years.
  - **PKU Lophlex**
    - L-tyrosine powder (Nutricia Ltd)
      - Berry, juicy berries, orange 1020 gram (ACBS) - NHS indicative price = £10.14
    - XP Maxamaid powder 50g sachets (Nutricia Ltd)
      - Orange cooler 20 liquid, purple cooler 20 liquid, red cooler 20 liquid, white cooler 20 liquid 174 mL (ACBS) - NHS indicative price = £9.02
    - XP Maxamaid powder (Nutricia Ltd)
      - Berry, juicy berries, orange 100 gram (ACBS) - NHS indicative price = £4.51
  - **PKU Lophlex LQ 10 liquid juicy** (Nutricia Ltd)
    - Berries, orange 62.5 ml (ACBS) - NHS indicative price = £5.08
  - **PKU Lophlex LQ 20**
    - Nutritional supplement for the dietary management of phenylketonuria in children over 4 years and adults including pregnant women.
    - L-tyrosine 20 g, energy 768 kJ (183 kcal) with vitamins, minerals, and trace elements.
  - **PKU Lophlex Sensation 20**
    - Nutritional supplement for the dietary management of phenylketonuria in children over 4 years and adults including pregnant women.
    - L-tyrosine 20 g, energy 768 kJ (183 kcal) with vitamins, minerals, and trace elements.
    - **PKU Lophlex LQ 20 liquid** (Nutricia Ltd)
      - Berry, juicy berries, orange 125 ml (ACBS) - NHS indicative price = £32.37
    - **PKU Lophlex Sensation 20** (Nutricia Ltd)
      - Berry, juicy berries, orange 327 gram (ACBS) - NHS indicative price = £32.37
  - **PKU Lophlex LQ 10 liquid juicy** (Nutricia Ltd)
    - Berries, orange 62.5 ml (ACBS) - NHS indicative price = £5.08
  - **PKU Lophlex LQ 20**
    - Nutritional supplement for the dietary management of phenylketonuria in children over 4 years and adults including pregnant women.
    - L-tyrosine 20 g, energy 768 kJ (183 kcal) with vitamins, minerals, and trace elements.
    - **PKU Lophlex Sensation 20** (Nutricia Ltd)
      - Berry, juicy berries, orange 327 gram (ACBS) - NHS indicative price = £32.37
  - **PKU Lophlex LQ 20 liquid** (Nutricia Ltd)
    - Berry, juicy berries, orange 125 ml (ACBS) - NHS indicative price = £32.37
  - **PKU Lophlex Sensation 20** (Nutricia Ltd)
    - Berry, juicy berries, orange 327 gram (ACBS) - NHS indicative price = £32.37
  - **PKU Lophlex LQ 10 liquid juicy** (Nutricia Ltd)
    - Berries, orange 62.5 ml (ACBS) - NHS indicative price = £5.08
  - **PKU Lophlex LQ 20**
    - Nutritional supplement for the dietary management of phenylketonuria in children over 4 years and adults including pregnant women.
    - L-tyrosine 20 g, energy 768 kJ (183 kcal) with vitamins, minerals, and trace elements.
    - **PKU Lophlex Sensation 20** (Nutricia Ltd)
      - Berry, juicy berries, orange 327 gram (ACBS) - NHS indicative price = £32.37
  - **PKU Lophlex LQ 20 liquid** (Nutricia Ltd)
    - Berry, juicy berries, orange 125 ml (ACBS) - NHS indicative price = £32.37
  - **PKU Lophlex Sensation 20** (Nutricia Ltd)
    - Berry, juicy berries, orange 327 gram (ACBS) - NHS indicative price = £32.37
  - **PKU Lophlex LQ 10 liquid juicy** (Nutricia Ltd)
    - Berries, orange 62.5 ml (ACBS) - NHS indicative price = £5.08
  - **PKU Lophlex LQ 20**
    - Nutritional supplement for the dietary management of phenylketonuria in children over 4 years and adults including pregnant women.
    - L-tyrosine 20 g, energy 768 kJ (183 kcal) with vitamins, minerals, and trace elements.
    - **PKU Lophlex Sensation 20** (Nutricia Ltd)
      - Berry, juicy berries, orange 327 gram (ACBS) - NHS indicative price = £32.37
  - **PKU Lophlex LQ 20 liquid** (Nutricia Ltd)
    - Berry, juicy berries, orange 125 ml (ACBS) - NHS indicative price = £32.37
  - **PKU Lophlex Sensation 20** (Nutricia Ltd)
    - Berry, juicy berries, orange 327 gram (ACBS) - NHS indicative price = £32.37
  - **PKU Lophlex LQ 10 liquid juicy** (Nutricia Ltd)
    - Berries, orange 62.5 ml (ACBS) - NHS indicative price = £5.08
  - **PKU Lophlex LQ 20**
    - Nutritional supplement for the dietary management of phenylketonuria in children over 4 years and adults including pregnant women.
    - L-tyrosine 20 g, energy 768 kJ (183 kcal) with vitamins, minerals, and trace elements.
    - **PKU Lophlex Sensation 20** (Nutricia Ltd)
      - Berry, juicy berries, orange 327 gram (ACBS) - NHS indicative price = £32.37
  - **PKU Lophlex LQ 20 liquid** (Nutricia Ltd)
    - Berry, juicy berries, orange 125 ml (ACBS) - NHS indicative price = £32.37
  - **PKU Lophlex Sensation 20** (Nutricia Ltd)
    - Berry, juicy berries, orange 327 gram (ACBS) - NHS indicative price = £32.37
  - **PKU Lophlex LQ 10 liquid juicy** (Nutricia Ltd)
    - Berries, orange 62.5 ml (ACBS) - NHS indicative price = £5.08
  - **PKU Lophlex LQ 20**
    - Nutritional supplement for the dietary management of phenylketonuria in children over 4 years and adults including pregnant women.
    - L-tyrosine 20 g, energy 768 kJ (183 kcal) with vitamins, minerals, and trace elements.
    - **PKU Lophlex Sensation 20** (Nutricia Ltd)
      - Berry, juicy berries, orange 327 gram (ACBS) - NHS indicative price = £32.37
  - **PKU Lophlex LQ 20 liquid** (Nutricia Ltd)
    - Berry, juicy berries, orange 125 ml (ACBS) - NHS indicative price = £32.37
  - **PKU Lophlex Sensation 20** (Nutricia Ltd)
    - Berry, juicy berries, orange 327 gram (ACBS) - NHS indicative price = £32.37
  - **PKU Lophlex LQ 10 liquid juicy** (Nutricia Ltd)
    - Berries, orange 62.5 ml (ACBS) - NHS indicative price = £5.08
  - **PKU Lophlex LQ 20**
    - Nutritional supplement for the dietary management of phenylketonuria in children over 4 years and adults including pregnant women.
    - L-tyrosine 20 g, energy 768 kJ (183 kcal) with vitamins, minerals, and trace elements.
POWDER, protein equivalent (essential and non-essential amino acids except methionine, phenylalanine, and tyrosine) 13.1 g, carbohydrate 49.5 g, fat 23 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.

TYR Anamix Infant methionine free powder (Nutricia Ltd) 400 gram (ACBS) - NHS indicative price = £38.18

TYR Anamix® Infant
> Nutritional supplement for the dietary management of proven tyrosinaemia where plasma-methionine concentrations are normal in children from birth to 3 years.

POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine and tyrosine) 15.1 g, carbohydrate 49.5 g, fat 23 g, fibre 5.3 g, energy 1915 kJ (457 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 2 g, carbohydrate 7.4 g, fat 3.5 g, fibre 800 mg, energy 287 kJ (69 kcal)/100 mL.

TYR Anamix Infant (Nutricia Ltd) methionine free powder, powder 400 gram (ACBS) - NHS indicative price = £38.18

TYR Anamix® Junior
> Nutritional supplement for the dietary management of proven tyrosinaemia in children 1–10 years.

POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine and tyrosine) 8.4 g, carbohydrate 11 g, fat 5.9 g, energy 475 kJ (115 kcal)/29-g sachet, with vitamins, minerals, and trace elements.

TYR Anamix Junior oral powder 29g sachets (Nutricia Ltd) 30 sachet (ACBS) - NHS Indicative Price = £202.50

TYR Anamix® Junior LQ
> Nutritional supplement for the dietary management of tyrosinaemia type 1 (when nitisinone (NTBC) is used, see ), type II, and type III, in children over 1 year.

LIQUID, protein equivalent (essential and non-essential amino acids except phenylalanine and tyrosine) 10 g, carbohydrate 8.8 g, fat 4.8 g, fibre 510 mg, energy 500 kJ (121 kcal)/125 mL, with vitamins, minerals and trace elements.

TYR Anamix Junior LQ liquid (Nutricia Ltd) 125 ml (ACBS) - NHS Indicative price = £8.85

TYR cooler® 15
> Nutritional supplement for the dietary management of tyrosinaemia in children over 3 years and adults.

LIQUID, protein equivalent (essential and non-essential amino acids except phenylalanine and tyrosine) 15 g, carbohydrate 7 g, fat 500 mg, energy 395 kJ (92 kcal)/130 mL, with vitamins, minerals, and trace elements.

TYR orange cooler 15 liquid (Vitafluo International Ltd) 130 ml (ACBS) - NHS indicative price = £11.09

TYR red cooler (Vitafluo International Ltd) 15 liquid 130 ml (ACBS) - NHS indicative price = £11.09

TYR express®
> Nutritional supplement for the dietary management of tyrosinaemia in children over 8 years and adults.

POWDER, protein equivalent (essential and non-essential amino acids except tyrosine and phenylalanine) 15 g, carbohydrate 3.4 g, fat less than 100 mg, energy 510 kJ (74 kcal)/25 g, with vitamins, minerals, and trace elements.

TYR express 15 oral powder 25g sachets (Vitafluo International Ltd) 30 sachet (ACBS) - NHS indicative price = £326.30

TYR express®
> Nutritional supplement for the dietary management of tyrosinaemia. Not recommended for children under 8 years.

POWDER, protein equivalent (essential and non-essential amino acids except tyrosine and phenylalanine) 20 g, carbohydrate 4.7 g, fat less than 100 mg, energy 416 kJ (99 kcal)/54 g, with vitamins, minerals, and trace elements.

TYR express 20 oral powder 34g sachets (Vitafluo International Ltd) 30 sachet (ACBS) - NHS indicative price = £421.57

TYR Gel®
> Nutritional supplement for the dietary management of tyrosinaemia in children 1–10 years.

GEL, protein equivalent (essential and non-essential amino acids except tyrosine and phenylalanine) 10 g, carbohydrate 10.5 g, fat less than 100 mg, energy 339 kJ (81 kcal)/24 g, with vitamins, minerals, and trace elements.

TYR gel oral powder 24g sachets (Vitafluo International Ltd) 30 sachet (ACBS) - NHS indicative price = £210.07

TYR Lophlex® LQ 20
> Nutritional supplement for the dietary management of tyrosinaemia in children over 5 years and adults.

LIQUID, protein equivalent (essential and non-essential amino acids except phenylalanine and tyrosine) 20 g, carbohydrate 8.8 g, fat less than 500 mg, energy 509 kJ (121 kcal)/125 mL, with vitamins, minerals, and trace elements.

TYR Lophlex LQ 20 liquid (Nutricia Ltd) 125 ml (ACBS) - NHS indicative price = £15.75

XPHEN TYR Maxamaid®
> Nutritional supplement for the dietary management of tyrosinaemia in children 1–8 years.

POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine and tyrosine) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1511 kJ (361 kcal)/100 g, with vitamins, minerals, and trace elements.

XPHEN TYR Tyrosidan®
> Nutritional supplement for the dietary management of tyrosinaemia in children 1–8 years.

POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine and tyrosine) 77 g, carbohydrate 4.5 g, fat nil, energy 1386 kJ (326 kcal)/100 g.

XPHEN TYR Tyrosidan Free AA Mix powder (Nutricia Ltd) 500 gram (ACBS) - NHS indicative price = £182.61

XPTM Tyrosidan®
> Nutritional supplement for the dietary management of tyrosinaemia type I in children and adults where plasma-methionine concentrations are normal.

POWDER, protein equivalent (essential and non-essential amino acids except phenylalanine and tyrosine) 77 g, carbohydrate 4.5 g, fat nil, energy 1386 kJ (326 kcal)/100 g.

XPTM Tyrosidan powder (Nutricia Ltd) 500 gram (ACBS) - NHS indicative price = £91.31
Appendix 3

Cautionary and advisory labels for dispensed medicines

Guidance for cautionary and advisory labels

Medicinal forms within BNF publications include code numbers of the cautionary labels that pharmacists are recommended to add when dispensing. It is also expected that pharmacists will counsel patients and carers when necessary.

Counselling needs to be related to the age, experience, background, and understanding of the individual patient or carer. The pharmacist should ensure understanding of how to take or use the medicine and how to follow the correct dosage schedule. Any effects of the medicine on co-ordination, performance of skilled tasks (e.g. driving or work), any foods or medicines to be avoided, and what to do if a dose is missed should also be explained. Other matters, such as the possibility of staining of the clothes or skin, or discoloration of urine or stools by a medicine should also be mentioned.

For some medicines there is a special need for counselling, such as an unusual method or time of administration or a potential interaction with a common food or domestic remedy, and this should be mentioned where necessary.

Original packs

Most preparations are dispensed in unbroken original packs that include further advice for the patient in the form of patient information leaflets. A label 10 may be of value where appropriate. More general leaflets advising on the administration of preparations such as eye drops, eye ointments, inhalers, and suppositories are also available.

Scope of labels

In general no label recommendations have been made for injections on the assumption that they will be administered by a healthcare professional or a well-instructed patient. The labelling is not exhaustive and pharmacists are recommended to use their professional discretion in labelling new preparations and those for which no labels are shown.

Individual labelling advice is not given on the administration of the large variety of antacids. In the absence of instructions from the prescriber, and if no specific order is given by the patient, the directions given under 'Dose' should be used on the label.

It is recognised that there may be occasions when pharmacists will use their knowledge and professional discretion and decide to omit one or more of the recommended labels for a particular patient. In this case counselling is of the utmost importance. There may also be an occasion when a prescriber does not wish additional cautionary labels to be used, in which case the prescription should be endorsed 'NCL' (no cautionary labels). The exact wording that is required instead should then be specified on the prescription.

Pharmacists label medicines with various wordings in addition to those directions specified on the prescription. Such labels include 'Shake the bottle', 'For external use only', and 'Store in a cool place', as well as 'Discard.... days after opening' and 'Do not use after....', which apply particularly to antibiotic mixtures, diluted liquid and topical preparations, and to eye-drops. Although not listed in the BNF these labels should continue to be used when appropriate; indeed, 'For external use only' is a legal requirement on external liquid preparations, while 'Keep out of the reach of children' is a legal requirement on all dispensed medicines. Care should be taken not to obscure other relevant information with adhesive labelling.

It is the usual practice for patients to take standard tablets with water or other liquid and for this reason no separate label has been recommended.

The label wordings recommended by the BNF apply to medicines dispensed against a prescription. Patients should be aware that a dispensed medicine should never be taken by, or shared with, anyone other than for whom the prescriber intended it. Therefore, the BNF does not include warnings against the use of a dispensed medicine by persons other than for whom it was specifically prescribed.

The label or labels for each preparation are recommended after careful consideration of the information available. However, it is recognised that in some cases this information may be either incomplete or open to a different interpretation. The BNF will therefore be grateful to receive any constructive comments on the labelling suggested for any preparation.

Recommended label wordings

For BNF 61 (March 2011), a revised set of cautionary and advisory labels were introduced. All of the existing labels were user-tested, and the revised wording selected reflects terminology that is better understood by patients.

Wordings which can be given as separate warnings are labels 1–19, 29–30, and 32. Wordings which can be incorporated in an appropriate position in the directions for dosage or administration are labels 21–28. A label has been omitted for number 20; labels 31 and 33 no longer apply to any medicines in the BNF and have therefore been deleted.

If separate labels are used it is recommended that the wordings be used without modification. If changes are made to suit computer requirements, care should be taken to retain the sense of the original.

Labels

1 Warning: This medicine may make you sleepy

To be used on preparations for children containing antihistamines, or other preparations given to children where the warnings of label 2 on driving or alcohol would not be appropriate.

2 Warning: This medicine may make you sleepy. If this happens, do not drive or use tools or machines. Do not drink alcohol

To be used on preparations for adults that can cause drowsiness, thereby affecting coordination and the ability to drive and operate hazardous machinery; label 1 is more appropriate for children. It is an offence to drive while under the influence of drink or drugs.

Some of these preparations only cause drowsiness in the first few days of treatment and some only cause drowsiness in higher doses. In such cases the patient should be told that the advice applies until the effects have worn off. However many of these preparations can produce a slowing of reaction time and a loss of mental concentration that can have the same effects as drowsiness.

Avoidance of alcoholic drink is recommended because the effects of CNS depressants are enhanced by alcohol. Strict prohibition however could lead to some patients not taking the medicine. Pharmacists should therefore explain the risk and encourage compliance, particularly in patients who may think they already tolerate the effects of alcohol (see also label 3). Queries from patients with epilepsy regarding fitness to drive should be referred back to the patient’s doctor.
Side-effects unrelated to drowsiness that may affect a patient’s ability to drive or operate machinery safely include blurred vision, dizziness, or nausea. In general, no label has been recommended to cover these cases, but the patient should be suitably counselled.

3 Warning: This medicine may make you sleepy. If this happens, do not drive or use tools or machines

To be used on preparations containing monoamine-oxidase inhibitors; the warning to avoid alcohol and deaehololised (low alcohol) drink is covered by the patient information leaflet. Also to be used as for label 2 but where alcohol is not an issue.

4 Warning: Do not drink alcohol

To be used on preparations where a reaction such as flushing may occur if alcohol is taken (e.g. metronidazole). Alcohol may also enhance the hypoglycaemia produced by some oral antidiabetic drugs but routine application of a warning label is not considered necessary. Patients should be advised not to drink alcohol for as long as they are receiving/using a course of medication, and in some cases for a period of time after the course is finished.

5 Do not take indigestion remedies 2 hours before or after you take this medicine

To be used with label 25 on preparations coated to resist gastric acid (e.g. enteric-coated tablets). This is to avoid the possibility of premature dissolution of the coating in the presence of an alkaline pH.

Label 5 also applies to drugs such as gabapentin where the absorption is significantly affected by antacids. Pharmacists will be aware (from a knowledge of physiology) that the usual time during which indigestion remedies should be avoided is at least 2 hours before and after the majority of medicines have been taken; when a manufacturer advises a different time period, this can be followed, and should be explained to the patient.

6 Do not take indigestion remedies, or medicines containing iron or zinc, 2 hours before or after you take this medicine

To be used on preparations containing ofloxacin and some other quinolones, doxycycline, lymecycline, minocycline, and penicillamine. These drugs chelate calcium, iron, and zinc and are less well absorbed when taken with calcium-containing antacids or preparations containing iron or zinc. Pharmacists will be aware (from a knowledge of physiology) that these incompatible preparations should be taken at least 2 hours apart for the majority of medicines; when a manufacturer advises a different time period, this can be followed, and should be explained to the patient.

7 Do not take milk, indigestion remedies, or medicines containing iron or zinc, 2 hours before or after you take this medicine

To be used on preparations containing ciprofloxacin, norfloxacin, tetracyclines that chelate calcium, iron, magnesium, and zinc, and are thus less available for absorption. Pharmacists will be aware (from a knowledge of physiology) that these incompatible preparations should be taken at least 2 hours apart for the majority of medicines; when a manufacturer advises a different time period, this can be followed, and should be explained to the patient.

8 Warning: Do not stop taking this medicine unless your doctor tells you to stop

To be used on preparations that contain a drug which is required to be taken over long periods without the patient necessarily perceiving any benefit (e.g. antituberculous drugs). Also to be used on preparations that contain a drug whose withdrawal is likely to be a particular hazard (e.g. clonidine for hypertension). Label 10 (see below) is more appropriate for corticosteroids.

9 Space the doses evenly throughout the day. Keep taking this medicine until the course is finished, unless you are told to stop

To be used on preparations where a course of treatment should be completed to reduce the incidence of relapse or failure of treatment. The preparations are antimicrobial drugs given by mouth. Very occasionally, some may have severe side-effects (e.g. diarrhoea in patients receiving clindamycin) and in such cases the patient may need to be advised of reasons for stopping treatment quickly and returning to the doctor.

10 Warning: Read the additional information given with this medicine

To be used particularly on preparations containing anticoagulants, lithium, and oral corticosteroids. The appropriate treatment card should be given to the patient and any necessary explanations given. This label may also be used on other preparations to remind the patient of the instructions that have been given.

11 Protect your skin from sunlight—even on a bright but cloudy day. Do not use sunbeds

To be used on preparations that may cause phototoxic or photoallergic reactions if the patient is exposed to ultraviolet radiation. Many drugs other than those listed in Appendix 3 (e.g. phenothiazines and sulfonamides) may, on rare occasions, cause reactions in susceptible patients. Exposure to high intensity ultraviolet radiation from sunray lamps and sunbeds is particularly likely to cause reactions.

12 Do not take anything containing aspirin while taking this medicine

To be used on preparations containing sulfipyrazone whose activity is reduced by aspirin. Label 12 should not be used for anticoagulants since label 10 is more appropriate.

13 Dissolve or mix with water before taking

To be used on preparations that are intended to be dissolved in water (e.g. soluble tablets) or mixed with water (e.g. powders, granules) before use. In a few cases other liquids such as fruit juice or milk may be used.

14 This medicine may colour your urine. This is harmless

To be used on preparations that may cause the patient’s urine to turn an unusual colour. These include triamterene (blue under some lights), levodopa (dark reddish), and rifampicin (red).

15 Caution: flammable. Keep your body away from fire or flames after you have put on the medicine

To be used on preparations containing sufficient flammable solvent to render them flammable if exposed to a naked flame.

16 Dissolve the tablet under your tongue—do not swallow. Store the tablets in this bottle with the cap tightly closed. Get a new supply 8 weeks after opening

To be used on glyceryl trinitrate tablets to remind the patient not to transfer the tablets to plastic or less suitable containers.

17 Do not take more than... in 24 hours

To be used on preparations for the treatment of acute migraine except those containing ergotamine, for which label 18 is used. The dose form should be specified, e.g. tablets or capsules. It may also be used on preparations for which no dose has been specified by the prescriber.

18 Do not take more than... in 24 hours. Also, do not take more than... in any one week

To be used on preparations containing ergotamine. The dose form should be specified, e.g. tablets or suppositories.

19 Warning: This medicine makes you sleepy. If you still feel sleepy the next day, do not drive or use tools or machines. Do not drink alcohol

To be used on preparations containing hypnotics (or some other drugs with sedative effects) prescribed to be taken at night. On the rare occasions when hypnotics are prescribed...
for daytime administration (e.g. nitrazepam in epilepsy), this label would clearly not be appropriate. Also to be used as an alternative to the label 2 wording (the choice being at the discretion of the pharmacist) for anxiolytics prescribed to be taken at night. It is hoped that this wording will convey adequately the problem of residual morning sedation after taking ‘sleeping tablets’.

21 Take with or just after food, or a meal
   To be used on preparations that are liable to cause gastric irritation, or those that are better absorbed with food.
   Patients should be advised that a small amount of food is sufficient.

22 Take 30 to 60 minutes before food
   To be used on some preparations whose absorption is thereby improved.
   Most oral antibacterials require label 23 instead (see below).

23 Take this medicine when your stomach is empty. This means an hour before food or 2 hours after food
   To be used on oral antibacterials whose absorption may be reduced by the presence of food and acid in the stomach.

24 Suck or chew this medicine
   To be used on preparations that should be sucked or chewed. The pharmacist should use discretion as to which of these words is appropriate.

25 Swallow this medicine whole. Do not chew or crush
   To be used on preparations that are enteric-coated or designed for modified-release.
   Also to be used on preparations that taste very unpleasant or may damage the mouth if not swallowed whole.
   Patients should be advised (where relevant) that some modified-release preparations can be broken in half, but that the halved tablet should still be swallowed whole, and not chewed or crushed.

26 Dissolve this medicine under your tongue
   To be used on preparations designed for sublingual use.
   Patients should be advised to hold under the tongue and avoid swallowing until dissolved. The buccal mucosa between the gum and cheek is occasionally specified by the prescriber.

27 Take with a full glass of water
   To be used on preparations that should be well diluted (e.g. chloral hydrate), where a high fluid intake is required (e.g. sulfonamides), or where water is required to aid the action (e.g. methylcellulose). The patient should be advised that ‘a full glass’ means at least 150 mL. In most cases fruit juice, tea, or coffee may be used.

28 Spread thinly on the affected skin only
   To be used on external preparations that should be applied sparingly (e.g. corticosteroids, dithranol).

29 Do not take more than 2 at any one time. Do not take more than 8 in 24 hours
   To be used on containers of dispensed solid dose preparations containing paracetamol for adults when the instruction on the label indicates that the dose can be taken on an ‘as required’ basis. The dose form should be specified, e.g. tablets or capsules.
   This label has been introduced because of the serious consequences of overdosage with paracetamol.

30 Contains paracetamol. Do not take anything else containing paracetamol while taking this medicine. Talk to a doctor at once if you take too much of this medicine, even if you feel well
   To be used on all containers of dispensed preparations containing paracetamol.

32 Contains aspirin. Do not take anything else containing aspirin while taking this medicine
   To be used on containers of dispensed preparations containing aspirin when the name on the label does not include the word ‘aspirin’.
Appendix 4
Wound management products and elasticated garments

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The correct dressing for wound management depends not only on the type of wound but also on the stage of the healing process. The principal stages of healing are: cleansing, removal of debris; granulation, vascularisation; epithelialisation. The ideal dressing for moist wound healing needs to ensure that the wound remains: moist with exudate, but not macerated; free of clinical infection and excessive slough; free of toxic chemicals, particles or fibres; at the optimum temperature for healing; undisturbed by the need for frequent changes; at the optimum pH value. As wound healing passes through its different stages, different types of dressings may be required to satisfy better one or other of these requirements. Under normal circumstances, a moist environment is a necessary part of the wound healing process; exudate provides a moist environment and promotes healing, but excessive exudate can cause maceration of the wound and surrounding healthy tissue. The volume and viscosity of exudate changes as the wound heals. There are certain circumstances where moist wound healing is not appropriate (e.g. gangrenous toes associated with vascular disease). Advanced wound dressings, p. 1297 are designed to control the environment for wound healing, for example to donate fluid (hydrogels), maintain hydration (hydrocolloids), or to absorb wound exudate (alginites, foams). Practices such as the use of irritant cleansers and deesloughing agents may be harmful and are largely obsolete; removal of debris and dressing remnants should need minimal irrigation with lukewarm sterile sodium chloride 0.9% solution or water. Hydrogel, hydrocolloid, and medical grade honey dressings can be used to deslough wounds by promoting autolytic debridement; there is insufficient evidence to support any particular method of debridement for difficult-to-heal surgical wounds. Sterile larvae (maggots) are also available for biosurgical removal of wound debris. There have been few clinical trials able to establish a clear advantage for any particular product. The choice between different dressings depends not only on the type and stage of the wound, but also on patient preference or tolerance, site of the wound, and cost. For further information, see Buyers’ Guide: Advanced wound dressings (October 2008); NHS Purchasing and Supply Agency, Centre for Evidence-based Purchasing. Prices quoted in Appendix 4 are basic NHS net prices; for further information see Prices in the BNF. The table below gives suggestions for choices of primary dressing depending on the type of wound (a secondary dressing may be needed in some cases).

Basic wound contact dressings

Low adherence dressings

Low adherence dressings are used as interface layers under secondary absorbent dressings. Placed directly on the wound bed, non-absorbent, low adherence dressings are suitable for clean, granulating, lightly exuding wounds without necrosis, and protect the wound bed from direct contact with secondary dressings. Care must be taken to avoid granulation tissue growing into the weave of these dressings. Tulle dressings are manufactured from cotton or viscose fibres which are impregnated with white or yellow soft paraffin to prevent the fibres from sticking, but this is only
### Wound contact material for different types of wounds

#### Wound PINK (epitheliasing)

<table>
<thead>
<tr>
<th>Low Exudate</th>
<th>Moderate Exudate</th>
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<tbody>
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<td>Low adherence p. 1294</td>
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<tr>
<td>Hydrocolloid p. 1301</td>
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#### Wound RED (granulating)

Symptoms or signs of infection, see Wounds with signs of infection

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<thead>
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<th>Low Exudate</th>
<th>Moderate Exudate</th>
<th>Heavy Exudate</th>
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<td>Alginate p. 1304</td>
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<td>Foam, low absorbent p. 1302</td>
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<td>capillary-action p. 1305</td>
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#### Wound YELLOW (Sloughy) (granulating)

Symptoms or signs of infection, see Wounds with signs of infection

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<th>Low Exudate</th>
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<tbody>
<tr>
<td>Hydrogel p. 1297</td>
<td>Hydrocolloid-fibrous p. 1301</td>
<td>Seek advice from wound care specialist</td>
</tr>
<tr>
<td>Hydrocolloid p. 1301</td>
<td>Alginate p. 1301</td>
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</tr>
<tr>
<td>Hydrocolloid-fibrous p. 1301</td>
<td>Foam p. 1302</td>
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<tr>
<td>Hydrocolloid-fibrous p. 1301</td>
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#### Wound BLACK (Necrotic/Eschar)

Consider mechanical debridement alongside autolytic debridement

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<tr>
<th>Low Exudate</th>
<th>Moderate Exudate</th>
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<tbody>
<tr>
<td>Hydrogel p. 1297</td>
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<td>Hydrocolloid p. 1301</td>
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<td>Hydrocolloid-fibrous p. 1301</td>
<td>Foam with silver p. 1308</td>
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<tr>
<td>Hydrocolloid-fibrous p. 1301</td>
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#### Wounds with signs of infection

Consider systemic antibacterials if appropriate; also consider odour-absorbent dressings. For malodorous wounds with slough or necrotic tissue, consider mechanical or autolytic debridement

<table>
<thead>
<tr>
<th>Low Exudate</th>
<th>Moderate Exudate</th>
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<tbody>
<tr>
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#### Note

In each section of this table the dressings are listed in order of increasing absorbency. Some wound contact (primary) dressings require a secondary dressing.

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Partly successful and it may be necessary to change the dressings frequently. The paraffin reduces absorbency of the dressing. Dressings with a reduced content (light loading) of soft paraffin are less liable to interfere with absorption; dressings with ‘normal loading’ (such as Jelonet®) have been used for skin graft transfer.

Knitted viscose primary dressing is an alternative to tulle dressings for exuding wounds; it can be used as the initial layer of multi-layer compression bandaging in the treatment of venous leg ulcers.

**Knitted polyester primary dressing**

**Atrauman**

Non-adherent knitted polyester primary dressing impregnated with neutral triglycerides

**Atrauman dressing** (Paul Hartmann Ltd) 10cm x 20cm = £0.63, 20cm x 30cm = £1.72, 5cm x 5cm = £0.27, 7.5cm x 10cm = £0.28

**Knitted viscose primary dressing**

**N-A Dressing**

Warp knitted fabric manufactured from a bright viscose monofilament.

**N-A dressing** (Systagenix Wound Management Ltd) 19cm x 9.5cm = £0.67, 9.5cm x 9.5cm = £0.35

**N-A Ultra**

Warp knitted fabric manufactured from a bright viscose monofilament.

**N-A Ultra dressing** (Systagenix Wound Management Ltd) 19cm x 9.5cm = £0.63, 9.5cm x 9.5cm = £0.33

**Profore**

Warp knitted fabric manufactured from a bright viscose monofilament.

**Profore** (Smith & Nephew Healthcare Ltd) wound contact layer 14cm x 20cm = £0.32

**Tricotex**

Warp knitted fabric manufactured from a bright viscose monofilament.

**Tricotex dressing** (Smith & Nephew Healthcare Ltd) 9.5cm x 9.5cm = £0.34

**Paraffin Gauze Dressing**

**Cuticell**

(Tulle Gras). Fabric of leno weave, weft and warp threads of cotton and/or viscose yarn, impregnated with white or yellow soft paraffin

**Cuticell** (BSN medical Ltd) Classic dressing 10cm x 10cm = £0.29

**Jelonet**

(Tulle Gras). Fabric of leno weave, weft and warp threads of cotton and/or viscose yarn, impregnated with white or yellow soft paraffin

**Jelonet dressing** (Smith & Nephew Healthcare Ltd) 10cm x 10cm = £0.41

**Neotulle**

(Tulle Gras). Fabric of leno weave, weft and warp threads of cotton and/or viscose yarn, impregnated with white or yellow soft paraffin

**Neotulle** (Neomedic Ltd) dressing 10cm x 10cm = £0.29
Paragauze
(Tulle Gras). Fabric of leno weave, weft and warp threads of cotton and/or viscose yarn, impregnated with white or yellow soft paraffin. Paragauze (C D Medical Ltd) dressing 10cm x 10cm = £0.28
Paranet
(Tulle Gras). Fabric of leno weave, weft and warp threads of cotton and/or viscose yarn, impregnated with white or yellow soft paraffin. Paranet (Synergy Health Plc) dressing 10cm x 10cm = £0.25
Absorbent dressings
Perforated film absorbent dressings are suitable only for wounds with mild to moderate amounts of exudate; they are not appropriate for leg ulcers or for other lesions that produce large quantities of viscous exudate. Dressings with an absorbent cellulose or polymer wadding layer are suitable for use on moderately to heavily exuding wounds.
Absorbent cellulose dressing
CelluDress
Absorbent Cellulose Dressing with Fluid Repellent Backing. CelluDress dressing (Medicareplus International Ltd) 10cm x 10cm = £0.19, 10cm x 15cm = £0.20, 15cm x 20cm = £0.22, 15cm x 20cm = £0.20, 20cm x 25cm = £0.40, 20cm x 30cm = £0.45
Exu-Dry
Absorbent Cellulose Dressing with Fluid Repellent Backing. Exu-Dry dressing (Smith & Nephew Healthcare Ltd) 10cm x 15cm = £1.12, 15cm x 23cm = £2.29, 23cm x 38cm = £5.32
Mesorb
Cellulose wadding pad with gauze wound contact layer and non-woven repellent backing. Mesorb dressing (Mohlyche Health Care Ltd) 10cm x 10cm = £0.62, 10cm x 15cm = £0.81, 10cm x 20cm = £1.00, 15cm x 20cm = £1.42, 20cm x 25cm = £2.24, 20cm x 30cm = £2.54
Telfa Max
Absorbent Cellulose Dressing with Fluid Repellent Backing. Zetuvit E
Absorbent Cellulose Dressing with Fluid Repellent Backing; sterile or non-sterile. Zetuvit E (Paul Hartmann Ltd) non-sterile dressing 10cm x 10cm = £0.07, 10cm x 20cm = £0.09, 20cm x 20cm = £0.14, 20cm x 40cm = £0.27, sterile dressing 10cm x 10cm = £0.21, 10cm x 20cm = £0.25, 20cm x 20cm = £0.39, 20cm x 40cm = £1.10,
Absorbent perforated dressing
Adpore
Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive border. Adpore dressing (Medicareplus International Ltd) 10cm x 10cm = £0.10, 10cm x 15cm = £0.16, 10cm x 20cm = £0.30, 10cm x 25cm = £0.34, 10cm x 30cm = £0.42, 10cm x 35cm = £0.50, 7cm x 8cm = £0.08
Cosmopore E
Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive border. Cosmopore E dressing (Paul Hartmann Ltd) 10cm x 20cm = £0.45, 10cm x 25cm = £0.56, 10cm x 35cm = £0.78, 5cm x 7.2cm = £0.08, 8cm x 10cm = £0.17, 8cm x 15cm = £0.28
Cutiplast Steril
Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive border. Cutiplast Steril dressing (Smith & Nephew Healthcare Ltd) 10cm x 20cm = £0.31, 10cm x 25cm = £0.32, 10cm x 30cm = £0.42, 8cm x 10cm = £0.11, 8cm x 15cm = £0.24
Leukomed
Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive border. Leukomed dressing (B5N medical Ltd) 10cm x 20cm = £0.43, 10cm x 25cm = £0.48, 10cm x 30cm = £0.62, 10cm x 35cm = £0.72, 5cm x 7.2cm = £0.09, 8cm x 10cm = £0.18, 8cm x 15cm = £0.32
Medipore + Pad
Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive border. Medipore + Pads dressing (3M Health Care Ltd) 10cm x 10cm = £0.15, 10cm x 15cm = £0.25, 10cm x 20cm = £0.37, 10cm x 25cm = £0.46, 10cm x 35cm = £0.64, 5cm x 7.2cm = £0.07
Medisafe
Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive border. Medisafe dressing (Neomedic Ltd) 6cm x 8cm = £0.08, 8cm x 10cm = £0.13, 8cm x 12cm = £0.23, 9cm x 15cm = £0.29, 9cm x 25cm = £0.34, 9cm x 25cm = £0.36
Mepore
Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive border. Mepore dressing (Paul Hartmann Ltd) 10cm x 11cm = £0.22, 11cm x 15cm = £0.36, 7cm x 8cm = £0.11, 9cm x 20cm = £0.44, 9cm x 25cm = £0.61, 9cm x 30cm = £0.70, 9cm x 35cm = £0.76
PremierPore
Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive border. PremierPore dressing (Shermond) 10cm x 10cm = £0.12, 10cm x 15cm = £0.18, 10cm x 20cm = £0.32, 10cm x 25cm = £0.36, 10cm x 30cm = £0.45, 10cm x 35cm = £0.52, 5cm x 7cm = £0.05
Primapore
Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive border. Primapore dressing (Smith & Nephew Healthcare Ltd) 10cm x 20cm = £0.43, 10cm x 25cm = £0.50, 10cm x 30cm = £0.62, 10cm x 35cm = £0.76, 6cm x 8.5cm = £0.18, 8cm x 10cm = £0.19, 8cm x 15cm = £0.33
Softpore
Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive border. Softpore dressing (Richardson Healthcare Ltd) 10cm x 10cm = £0.13, 10cm x 15cm = £0.20, 10cm x 20cm = £0.35, 10cm x 25cm = £0.40, 10cm x 30cm = £0.49, 10cm x 35cm = £0.58, 6cm x 7cm = £0.06
Sterifix
Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive border. Sterifix dressing (Paul Hartmann Ltd) 10cm x 14cm = £0.58, 5cm x 7cm = £0.26, 7cm x 10cm = £0.32
Telfa Island
Low-adherence primary dressing consisting of viscose and rayon absorbent pad with adhesive border. Telfa Island dressing (Aria Medical Ltd) 10cm x 12.5cm = £0.27, 10cm x 20cm = £0.35, 10cm x 25.5cm = £0.45, 10cm x 35cm = £0.62, 5cm x 10cm = £0.08
Absorbent perforated plastic film faced dressing
Absopad
Low-adherence primary dressing consisting of 3 layers—perforated polyester film wound contact layer, absorbent cotton pad, and hydrophobic backing. Absopad dressing (Medicareplus International Ltd) 10cm x 10cm = £0.13, 20cm x 10cm = £0.28
Askina Pad
Low-adherence primary dressing consisting of 3 layers—perforated polyester film wound contact layer, absorbent cotton pad, and hydrophobic backing. Askina (B.Braun Medical Ltd) Pad dressing 10cm x 10cm = £0.21
Melolin
Low-adherence primary dressing consisting of 3 layers—perforated polyester film wound contact layer, absorbent cotton pad, and hydrophobic backing. Melolin dressing (Smith & Nephew Healthcare Ltd) 10cm x 10cm = £0.27, 20cm x 10cm = £0.53, 5cm x 5cm = £0.17
Hydrogel dressings

Hydrogel dressings are most commonly supplied as an amorphous, cohesive topical application that can take up the shape of a wound. A secondary, non-absorbent dressing is needed. These dressings are generally used to donate liquid to dry sloughy wounds and facilitate autolytic debridement of necrotic tissue; some also have the ability to absorb very small amounts of exudate. Hydrogel products that do not contain propylene glycol should be used if the wound is to be treated with larval therapy. Hydrogel sheets have a fixed structure and limited fluid-handling capacity; hydrogel sheet dressings are best avoided in the presence of infection, and are unsuitable for heavily exuding wounds.

Hydrogel application (amorphous)

**ActiveHeal Hydrogel**

Hydrogel containing guar gum and propylene glycol

*ActiveHeal* (Advanced Medical Solutions Ltd) Hydrogel dressing = £1.41

**Aquaform**

Hydrogel containing modified starch copolymer

*Aquaform* (Aspen Medical Europe Ltd) Hydrogel dressing = £2.02

**Askina Gel**

Hydrogel containing modified starch and glycerol

*Askina* (B.Braun Medical Ltd) Gel dressing = £2.00

**Cutimed**

Hydrogel

*Cutimed* (BSN medical Ltd) Gel dressing = £2.99

**Flexigran**

Hydrogel containing modified starch and glycerol

*Flexigran* (A1 Pharmaceuticals) Gel dressing = £1.90

**GranuGel**

Hydrogel containing carboxymethylcellulose, pectin and propylene glycol

*GranuGel* (ConvaTec Ltd) Hydrocolloid Gel dressing = £2.32

**Intrasite Gel**

Hydrogel containing modified carmellose polymer and propylene glycol

*Intrasite* (Smith & Nephew Healthcare Ltd) Gel dressing = £3.57

**Nu-Gel**

Hydrogel containing alginate and propylene glycol

*Nu-Gel* (Systagenix Wound Management Ltd) dressing = £2.09

**Purilon Gel**

Hydrogel containing carboxymethylcellulose and calcium alginate

*Purilon* (Coloplast Ltd) Gel dressing = £2.26

**Hydrogel sheet dressings**

**ActiFormCool**

Hydrogel dressing

*ActiFormCool sheet* (Activa Healthcare Ltd) 10cm x 10cm square = £6.63, 10cm x 15cm rectangular = £3.79, 20cm x 20cm square = £7.93, 5cm x 6.5cm rectangular = £1.79

**Aquaflo**

Hydrogel dressing

*Aquaflo* (Covidien (UK) Commercial Ltd) sheet 7.5cm discs = £2.60

**Coolie**

Hydrogel dressing (without adhesive border)

*Coolie* (Zerderma Ltd) sheet 7cm discs = £1.96

**Gel FX**

Hydrogel dressing (without adhesive border)

*Gel FX sheet* (Synergy Health Pk) 6cm x 10cm square = £1.60, 6cm x 15cm rectangular = £3.20

**Geliperm**

Hydrogel sheets

*Geliperm* (Geistlich Sono Ltd) sheet 10cm x 10cm square = £2.53

**Hydrosorb**

Absorbent, transparent, hydrogel sheets containing polyurethane polymers covered with a semi-permeable film

*Hydrosorb sheet* (Paul Hartmann Ltd) 10cm x 10cm square = £2.24, 20cm x 20cm square = £6.71, 5cm x 7.5cm rectangular = £1.56
Wound management products and elasticated garments

**Hydrosorb Comfort**
Absorbent, transparent, hydrogel sheets containing polyurethane polymers covered with a semi-permeable film (with adhesive border, waterproof).

**Hydrosorb Comfort sheet** (Paul Hartmann Ltd) 12.5cm x 12.5cm square = £3.58, 4.5cm x 6.5cm rectangular = £1.85, 7.5cm x 10cm rectangular = £2.46.

**Intrasite Conformable**
Soft non-woven dressing impregnated with Intrasite gel.

**Intrasite Conformable dressing 10cm x 10cm** (Smith & Nephew Healthcare Ltd) 10cm square = £1.80, 20cm rectangular = £2.42, 40cm rectangular = £4.33.

**Novogel**
Glycerol-based hydrogel sheets (standard or thin).

**Novogel sheet** (Ford Medical Associates Ltd) 10cm x 10cm square = £3.18, 15cm x 20cm rectangular = £6.07, 20cm x 40cm rectangular = £11.56, 30cm x 30cm (0.15cm thickness) square = £12.71, (0.30cm thickness) square = £13.47, 5cm x 7.5cm rectangular = £1.99, 7.5cm diameter circular = £2.89.

**Sanoskin NET**
Hydrogel sheet (without adhesive border).

**Sanoskin (Ideal Medical Solutions Ltd)** NET sheet 8.5cm x 12cm rectangular = £2.28.

**Vacunet**
Non-adherent, hydrogel coated polyester net dressing.

**Vacunet dressing 10cm** x 1 (Pro-Tex Capillary Dressings Ltd) 10cm square = £1.93, 5cm rectangular = £2.86.

**Sodium hyaluronate dressings**
The hydrating properties of sodium hyaluronate promote wound healing, and dressings can be applied directly to the wound, or to a primary dressing (a secondary dressing should also be applied). The iodine and potassium iodide in these dressings prevent the bacterial decay of sodium hyaluronate in the wound.

**Hyiodine**
Sodium hyaluronate 1.5%, potassium iodide 0.15%, iodine 0.1%, in a viscous solution.

**Hyiodine (H & R Healthcare Ltd)** dressing = £35.00.

**Vapour-permeable films and membranes**
Vapour-permeable films and membranes allow the passage of water vapour and oxygen but are impermeable to water and micro-organisms, and are suitable for lightly exuding wounds. They are highly conformable, provide protection, and a moist healing environment; transparent film dressings permit constant observation of the wound. Water vapour loss can occur at a slower rate than exudate is generated, so that fluid accumulates under the dressing, which can lead to tissue maceration and to wrinkling at the adhesive contact site (with risk of bacterial entry). Newer versions of these dressings have increased moisture vapour permeability. Despite these advances, vapour-permeable films and membranes are unsuitable for infected, large heavily exuding wounds, and chronic leg ulcers.

Vapour-permeable films and membranes are suitable for partial-thickness wounds with minimal exudate, or wounds with eschar. Most commonly, they are used as a secondary dressing over alginates or hydrogels; film dressings can also be used to protect the fragile skin of patients at risk of developing minor skin damage caused by friction or pressure.

**Novo Fix**
For intravenous and subcutaneous catheter sites.

**Niko** (Unomedical Ltd) Fix dressing 7cm x 8.5cm = £0.19.

**Vapour-permeable Adhesive Film Dressing (Semi-permeable Adhesive Dressing)**
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces.

**Askina Derm**
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces.

**Askina Derm dressing** (B. Braun Medical Ltd) 10cm x 12cm = £1.08, 15cm x 20cm = £2.05, 15cm x 20cm = £2.49, 20cm x 30cm = £4.44, 6cm x 7cm = £0.37.

**Biocclusiv**
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces.

**Biocclusiv dressing** (Systagenix Wound Management Ltd) dressing 10.2cm x 12.7cm = £1.54.

**C-View**
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces.

**C-View dressing** (Aspen Medical Europe Ltd) 10cm x 12cm = £1.02, 12cm x 12cm = £1.09, 15cm x 20cm = £2.36, 6cm x 7cm = £0.38.

**Dressfilm**
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces.

**Dressfilm dressing** (St Georges Medical Ltd) 12cm x 12cm = £0.93, 15cm x 20cm = £1.90, 6cm x 7cm = £0.30.

**Hydrosorb Comfort**
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces.

**Hydrosorb Comfort dressing** (Paul Hartmann Ltd) 10cm x 12.5cm = £0.42, 10cm x 15cm = £0.52, 10cm x 25cm = £0.61, 12cm x 25cm = £0.86, 15cm x 20cm = £0.96, 20cm x 30cm = £1.60, 6cm x 7cm = £0.22.

**Hypafix Transparent**
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces.

**Hypafix Transparent dressing** (BSN medical Ltd) dressing 10cm x 2m = £8.71.

**Leukomed T**
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces.

**Leukomed T dressing** (BSN medical Ltd) 10cm x 12.5cm = £1.01, 11cm x 14cm = £1.23, 15cm x 20cm = £2.35, 15cm x 25cm = £2.51, 7.2cm x 5cm = £0.37, 8cm x 10cm = £0.69.

**Mepitel Film**
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces.

**Mepitel Film dressing** (Molnlycke Health Care Ltd) 10.5cm x 12cm = £1.31, 10.5cm x 25cm = £2.55, 15.5cm x 20cm = £3.24, 6.5cm x 7cm = £0.49.

**Mepore Film**
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces.

**Mepore Film dressing** (Molnlycke Health Care Ltd) 10cm x 12cm = £1.23, 10cm x 25cm = £2.39, 15cm x 20cm = £3.04, 6cm x 7cm = £0.46.

**OpSite Flexifix**
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces.

**OpSite Flexifix dressing** (Smith & Nephew Healthcare Ltd) 10cm x 1m = £6.57, 5cm x 1m = £3.89.

**OpSite Flexigrid**
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces.

**OpSite Flexigrid dressing** (Smith & Nephew Healthcare Ltd) 12cm x 12cm = £1.12, 15cm x 20cm = £2.84, 6cm x 7cm = £0.40.
Polyskin II
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

Kendall Film dressing (Aria Medical Ltd) 10cm x 12cm = £1.03, 10cm x 20cm = £2.04, 15cm x 20cm = £2.35, 20cm x 25cm = £4.11, 4cm x 4cm = £0.36, 6cm x 7cm = £0.40

ProtectFilm
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

ProtectFilm dressing (Wallace, Cameron & Company Ltd) 10cm x 12cm = £0.20, 15cm x 20cm = £0.40, 6cm x 7cm = £0.11

Suprasorb F
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

Suprasorb F dressing (Johann & Rauscher (UK) Ltd) 10cm x 12cm = £0.80, 15cm x 20cm = £2.50, 5cm x 7cm = £0.33

Tegaderm
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

Tegaderm Diamond dressing (3M Health Care Ltd) 12cm x 12cm = £1.11, 15cm x 20cm = £2.41, 6cm x 7cm = £0.39

Vacuskin
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

Vacuskin dressing (Pro-Tex Capillary Dressings Ltd) 10cm x 12cm = £1.06, 10cm x 25cm = £2.06, 6cm x 7cm = £0.40

Vellafilm
Extensible, waterproof, water vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces

Vellafilm dressing 1 (Advancis Medical) 2cm x 12cm = £1.10, 2cm x 35cm = £2.75, 5cm x 20cm = £2.10

Vapour-permeable Adhesive Film Dressing with absorbent pad

Adapore Ultra dressing (Medicareplus International Ltd) 10cm x 10cm = £0.14, 10cm x 15cm = £0.22, 10cm x 20cm = £0.33, 15cm x 25cm = £0.35, 10cm x 30cm = £0.52, 7cm x 8cm = £0.12

Alldress
Film dressing with absorbent pad

Alldress dressing 1 (Molynckye Health Care Ltd) 1cm x 10cm = £0.95, 5cm x 15cm = £2.07, 6cm x 20cm = £2.56

C-View Post-Op
Film dressing with absorbent pad

C-View Post-Op dressing (Aspen Medical Europe Ltd) 10cm x 12cm = £1.10, 10cm x 25cm = £1.60, 10cm x 35cm = £2.60, 6cm x 7cm = £0.40

Clearpore
Film dressing with absorbent pad

Clearpore dressing (Richardson Healthcare Ltd) 10cm x 10cm = £0.20, 10cm x 15cm = £0.24, 10cm x 20cm = £0.36, 10cm x 25cm = £0.40, 10cm x 30cm = £0.65, 6cm x 10cm = £0.15, 6cm x 7cm = £0.12

Hydrofilm Plus
Film dressing with absorbent pad

Hydrofilm Plus dressing (Paul Hartmann Ltd) 10cm x 20cm = £0.45, 10cm x 25cm = £0.60, 10cm x 30cm = £0.68, 7.2cm x 5cm = £0.18, 9cm x 10cm = £0.27, 9cm x 15cm = £0.30

Leukomed T Plus
Film dressing with absorbent pad

Leukomed T Plus dressing (BSN medical Ltd) 10cm x 20cm = £1.34, 10cm x 25cm = £1.50, 10cm x 30cm = £2.51, 10cm x 35cm = £3.04, 7.2cm x 5cm = £0.27, 8cm x 10cm = £0.53, 8cm x 15cm = £0.80

Mepore Film & Pad
Film dressing with absorbent pad

Mepore Film & Pad dressing (Molynckye Health Care Ltd) 4cm x 5cm = £0.24, 5cm x 7cm = £0.24, 6cm x 10cm = £0.62, 5cm x 15cm = £0.92, 9cm x 20cm = £1.36, 9cm x 25cm = £1.50, 9cm x 30cm = £2.00, 9cm x 35cm = £2.49

Mepore Ultra
Film dressing with absorbent pad

Mepore Ultra dressing (Molynckye Health Care Ltd) 10cm x 11cm = £0.79, 11cm x 15cm = £1.17, 7cm x 8cm = £0.40, 9cm x 20cm = £1.51, 10cm x 25cm = £1.67, 9cm x 30cm = £2.75

OpSite Plus
Film dressing with absorbent pad

OpSite Plus dressing (Smith & Nephew Healthcare Ltd) 10cm x 12cm = £1.19, 10cm x 20cm = £2.01, 10cm x 30cm = £3.33, 6.5cm x 5cm = £0.32, 8.5cm x 9.5cm = £0.88

OpSite Post-op
Film dressing with absorbent pad

OpSite Post-Op dressing (Smith & Nephew Healthcare Ltd) 10cm x 12cm = £1.17, 10cm x 20cm = £1.97, 10cm x 25cm = £2.48, 10cm x 30cm = £2.92, 10cm x 35cm = £3.27, 8.5cm x 15.5cm = £1.19, 8.5cm x 9.5cm = £0.86

Pharmapore-PU
Film dressing with absorbent pad

Pharmapore-PU dressing (Wallace, Cameron & Company Ltd) 10cm x 25cm = £0.38, 10cm x 30cm = £0.58, 8.5cm x 15.5cm = £0.20

PremierPore VP
Film dressing with absorbent pad

PremierPore VP dressing (Shermon) 10cm x 10cm = £0.16, 10cm x 15cm = £0.24, 10cm x 20cm = £0.36, 10cm x 25cm = £0.38, 10cm x 30cm = £0.57, 10cm x 35cm = £0.69, 5cm x 7cm = £0.13

Tegaderm
Film dressing with absorbent pad

Tegaderm + Pad dressing (3M Health Care Ltd) 5cm x 7cm = £0.26, 9cm x 10cm = £0.65, 9cm x 15cm = £0.95, 9cm x 20cm = £1.40, 9cm x 25cm = £1.57, 9cm x 35cm = £2.60

Tegaderm Absorbent Clear
Film dressing with clear acrylic polymer oval-shaped pad or rectangular-shaped pad

Tegaderm Absorbent Clear Acrylic dressing (3M Health Care Ltd) 11.1cm x 12.7cm oval = £4.11, 14.2cm x 15.8cm oval = £5.78, 14.9cm x 15.2cm rectangular = £8.66, 16.8cm x 19cm sacral = £10.37, 20cm x 20cm rectangular = £13.91, 7.6cm x 9.5cm oval = £3.17

Vapour-permeable transparent film dressing with adhesive foam border.

Central Gard
For intravenous and subcutaneous catheter sites

Central Gard dressing 16cm x (Union Medical Ltd) 7cm = £0.94, 8.8cm = £1.03

East-V
For intravenous and subcutaneous catheter sites

East-V (Convatec Ltd) dressing 7cm x 7.5cm = £0.38

Vapour-permeable transparent, adhesive film dressing.

Hydrofilm I.V. Control
For intravenous and subcutaneous catheter sites

Hydrofilm (Paul Hartmann Ltd) I.V. Control dressing 7cm x 9cm = £0.31

IV3000
For intravenous and subcutaneous catheter sites

IV3000 dressing (Smith & Nephew Healthcare Ltd) 10cm x 12cm = £1.39, 5cm x 6cm = £0.42, 6cm x 7cm = £0.55, 7cm x 9cm = £0.73, 9cm x 12cm = £1.44

Mepore IV
For intravenous and subcutaneous catheter sites

Mepore IV dressing (Molynckye Health Care Ltd) 10cm x 11cm = £1.06, 5cm x 5.5cm = £0.31, 8cm x 9cm = £0.40
Wound management

Pharmapure-PIV
For intravenous and subcutaneous catheter sites
Pharmapure-PIV dressing (Wallace, Cameron & Company Ltd) 6cm x 7cm = £0.08, 7cm x 8.5cm = £0.07, 7cm x 9cm = £0.17

Tegaderm IV
For intravenous and subcutaneous catheter sites
Tegaderm IV dressing with securing tapes (3M Health Care Ltd) 10cm x 15.5cm = £1.67, 7cm x 8.5cm = £0.59, 8.5cm x 10.5cm = £1.16

Soft polymer dressings
Dressings with soft polymer, often a soft silicone polymer, in a non-adherent or gently adherent layer are suitable for use on lightly to moderately exuding wounds. For moderately to heavily exuding wounds, an absorbent secondary dressing can be added, or a soft polymer dressing with an absorbent pad can be used. Wound contact dressings coated with soft silicone have gentle adhesive properties and can be used on fragile skin areas or where it is beneficial to reduce the frequency of primary dressing changes. Soft polymer dressings should not be used on heavily bleeding wounds; blood clots can cause the dressing to adhere to the wound surface. For silicone keloid dressings see p. 1309.

Cellulose dressings
Sorbion Sachet Border
Absorbent polymers in cellulose matrix, hypoallergenic polypropylene envelope, with adhesive border
sorbion sachet border dressing (H & R Healthcare Ltd) 10cm x 10cm square = £2.95, 15cm x 15cm square = £4.49, 25cm x 15cm rectangular = £6.99
Sorbion Sachet EXTRA
Absorbent polymers in cellulose matrix, hypoallergenic polypropylene envelope
sorbion sachet EXTRA dressing (H & R Healthcare Ltd) 10cm x 10cm = £2.71, 15cm x 10cm = £3.73, 20cm x 20cm = £7.00, 30cm x 20cm = £9.99, 5cm x 5cm = £1.45, 7.5cm x 7.5cm = £1.78
Sorbion Sachet Multi Star
Absorbent polymers in cellulose matrix, hypoallergenic polypropylene envelope
sorbion sachet multi star dressing (H & R Healthcare Ltd) 14cm x 14cm = £4.89, 8cm x 8cm = £2.99
Sorbion Sachet 5 Drainage
Absorbent polymers in cellulose matrix, hypoallergenic polypropylene envelope (‘Y’ shaped dressing)
sorbin (H & R Healthcare Ltd) sachet 5 drainage dressing 10cm x 10cm = £2.64
Suprasorb X
Biosynthetic cellulose fibre dressing
Suprasorb X dressing (Lohmann & Rauscher (UK) Ltd) 14cm x 20cm rectangular = £8.38, 20cm x 20cm rope = £6.51, 5cm x 5cm square = £2.03, 9cm x 9cm square = £4.23
With absorbent pad
Advazorb Border
Soft silicone wound contact dressing with polyurethane foam film backing and adhesive border
Advazorb Border dressing (Advancis Medical) 10cm x 10cm = £2.10, 15cm x 10cm = £2.90, 10cm x 20cm = £4.25, 12.5cm x 12.5cm = £2.58, 15cm x 15cm = £3.15, 20cm x 20cm = £5.46, 7.5cm x 7.5cm = £1.19
Advazorb Border Lite
Soft silicone wound contact dressing with polyurethane foam film backing and adhesive border
Advazorb Border Lite dressing (Advancis Medical) 10cm x 10cm = £1.89, 10cm x 20cm = £2.61, 10cm x 30cm = £3.83, 12.5cm x 12.5cm = £2.32, 15cm x 15cm = £2.84, 20cm x 20cm = £4.91, 7.5cm x 7.5cm = £1.07
Advazorb Silfix
Soft silicone wound contact dressing with polyurethane foam film backing
Advazorb Silfix dressing (Advancis Medical) 10cm x 10cm = £1.85, 10cm x 20cm = £3.18, 12.5cm x 12.5cm = £2.59, 15cm x 15cm = £3.36, 20cm x 20cm = £4.98, 7.5cm x 7.5cm = £0.99
Advazorb Silfix Lite
Soft silicone wound contact dressing with polyurethane foam film backing
Advazorb Silfix Lite dressing (Advancis Medical) 10cm x 10cm = £1.67, 10cm x 20cm = £2.86, 12.5cm x 12.5cm = £3.33, 15cm x 15cm = £3.02, 20cm x 20cm = £4.48, 7.5cm x 7.5cm = £0.89
Allevyn Gentle
Soft gel wound contact dressing, with polyurethane foam film backing
Allevyn Gentle dressing (Smith & Nephew Healthcare Ltd) 10cm x 10cm = £2.49, 10cm x 20cm = £4.01, 15cm x 15cm = £4.18, 20cm x 20cm = £6.68, 5cm x 5cm = £1.26
Allevyn Gentle Border
Silicone gel wound contact dressing, with polyurethane foam film backing
Allevyn Gentle Border dressing (Smith & Nephew Healthcare Ltd) Heel dressing 23cm x 23.2cm = £9.59, dressing 10cm x 10cm = £2.18, 12.5cm x 12.5cm = £2.67, 17.5cm x 17.5cm = £5.26, 7.5cm x 7.5cm = £1.48
Allevyn Gentle Border Lite
Silicone gel wound contact dressing, with polyurethane foam film backing
Allevyn Gentle Border Lite dressing (Smith & Nephew Healthcare Ltd) 10cm x 10cm = £2.15, 15cm x 15cm = £3.79, 5.5cm x 12cm = £1.84, 5cm x 5cm = £0.89, 9cm x 15cm = £3.41
Allevyn Life
Soft silicone wound contact dressing, with central mesh screen, polyurethane foam film backing and adhesive border
Allevyn Life dressing (Smith & Nephew Healthcare Ltd) 10.3cm x 10.3cm = £1.68, 12.9cm x 12.9cm = £2.47, 15.4cm x 15.4cm = £3.02, 21cm x 21cm = £5.95
Cutimed Siltec
Soft silicone wound contact dressing, with polyurethane foam film backing
Cutimed Siltec (BSN medical Ltd) Heel dressing 16cm x 24cm = £7.15, Sacrum dressing 17.5cm x 17.5cm = £4.55, 23cm x 23cm = £7.29, dressing 10cm x 10cm = £2.46, 10cm x 20cm = £4.06, 15cm x 15cm = £4.59, 20cm x 20cm = £6.97, 5cm x 6cm = £3.31
Cutimed Siltec B
Soft silicone wound contact dressing, with polyurethane foam film backing, with adhesive border, for lightly to moderately exuding wounds
Cutimed Siltec B dressing (BSN medical Ltd) 12.5cm x 12.5cm = £3.24, 15cm x 15cm = £4.16, 17.5cm x 17.5cm = £5.25, 22.5cm x 22.5cm = £8.47, 7.5cm x 7.5cm = £1.53
Cutimed Siltec L
Soft silicone wound contact dressing, with polyurethane foam film backing, for lightly to moderately exuding wounds
Cutimed Siltec L dressing (BSN medical Ltd) 10cm x 10cm = £2.12, 15cm x 15cm = £3.48, 5cm x 6cm = £1.05
Eclipse Adherent
Soft silicone wound contact layer with absorbent pad and film backing
Eclipse Adherent dressing (Advancis Medical) 10cm x 10cm = £2.99, 10cm x 20cm = £3.75, 15cm x 15cm = £4.99, 20cm x 20cm = £9.99, 17cm x 19cm sacral = £3.76, 22cm x 23cm sacral = £6.23
Flivarsorb
Absorbent polymer dressing with non-adherent wound contact layer
Flivarsorb dressing (Lohmann & Rauscher (UK) Ltd) 10cm x 10cm square = £0.88, 10cm x 20cm rectangular = £1.05, 20cm x 20cm square = £1.86, 20cm x 30cm rectangular = £2.35
Flivarsorb Adhesive
Absorbent polymer dressing with non-adherent wound contact layer and adhesive border
Flivarsorb Adhesive dressing (Lohmann & Rauscher (UK) Ltd) 2cm x 12cm square = £3.32, 5cm x 15cm square = £4.54
Mepilex
Absorbent soft silicone dressing with polyurethane foam film backing
Mepilex (Molnlycke Health Care Ltd) Heel dressing 13cm x 20cm = £5.41, 15cm x 22cm = £6.22, XT dressing 10cm x 11cm = £2.66, 11cm x 20cm = £4.39, 15cm x 16cm = £4.82, 20cm x 21cm = £7.28, dressing 5cm x 5cm = £1.21.

**Mepilex Border**
Absorbt soft silicone dressing with polyurethane foam film backing and adhesive border.

**Mepilex Border** (Molnlycke Health Care Ltd) Heel dressing 18.5cm x 24cm = £5.00, Sacrum dressing 18cm x 18cm = £8.45, 23cm x 23cm = £7.91, dressing 10cm x 12.5cm = £2.72, 10cm x 20cm = £3.69, 10cm x 30cm = £5.55, 15cm x 17.5cm = £4.74, 17cm x 20cm = £5.07.

**Mepilex Border Lite**
Thin absorbent soft silicone dressing with polyurethane foam film backing and adhesive border.

**Mepilex Border dressing** (Molnlycke Health Care Ltd) 10cm x 10cm = £2.53, 15cm x 15cm = £4.13, 4cm x 5cm = £0.92, 5cm x 12.5cm = £2.51, 7.5cm x 7.5cm = £1.39.

**Mepilex Lite**
Thin absorbent soft silicone dressing with polyurethane foam film backing.

**Mepilex Lite Dressing** (Molnlycke Health Care Ltd) 10cm x 10cm = £2.17, 15cm x 15cm = £4.22, 20cm x 20cm = £26.66, 6cm x 8.5cm = £1.92.

**Mepilex Transfer**
Soft silicone exudate transfer dressing.

**Mepilex Transfer dressing** (Molnlycke Health Care Ltd) 10cm x 12cm = £3.51, 15cm x 20cm = £10.64, 20cm x 50cm = £27.20, 7.5cm x 8.5cm = £2.23.

**Sorban Sana**
Non-adherent polyethylene wound contact dressing with absorbent core.

**Sorban Sana Gentle dressing** (H & R Healthcare Ltd) 12cm x 12cm = £2.49, 12cm x 22cm = £4.49, 22cm x 22cm = £7.99, 8.5cm x 8.5cm = £1.99.

**Urgotol Duo**
Non-adherent soft polyethylene wound contact dressing with absorbent pad.

**UrgotolDuo dressing** (Urgo Ltd) 10cm x 12cm = £3.81, 15cm x 20cm = £8.85, 5cm x 10cm = £2.46.

**Without absorbent pad**

**Adaptic Touch**
Non-adherent soft silicone wound contact dressing.

**Adaptic Touch dressing** (Systagenix Wound Management Ltd) 12.7cm x 15cm = £4.65, 20cm x 32cm = £12.50, 5cm x 7.5cm = £1.13, 7.5cm x 11cm = £2.25.

**Askina SilNet**
Soft silicone-coated wound contact dressing.

**Askina SilNet dressing** (B.Braun Medical Ltd) 10cm x 18cm = £4.98, 20cm x 30cm = £12.20, 5cm x 7.5cm = £1.13, 7.5cm x 10cm = £2.28.

**Meptel**
Soft silicone, semi-transparent wound contact dressing.

**Meptel dressing** (Molnlycke Health Care Ltd) 12cm x 15cm = £6.45, 5cm x 7cm = £1.59, 8cm x 10cm = £2.19.

**Meptel One**
Soft silicone, thin, transparent wound contact dressing.

**Meptel One dressing** (Molnlycke Health Care Ltd) 13cm x 15cm = £6.45, 24cm x 27.5cm = £17.38, 6cm x 7cm = £1.59, 9cm x 10cm = £3.19.

**Physiostyle**
Non-adherent soft polyurethane wound contact dressing.

**Physiostyle dressing 1** (Coloplast Ltd) 0cm x 10cm = £2.25, 5cm x 20cm = £6.86.

**Silflex**
Soft silicone-coated polyester wound contact dressing.

**Silflex dressing** (Advancis Medical) 12cm x 15cm = £4.58, 20cm x 30cm = £12.79, 35cm x 60cm = £39.54, 5cm x 7cm = £2.11, 8cm x 10cm = £2.27.

**Silon- TSR**
Soft silicone polymer wound contact dressing.

**Silon- TSR dressing** (Bio Med Sciences) 13cm x 13cm = £3.52, 13cm x 25cm = £5.47, 28cm x 30cm = £7.37.

**Sohion Contact**
Non-adherent soft polymer wound contact dressing.

**Sohion Contact dressing** (H & R Healthcare Ltd) 10cm x 10cm = £1.99, 10cm x 20cm = £3.39, 20cm x 20cm = £5.99, 20cm x 30cm = £8.99, 7.5cm x 7.5cm = £1.49.

**Tegaderm Contact**
Non-adherent soft polyurethane wound contact dressing.

**Tegaderm Contact dressing** (3M Health Care Ltd) 20cm x 25cm = £10.86, 7.5cm x 10cm = £2.27, 7.5cm x 20cm = £4.46.

**Urgotol**
Non-adherent soft polyurethane wound contact dressing.

**Urgotol dressing** (Urgo Ltd) 10cm x 10cm = £3.06, 10cm x 40cm = £10.29, 15cm x 15cm = £5.50, 15cm x 20cm = £8.66, 20cm x 30cm = £13.92, 5cm x 5cm = £1.53.

**Hydrocolloid dressings**
Hydrocolloid dressings are usually presented as a hydrocolloid layer on a vapour-permeable film or foam pad. Semi-permeable to water vapour and oxygen, these dressings form a gel in the presence of exudate to facilitate rehybridation in lightly to moderately exuding wounds and promote autolytic debridement of dry, sloughy, or necrotic wounds; they are also suitable for promoting granulation. Hydrocolloid-fibrous dressings made from modified carmellose fibres resemble alginate dressings; hydrocolloid-fibrous dressings are more absorbent and suitable for moderately to heavily exuding wounds.

**Hydrocolloid-fibrous dressings**

**Aquacel**
Soft non-woven pad containing hydrocolloid-fibres.

**Aquacel** (Convatec Ltd) Ribbon dressing 1cm x 45cm = £1.83, 2cm x 45cm = £2.44, dressing 10cm x 10cm square = £2.41, 15cm x 15cm square = £4.53, 4cm x 10cm rectangular = £1.30, 4cm x 20cm rectangular = £1.91, 4cm x 30cm rectangular = £2.88, 5cm x 5cm square = £1.01.

**Aquacel Foam**
Soft non-woven pad containing hydrocolloid-fibres with foam layer; with or without adhesive border.

**Aquacel Foam dressing** (Convatec Ltd) adhesive 10cm x 10cm = £2.34, 12.5cm x 12.5cm = £2.65, 17.5cm x 17.5cm = £5.30, 19.8cm x 14cm heel = £5.43, 20cm x 16.5cm sacral = £4.87, 21cm x 21cm = £7.76, 25cm x 30cm = £10.05, 6cm x 6cm = £1.38, non-adhesive 10cm x 10cm = £2.53, 15cm x 15cm = £4.25, 15cm x 20cm = £5.81, 20cm x 20cm = £6.94.

**UrgoClean Pad**
Pad, hydrocolloid fibres coated with soft-adherent lipo-colloidal wound contact layer.

**UrgoClean Pad dressing** (Urgo Ltd) 10cm x 10cm square = £2.11, 20cm x 15cm rectangular = £3.96, 6cm x 6cm square = £0.95.

**UrgoClean Rope**
Rope, non-woven rope containing hydrocolloid fibres.

**UrgoClean rope dressing** (Urgo Ltd) 2.5cm x 40cm = £2.37, 5cm x 40cm = £3.14.

**Versiva XC, non-adhesive**
Hydrocolloid gelling foam dressing; with or without adhesive border.

**Versiva XC dressing** (Convatec Ltd) 10cm x 10cm square = £2.50, 11cm x 11cm square = £2.44, 14cm x 14cm square = £3.13, 15cm x 15cm square = £4.50, 15cm x 19cm square = £5.37, 20cm x 20cm square = £6.73, 21cm x 25cm sacral = £6.40, 22cm x 22cm square = £6.39, 7.5cm x 7.5cm square = £1.47.

**Polyurethane matrix dressing**

**Cutinova Hydro**
Polyurethane matrix with absorbent particles and waterproof polyurethane film.

**Cutinova Hydro dressing** (Smith & Nephew Healthcare Ltd) 10cm x 10cm square = £2.53, 15cm x 20cm rectangular = £5.36, 5cm x 6cm rectangular = £1.26.
With adhesive border

**Biatain Super**
Semi-permeable hydrocolloid dressing; without adhesive border

**Biatain Super dressing (adhesive)** (Coloplast Ltd) 10cm x 10cm square = £2.16, 12.5cm x 12.5cm square = £3.57, 15cm x 15cm square = £3.93, 18cm x 18cm rectangular = £3.58, 15cm x 15cm square = £4.30, 20cm x 20cm square = £6.71

**Granuflex Border**
Hydrocolloid wound contact layer bonded to plastic foam layer, with outer semi-permeable polyurethane film

**Granuflex Border dressing (Convatec Ltd) 10cm x 10cm square = £3.32, 10cm x 18cm triangular = £3.91, 15cm x 15cm square = £6.33, 15cm x 18cm triangular = £6.10, 6cm x 6cm square = £1.75

**Hydrocoll Border**
Hydrocolloid dressing with adhesive border and absorbent wound contact pad

**Hydrocoll Border (bevelled edge) dressing** (Paul Hartmann Ltd) 10cm x 10cm square = £2.41, 12cm x 12cm square = £3.60, 15cm x 15cm square = £4.53, 5cm x 5cm square = £1.01, 7.5cm x 7.5cm square = £1.65, 8cm x 12cm concave = £2.12

**Tegaderm Hydrocolloid**
Hydrocolloid dressing with adhesive border; normal or thin

**Tegaderm Hydrocolloid (3M Health Care Ltd) Thin dressing** 10cm x 12cm oval = £1.55, 13cm x 15cm oval = £2.08, dressing 10cm x 12cm oval = £2.33, 13cm x 15cm oval = £4.34, 17.1cm x 16.1cm sacral = £4.85,

**Ultec Pro**
Semi-permeable hydrocolloid dressing with adhesive border

**Ultec Pro dressing (adhesive)** (Covidien (UK) Commercial Ltd) 15cm x 18cm sacral = £3.30, 19.5cm x 23cm sacral = £4.98, 21cm x 21cm square = £4.67

Without adhesive border

**ActiveHeal Hydrocolloid**
Semi-permeable polyurethane film backing, hydrocolloid wound contact layer, with or without polyurethane foam later

**ActiveHeal Hydrocolloid (Advanced Medical Solutions Ltd) dressing**
10cm x 10cm square = £1.58, 15cm x 15cm square = £3.43, 15cm x 18cm sacral = £3.98, 5cm x 7.5cm rectangular = £0.78, foam backed dressing 10cm x 10cm square = £1.55, 15cm x 15cm square = £2.91, 15cm x 18cm sacral = £3.36, 5cm x 7.5cm rectangular = £0.97,

**Askins Biofilm Transparent**
Semi-permeable, polyurethane film dressing with hydrocolloid adhesive

**Askins Biofilm Transparent dressing** (B.Braun Medical Ltd) 10cm x 10cm square = £1.07, 20cm x 20cm square = £1.15

**Biatain Super**
Semi-permeable, hydrocolloid film dressing without adhesive border

**Biatain Super dressing (non-adhesive)** (Coloplast Ltd) 10cm x 10cm square = £2.16, 12.5cm x 12.5cm square = £3.57, 12cm x 20cm rectangular = £3.58, 15cm x 15cm square = £4.30, 20cm x 20cm square = £6.71

**Comfeel Plus Contour**
Hydrocolloid dressings containing carmellose sodium and calcium alginate

**Comfeel Plus Contour dressing** (Coloplast Ltd) 6cm x 8cm = £2.19, 9cm x 11cm = £3.81

**Comfeel Plus Pressure Relieving**
Hydrocolloid dressings containing carmellose sodium and calcium alginate

**Comfeel Plus Pressure Relieving dressing** (Coloplast Ltd) 10cm diameter circular = £4.59, 15cm diameter circular = £6.91, 7cm diameter circular = £3.43

**Comfeel Plus Transparent**
Hydrocolloid dressings containing carmellose sodium and calcium alginate

**Comfeel Plus Transparent dressing** (Coloplast Ltd) 10cm x 10cm square = £1.26, 15cm x 15cm square = £3.30, 15cm x 20cm rectangular = £3.35, 20cm x 20cm square = £3.37, 5cm x 15cm rectangular = £1.57, 5cm x 25cm rectangular = £2.55, 5cm x 7cm rectangular = £0.66, 9cm x 14cm rectangular = £2.41, 9cm x 25cm rectangular = £3.42

**Comfeel Plus Ulcer**
Hydrocolloid dressings containing carmellose sodium and calcium alginate

**Comfeel Plus Ulcer (bevelled edge) dressing** (Coloplast Ltd) 10cm x 10cm square = £2.42, 18cm x 20cm triangular = £5.65, 20cm x 20cm square = £7.47, 4cm x 5cm rectangular = £0.95

**DuoDERM Extra Thin**
Semi-permeable hydrocolloid dressing

**DuoDERM Extra Thin dressing** (Convatec Ltd) 10cm x 10cm square = £1.31, 15cm x 15cm square = £2.84, 5cm x 10cm rectangular = £0.76, 7.5cm x 7.5cm square = £0.79, 9cm x 15cm rectangular = £1.76, 9cm x 25cm rectangular = £2.81, 9cm x 35cm rectangular = £3.93

**DuoDERM Signal**
Semi-permeable hydrocolloid dressing with "Time to change" indicator

**DuoDERM Signal dressing** (Convatec Ltd) 10cm x 10cm square = £2.12, 11cm x 10cm oval = £1.22, 14cm x 14cm square = £3.71, 18.5cm x 19.5cm heel = £5.19, 20cm x 20cm square = £7.38, 22.5cm x 20cm sacral = £6.07

**Flexigran**
Semi-permeable hydrocolloid dressing without adhesive border; normal or thin

**Flexigran (A1 Pharmaceuticals) Thin dressing** 10cm x 10cm square = £1.08, dressing 10cm x 10cm square = £2.19

**Granuflex**
Hydrocolloid wound contact layer bonded to plastic foam layer, with outer semi-permeable polyurethan film

**Granuflex (modified) dressing** (Convatec Ltd) 10cm x 10cm square = £2.78, 15cm x 15cm square = £5.28, 15cm x 20cm rectangular = £5.72, 20cm x 20cm square = £7.95

**Hydrocoll Basic**
Hydrocolloid dressing with absorbent wound contact pad

**Hydrocoll (Paul Hartmann Ltd) Basic dressing** 10cm x 10cm square = £2.45

**Hydrocoll Thin Film**
Thin hydrocolloid dressing with absorbent wound contact pad

**Hydrocoll Thin Film dressing** (Paul Hartmann Ltd) 10cm x 10cm square = £1.15, 15cm x 15cm square = £2.59, 7.5cm x 7.5cm square = £0.70

**Nu-Derm**
Semi-permeable hydrocolloid dressing (normal and thin)

**Nu-Derm dressing** (Syntagenex Wound Management Ltd) 10cm x 10cm square = £1.56, 15cm x 15cm square = £3.18, 15cm x 18cm sacral = £4.45, 20cm x 20cm square = £6.36, 5cm x 5cm square = £0.85, 8cm x 12cm heel/elbow = £3.18, thin 10cm x 10cm square = £1.06

**Tegaderm Hydrocolloid**
Hydrocolloid dressing without adhesive border; normal and thin

**Tegaderm Hydrocolloid (3M Health Care Ltd) Thin dressing** 10cm x 10cm square = £1.55, dressing 10cm x 10cm square = £2.37, 15cm x 15cm square = £4.59,

**Ultec Pro**
Semi-permeable hydrocolloid dressing; without adhesive border

**Ultec Pro dressing** (Covidien (UK) Commercial Ltd) 10cm x 10cm square = £2.28, 15cm x 15cm square = £4.44, 20cm x 20cm square = £6.69

**Foam dressings**
Dressings containing hydrophilic polyurethane foam (adhesive or non-adhesive), with or without plastic film-backing, are suitable for all types of exuding wounds, but not for dry wounds; some foam dressings have a moisture-sensitive film backing with variable permeability dependent on the level of exudate.
Foam dressings vary in their ability to absorb exudate; some are suitable only for lightly to moderately exuding wounds, others have greater fluid-handling capacity and are suitable for heavily exuding wounds. Saturated foam dressings can cause maceration of healthy skin if left in contact with the wound.

Foam dressings can be used in combination with other primary wound contact dressings. If used under compression bandaging or compression garments, the fluid-handling capacity of the foam dressing may be reduced. Foam dressings can also be used to provide a protective cushion for fragile skin. A foam dressing containing ibuprofen is available and may be useful for treating painful exuding wounds.

Cavi-Care
Soft, conforming cavity wound dressing prepared by mixing Cavi-Care exuding wounds. The handling capacity of the foam dressing may be reduced.

**Primary wound contact dressings.** If used under
others have greater fluid-handing capacity and are suitable
Foam dressings vary in their ability to absorb exudate; some

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- **PolyMem dressing (Aspen Medical Europe Ltd) (adhesive)**
  - 10cm x 13cm rectangular = £2.18, 15cm x 15cm square = £2.93, 16.5cm x 20.9cm oval = £6.74, 18.4cm x 20cm square = £4.53, 5cm x 7.6cm oval = £1.15, 8.8cm x 12.7cm oval = £2.05,
  - **PolyMem dressing (Aspen Medical Europe Ltd) (adhesive)**
  - 5cm x 5cm square = £0.52

- **Tegaderm Foam Adhesive**
  - **Tegaderm Foam dressing (adhesive)**
  - 3M Health Care Ltd 10cm x 11cm oval = £0.39, 13.9cm x 13.9cm circular (heel) = £4.22, 14.3cm x 14.3cm square = £3.54, 14.3cm x 13.6cm oval = £4.24, 19cm x 22.2cm oval = £6.96, 9.6cm x 6.9cm soft cloth border = £1.71, 9.6cm x 7.6cm oval = £1.46

- **Tielit**:
  - **Tielit Lite**: (Syntegens Wound Management Ltd) Lite dressing 11cm x 11cm square = £2.28, dressing 15cm x 15cm square = £3.89, 15cm x 20cm rectangular = £4.87, 18cm x 18cm square = £4.95, 7cm x 9cm rectangular = £1.29,
  - **Tielit Lite**: (Syntegens Wound Management Ltd) Lite dressing 11cm x 11cm square = £2.28, 7cm x 9cm rectangular = £1.21, 8cm x 15cm rectangular = £2.81, 8cm x 20cm rectangular = £2.97

- **Tielit Plus**: (Syntegens Wound Management Ltd) 11cm x 11cm square = £2.63, 15cm x 15cm square = £3.13, square = £4.30, 15cm x 20cm rectangular = £5.39, 20cm x 26.5cm heel = £4.45,
  - **Trufoam**: 11cm x 11cm square = £1.70, 15cm x 15cm square = £2.23, 15cm x 20cm rectangular = £4.04, 7cm x 9cm rectangular = £1.16

- **Polyurethane Foam Film Dressing without Adhesive Border**
  - **ActivHeal Foam Adhesive**
  - **ActivHeal Foam Adhesive dressing (Advanced Medical Solutions Ltd)** 10cm x 10cm square = £1.13, 10cm x 20cm rectangular = £2.34, 20cm x 20cm square = £3.92, 5cm x 5cm square = £0.75

- **Advazorb**: 10cm x 10cm square = £0.97, 10cm x 20cm rectangular = £3.45, 20cm x 20cm square = £6.05, 5cm x 5cm square = £0.75

- **Advazorb**: Heel dressing 17cm x 21cm = £4.75, dressing 10cm x 10cm square = £1.08, 10cm x 20cm rectangular = £3.35, 12.5cm x 12.5cm square = £1.59, 15cm x 15cm square = £2.10, 20cm x 20cm square = £3.75, 5cm x 5cm square = £0.65, 7.5cm x 7.5cm square = £0.78,

- **Advazorb Lite**: 10cm x 10cm square = £0.97, 10cm x 20cm rectangular = £3.45, 20cm x 20cm square = £6.05, 5cm x 5cm square = £0.75

- **Allevyn Cavity, circular**: 10cm x 10cm square = £1.13, 12cm x 4cm circular = £1.60, 12cm x 4cm circular = £1.76, 5cm x 5cm square = £0.65

- **Allevyn Cavity, circular**: 10cm x 10cm square = £1.13, 12cm x 4cm circular = £1.60, 12cm x 4cm circular = £1.76, 5cm x 5cm square = £0.65

- **Allevyn Sillicone**: 7.5cm x 7.5cm square = £0.47, 15cm x 15cm square = £0.77

- **Biatain Silicone**: 7.5cm x 7.5cm square = £0.47, 15cm x 15cm square = £0.77

- **Kendall Island**: 30cm x 10cm square = £2.13, 25cm x 25cm square = £2.60, 15cm x 15cm = £3.86, 17.5cm x 17.5cm = £5.13

- **Kendall Foam Island dressing**: 10cm x 10cm square = £2.90, 20cm x 20cm square = £5.46

- **PermaFoam dressing (adhesive)**
  - 16.5cm x 18cm concave = £0.36, 18cm x 18cm square = £3.31, 22cm x 22cm square = £3.80

- **PermaFoam Comfort dressing**: 10cm x 20cm rectangular = £3.35, 11cm x 11cm square = £2.12, 15cm x 15cm square = £3.46, 20cm x 20cm square = £5.03, 8cm x 8cm square = £1.12

**Brand names and descriptions**
- **BNF medical Ltd**
- **Coloplast Ltd**
- **Cavi-Care**
- **Askina Foam**

**Product descriptions**
- **ActivHeal Foam dressing**: (Advanced Medical Solutions Ltd) 10cm x 10cm square = £1.13, 25cm x 25cm square = £2.60, 15cm x 15cm square = £3.31, 22cm x 22cm square = £3.80

**Other products**
- **Advancis Medical**: 10cm x 10cm square = £1.08, 10cm x 20cm rectangular = £3.35, 12.5cm x 12.5cm square = £1.59, 15cm x 15cm square = £2.10, 20cm x 20cm square = £3.75, 5cm x 5cm square = £0.65, 7.5cm x 7.5cm square = £0.78,

**Additional information**
- **BNF medical Ltd**
- **Smith & Nephew Healthcare Ltd**
- **B.Braun Medical Ltd**
- **Coloplast Ltd**
- **Smith & Nephew Healthcare Ltd**
- **Advancis Medical**: 10cm x 10cm square = £1.08, 10cm x 20cm rectangular = £3.35, 12.5cm x 12.5cm square = £1.59, 15cm x 15cm square = £2.10, 20cm x 20cm square = £3.75, 5cm x 5cm square = £0.65, 7.5cm x 7.5cm square = £0.78,
### Wound management products and elasticated garments

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<td>10cm x 10cm square</td>
<td>£7.06</td>
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<td><strong>Kaltostat Calcium alginate dressing</strong></td>
<td>10cm x 10cm square</td>
<td>£7.06</td>
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<tr>
<td><strong>Kendall Calcium alginate dressing</strong></td>
<td>10cm x 10cm square</td>
<td>£7.06</td>
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**Notes:**
- Prices are approximate and subject to change.
- Sizes and prices vary depending on the supplier and location.
- Always check with suppliers for the most current information.
- For detailed information, please refer to the respective product details from the suppliers.

**References:**
- Paul Hartmann Ltd
- Systagenix Wound Management Ltd
- Molnlycke Health Care Ltd
- Coloplast Ltd
- Advanced Medical Solutions Ltd
- Advanced Medical Solutions Ltd
- Advanced Medical Solutions Ltd
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Melagisorb
Calcium sodium alginate fibre, highly absorbent, gelling dressing, non-woven

Melagisorb (Molynex Health Care Ltd) Cavity dressing 2.2cm x 32cm = £3.55, dressing 10cm x 10cm = £1.88, 10cm x 20cm = £3.52, 5cm x 5cm = £0.80.

Sorbalgan
Calcium alginate dressing
Sorbalgan (Paul Hartmann Ltd) T dressing 2g = £3.47, dressing 10cm x 10cm = £1.70, 5cm x 5cm = £0.81.

Sorbsan Flat
Calcium alginate fibre, highly absorbent, flat non-woven pads

Sorbsan Flat dressing (Aspen Medical Europe Ltd) 10cm x 10cm = £1.71, 10cm x 20cm = £3.20, 5cm x 5cm = £0.81.

Sorbsan Plus
Alginate dressing bonded to a secondary absorbent viscose pad

Sorbsan Plus dressing (Aspen Medical Europe Ltd) 10cm x 10cm = £3.10, 10cm x 20cm = £3.96, 15cm x 20cm = £5.49, 7.5cm x 10cm = £1.76.

Sorbsan Ribbon
Alginate dressing bonded to a secondary absorbent viscose pad

Sorbsan (Aspen Medical Europe Ltd) Ribbon dressing 40cm = £2.04.

Sorbsan Surgical Packing
Alginate dressing bonded to a secondary absorbent viscose pad

Sorbsan (Aspen Medical Europe Ltd) Packing dressing 2g = £3.47.

Suprasorb A
Calcium alginate dressing

Suprasorb A (Lohmann & Rauscher (UK) Ltd) alginate dressing 10cm x 10cm = £1.22, 5cm x 5cm = £0.62, cavity dressing 2g = £2.26.

Tegaderm Alginate
Calcium alginate dressing

Tegaderm Alginate dressing (3M Health Care Ltd) 10cm x 10cm = £1.72, 2cm x 30.4cm = £2.87, 5cm x 5cm = £0.81.

Urgosorb
Alginate and carboxymethylcellulose dressing without adhesive border

Urgosorb (Urgo Ltd) Pad dressing 10cm x 10cm = £2.10, 10cm x 20cm = £3.85, 5cm x 5cm = £0.87. Rope dressing 30cm = £2.75.

Capillary-action dressings
Capillary-action dressings consist of an absorbent core of hydrophilic fibres sandwiched between two low-adherent wound-contact layers to ensure no fibres are shed on to the wound surface. Wound exudate is taken up by the dressing and retained within the highly absorbent central layer. The dressing may be applied intact to relatively superficial areas, but for deeper wounds or cavities it may be cut to shape to ensure good contact with the wound base. Multiple layers may be applied to heavily exuding wounds to further increase the fluid-absorbing capacity of the dressing. A secondary adhesive dressing is necessary. Capillary-action dressings are suitable for use on all types of exuding wounds, but particularly on sloughy wounds where removal of fluid from the wound aids debridement; capillary-action dressings are contra-indicated for heavily bleeding wounds or arterial bleeding.

Advadraw
Non-adherent dressing consisting of a soft viscose and polyester absorbent pad with central wicking layer between two perforated permeable wound contact layers

Advadraw dressing (Advancis Medical) 10cm x 10cm = £0.88, 10cm x 15cm = £1.19, 15cm x 15cm = £1.57, 5cm x 7.5cm = £0.57.

Advadraw Spiral

Advadraw (Advancis Medical) Spiral dressing 0.5cm x 40cm = £0.82.

Cerdak Aerocloth
Non-adhesive wound contact sachet containing ceramic spheres, with non-woven fabric adhesive backing

Cerdak Aerocloth dressing 5cm x (Apollo Medical Products Ltd) 10cm = £1.94, 5cm = £1.37.

Cerdak Aerofilin
Non-adhesive wound contact sachet containing ceramic spheres, with waterproof transparent adhesive film backing

Cerdak Aerofilin dressing 5cm x (Apollo Medical Products Ltd) 10cm = £2.07, 5cm = £1.51.

Cerdak Basic
Non-adhesive wound contact sachet containing ceramic spheres

Cerdak Basic dressing (Apollo Medical Products Ltd) 10cm x 10cm = £1.56, 10cm x 15cm = £2.08, 5cm x 5cm = £0.70.

Sumar Lite

Sumar Lite dressing (Lantor (UK) Ltd) 10cm x 10cm = £1.59, 10cm x 15cm = £2.12, 5cm x 5cm = £0.93.

Sumar Max

Sumar Max dressing (Lantor (UK) Ltd) 10cm x 10cm = £1.61, 10cm x 15cm = £2.15, 5cm x 5cm = £0.95.

Sumar Spiral

Sumar (Lantor (UK) Ltd) Spiral dressing 0.5cm x 40cm = £1.57.

Vacutex
Low-adherent dressing consisting of two external polyester wound contact layers with central wicking polyester/cotton mix absorbent layer

Vacutex dressing (Pro-Tex Capillary Dressings Ltd) 10cm x 10cm = £1.66, 10cm x 15cm = £2.23, 10cm x 20cm = £2.68, 15cm x 20cm = £3.14, 20cm x 20cm = £4.89, 5cm x 5cm = £0.94.

Odour absorbent dressings

Dressings containing activated charcoal are used to absorb odour from wounds. The underlying cause of wound odour should be identified. Wound odour is most effectively reduced by debridement of slough, reduction in bacterial levels, and frequent dressing changes. Fungating wounds and chronic infected wounds produce high volumes of exudate which can reduce the effectiveness of odour absorbent dressings. Many odour absorbent dressings are intended for use in combination with other dressings; odour absorbent dressings with a suitable wound contact layer can be used as a primary dressing.

Askina Carbosorb
Activated charcoal and non-woven viscose rayon dressing

Askina Carbosorb dressing 10cm x (B. Braun Medical Ltd) 10cm = £2.88, 20cm = £3.56.

CarboFLEX
Dressing in 5 layers: wound-facing absorber layer containing alginate and hydrocolloid; water-resistant second layer; third layer containing activated charcoal; non-woven absorbent fourth layer; water-resistant backing layer

CarboFLEX dressing (Convatec Ltd) 10cm x 10cm = £3.18, 15cm x 20cm = £7.23, 8cm x 15cm oval = £3.82.

Carbopad VC
Activated charcoal non-absorbent dressing

Carbopad VC dressing 10cm x (Synergy Health Plc) 10cm = £1.62, 20cm = £2.19.

CliniSorb Odour Control Dressings
Activated charcoal cloth enclosed in viscose rayon with outer polyamide coating

CliniSorb dressing 1 (CliniMed Ltd) 5cm x 10cm = £1.88, 5cm x 20cm = £2.50, 5cm x 25cm = £4.03.

Sorbsan Plus Carbon
Alginate dressing with activated carbon

Sorbsan Plus Carbon dressing (Aspen Medical Ltd) 10cm x 15cm = £4.96, 10cm x 20cm = £5.94, 15cm x 20cm = £6.84, 7.5cm x 15cm = £2.56.

Antimicrobial dressings

Spreading infection at the wound site requires treatment with systemic antibacterials. For local wound infection, a topical antimicrobial dressing can be used to reduce the level of bacteria at the wound
Wound management

where removal of waxes may be difficult.

Knitted viscose impregnated with medical grade manuka
Activon Tulle

10
Actilite gauze dressing
honey and manuka oil

Knitted viscose impregnated with medical grade manuka

Activon Honey

medical grade honey

Honey

Medical grade honey has antimicrobial and anti-
inflammatory properties and can be used for acute or
chronic wounds. Medical grade honey has osmotic
properties, producing an environment that promotes
autolytic debridement; it can help control wound malodour.
Honey dressings should not be used on patients with
extreme sensitivity to honey, bee stings or bee products.
Patients with diabetes should be monitored for changes in
blood-glucose concentrations during treatment with topical
honey or honey-impregnated dressings. For Activon Tulle®,
where no size is stated by the prescriber the 5 cm size is to
be supplied. Medihoney® Antimicrobial Wound Gel is not
recommended for use in deep wounds or body cavities
where removal of waxes may be difficult.

Honey-based topical application

Activon Honey

Medical grade manuka honey

L-Mesitran SOFT ointment dressing
Honey (medical grade) 40%

L-Mesitran (Aspen Medical Europe Ltd) SOFT ointment dressing = £3.59

MANUKA Honeys

Medical grade manuka honey

MANUKA Honeys (Manuka Medical Ltd) dressing = £5.90

Medihoney Antibacterial Medical Honey

Medical grade, Leptospermum sp.

Medihoney (Derma Sciences Europe, Ltd) Antibacterial Medical Honey dressing = £9.90

Medihoney Antibacterial Wound Gel

Medical grade, Leptospermum sp. 80% in natural waxes and oils

Medihoney (Derma Sciences Europe, Ltd) Antibacterial Wound Gel dressing = £4.02

MelMax Plus Honey

Medical grade; Bulgarian, mountain flower) 45% in basis

containing polyethylene glycol

Mesitran Ointment
Honey (medical grade) 47% Excipients include lanolin

Mesitran (Aspen Medical Europe Ltd) ointment dressing = £9.90

Sheet dressing

Actilite

Knitted viscose impregnated with medical grade manuka
honey and manuka oil

Actilite gauze dressing (Advancis Medical) 10 cm x 10 cm = £0.98,
10 cm x 20 cm = £1.90, 5 cm x 5 cm = £0.57

Activon Tulle

Knitted viscose impregnated with medical grade manuka
honey

Activon Tulle gauze dressing (Advancis Medical) 10 cm x 10 cm = £2.97, 5 cm x 5 cm = £1.80

Algovon
Absorbent, non-adherent calcium alginate dressing
impregnated with medical grade manuka honey

Algovon dressing (Advancis Medical) 10 cm x 10 cm = £3.40, 5 cm x 5 cm = £1.98

Algovon Plus
Reinforced calcium alginate dressing impregnated with medical grade manuka honey

Algovon Plus (Advancis Medical) Ribbon dressing 2.5 cm x 20 cm = £3.36, dressing 10 cm x 10 cm = £3.36, 5 cm x 5 cm = £1.96,

L-Mesitran Border
Hydrogel, semi-permeable dressing impregnated with medical grade honey, with adhesive border

L-Mesitran (Aspen Medical Europe Ltd) Border sheet 10 cm x 10 cm square = £2.74

L-Mesitran Hydro
Hydrogel, semi-permeable dressing impregnated with medical grade honey, without adhesive border

L-Mesitran Hydro sheet 1 (Aspen Medical Europe Ltd) 0 cm x 10 cm square = £2.63, 5 cm x 20 cm rectangular = £5.48

L-Mesitran Net
Hydrogel, non-adherent wound contact layer, without
adhesive border

L-Mesitran (Aspen Medical Europe Ltd) Net sheet 10 cm x 10 cm square = £2.53

Medihoney Antibacterial Honey Apinate
Non-adherent calcium alginate dressing, impregnated with medical grade honey

Medihoney Antibacterial Honey Apinate (Derma Sciences Europe, Ltd) dressing 10 cm x 10 cm square = £3.40, 5 cm x 5 cm square = £2.00,

Medihoney Antibacterial Honey Tulle
Woven fabric impregnated with medical grade manuka honey

Medihoney (Derma Sciences Europe, Ltd) Tulle dressing 10 cm x 10 cm = £2.98

Medihoney Gel sheet
Sodium alginate dressing impregnated with medical grade honey

Medihoney Gel Sheet dressing (Derma Sciences Europe, Ltd) 10 cm x 10 cm = £4.20, 5 cm x 5 cm = £1.75

MelMax
Acetate wound contact layer impregnated with buckwheat
honey 75% in ointment basis

MelMax dressing (CliniMed Ltd) 5 cm x 6 cm rectangular = £4.82, 8 cm x 10 cm rectangular = £9.90, 8 cm x 20 cm rectangular = £19.79

Meladerm Plus Tulle
Knitted viscose impregnated with medical grade honey

(Bulgarian, mountain flower) 45% in a basis containing
polyethylene glycol

Meladerm (SanoMed Manufacturing BV) Plus Tulle dressing 10 cm x 10 cm = £2.10

Iodine
Cadeoximer–iodine, like povidone–iodine, releases free
iodine when exposed to wound exudate. The free iodine acts
as an antisepic on the wound surface, the cadeoximer
absorbs wound exudate and encourages de-sloughing.
Two-component hydrogel dressings containing glucose
oxidase and iodide ions generate a low level of free iodine in
the presence of moisture and oxygen.

Povidone–iodine fabric dressing is a knitted viscose
dressing with povidone–iodine incorporated in a
hydrophilic polyethylene glycol basis; this facilitates
diffusion of the iodine into the wound and permits removal of
the dressing by irrigation. The iodine has a wide
spectrum of antimicrobial activity but it is rapidly
 deactivated by wound exudate. Systemic absorption of iodine may occur, particularly from
large wounds or with prolonged use.
Iodosflex® and Iodosorb® are used for the treatment of chronic exuding wounds; max. single application 50 g, max. weekly application 150 g; max. duration up to 3 months in any single course of treatment. They are contra-indicated in patients receiving lithium, in thyroid disorders, in pregnancy and breast feeding, and in children; they should be used with caution in patients with severe renal impairment or history of thyroid disorder. Iodozyme® is an antimicrobial dressing used for lightly to moderately exuding wounds. It is contra-indicated in thyroid disorders and in patients receiving lithium; it should be used with caution in children and in women who are pregnant or breast-feeding. Oxyzyme® is used for non-infected, dry to moderately exuding wounds. It is contra-indicated in thyroid disorders and in patients receiving lithium; it should be used with caution in children and in women who are pregnant or breast-feeding. Povidone-iodine Fabric Dressing is used as a wound contact layer for abrasions and superficial burns. It is contra-indicated in patients with severe renal impairment and in children under 6 months.

Iodosflex Paste
Iodine 0.9% as cadexomer–iodine in a paste basis with gauze backing
Iodosorb Ointment
Iodine 0.9% as cadexomer–iodine in an ointment basis
Iodosorb (Smith & Nephew Healthcare Ltd) ointment dressing = £3.03
Iodosorb Powder
Iodine 0.9% as cadexomer–iodine microbeads, 3-g sachet
Iodosorb (Smith & Nephew Healthcare Ltd) powder dressing sachets = £1.93
Iodozyme Hydrogel
Hydrogel (two-component dressing containing glucose oxidase and iodide ions)
Iodozyme dressing (Archimed Llp) 10 cm x 10 cm square = £12.50, 6.5 cm x 5 cm rectangular = £7.50
Oxyzyme Hydrogel
Hydrogel (two-component dressing containing glucose oxidase and iodide ions)
Oxyzyme dressing (Archimed Llp) 10 cm x 10 cm square = £10.00, 6.5 cm x 5 cm rectangular = £6.00
Povidone-iodine fabric dressing
Inadine
(Drug Tariff specification 43). Knitted viscose primary dressing impregnated with povidone–iodine ointment 10%
Inadine dressing (Systagenix Wound Management Ltd) 5 cm x 5 cm = £0.33, 9.5 cm x 9.5 cm = £0.49

Silver
Antimicrobial dressings containing silver should be used only when infection is suspected as a result of clinical signs or symptoms (see also notes above). Silver ions exert an antimicrobial effect in the presence of wound exudate; the volume of wound exudate as well as the presence of infection should be considered when selecting a silver-containing dressing. Silver-impregnated dressings should not be used routinely for the management of uncomplicated ulcers. It is recommended that these dressings should not be used on acute wounds as there is some evidence to suggest they delay wound healing. Dressings impregnated with silver sulfadiazine have broad antimicrobial activity; if silver sulfadiazine is applied to large areas, or used for prolonged periods, there is a risk of blood disorders and skin discoloration (see p. 1010). The use of silver sulfadiazine-impregnated dressings is contra-indicated in neonates, in pregnancy, and in patients with significant renal or hepatic impairment, sensitivity to sulfonamides, or G6PD deficiency. Large amounts of silver sulfadiazine applied topically may interact with other drugs—see Appendix 1 (sulfonamides).

Alginate dressings

Acticoat Absorbent
Calcium alginate dressing with a silver coated antimicrobial barrier
Acticoat Absorbent (Smith & Nephew Healthcare Ltd) cavity dressing 2 cm x 3 cm = £12.87, dressing 10 cm x 12.5 cm rectangular = £12.79, 5 cm x 5 cm square = £5.33.

Algisite Ag
Calcium alginate dressing, with silver
Algisite Ag dressing (Smith & Nephew Healthcare Ltd) 10 cm x 10 cm = £4.12, 10 cm x 20 cm = £7.57, 2 g = £5.69, 5 cm x 5 cm = £1.65

Askina Calgitrol Ag
Calcium alginate and silver alginate dressing with polysurethane foam backing
Askina Calgitrol Ag dressing (B.Braun Medical Ltd) 10 cm x 10 cm square = £3.21, 15 cm x 15 cm square = £6.21, 20 cm x 20 cm square = £14.48

Askina Calgitrol Thin
Calcium alginate and silver alginate matrix, for use with absorptive secondary dressings
Askina Calgitrol Thin dressing (B.Braun Medical Ltd) 10 cm x 10 cm square = £4.06, 15 cm x 15 cm square = £9.12, 20 cm x 20 cm square = £16.11, 5 cm x 5 cm square = £1.96

Melgisorb Ag
Alginate and carboxymethylcellulose dressing, with ionic silver
Melgisorb Ag (Molyncke Health Care Ltd) Cavity dressing 3 cm x 4 cm = £4.47, dressing 10 cm x 10 cm = £3.59, 15 cm x 15 cm = £7.60, 5 cm x 5 cm = £1.79.

Silvercel
Alginate and carboxymethylcellulose dressing impregnated with silver
Silvercel dressing (Systagenix Wound Management Ltd) 10 cm x 20 cm rectangular = £7.68, 11 cm x 11 cm square = £4.14, 2.5 cm x 30.5 cm rectangular = £4.45, 5 cm x 5 cm square = £1.68

Silvercel Non-adherent
Alginate and carboxymethylcellulose dressing with film wound contact layer, impregnated with silver
Silvercel Non-Adherent (Systagenix Wound Management Ltd) cavity dressing 2.5 cm x 30.5 cm = £3.94, dressing 10 cm x 20 cm rectangular = £7.25, 11 cm x 11 cm square = £3.89, 5 cm x 5 cm square = £1.62.

Sorbax Silver Flat
Calcium alginate fibre, highly absorbent, flat non-woven pads, with silver
Sorbax Silver Flat dressing (Aspen Medical Europe Ltd) 10 cm x 10 cm = £3.97, 10 cm x 20 cm = £7.26, 5 cm x 5 cm = £1.57

Sorbax Silver Plus
Calcium alginate dressing with absorbent backing, with silver
Sorbax Silver Plus dressing (Aspen Medical Europe Ltd) 10 cm x 15 cm = £5.56, 10 cm x 20 cm = £6.77, 15 cm x 20 cm = £9.08, 7.5 cm x 10 cm = £3.35

Sorbax Silver Plus SA
Calcium alginate dressing with absorbent backing and adhesive border, with silver
Sorbax (Aspen Medical Europe Ltd) Silver Plus SA dressing 11.5 cm x 14 cm = £5.44

Sorbax Silver Ribbon
With silver
Sorbax (Aspen Medical Europe Ltd) Silver Ribbon dressing 1 g = £4.15

Sorbax Silver Surgical Packaging
With silver
Sorbax (Aspen Medical Europe Ltd) Silver Packaging dressing 7 cm x 5 cm = £5.76

Suprasorb A + Ag
Calcium alginate dressing, with silver
Suprasorb A + Ag (Lohmann & Rauscher (UK) Ltd) dressing 10cm x 10cm = £4.07, 10cm x 20cm = £7.52, 5cm x 5cm = £1.62, rose dressing 2g = £6.02.

Tegaderm Alginat Ag
Calcium alginate and carboxymethylcellulose dressing, with silver

Tegaderm Alginat Ag dressing (3M Health Care Ltd) 10cm x 10cm = £3.24, 3cm x 30cm = £3.70, 5cm x 5cm = £1.39

Urgosor Silver
Alginat and carboxymethylcellulose dressing, impregnated with silver
Urgosor Silver ( Urgo Ltd) Rope dressing 2.5cm x 30cm = £3.65, dressing 10cm x 10cm = £3.63, 10cm x 20cm = £6.85, 5cm x 5cm = £1.52

Foam dressings

Acticoat Moisture Control
Three layer polyurethane dressing consisting of a silver coated layer, a foam layer, and a waterproof layer
Acticoat Moisture Control dressing (Smith & Nephew Healthcare Ltd) 10cm x 10cm square = £16.70, 10cm x 20cm rectangular = £22.55, 5cm x 5cm square = £7.14

Allevyn
Silver sulfadiazine impregnated polyurethane foam film dressing with or without adhesive border
Allevyn (Smith & Nephew Healthcare Ltd) Adhesive dressing 10cm x 10cm square = £5.45, 12.5cm x 12.5cm square = £7.16, 17.5cm x 17.5cm square = £13.77, 17cm x 17cm square = £10.75, 22cm x 22cm sacral = £14.40, 7.5cm x 7.5cm square = £3.46, Heel Non-Adhesive dressing 10.5cm x 13.5cm = £10.66, Non-Adhesive dressing 10cm x 10cm square = £6.08, 15cm x 15cm square = £11.55, 20cm x 20cm square = £16.68, 5cm x 5cm square = £3.23

Blatain Ag
Silver impregnated polyurethane foam film dressing, with or without adhesive border
Blatain Ag (Coloplast Ltd) cavity dressing 5cm x 8cm = £4.01, dressing 10cm x 10cm square = £8.04, 10cm x 20cm rectangular = £14.78, 12.5cm x 12.5cm square = £9.20, 15cm x 15cm square = £16.14, 18cm x 18cm square = £18.45, 19cm x 20cm heel = £18.20, 20cm x 20cm square = £22.76, 22cm x 22cm sacral = £19.34, 5cm x 7cm rectangular = £3.30

PolyMem Silver
Silver impregnated polyurethane foam film dressing, with or without adhesive border
PolyMem Silver (Aspen Medical Europe Ltd) WIC dressing 8cm x 8cm = £7.05, dressing 10.8cm x 10.8cm square = £8.56, 12.7cm x 12.7cm oval = £5.60, 17cm x 17cm rectangular = £17.76, 5cm x 7cm oval = £2.27

UrgoCell Silver
Non-adherent, polyurethane foam film dressing with silver in wound contact layer
UrgoCell Silver dressing (Urgo Ltd) 10cm x 10cm = £5.86, 15cm x 20cm = £10.74, 6cm x 6cm = £4.26

Hydrocolloid dressings

Aquacel Ag
Soft non-woven pad containing hydrocolloid fibres, (silver impregnated),
Aquacel Ag (Convatec Ltd) Ribbon dressing 1cm x 45cm = £3.08, 2cm x 45cm = £4.71, dressing 10cm x 10cm square = £6.69, 15cm x 15cm square = £8.82, 20cm x 20cm rectangular = £21.89, 4cm x 10cm rectangular = £2.85, 4cm x 20cm rectangular = £3.72, 4cm x 30cm rectangular = £5.57

Physiostulle Ag
Non-adherent polyester fabric with hydrocolloid and silver sulfadiazine
Physiostulle (Coloplast Ltd) dressing 10cm x 10cm = £2.25

Low adherence dressing

Acticoat
Three-layer antimicrobial barrier dressing consisting of a polyester core between low adherent silver-coated high density polyethylene mesh (for 3-day wear)
Acticoat dressing (Smith & Nephew Healthcare Ltd) 10cm x 10cm square = £8.52, 10cm x 20cm rectangular = £13.33, 20cm x 20cm rectangular = £45.60, 5cm x 5cm square = £3.49

Acticoat 7
Five-layer antimicrobial barrier dressing consisting of a polyester core between low adherent silver-coated high density polyethylene mesh (for 7-day wear)
Acticoat 7 dressing (Smith & Nephew Healthcare Ltd) 10cm x 10cm square = £18.07, 15cm x 15cm square = £32.48, 5cm x 5cm square = £6.07

Acticoat Flex 3
Conformable antimicrobial barrier dressing consisting of a polyester core between low adherent silver-coated high density polyethylene mesh (for 3-day wear)
Acticoat Flex 3 dressing (Smith & Nephew Healthcare Ltd) 10cm x 10cm square = £8.56, 10cm x 20cm rectangular = £13.37, 20cm x 40cm rectangular = £45.77, 5cm x 5cm square = £3.50

Acticoat Flex 7
Conformable antimicrobial barrier dressing consisting of a polyester core between low adherent silver-coated high density polyethylene mesh (for 7-day wear)
Acticoat Flex 7 dressing (Smith & Nephew Healthcare Ltd) 10cm x 12.5cm rectangular = £18.14, 15cm x 15cm square = £32.61, 5cm x 5cm square = £6.09

Atrauman Ag
Non-adherent polyamide fabric impregnated with silver and neutral triglycerides
Atrauman Ag dressing (Paul Hartmann Ltd) 10cm x 10cm = £1.25, 10cm x 20cm = £2.45, 5cm x 5cm = £0.51

Soft polymer dressings

Allevyn Ag Gentle
Soft polymer wound contact dressing, with silver sulfadiazine impregnated polyurethane foam layer, with or without adhesive border
Allevyn Ag Gentle (Smith & Nephew Healthcare Ltd) Border dressing 10cm x 10cm = £6.33, 12.5cm x 12.5cm = £8.14, 17.5cm x 17.5cm = £15.51, 7.5cm x 7.5cm = £4.21, dressing 10cm x 10cm = £6.15, 20cm x 20cm = £10.16, 15cm x 15cm = £11.44, 20cm x 20cm = £16.94, 5cm x 5cm = £3.39

Mepilex Ag
Soft silicone wound contact dressing with polyurethane foam film backing, with silver, with or without adhesive border
Mepilex (Mohrlycke Health Care Ltd) Ag dressing 10cm x 10cm = £6.12, 10cm x 20cm = £10.09, 15cm x 15cm = £11.36, 20cm x 20cm = £16.84, 20cm x 50cm = £63.20, Border Ag dressing 10cm x 12.5cm = £5.16, 10cm x 20cm = £8.97, 10cm x 30cm = £13.46, 15cm x 17.5cm = £11.31, 17cm x 20cm = £14.66, 7cm x 7.5cm = £3.41, Border Sacrum Ag dressing 18cm x 18cm = £11.83, 20cm x 20cm = £14.38, 23cm x 23cm = £18.89, Heel Ag dressing 13cm x 20cm = £12.78, 15cm x 22cm = £14.32

Urgotol 550
Non-adherent, soft polymer wound contact dressing, with silver sulfadiazine
Urgotol Silver
Non-adherent soft polymer wound contact dressing, with silver
Urgotol Silver dressing 1 (Urgo Ltd) 5cm x 12cm = £3.53, 5cm x 20cm = £9.61

With charcoal

Actisorb Silver 220
Knitted fabric of activated charcoal, with one-way stretch, with silver residues, within spun-bonded nylon sleeve
Actisorb Silver 220 dressing (Systagenix Wound Management Ltd) 10.5cm x 10.5cm = £2.58, 10.5cm x 19cm = £4.70, 6.5cm x 9.5cm = £1.64

Other antimicrobials

Cutimed Siltec Sorbact
Polyurethane foam dressing with acetate fabric coated with diallylcarbamoyl chloride, with adhesive border
Cutimed Siltec Sorbact dressing (BSN medical Ltd) 12.5cm x 12.5cm = £6.38, 15cm x 15cm = £7.91, 17.5cm x 17.5cm = £11.06, 22.5cm x 22.5cm = £16.83, 7.5cm x 7.5cm = £2.49, 17.5cm x 17.5cm sacral = £8.00, 23cm x 23cm sacral = £12.02.

**Cutimed Sorbact**

Low adherence acetate tissue impregnated with dialky carbamoyl chloride; dressign pad, swabs, round swabs or ribbon gauze, cotton

**Cutimed Sorbact** (BSN medical Ltd) Ribbon dressing 2cm x 50cm = £4.00, 5cm x 200cm = £7.87, Round swab 3cm = £3.27, dressing pad 10cm x 10cm = £5.45, 10cm x 20cm = £8.49, 7cm x 9cm = £3.49, swab 4cm x 6cm = £1.63, 7cm x 9cm = £2.72,

**Cutimed Sorbact Gel**

Hydrogel dressing impregnated with dialky carbamoyl chloride

**Cutimed Sorbact Gel dressing** 7.5cm x (BSN medical Ltd) 15cm rectangular = £4.43, 7.5cm square = £2.63

**Cutimed Sorbact Hydroactive**

Non-adhesive gel dressing with hydropolymer matrix and acetate fabric coated with dialky carbamoyl chloride

**Cutimed Sorbact Hydroactive dressing** (BSN medical Ltd) 14cm x 14cm = £5.31, 14cm x 24cm = £8.52, 19cm x 19cm = £10.01, 24cm x 24cm = £15.17, 7cm x 8.5cm = £3.64

**Cutimed Sorbact Hydroactive B**

Gel dressing with hydropolymer matrix and acetate fabric coated with dialky carbamoyl chloride, with adhesive border

**Cutimed Sorbact Hydroactive B dressing** (BSN medical Ltd) 10cm x 10cm = £7.02, 10cm x 20cm = £11.24, 15cm x 15cm = £13.21, 20cm x 20cm = £20.02, 5cm x 6.5cm = £3.94

**Flaminal Forte gel**

Alginate with glucose oxidase and lactoperoxidase, for moderately to heavily exuding wounds

**Flaminal Hydro gel**

Alginate with glucose oxidase and lactoperoxidase, for lightly to moderately exuding wounds

**Kendall AMD**

Foam dressing with polyhexanide, without adhesive border

**Kendall AMD Antimicrobial foam dressing** (Aria Medical Ltd) 10cm x 10cm square = £4.71, 10cm x 20cm rectangular = £8.92, 15cm x 15cm square = £8.92, 20cm x 20cm square = £13.07, 5cm x 5cm square = £2.56, 8.8cm x 7.5cm rectangular (fenestrated) = £4.43

**Kendall AMD Plus**

Foam dressing with polyhexanide, without adhesive border

**Kendall AMD Antimicrobial Plus foam dressing** (Aria Medical Ltd) 10cm x 10cm square = £4.94, 8.8cm x 7.5cm rectangular (fenestrated) = £4.43

**Octenilin Wound gel**

Wound gel, hydroxyethylcellulose and propylene glycol, with octenidine hydrochloride

**Prontosan Wound Gel**

Hydrogel containing betaine surfactant and polyhexanide

**Suprasorb X + PHMB**

Biosynthetic cellulose fibre dressing with polyhexanide

**Suprasorb X + PHMB dressing** (Lohmann & Rauscher (UK) Ltd) 14cm x 20cm rectangular = £11.53, 2cm x 21cm rope = £7.18, 5cm x 5cm square = £2.59, 8cm x 9cm square = £2.07

**Telfa AMD**

Low adherence absorbent perforated plastic film faced dressing with polyhexanide

**Telfa AMD dressing** (Aria Medical Ltd) 10cm x 7.5cm = £0.18, 20cm x 7.5cm = £0.28

**Telfa AMD Island**

Low adherence dressing with adhesive border and absorbent pad, with polyhexanide

**Telfa AMD Island dressing** 10cm x (Aria Medical Ltd) 12.5cm = £0.59, 20cm = £0.86, 25.5cm = £0.98, 35cm = £1.22

**Chlorhexidine gauze dressing**

**Bactigras**

Fabric of linen weave, wet and warp threads of cotton and/or viscose yarn, impregnated with ointment containing chlorhexidine acetate

**Bactigras gauze dressing** (Smith & Nephew Healthcare Ltd) 5cm x 5cm = 28p, 10cm x 10cm = 59p

**Irrigation fluids**

**Octenilin Wound irrigation solution**

Aqueous solution containing glycerol, ethylhexylglycerin and octenidine hydrochloride

**Prontosan Wound Irrigation Solution**

Aqueous solution containing betaine surfactant and polyhexanide

**Prontosan irrigation solution** (B.Braun Medical Ltd) 350ml bottles = £4.75, 40ml unit dose = £14.12

**Specialised dressings**

**Protease-modulating matrix dressings**

**Cadesorb Ointment**

Cadesorb (Smith & Nephew Healthcare Ltd) ointment = £9.18

**Catrix**

Catrix dressing (Cranage Healthcare Ltd) sachets = £3.80

**Promogran**

Collagen and oxidised regenerated cellulose matrix, applied directly to wound and covered with suitable dressing

**Promogran dressing** (Systagenix Wound Management Ltd) 123 square cm = £15.62, 28 square cm = £5.19

**Promogran Prisma Matrix**

Collagen, silver and oxidised regenerated cellulose matrix, applied directly to wound and covered with suitable dressing

**Promogran Prisma dressing** (Systagenix Wound Management Ltd) 123 square cm = £17.98, 28 square cm = £6.31

**Tegaderm Matrix**

Cellulose acetate matrix, impregnated with polyhydrated ionogens ointment in polyethylene glycol basis

**Tegaderm Matrix dressing** (3M Health Care Ltd) 5cm x 5cm = £4.98, 8cm x 10cm = £10.23

**UroStart**

Soft adherent polymer matrix containing nano-oligosaccharide factor (NOSF), with polyurethane foam film backing

**UroStart dressing** (Urgo Ltd) 10cm x 10cm = £6.07, 15cm x 20cm = £10.92, 6cm x 6cm = £4.39, 12cm x 19cm heel = £8.36

**UroStart Contact**

Non-adherent soft polymer wound contact dressing containing nano-oligosaccharide factor (NOSF)

**UroStart (Urgo Ltd) Contact dressing** 5cm x 7cm = £2.96

**Silicone keloid dressings**

Silicone gel and gel sheets are used to reduce or prevent hypertrophic and keloid scarring. They should not be used on open wounds. Application times should be increased gradually. Silicone sheets can be washed and reused.

**Silicone gel**

**Bapscarcare**

Silicone gel

**Bapscarcare (BAP Medical UK Ltd) gel** = £17.00

**Cilitech**

Silicone gel

**Cilitech (Su-Med International (UK) Ltd) gel** = £50.00

**Dermatix**

Silicone gel

**Dermatix gel** (Meda Pharmaceuticals Ltd) = £60.53

**Kelo-cote UV**

Silicone gel with SPF 30 UV protection

**Kelo-cote** (Sinclair IS Pharma Plc) UV gel = £17.88

**Kelo-cote gel**

Silicone gel
Wound management

NewGel E
Silicone gel with vitamin E
NewGel E (AdvanTec Surgical Ltd) gel = £17.70

Scarsil
Silicone gel
Scarsil (Jobskin Ltd) gel = £15.19

Silgel
Silicone gel
Silgel (Nagor Ltd) STC-SE gel = £19.00

Silicone sheets
Advasil Conform
Self-adhesive silicone gel sheet with polyurethane film backing
Advasil Conform sheet I (AdvanTec Medical) 10cm x 10cm square = £5.20, 5cm x 10cm rectangular = £9.17

Bapsccare T
Self-adhesive silicone gel sheet
Bapsccare T sheet (BAP Medical UK Ltd) 10cm x 15cm rectangular = £9.00, 5cm x 30cm rectangular = £9.00, 5cm x 7cm rectangular = £3.15

Cica-Care
Soft, self-adhesive, semi-occlusive silicone gel sheet with backing
Cica-Care sheet (Smith & Nephew Healthcare Ltd) 15cm x 12cm rectangular = £28.40, 6cm x 12cm rectangular = £14.57

Ciltech
Silicone gel sheet
Ciltech sheet 1 (Su-Med International (UK) Ltd) 10cm x 10cm square = £7.50, 0cm x 20cm rectangular = £12.50, 5cm x 15cm square = £14.00

Dermafix
Self-adhesive silicone gel sheet (clear- or fabric-backed)
Dermafix (Meda Pharmaceuticals Ltd) Clear sheet 13cm x 13cm square = £15.79, 13cm x 25cm rectangular = £28.53, 20cm x 30cm rectangular = £51.97, 4cm x 13cm rectangular = £6.88. Fabric sheet 13cm x 13cm square = £15.79, 13cm x 25cm rectangular = £28.53, 20cm x 30cm rectangular = £51.97, 4cm x 13cm rectangular = £6.88

Mepiform
Self-adhesive silicone gel sheet with polyurethane film backing
Mepiform sheet (Molnlycke Health Care Ltd) 4cm x 31cm rectangular = £16.80, 5cm x 7cm rectangular = £3.42, 9cm x 18cm rectangular = £13.37

Scar FX
Self-adhesive, transparent, silicone gel sheet
Scar FX sheet (Jobskin Ltd) 10cm x 20cm rectangular = £16.00, 22.5cm x 14.5cm shaped = £12.00, 25.5cm x 30.5cm rectangular = £50.00, 3.75cm x 2.25cm rectangular = £12.00, 7.5cm diameter shaped = £8.50

Silgel
Silicone gel sheet
Silgel sheet (Nagor Ltd) 10cm x 10cm square = £13.50, 10cm x 30cm rectangular = £31.50, 10cm x 5cm rectangular = £7.50, 15cm x 10cm rectangular = £19.50, 20cm x 20cm square = £40.00, 25cm x 15cm shaped = £21.12, 30cm x 5cm rectangular = £19.50, 40cm x 40cm square = £144.00, 46cm x 8.5cm shaped = £39.46, 5.5cm diameter shaped = £4.00

Adjunct dressings and appliances

Surgical absorbents
Surgical absorbents applied directly to the wound have many disadvantages—dehydration of and adherence to the wound, shedding of fibres, and the leakage of exudate (‘strike through’) with an associated risk of infection. Gauze and cotton absorbent dressings can be used as secondary layers in the management of heavily exuding wounds (but see also Capillary-action dressings, p. 1305). Absorbent cotton gauze fabric can be used for swabbing and cleaning skin. Ribbon gauze can be used post-operatively to pack wound cavities, but adherence to the wound bed will cause bleeding and tissue damage on removal of the dressing—an advanced wound dressing (e.g. hydrocolloid-fibrous p. 1301, foam p. 1302, or alginate p. 1304) layered into the cavity is often more suitable.

Cotton

Absorbent Cotton, BP
Carded cotton fibres of not less than 10 mm average staple length, available in rolls and balls

Absorbent (Robert Bailey & Son Plc) cotton BP 1988

Absorbent Cotton, Hospital Quality
As for absorbent cotton but lower quality materials, shorter staple length etc.

Absorbent (Robert Bailey & Son Plc) cotton hospital quality

Gauze and cotton tissue

Gamgee Tissue (blue)
Consists of absorbent cotton enclosed in absorbent cotton gauze type 2 or absorbent cotton and viscose gauze type 2

Gamgee (Robinson Healthcare) tissue blue label

Gamgee Tissue (pink)
Consists of absorbent cotton enclosed in absorbent cotton gauze type 2 or absorbent cotton and viscose gauze type 2

Gamgee (Robinson Healthcare) tissue pink label DF

Gauze and tissue

Absorbent Cotton Gauze, BP 1988
Cotton fabric of plain weave, in rolls and as swabs (see below), usually Type 13 light, sterile

Absorbent (Robert Bailey & Son Plc) cotton BP 1988

Alvita (Alliance Healthcare (Distribution) Ltd) absorbent cotton BP 1988

Clini (Clinisupplies Ltd) absorbent cotton BP 1988

Vermaid (Synergy Health Plc) absorbent cotton BP 1988

Absorbent Cotton and Viscose Ribbon Gauze, BP 1988
Woven fabric in ribbon form with fast selvedge edges, warp threads of cotton, weft threads of viscose or combined cotton and viscose yarn, sterile

Vermaid Fast Edge ribbon gauze sterile (Synergy Health Plc) 1.25cm, 2.5cm

Lint

Absorbent Lint, BPC
Cotton cloth of plain weave with nap raised on one side from warp yarns

Absorbent (Robinson Healthcare) lint

Alvita (Alliance Healthcare (Distribution) Ltd) absorbent lint BPC

Clini (Clinisupplies Ltd) absorbent lint BPC

Pads

Drisorb
Absorbent Dressing Pads, Sterile
Drisorb (Synergy Health Plc) dressing pad 10cm x 20cm = £0.17

PremierPad
Absorbent Dressing Pads, Sterile
PremierPad dressing pad (Shermond) 10cm x 20cm = £0.18, 20cm x 20cm = £0.25

Xupad
Absorbent Dressing Pads, Sterile
Xupad dressing pad (Richardson Healthcare Ltd) 10cm x 20cm = £0.17, 20cm x 20cm = £0.28, 20cm x 40cm = £0.40

Wound drainage pouches
Wound drainage pouches can be used in the management of wounds and fistulas with significant levels of exudate.

Biotrol Draina S
Wound drainage pouch

Biotrol Draina S wound drainage bag (B.Braun Medical Ltd) large (Transparent) = £94.55, medium (Transparent) = £76.88, mini (Transparent) = £77.11
Biotrol Draina S Vision
Wound drainage pouch
Draina S Vision (B. Braun Medical Ltd) 100 wound drainage bag = £123.38, 50 wound drainage bag = £100.66, 75 wound drainage bag = £106.34

Eakin Access window
For use with Eakin pouches
Eakin (Pelican Healthcare Ltd) access window = £37.39

Eakin Wound pouch, bung closure
Wound pouch, bung closure
Eakin wound drainage bag with bung closure (Pelican Healthcare Ltd) £101.48, medium = £74.78, small = £53.41, and access window for horizontal wounds, extra large = £101.48, for horizontal wounds, extra large = £90.80; for vertical incision wounds, extra large = £90.80, wounds, extra large = £90.80,

Eakin Wound pouch, fold and tuck closure
Wound pouch, fold and tuck closure
Eakin wound drainage bag with fold and tuck closure, (Pelican Healthcare Ltd) £90.80, medium = £69.94, small = £48.07, extra large = £80.12,

Option Wound Manager
Wound drainage bag
Option wound manager bag (Oxamed Ltd) £158.71, medium = £133.16, small = £130.26, square = £138.95, extra small = £117.12.

Option Wound Manager with access port
Wound drainage bag, with access port
Option wound manager bag with access port, (Oxamed Ltd) large = £169.65, medium = £138.95, small = £136.05, square = £144.74, extra small = £128.06.

Option Wound Manager, cut to fit
Wound drainage bag, cut to fit
Option wound manager bag (Oxamed Ltd) large = £83.44, medium = £79.66, small = £71.91

Welland Fistula bag
Wound drainage bag, cut-to-fit
Welland (Welland Medical Ltd) Fistula wound drainage bag = £81.29

Physical debridement pads
Debrisoft® is a pad that is used for the debridement of superficial wounds containing loose slough and debris, and for the removal of hyperkeratosis from the skin. Debrisoft® must be fully moistened with a wound cleansing solution before use and is not appropriate for use as a wound dressing.

Debrisoft Pad
Polyester fibres with bound edges and knitted outer surface coated with polyacrylate
Debrisoft (Activa Healthcare Ltd) pad 10cm x 10cm = £6.39

Complex adjunct therapies
Topical negative pressure therapy
Accessories
Renasys
Soft port and connector
Renasys (Smith & Nephew Healthcare Ltd) Soft Port = £11.11, connector for use with soft port = £3.24

V.A.C.
Drape, gel for canister, Sensa T.R.A.C. Pad
SensaT.R.A.C. (KCI Medical Ltd) pad = £10.95
T.R.A.C. (KCI Medical Ltd) connector = £3.13
V.A.C. (KCI Medical Ltd) drape = £9.39, gel strips = £3.76
Venturi
Gel patches, adhesive, and connector
Venturi (Talley Group Ltd) adhesive gel patch = £15.00, connector = £15.00

WoundASSIST gel strip
WoundASSIST (Huntleigh Healthcare Ltd) TNP gel strip = £3.37

Vacuum assisted closure products
Exsu-Fast kit 1
Dressing Kit
Exsu-Fast (Synergy Health Plc) dressing kit 1 = £28.04
Exsu-Fast kit 2
Dressing Kit
Exsu-Fast (Synergy Health Plc) dressing kit 2 = £35.83
Exsu-Fast kit 3
Dressing Kit
Exsu-Fast (Synergy Health Plc) dressing kit 3 = £35.83
Exsu-Fast kit 4
Dressing Kit
Exsu-Fast (Synergy Health Plc) dressing kit 4 = £28.04

V.A.C. GranaFoam
Polypolyurethane foam dressing (with adhesive drapes and pad connector); with or without silver
V.A.C. GranaFoam (KCI Medical Ltd) Bridge dressing kit = £32.04, Silver with SensaT.R.A.C dressing kit medium = £38.04, small = £32.78, dressing kit large = £31.70, medium = £27.32, small = £22.95,

V.A.C. Simplace
Spiral-cut polyurethane foam dressings, vapour-permeable adhesive film dressings (with adhesive drapes and pad connector)
V.A.C. Simplace EX dressing kit (KCI Medical Ltd) medium = £30.58, small = £26.60

V.A.C. WhiteFoam
Polyvinyl alcohol foam dressing or dressing kit
V.A.C. WhiteFoam dressing (KCI Medical Ltd) large = £17.04, small = £10.64, kit large = £33.54, small = £25.91,
Venturi
Wound sealing kit, flat drain; with or without channel drain
Venturi wound sealer with steel (Talley Group Ltd) channel drain = £15.00, flat drain, large = £17.50, standard = £15.00,

WoundASSIST
Wound pack and channel drain
WoundASSIST TNP dressing pack (Huntleigh Healthcare Ltd) medium/large = £23.85, small/medium = £20.81, channel drain medium/large = £23.85, small/medium = £20.81, extra large = £34.05,

Wound drainage collection devices
ActiV.A.C.
Canister with gel
ActiV.A.C (KCI Medical Ltd) canister with gel = £28.42

S-Canister
Canister kit
S-Canister (Smith & Nephew Healthcare Ltd) kit = £19.00

V.A.C. Freedom
Canister with gel
V.A.C. (KCI Medical Ltd) Freedom Canister with gel = £28.85
Venturi
Canister kit with solidifier
Venturi (Talley Group Ltd) Compact canister kit = £12.50, canister kit = £12.50

WoundASSIST wound pack
Canister
WoundASSIST (Huntleigh Healthcare Ltd) TNP canister = £20.30

Wound care accessories
Dressing packs
The role of dressing packs is very limited. They are used to provide a clean or sterile working surface; some packs shown below include cotton wool balls, which are not recommended for use on wounds.

Multiple Pack Dressing No. 1
Contains absorbent cotton, absorbent cotton gauze type 13 light (sterile), open-wove bandages (banded)

Vernaid (Synergy Health Plc) multiple pack dressing
Non-drug tariff specification sterile dressing packs

Dressit
Vitrex gloves, large apron, disposable bag, paper towel, softswabs, adsorbent pad, sterile field
Dressit sterile dressing pack with (Richardson Healthcare Ltd) medium/large gloves = £0.60, small/medium gloves = £0.60

Nurse It
Contains latex-free, powder-free nitrile gloves, sterile laminated paper sheet, large apron, non-sterile swabs, paper towel, disposable bag, compartmented tray, disposable forceps, paper measuring tape

Nurse It sterile dressing pack with (Medicaplus International Ltd) medium/large gloves = £0.54, small/medium gloves = £0.54

Polyfield Nitrile Patient Pack
Contains powder-free nitrile gloves, laminate sheet, non-sterile or non-sterile 4 ply absorbent paper towel, water repellent inner wrapper

Polyfield Nitrile Patient Pack with (Shermond) large gloves = £0.52, medium gloves = £0.52, small gloves = £0.52

Sovereign medium gloves = £0

Softswab non-sterile fabric swab 4ply (Richardson Healthcare Ltd) non-sterile 10cm x 10cm, sterile 7.5cm x 7.5cm

Softswab non-sterile fabric swab 4ply (Synergy Health Plc) non-sterile 10cm x 10cm, sterile 7.5cm x 7.5cm

Topper 8 non-sterile fabric swabs 4ply (Syntagenix Wound Management Ltd) non-sterile 10cm x 10cm, sterile 7.5cm x 7.5cm

Filamated gauze swabs

Cotfil
As for Gauze Swab, but with thin layer of Absorbent Cotton enclosed within, non-sterile
Cotfil (Synergy Health Plc) filamated gauze swab 8ply non-sterile 10cm x 10cm

Filamated non-woven Fabric Swab

Regal
(Drug Tariff specification 29). Film of viscose fibres enclosed within non-sterile viscose fabric folded 8-ply, non-sterile
Regal (Syntagenix Wound Management Ltd) filamated swab 8ply 10cm x 10cm

Surgical adhesive tapes

Adhesive tapes are useful for retaining dressings on joints or awkward body parts. These tapes, particularly those containing rubber, can cause irritant and allergic reactions in susceptible patients; synthetic adhesives have been developed to overcome this problem, but they, too, may sometimes be associated with reactions. Synthetic adhesive, or silicon adhesive, tapes can be used for patients with skin reactions to plasters and strapping containing rubber, or undergoing prolonged treatment. Adhesive tapes that are occlusive may cause skin maceration. Care is needed not to apply these tapes under tension, to avoid creating a tourniquet effect. If applied over joints they need to be orientated so that the area of maximum extensibility of the fabric is in the direction of movement of the limb.

Occlusive adhesive tapes

Blender
(Impermeable Plastic Adhesive Tape, BP 1988). Extensible water-impermeable plastic film spread with a polymeric adhesive mass
Blender tape (3M Health Care Ltd) 2.5cm = £1.77, 5cm = £3.37

Sleek
(Impermeable Plastic Adhesive Tape, BP 1988). Extensible water-impermeable plastic film spread with an adhesive mass
Leukoplast Sleek tape (BSN medical Ltd) 2.5cm, 5cm, 7.5cm

Permeable adhesive tapes

3m Kid Removal Silicone Tape
Soft silicone, water-resistant, knitted fabric, polyurethane film adhesive tape
3m Kid removal tape (3M Health Care Ltd) 2.5cm = £3.58, 5cm = £6.48

Chemifix
(Permeable, Apertured Non-Woven Synthetic Adhesive Tape, BP 1988). Non-sterile fabric with a polyacrylate adhesive
Chemifix tape (Medicareplus International Ltd) 10cm = £2.10, 2.5cm = £0.90, 5cm = £1.40

Chemipore
(Permeable Non-Woven Synthetic Adhesive Tape, BP 1988). Backing of paper-based or non-sterile textile material spread with a polymeric adhesive mass
Chemipore tape (Medicareplus International Ltd) 1.25cm = £0.27, 2.5cm = £0.70, 5cm = £0.95

Clinipore
(Permeable Non-Woven Synthetic Adhesive Tape, BP 1988). Backing of paper-based or non-sterile textile material spread with a polymeric adhesive mass
Clinipore tape (CliniSupplies Ltd) 1.25cm = £0.35, 2.5cm = £0.73, 5cm = £0.99

Elastoplast
(Elastic Adhesive Tape, BP 1988). Woven fabric, elastic in warp (crepe-twisted cotton threads), weft of cotton and/or viscose threads, spread with adhesive mass containing zinc oxide
Tensoplast (BSN medical Ltd) elastic adhesive tape 2.5cm

Hypafix tape (BSN medical Ltd) 10cm = £4.63, 15cm = £6.86, 2.5cm = £1.67, 5cm = £9.10, 10cm = £13.15, 5cm = £2.65

Insil (Soft silicone, water-resistant, knitted fabric, polyurethane film adhesive tape.

Insil tape (Insight Medical Products Ltd) 2cm = £5.77, 4cm = £5.77

Leukofix (Permeable Non-Woven Synthetic Adhesive Tape, BP 1988). Backing of paper-based or non-woven textile material spread with a polymeric adhesive mass.

Leukofix tape (BSN medical Ltd) 1.25cm = £0.55, 2.5cm = £0.89, 5cm = £1.55

Leukopor (Permeable Non-Woven Synthetic Adhesive Tape, BP 1988). Backing of paper-based or non-woven textile material spread with a polymeric adhesive mass.

Leukopor tape (Robert Bailey & Son Plc) 1.25cm = £0.49, 2.5cm = £0.76, 5cm = £1.34

Mediplast (Permeable Non-Woven Synthetic Adhesive Tape, BP 1988). Backing of paper-based or non-woven textile material spread with a polymeric adhesive mass.

Mediplast tape (Neomedic Ltd) 1.25cm = £0.30, 2.5cm = £0.50

Mediplast (Fabric, plain weave, warp and weft of cotton and/or viscose, spread with an adhesive containing zinc oxide.

Mediplast Zinc Oxide plaster (Neomedic Ltd) 1.25cm = £0.82, 2.5cm = £1.19, 5cm = £1.99, 7.5cm = £2.99


Mefix tape (Molnlycke Health Care Ltd) 10cm = £2.89, 15cm = £3.94, 2.5cm = £1.02, 20cm = £5.04, 30cm = £7.24, 5cm = £1.81

Mepitac (Soft silicone, water-resistant, knitted fabric, polyurethane film adhesive tape.

Mepitac tape (Molnlycke Health Care Ltd) 2cm = £0.93, 4cm = £0.93

Micropore (Permeable Non-Woven Synthetic Adhesive Tape, BP 1988). Backing of paper-based or non-woven textile material spread with a polymeric adhesive mass.

Micropore tape (3M Health Care Ltd) 1.25cm = £0.62, 2.5cm = £0.92, 5cm = £1.62


Omnifix tape (Paul Hartmann Ltd) 10cm = £4.04, 15cm = £5.97, 5cm = £2.40

OpSite Flexifix Gentle (Soft silicone, water-resistant, knitted fabric, polyurethane film adhesive tape.

OpSite Flexifix Gentle tape (Smith & Nephew Healthcare Ltd) 2.5cm = £10.20, 5cm = £19.13


Primaflex tape (Smith & Nephew Healthcare Ltd) 10cm = £2.32, 15cm = £3.43, 20cm = £4.22, 5cm = £1.58

Scanpor (Permeable Non-Woven Synthetic Adhesive Tape, BP 1988). Backing of paper-based or non-woven textile material spread with a polymeric adhesive mass.

Scanpor tape (Bio-Diagnostics Ltd) 1.25cm = £0.55, 2.5cm = £0.92, 5cm = £1.75, 7.5cm = £2.56

Siltape (Soft silicone, water-resistant, knitted fabric, polyurethane film adhesive tape.

Siltape (Advancis Medical) 2cm = £5.60, 4cm = £5.60

Strappal (Fabric, plain weave, warp and weft of cotton and/or viscose, spread with an adhesive containing zinc oxide.

Strappal adhesive tape (BSN medical Ltd) 2.5cm = £1.37, 5cm = £2.32, 7.5cm = £3.49

Transpore (Permeable Non-Woven Synthetic Adhesive Tape, BP 1988). Backing of paper-based or non-woven textile material spread with a polymeric adhesive mass.

Transpore tape (3M Health Care Ltd) 1.25cm = £0.52, 2.5cm = £0.84, 5cm = £1.48

Zinc Oxide Adhesive Tape, BP 1988 (Fabric, plain weave, warp and weft of cotton and/or viscose, spread with an adhesive containing zinc oxide.

Fast Aid zinc oxide adhesive tape (Robinson Healthcare) 1.25cm, 2.5cm, 5cm, 7.5cm

Skin closure dressings
Skin closure strips are used as an alternative to sutures for minor cuts and lacerations. Skin tissue adhesive can be used for closure of minor skin wounds and for additional suture support.

Skin closure strips, sterile

Leukostrip (Drug Tariff specifies that these are specifically for personal administration by the prescriber.

Leukostrip (Smith & Nephew Healthcare Ltd) skin closure strips 6.4mm x 76mm = £6.28

Omnistrip (Drug Tariff specifies that these are specifically for personal administration by the prescriber.

Omnistrip (Paul Hartmann Ltd) skin closure strips sterile 6mm x 76mm = £24.11

Steri-strip (Drug Tariff specifies that these are specifically for personal administration by the prescriber.

Steri-strip (3M Health Care Ltd) skin closure strips 6mm x 75mm = £8.77

Bandages
Non-extendable bandages
Skin closure strips are used as an alternative to sutures for minor cuts and lacerations. Skin tissue adhesive can be used for closure of minor skin wounds and for additional suture support.

Open-wound Bandage, Type 1 BP 1988
Cotton cloth, plain weave, warp of cotton, weft of cotton, viscose, or combination, one continuous length.

Clini open wave bandage Type 1 BP 1988 (CliniSupplies Ltd) 10cm x 5m, 2.5cm x 5m, 5cm x 5m, 7.5cm x 5m.

Vernaoid white open wave bandage (Synergy Health Plc) 10cm x 5m, 2.5cm x 5m, 5cm x 5m, 7.5cm x 5m.

White open wave bandage (Robert Bailey & Son Plc) 10cm x 5m, 2.5cm x 5m, 5cm x 5m, 7.5cm x 5m.

Triangular Calico Bandage, BP 1980
Unbleached calico right-angled triangle.

Clini (CliniSupplies Ltd) triangular calico bandage BP 1980 90cm x 127cm.

Triangular (BSN medical Ltd) calico bandage 90cm x 127cm.

Light-weight conforming bandages
Lightweight conforming bandages are used for dressing retention, with the aim of keeping the dressing close to the wound without inhibiting movement or restricting blood flow. The elasticity of conforming-stretch bandages (also termed contour bandages) is greater than that of cotton conforming bandages.
Wound management
Appendix 4

Acti-Wrap
Fabric, plain weave, warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length, 4 m stretched (all)

Acti-Wrap (cohesive/latex free) bandage (Activa Healthcare Ltd) 10cm x 4m = £0.80, 6cm x 4m = £0.65, 8cm x 4m = £0.68

Cotton Conforming Bandage, BP 1988
Cotton fabric, plain weave, treated to impart some elasticity to warp and weft

Easifix
Fabric, plain weave, warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length, 4 m stretched (all)

Easifix (BN medical Ltd) 10cm x 4m = £0.50, 15cm x 4m = £0.85, 5cm x 4m = £0.35, 7.5cm x 4m = £0.42

Easifix K
Fabric, knitted warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length. 4 m stretched

Easifik bandage (BSN medical Ltd) 10cm x 4m = £0.18, 15cm x 4m = £0.32, 2.5cm x 4m = £0.10, 5cm x 4m = £0.11, 7.5cm x 4m = £0.16

Hospiform
Fabric, plain weave, warp of polyamide, weft of viscose

Hospiform bandage (Paul Hartmann Ltd) 10cm x 4m = £0.19, 12cm x 4m = £0.23, 6cm x 4m = £0.13, 8cm x 4m = £0.17

K-Band
Fabric, knitted warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length. 4 m stretched

K-Band bandage (Urgo Ltd) 10cm x 4m = £0.28, 15cm x 4m = £0.49, 5cm x 4m = £0.20, 7cm x 4m = £0.26

Knit Fix
Fabric, knitted warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length. 4 m stretched

Knit Fix bandage (Robert Bailey & Son Plc) 10cm x 4m = £0.17, 15cm x 4m = £0.33, 5cm x 4m = £0.12, 7cm x 4m = £0.17

Knit-Band
Fabric, knitted warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length. 4 m stretched

Knit-Band bandage (CliniSupplies Ltd) 10cm x 4m = £0.17, 15cm x 4m = £0.30, 5cm x 4m = £0.10, 7cm x 4m = £0.15

Kontour
Fabric, plain weave, warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length, 4 m stretched (all)

Kontour bandage (EasiGrip Ltd) 10cm x 4m = £0.40, 15cm x 4m = £0.66, 5cm x 4m = £0.28, 7.5cm x 4m = £0.35

Mollelast
Fabric, plain weave, warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length, 4 m stretched (all)

Mollelast (Lohmann & Rauscher (UK) Ltd) bandage 4cm x 4m = £0.30

Peha-haft
Polyamide and Cellulose Contour Bandage, cohesive, latex-free

Peha-haft bandage (Paul Hartmann Ltd) 10cm x 4m = £0.76, 12cm x 4m = £0.90, 2.5cm x 4m = £0.73, 4cm x 4m = £0.47, 6cm x 4m = £0.56, 8cm x 4m = £0.66

PremierBand
Polyamide and Cellulose Contour Bandage

PremierBand bandage (Shermond) 10cm x 4m = £0.17, 15cm x 4m = £0.25, 5cm x 4m = £0.12, 7.5cm x 4m = £0.14

Slinky
Fabric, plain weave, warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length, 4 m stretched (all)

Slinky bandage (Molnycke Health Care Ltd) 10cm x 4m = £0.71, 15cm x 4m = £1.02, 7.5cm x 4m = £0.59

Stayform
Fabric, plain weave, warp of polyamide filament, weft of cotton or viscose, fast edges, one continuous length, 4 m stretched (all)

Stayform bandage (Robinson Healthcare) 10cm x 4m = £0.40, 15cm x 4m = £0.68, 5cm x 4m = £0.29, 7.5cm x 4m = £0.36

Tubular bandages and garments
Tubular bandages are available in different forms, according to the function required of them. Some are used under orthopaedic casts and some are suitable for protecting areas to which creams or ointments (other than those containing potent corticosteroids) have been applied. The conformability of the elasticated versions makes them particularly suitable for retaining dressings on difficult parts of the body or for soft tissue injury, but their use as the only means of applying pressure to an oedematous limb or to a varicose ulcer is not appropriate, since the pressure they exert is inadequate.

Compression hosiery reduces the recurrence of venous leg ulcers and should be considered for use after wound healing.

Silk clothing is available as an alternative to elasticated viscose stockinet garments, for use in the management of severe eczema and allergic skin conditions.

Elasticated Surgical Tubular Stockinette, Foam padded is used for relief of pressure and elimination of friction in relevant area; porosity of foam lining allows normal water loss from skin surface.

For Elasticated Tubular Bandage, BP 1993, where no size stated by the prescriber, the 30 cm length should be supplied and width endorsed. Non-elasticated Cotton Stockinette, Bleached, BP 1988 1m lengths is used as basis (with wadding) for Plaster of Paris bandages etc.; 6 m length, compression bandage.

For Non-elasticated Ribbed Cotton and Viscose Surgical Tubular Stockinette, BP 1988, the Drug Tariff specifies various combinations of sizes to provide sufficient material for part or full body coverage. It is used as protective dressings with tar-based and other steroid ointments.

Elasticated

Acti-Fast
(Drug Tariff specification 46). Lightweight plain-knitted elasticated tubular bandage

Acti-Fast 2-way stretch stockinette (Activa Healthcare Ltd) 10.75cm = £6.04, 17.5cm = £1.83, 20cm = £3.20, 3.5cm = £0.56, 5cm = £0.58, 7.5cm = £0.77

Clinifast
(Drug Tariff specification 46). Lightweight plain-knitted elasticated tubular bandage; various colours and sizes

Clinifast stockinette (CliniSupplies Ltd) 10.75cm = £5.04, 17.5cm = £1.83, 3.5cm = £0.56, 5cm = £0.58, 7.5cm = £0.77

Comfifast
(Drug Tariff specification 46). Lightweight plain-knitted elasticated tubular bandage; various colours and sizes

Comfifast stockinette (Synergy Health Plc) 10.75cm = £6.04, 17.5cm = £1.83, 3.5cm = £0.56, 5cm = £0.58, 7.5cm = £0.77

Comfifast Easywrap
(Drug Tariff specification 46). Lightweight plain-knitted elasticated tubular bandage; various colours and sizes
Comfifast Multistretch Tubular Bandage with polyurethane foam lining.

Coverflex Lightweight plain-knitted elasticated tubular bandage; various colours and sizes

Coverflex stockinette (Paul Hartmann Ltd) 10.75cm = £0.81, 17.5cm = £0.89, 25.5cm = £0.95

Coverflex stockinette (Easyrip Ltd) 10.75cm = £0.90, 17.5cm = £0.91, 25.5cm = £0.96

Elasticated Surgical Tubular Stockinette, Foam padded or Topipad

DreamSkin Knitted silk fabric, hypoallergenic, sericin-free

DreamSkin (DreamSkin Health Ltd) baby leggins with foldaway feet 0–3 months = £24.95, 3–6 months = £27.81, 6–9 months = £28.32, 9–12 months = £28.77, 12–18 months = £29.87, 18–24 months = £32.43, 24–30 months = £34.49, 30–36 months = £36.63, 36–42 months = £38.87, 42–48 months = £41.21, 48–54 months = £43.65, 54–60 months = £46.19, 60–66 months = £48.83, 66–72 months = £51.64, 72–78 months = £54.62, 78–84 months = £57.77, 84–90 months = £60.95, 90–96 months = £64.21, 96–108 months = £67.62, 108–120 months = £71.15, 120–144 months = £74.81, 144–168 months = £78.64, 168–192 months = £82.60, 192–216 months = £86.66, 216–240 months = £90.83, 240–270 months = £95.10, 270–300 months = £99.48

Elasticated Tubular Bandage, BP 1993

Easystrip Cotton stockinette bleached heavyweight (E Salis Ltd) 10cm, 2.5cm, 5cm

Silk Clothing

Skinny

Stylist

Wound management products and elasticated garments
Support bandages

Light support bandages, which include the various forms of crepe bandage, are used in the prevention of oedema; they are also used to provide support for mild sprains and joints but their effectiveness has not been proven for this purpose. Since they have limited extensibility, they are able to provide light support without exerting undue pressure. For a warning against injudicious compression see p. 1317.

CliniLite

Knitted fabric, viscose and elastomer yarn. Type 2 (light support bandage)

CliniLite bandage (Clinisupplies Ltd) 10cm x 4.5m = £0.80, 15cm x 4.5m = £1.16, 5cm x 4.5m = £0.44, 7.5cm x 4.5m = £0.61

CliniPlus

Knitted fabric, viscose and elastomer yarn. Type 2 (light support bandage)

CliniPlus (Clinisupplies Ltd) bandage 10cm x 8.7m = £1.80

Cotton Crepe Bandage

Light support bandage, 4.5 m stretched (all)

Hospirecpe 2 (Paul Hartmann Ltd) 29 bandage 10cm x 4.5m = £0.81, 15cm x 4.5m = £1.18, 15cm x 5m = £0.65, 7.5cm x 4.5m = £0.62, 39 bandage 10cm x 4.5m = £0.80, 15cm x 4.5m = £1.17, 5cm x 4.5m = £0.44, 7.5cm x 4.5m = £0.62,

Cotton Crepe Bandage, BP 1988

Fabric, plain weave, warp of crepe-twisted cotton threads, weft of cotton threads; stretch bandage. 4.5 m stretched (both)

Elastocrepe bandage (BSN medical Ltd) 10cm x 4.5m, 7.5cm x 4.5m

Flexocrepe bandage (Robinson Healthcare) 10cm x 4.5m, 7.5cm x 4.5m

Sterocrepe bandage (Steroplast Healthcare Ltd) 10cm x 4.5m, 7.5cm x 4.5m

Cotton Suspensory Bandage

(Drug Tariff). Type 1: cotton net bag with draw tapes and webbing waistband; small, medium, and large (all)

Crepe Bandage, BP 1988

Fabric, plain weave, warp of wool threads and crepe-twisted cotton threads, weft of cotton threads; stretch bandage; 4.5 m stretched

Alvita crepe bandage (Alliance Healthcare (Distribution) Ltd) 10cm x 4.5m, 15cm x 4.5m, 5cm x 4.5m, 7.5cm x 4.5m

Clinicrepe bandage (Clinisupplies Ltd) 10cm x 4.5m, 15cm x 4.5m, 5cm x 4.5m, 7.5cm x 4.5m

Crepe bandage (Robert Bailey & Son Plc) 10cm x 4.5m, 15cm x 4.5m, 5cm x 4.5m, 7.5cm x 4.5m

Propax crepe bandage (BSN medical Ltd) 10cm x 4.5m, 15cm x 4.5m, 5cm x 4.5m, 7.5cm x 4.5m

Vernade crepe bandage (Synergy Health Plc) 10cm x 4.5m, 15cm x 4.5m, 5cm x 4.5m, 7.5cm x 4.5m

Elset

Knitted fabric, viscose and elastomer yarn. Type 2 (light support bandage)

Elset (Molnlycke Health Care Ltd) bandage 15cm x 12m = £5.52, bandage 10cm x 6m = £2.57, 10cm x 8m = £3.29, 15cm x 6m = £2.76.

Hospicrepe 233

Fabric, plain weave, warp of crepe-twisted cotton threads, weft of cotton threads; stretch bandage, lighter than cotton crepe, 4.5 m stretched (all)

Hosprise 233 bandage (Paul Hartmann Ltd) 10cm x 4.5m = £0.96, 15cm x 4.5m = £1.36, 5cm x 4.5m = £0.52, 7.5cm x 4.5m = £0.72

Hosplite

Fabric, cotton, polyamide, and elastane; light support bandage (Type 2), 4.5 m stretched (all)

Hosplite bandage (Paul Hartmann Ltd) 10cm x 4.5m = £0.61, 15cm x 4.5m = £0.90, 5cm x 4.5m = £0.36, 7.5cm x 4.5m = £0.50

K-Lite

Knitted fabric, viscose and elastomer yarn. Type 2 (light support bandage)

K-Lite (Urto Ltd) Long bandage 10cm x 5.25m = £1.14, bandage 10cm x 4.5m = £0.99, 15cm x 4.5m = £1.44, 5cm x 4.5m = £0.55, 7cm x 4.5m = £0.76

K-Plus

Knitted fabric, viscose and elastomer yarn. Type 2 (light support bandage)

K-Plus (Urto Ltd) Long bandage 10cm x 10.25m = £2.61, bandage 10cm x 8.7m = £2.26

Knit-Firm

Knitted fabric, viscose and elastomer yarn. Type 2 (light support bandage)

Knit-Firm bandage (Millsedge Healthcare) 10cm x 4.5m = £0.66, 15cm x 4.5m = £0.96, 5cm x 4.5m = £0.36, 7cm x 4.5m = £0.51

L3

Knitted fabric, viscose and elastomer yarn. Type 2 (light support bandage)

L3 (Smith & Nephew Healthcare Ltd) bandage 10cm x 8.6m = £2.19

Neosport

Fabric, cotton, polyamide, and elastane; light support bandage (Type 2), 4.5 m stretched (all)

Neosport bandage (Euromed Ltd) 10cm x 4.5m = £0.91, 15cm x 4.5m = £1.12, 5cm x 4.5m = £0.54, 7.5cm x 4.5m = £0.73

PremierBand

Fabric, plain weave, warp of crepe-twisted cotton threads, weft of cotton threads; stretch bandage, lighter than cotton crepe, 4.5 m stretched (all)

PremierBand bandage (Sherwood) 10cm x 4.5m = £0.79, 15cm x 4.5m = £1.18, 15cm x 4.5m = £0.65, 7.5cm x 4.5m = £0.63

Profore #2

Fabric, cotton, polyamide, and elastane; light support bandage (Type 2), 4.5 m stretched (all)

Profore #2 (Smith & Nephew Healthcare Ltd) bandage 10cm x 4.5m = £1.34, latex free bandage 10cm x 4.5m = £1.42

Profore #3

Knitted fabric, viscose and elastomer yarn. Type 2 (light support bandage)

Profore #3 (Smith & Nephew Healthcare Ltd) bandage 10cm x 8.7m = £3.90, latex free bandage 10cm x 8.7m = £4.24

Setocrepe

Fabric, cotton, polyamide, and elastane; light support bandage (Type 2), 4.5 m stretched (all)
Setocrepe (Molnlycke Health Care Ltd) bandage 10cm x 4.5m = £1.18

Selfcrepe
Fabric, cotton, polyamide, and elastane; light support bandage (Type 2), 4.5 m stretched (all)
Selfcrepe bandage (BSN medical Ltd) 10cm x 4.5m = £1.23, 15cm x 4.5m = £1.79, 5cm x 4.5m = £0.69, 7.5cm x 4.5m = £0.97

Adhesive bandages
Elastic adhesive bandages are used to provide compression in the treatment of varicose veins and for the support of injured joints; they should no longer be used for the support of fractured ribs and clavicles. They have also been used with zinc paste bandage in the treatment of venous ulcers, but they can cause skin reactions in susceptible patients and may not produce sufficient pressures for healing (significantly lower than those provided by other compression bandages).

Elastic Adhesive Bandage, BP 1993
Woven fabric, elastic in warp (crepe-twisted cotton threads), weft of cotton and/or viscose threads spread with adhesive mass containing zinc oxide. 4.5 m stretched
Tensoplast bandage (BSN medical Ltd) 10cm x 4.5m, 5cm x 4.5m, 7.5cm x 4.5m

Cohesive bandages
Cohesive bandages adhere to themselves, but not to the skin, and are useful for providing support for sports use where ordinary stretch bandages might become displaced and adhesive bandages are inappropriate. Care is needed in their application, however, since the loss of ability for movement between turns of the bandage to equalise local areas of high tension carries the potential for creating a tourniquet effect. Cohesive bandages can be used to support sprained joints and as an outer layer for multi-layer compression bandaging; they should not be used if arterial disease is suspected.

Cohesive extensible bandages
Coban Bandage
Coban (3M Health Care Ltd) self-adherent bandage 10cm x 6m = £2.93
K Press Bandage
K Press bandage (Urgo Ltd) 10cm x 6.5m = £2.89, 10cm x 7.5m = £3.37, 12cm x 7.5m = £4.25, 8cm x 7.5m = £3.18
Profore #4 Bandage
Profore #4 (Smith & Nephew Healthcare Ltd) bandage 10cm x 2.5m = £3.23, latex free bandage 10cm x 2.5m = £3.51
Ultra Fast Bandage
Ultra (Robinson Healthcare) Fast cohesive bandage 10cm x 6.3m = £2.39

Compression bandages
High compression products are used to provide the high compression needed for the management of gross varices, post-thrombotic venous insufficiency, venous leg ulcers, and gross oedema in average-sized limbs. Their use calls for an expert knowledge of the elastic properties of the products and experience in the technique of providing careful graduated compression. Incorrect application can lead to uneven and inadequate pressures or to hazardous levels of pressure. In particular, injudicious use of compression in limbs with arterial disease has been reported to cause severe skin and tissue necrosis (in some instances calling for amputation). Doppler testing is required before treatment with compression. Oral pentoxifylline, p. 207 can be used as adjunct therapy if a chronic venous leg ulcer does not respond to compression bandaging [unlicensed indication].

High compression bandages
High Compression Bandage
Cotton, viscose, nylon, and Lycra extensible bandage, 3 m (unstretched)
K-Three (Urgo Ltd) bandage 10cm x 3m = £2.81
SurePress (ConvaTec Ltd) bandage 10cm x 3m = £3.61
PEC High Compression Bandages
Polyamide, elastane, and cotton compression (high) extensible bandage, 3.5 m unstretched
Setopress (Molnlycke Health Care Ltd) bandage 10cm x 3.5m = £3.50
VEC High Compression Bandages
Viscose, elastane, and cotton compression (high) extensible bandage, 3 m unstretched (both)
Tensoplast bandage (BSN medical Ltd) 10cm x 3m = £3.43, 7.5cm x 3m = £2.67
Short stretch compression bandages
Actico Bandage
Actico bandage (Activa Healthcare Ltd) 10cm x 6m = £3.33, 12cm x 6m = £4.24, 4cm x 6m = £2.38, 6cm x 6m = £2.79, 8cm x 6m = £3.21
Comprian Bandage
Comprian bandage (BSN medical Ltd) 10cm x 5m = £3.36, 12cm x 5m = £4.09, 6cm x 5m = £2.66, 8cm x 5m = £3.12
Residal K Bandage
Residal K bandage (Lohmann & Rauscher (UK) Ltd) 10cm x 10m = £5.97, 10cm x 5m = £3.43, 12cm x 5m = £4.16, 6cm x 5m = £2.63, 8cm x 5m = £3.14
Sub-compression wadding bandage
Cellona Undercast Padding
Padding
Cellona Undercast padding bandage (Lohmann & Rauscher (UK) Ltd) 10cm x 2.75m = £0.47, 15cm x 2.75m = £0.60, 5cm x 2.75m = £0.31, 7.5cm x 2.75m = £0.38
Flexi-Ban Padding
Flexi-Ban (Activa Healthcare Ltd) bandage 10cm x 3.5m = £0.50
K Tech Reduced Padding
K Tech Reduced bandage 10cm x (Urgo Ltd) 6m = £4.68, 7.3m = £5.11
K-Soft Padding
K-Soft (Urgo Ltd) Long bandage 10cm x 4.5m = £0.56, bandage 10cm x 3.5m = £0.45
K-Tech (K Tech in DMD) Padding
K Tech (Urgo Ltd) Reduced bandage 10cm x 7.3m = £5.11, bandage 10cm x 5m = £3.90, 10cm x 6m = £4.68, 12cm x 6m = £5.91, 12cm x 7.3m = £6.45, 8cm x 6m = £4.42, 8cm x 7.3m = £4.82,
Ortho-Band Plus Padding
Ortho-Band (Millpledge Healthcare) Plus bandage 10cm x 3.5m = £0.37
Profore #1 Padding
Profore #1 (Smith & Nephew Healthcare Ltd) bandage 10cm x 3.5m = £0.70, latex free bandage 10cm x 3.5m = £0.76
Softexe Padding
Softexe (Molnlycke Health Care Ltd) bandage 10cm x 3.5m = £0.62
SurePres Padding
SurePres (ConvaTec Ltd) bandage 10cm x 3m = £3.61
Ultra Soft Padding
Ultra (Robinson Healthcare) Soft wadding bandage 10cm x 3.5m = £0.39
Wound management

**Multi-layer compression bandaging**

Multi-layer compression bandaging systems are an alternative to High Compression Bandages for the treatment of venous leg ulcers. Compression is achieved by the combined effects of two or three extensible bandages applied over a layer of orthopaedic wadding and a wound contact dressing.

**Four layer systems**

**K-Four**

Padding

**K-Four (Urgo Ltd)** Reduced Compression multi-layer compression bandage kit 18cm+ ankle circumference = £6.89, 25cm-32cm ankle circumference = £8.80, multi-layer compression bandage kit 18cm-25cm ankle circumference = £4.92, 25cm-30cm ankle circumference = £6.80, greater than 30cm ankle circumference = £3.96, less than 18cm ankle circumference = £7.11.

**Profore**

Wound contact layer

**Profore (Smith & Nephew Healthcare Ltd)** Lite latex free multi-layer compression bandage kit = £5.91, multi-layer compression bandage kit 18cm-25cm ankle circumference = £10.07, multi-layer compression bandage kit 18cm-25cm ankle circumference = £9.42, 25cm-30cm ankle circumference = £7.82, above 30cm ankle circumference = £11.71, up to 18cm ankle circumference = £10.11.

**Ultra Four**

Wound contact layer

**Ultra Four (Robinson Healthcare)** Reduced Compression multi-layer compression bandage kit = £6.44, latex free multi-layer compression bandage kit 18cm-25cm ankle circumference = £5.67, up to 18cm ankle circumference = £6.41.

**Zizoc**

Sterile rayon stocking impregnated with ointment containing zinc oxide 20%

**Zizoc (Smith & Nephew Healthcare Ltd)** stockings = £31.26

**Compression hosiery and garments**

Compression (elastic) hosiery is used to treat conditions associated with chronic venous insufficiency, to prevent recurrence of thrombosis, or to reduce the risk of further venous ulceration after treatment with compression bandaging. Doppler testing to confirm arterial sufficiency is required before recommending the use of compression hosiery.

Before elastic hosiery can be dispensed, the quantity (single or pair), article (including accessories), and compression class must be specified by the prescriber. There are different compression values for graduated compression hosiery and lymphoedema garments (see table below). All dispensed elastic hosiery articles must state on the packaging that they conform with Drug Tariff technical specification No. 40, for further details see Drug Tariff.

Graduated Compression hosiery, Class 1 Light Support is used for superficial or early varices, varicosis during pregnancy.

Graduated Compression hosiery, Class 2 Medium Support is used for varices of medium severity, ulcer treatment and prophylaxis, mild oedema, varicosis during pregnancy.

Graduated Compression hosiery, Class 3 Strong Support is used for gross varices, post thrombotic venous insufficiency, gross oedema, ulcer treatment and prophylaxis.

Compression values for hosiery and lymphoedema garments

**Class 1: Compression hosiery (British standard)**

14–17 mmHg, lymphoedema garments (European classification) 18–21 mmHg; Class 2 Compression hosiery (British standard) 18–24 mmHg, lymphoedema garments (European classification) 23–32 mmHg; Class 3 Compression hosiery (British standard) 25–35 mmHg, lymphoedema garments (European classification) 34–46 mmHg; Class 4 Compression hosiery (British standard)—not available, lymphoedema garments (European classification) 49–70 mmHg; Class 4 super Compression hosiery (British standard)—not available, lymphoedema garments (European classification) 60–90 mmHg.
Graduated compression hosiery

**Class 1 Light Support**
Hosiery, compression at ankle 14–17 mmHg, thigh length or below knee with knitted in heel

**Class 2 Light Support**
Hosiery, compression at ankle 14–17 mmHg, thigh length or below knee with knitted in heel

**Accessories**
- **Suspender**
  - Suspender, for thigh stockings

**Anklets**

**Class 2 Medium Support**
Anklets, compression 18–24 mmHg, circular knit (standard and made-to-measure),

**Class 3 Strong Support**
Anklets, compression 18–24 mmHg, circular knit (standard and made-to-measure),

**Knee caps**

**Class 2 Medium Support**
Kneecaps, compression 18–24 mmHg, circular knit (standard and made-to-measure)

**Class 3 Strong Support**
Kneecaps, compression 18–24 mmHg, circular knit (standard and made-to-measure)

**Lymphoedema garments**

Lymphoedema compression garments are used to maintain limb shape and prevent additional fluid retention. Either flat-bed or circular knitting methods are used in the manufacture of elasticated compression garments. Seamless, circular-knitted garments (in standard sizes) can be used to prevent swelling if the lymphoedema is well controlled and if the limb is in good shape and without skin folds. Flat-knitted garments (usually made-to-measure) with a seam, provide greater rigidity and stiffness to maintain reduction of lymphoedema following treatment with compression bandages.

A standard range of light, medium, or high compression garments are available, as well as low compression (12–16 mmHg) armsleeves, made-to-measure garments up to compression 90 mmHg, and accessories—see Drug Tariff for details. Note There are different compression values for lymphoedema garments and graduated compression hosiery, see above.
Dental Practitioners’ Formulary

List of Dental Preparations

The following list has been approved by the appropriate Secretaries of State, and the preparations therein may be prescribed by dental practitioners on form FP10D (GP14 in Scotland, WP10D in Wales). Licensed sugar-free versions, where available, are preferred. Licensed alcohol-free mouthwashes, where available, are preferred.

Azithromycin Tablets, Aciclovir Tablets, BP, Benzydamine Mouthwash, BP
Azithromycin Capsules, Aspirin Tablets, Dispersible, BP
Artificial Saliva Gel, DPF
Artificial Saliva Oral Spray, DPF
Artificial Saliva Pastilles, DPF
Artificial Saliva Protective Spray, DPF

Artificial Saliva Substitutes as listed below (to be prescribed only for indications approved by ACBS (patients suffering from dry mouth as a result of having or, having undergone, radiotherapy or sicca syndrome):

BioXtra® Gel Mouthwash
BioXtra® Moisturising Gel
Glandosane® Saliveze®

Artificial Saliva Substitute Spray, DPF
Aspirin Tablets, Dispersible, BP
Azithromycin Capsules, 250 mg, DPF
Azithromycin Oral Suspension, 200 mg/5 mL, DPF
Azithromycin Tablets, 250 mg, DPF
Azithromycin Tablets, 500 mg, DPF
Beclometasone Pressurised Inhalation, BP, 50 micrograms/ metered inhalation, CFC-free, as:

Clen Modulite®

Benzydamine Mouthwash, BP 0.15%
Benzydamine Oromucosal Spray, BP 0.15%
Betamethasone Soluble Tablets, 500 micrograms, DPF
Carbamazepine Tablets, BP
Cefalexin Capsules, BP
Cefalexin Oral Suspension, BP
Cefalexin Tablets, BP
Cefradine Capsules, BP
Cetirizine Oral Solution, BP, 5 mg/5 mL
Cetirizine Tablets, BP, 10 mg
Chlorhexidine Gluconate Gel, BP
Chlorhexidine Mouthwash, BP
Chlorhexidine Oral Spray, DPF
Chlorphenamine Tablets, BP
Choline Salicylate Dental Gel, BP
Clarithromycin Oral Suspension, 125 mg/5 mL, DPF
Clarithromycin Oral Suspension, 250 mg/5 mL, DPF
Clarithromycin Tablets, BP
Clindamycin Capsules, BP
Co-amoxiclav Tablets, BP, 250/125 (amoxicillin 250 mg as trihydrate, clavulanic acid 125 mg as potassium salt)
Co-amoxiclav Oral Suspension, BP, 125/31 (amoxicillin 125 mg as trihydrate, clavulanic acid 31.25 mg as potassium salt)/5 mL
Co-amoxiclav Oral Suspension, BP, 250/62 (amoxicillin 250 mg as trihydrate, clavulanic acid 62.5 mg as potassium salt)/5 mL
Diazepam Oral Solution, BP, 2 mg/5 mL
Diazepam Tablets, BP
Diclofenac Sodium Tablets, Gastro-resistant, BP
Dihydrocodeine Tablets, BP, 30 mg
Doxycycline Tablets, Dispersible, BP
Doxycycline Capsules, BP, 100 mg
Doxycycline Tablets, 20 mg, DPF
Ephedrine Nasal Drops, BP
Erythromycin Ethyl Succinate Oral Suspension, BP
Erythromycin Ethyl Succinate Tablets, BP
Erythromycin Stearate Tablets, BP
Erythromycin Tablets, Gastro-resistant, BP
Fluconazole Capsules, 50 mg, DPF
Fluconazole Oral Suspension, 50 mg/5 mL, DPF
Hydrocortisone Cream, BP, 1%
Hydrocortisone Oromucosal Tablets, BP
Hydrogen Peroxide Mouthwash, BP, 6%
Ibuprofen Oral Suspension, BP, sugar-free
Ibuprofen Tablets, BP
Lansoprazole Capsules, Gastro-resistant, BP
Lidocaine Ointment, BP, 5%
Lidocaine Spray 10%, DPF
Loratadine Syrup, 5 mg/5 mL, DPF
Loratadine Tablets, BP, 10 mg
Menthol and Eucalyptus Inhalation, BP 1980
Metronidazole Oral Suspension, BP
Metronidazole Tablets, BP
Miconazole Cream, BP
Miconazole Oromucosal Gel, BP
Miconazole and Hydrocortisone Cream, BP
Miconazole and Hydrocortisone Ointment, BP
Nystatin Oral Suspension, BP
Omeprazole Capsules, Gastro-resistant, BP
Oxycycline Tablets, BP
Paracetamol Oral Suspension, BP
Paracetamol Tablets, BP
Paracetamol Tablets, Soluble, BP
Phenoxymethylpenicillin Oral Solution, BP
Phenoxymethylpenicillin Tablets, BP
Promethazine Hydrochloride Tablets, BP
Promethazine Oral Solution, BP
Saliva Stimulating Tablets, DPF
Sodium Chloride Mouthwash, Compound, BP
Sodium Fluoride Mouthwash, BP
Sodium Fluoride Oral Drops, BP
Sodium Fluoride Tablets, BP
Sodium Fluoride Toothpaste 0.619%, DPF
Sodium Fluoride Toothpaste 1.1%, DPF
Sodium Fusidate Ointment, BP
Temazepam Oral Solution, BP
Temazepam Tablets, BP
Tetracycline Tablets, BP

Preparations in this list which are not included in the BP or BPC are described under Details of DPF preparations. For details of preparations that can be prescribed, see individual entries under the relevant drug monographs throughout the BNF publications.

Details of DPF preparations

Preparations on the List of Dental Preparations which are specified as DPF are described as follows in the DPF. Although brand names have sometimes been included for identification purposes preparations on the list should be prescribed by non-proprietary name.

Amoxicillin Oral Powder
amoxicillin (as trihydrate) 3 g sachet

Additional information on the use of these preparations is available in the BNF publications.
Artificial Saliva Gel
(proprietary product: Biotene Oralbalance), lactoperoxidase, lactoferrin, lysozyme, glucose oxidase, xylitol in a gel basis

Artificial Saliva Oral Spray
(proprietary product: Xerotin) consists of water, sorbitol, carmelllose (carboxymethylcellulose), potassium chloride, sodium chloride, potassium phosphate, magnesium chloride, calcium chloride and other ingredients, pH neutral

Artificial Saliva Pastilles
(proprietary product: Salivix), consists of acacia, malic acid, and other ingredients

Artificial Saliva Protective Spray
(proprietary product: Aquoral) consists of oxidised glycerol triesters, silicon dioxide, flavouring agents, aspartame

Artificial Saliva Substitute Spray
(proprietary product: AS Saliva Orthana Spray) consists of mucin, methylparaben, benzalkonium chloride, EDTA, xylitol, peppermint oil, spearmint oil, mineral salts

Azithromycin Capsules
azithromycin 250 mg

Azithromycin Oral Suspension
200 mg/5 mL.
azithromycin 200 mg/5 mL when reconstituted with water

Azithromycin Tablets
azithromycin 250 mg and 500 mg

Betamethasone Soluble Tablets
500 micrograms
betamethasone (as sodium phosphate) 500 micrograms

Chlorhexidine Oral Spray
(proprietary product: Corsodyl Oral Spray), chlorhexidine gluconate 0.2%

Clarithromycin Oral Suspension
125 mg/5 mL.
clarithromycin 125 mg/5 mL when reconstituted with water

Clarithromycin Oral Suspension
250 mg/5 mL.
clarithromycin 250 mg/5 mL when reconstituted with water

Doxycycline Tablets
20 mg
(proprietary product: Periostat), doxycycline (as hyclate) 20 mg

Fluconazole Capsules
50 mg
fluconazole 50 mg

Fluconazole Oral Suspension
50 mg/5 mL.
(proprietary product: Diflucan), fluconazole 50 mg/5 mL when reconstituted with water

Lidocaine Spray
10%
(proprietary product: Xylocaine Spray), lidocaine 10% supplying 10 mg lidocaine/spray

Loratadine Syrup
5 mg/5 mL.
loratadine 5 mg/5 mL

Saliva Stimulating Tablets
(proprietary product: SST), citric acid, malic acid and other ingredients in a sorbitol base

Sodium Fluoride Toothpaste
0.619%
(proprietary product: Duraphat '2800 ppm' Toothpaste), sodium fluoride 0.619%

Sodium Fluoride Toothpaste
1.1%
(proprietary product: Duraphat '5000 ppm' Toothpaste), sodium fluoride 1.1%
Nurse Prescribers’ Formulary

Nurse Prescribers’ Formulary for Community Practitioners

Nurse Prescribers’ Formulary Appendix (Appendix NPF). List of preparations approved by the Secretary of State which may be prescribed on form FP10P (form HS21(N) in Northern Ireland, form GP10(N) in Scotland, forms WP10CN and WP10PN in Wales) by Nurses for National Health Service patients.

Community practitioners who have completed the necessary training may only prescribe items appearing in the nurse prescribers’ list set out below. Community Practitioner Nurse Prescribers are recommended to prescribe generically, except where this would not be clinically appropriate or where there is no approved generic name.

Medicinal Preparations

Preparations on this list which are not included in the BP or BPC are described on p. 1323.

- Almond Oil Ear Drops, BP
- Arachis Oil Enema, NPF
- Aspirin Tablets, Dispersible, 300 mg, BP (max. 96 tablets; max. pack size 32 tablets)
- Bisacodyl Suppositories, BP (includes 5-mg and 10-mg strengths)
- Bisacodyl Tablets, BP
- Catheter Maintenance Solution, Sodium Chloride, NPF
- Catheter Maintenance Solution, Solution C’, NPF
- Catheter Maintenance Solution, ‘Solution R’, NPF
- Chlorhexidine Gluconate Alcoholic Solutions containing at least 0.05%
- Chlorhexidine Gluconate Aqueous Solutions containing at least 0.05%
- Choline Salicylate Dental Gel, BP
- Clotrimazole Cream 1%, BP
- Co-danthramer Capsules, NPF
- Co-danthramer Capsules, Strong, NPF
- Co-danthramer Oral Suspension, NPF
- Co-danthramer Oral Suspension, Strong, NPF
- Co-danthrusate Capsules, BP
- Co-danthrusate Oral Suspension, NPF
- Crotamiton Cream, BP
- Crotamiton Lotion, BP
- Diclofenac barrier creams containing at least 20%
- Diclofenac Lotion, BP
- Diclofenac Tablets, BP
- Diltiazem Tablets, BP
- Dimeticone Lotion, NPF
- Dimeticone barrier creams containing at least 0.5%
- Dimeticone barrier creams containing at least 1%
- Dimeticone Lotion, NPF
- Docosate Capsules, BP
- Docosate Enema, NPF
- Docosate Oral Solution, BP
- Docosate Oral Solution, Paediatric, BP
- Econazole Cream 1%, BP
- Emollients as listed below:
  - Aquadrate® 10% w/w Cream
  - Arachis Oil, BP
  - Balneum® Plus Cream
  - Cetraben® Emollient Cream
  - Dermamist
  - Diprobalse® Cream
  - Diprobalse® Ointment
  - Doublebase®
  - Doublebase® Dayleve Gel
  - E45® Cream
  - E45® Itch Relief Cream
  - Emulsifying Ointment, BP
  - Eucerin® Intensive 10% w/w Urea Treatment Cream
  - Eucerin® Intensive 10% w/w Urea Treatment Lotion
- Hydromol® Cream
- Hydromol® Intensive
- Hydrous Ointment, BP
- Lipobase®
- Liquid and White Soft Paraffin Ointment, NPF
- Neutrogena® Norwegian Formula Dermatological Cream
- Nutraplus® Cream
- Oilatum® Cream
- Oilatum® Junior Cream
- Paraffin, White Soft, BP
- Paraffin, Yellow Soft, BP
- Ultrabase®
- Ungsentum M®
- Emollient Bath and Shower Preparations as listed below:
  - Aqueous Cream, BP
  - Balneum® (except pack sizes that are not to be prescribed under the NHS (see Part XVIIIA of the Drug Tariff, Part XI of the Northern Ireland Drug Tariff))
  - Balneum® Plus® Bath Oil (except pack sizes that are not to be prescribed under the NHS (see Part XVIIIA of the Drug Tariff, Part XI of the Northern Ireland Drug Tariff))
  - Cetraben® Emollient Bath Additive
  - Dermalo® Bath Emollient
  - Doublebase® Emollient Bath Additive
  - Doublebase® Emollient Shower Gel
  - Doublebase® Emollient Wash Gel
  - Hydromol® Bath and Shower Emollient
  - Oilatum® Emollient
  - Oilatum® Gel
  - Ointate® Emollient
  - Zerolatum® Emollient Medicinal Bath Oil
- Folic Acid Tablets 400 micrograms, BP
- Glycerol Suppositories, BP
- Ibuprofen Oral Suspension, BP (except for indications and doses that are PoM)
- Ibuprofen Tablets, BP (except for indications and doses that are PoM)
- Ispaghula Husk Granules, BP
- Ispaghula Husk Granules, Effervescent, BP
- Ispaghula Husk Oral Powder, BP
- Lactulose Solution, BP
- Lidocaine Ointment, BP
- Lidocaine and Chlorhexidine Gel, BP
- Macroglol Oral Liquid, Compound, NPF
- Macroglol Oral Powder, Compound, NPF
- Macrogol Oral Powder, Compound, Half-strength, NPF
- Magnesium Hydroxide Mixture, BP
- Magnesium Sulfate Pante, BP
- Malathion aqueous lotions containing at least 0.5%
- Mecobalamin Oral Suspension, NPF
- Mecobalamin Tablets, NPF
- Methylcellulose Tablets, BP
- Miconazole Cream 2%, BP
- Miconazole Oromucosal Gel, BP
- Mouthwash Solution-tablets, NPF
- Nicotine Inhalation Cartridge for Oromucosal Use, NPF
- Nicotine Lozenge, NPF
- Nicotine Medicated Chewing Gum, NPF
- Nicotine Nasal Spray, NPF
- Nicotine Oral Spray, NPF
- Nicotine Sublingual Tablets, NPF
- Nicotine Transdermal Patches, NPF
- Nystatin Oral Suspension, BP
- Olive Oil Ear Drops, BP
Paracetamol Oral Suspension, BP (includes 120 mg/5 mL and 250 mg/5 mL strengths—both of which are available as sugar-free formulations)
Paracetamol Tablets, BP (max. 96 tablets; max. pack size 32 tablets)
Paracetamol Tablets, Soluble, BP (includes 120-mg and 500-mg tablets); (max. 96 tablets; max. pack size 32 tablets)
Permethrin Cream, NPF
Phosphates Enema, BP
Povidone-Iodine Solution, BP
Senna Oral Solution, NPF
Senna Tablets, BP
Senna and Ispaghula Granules, NPF
Sodium Chloride Solution, Sterile, BP
Sodium Citrate Compound Enema, NPF
Sodium Picosulfate Capsules, NPF
Sodium Picosulphate Elixir, NPF
Spermicidal contraceptives as listed below:

Gygel® Contraceptive Jelly
Sterculia Granules, NPF
Sterculia and Frangula Granules, NPF
Titanium Ointment, BP
Water for Injections, BP
Zinc and Castor Oil Ointment, BP
Zinc Oxide and Dimeticone Spray, NPF
Zinc Oxide Impregnated Medicated Bandage, NPF
Zinc Oxide Impregnated Medicated Stocking, NPF
Zinc Paste Bandage, BP 1993
Zinc Paste and Ichthammol Bandage, BP 1993

Appliances and Reagents (including Wound Management Products)
Community Practitioner Nurse Prescribers in England, Wales and Northern Ireland can prescribe any appliance or reagent in the relevant Drug Tariff. In the Scottish Drug Tariff, Appliances and Reagents which may not be prescribed by Nurses are annotated Nx.

Appliances (including Contraceptive Devices)—where it is not appropriate for nurse prescribers in family planning clinics to prescribe contraceptive devices using form FP10(P) (forms WP10CN and WP10PN in Wales), they may prescribe using the same system as doctors in the clinic) as listed in Part IXC of the Drug Tariff (Part III of the Northern Ireland Drug Tariff, Part 3 (Appliances) and Part 2 (Dressings) of the Scottish Drug Tariff).

Incontinence Appliances as listed in Part IXA of the Drug Tariff (Part III of the Northern Ireland Drug Tariff, Part 5 of the Scottish Drug Tariff).
Stoma Appliances and Associated Products as listed in Part IXC of the Drug Tariff (Part III of the Northern Ireland Drug Tariff, Part 6 of the Scottish Drug Tariff).

Chemical Reagents as listed in Part IX of the Drug Tariff (Part II of the Northern Ireland Drug Tariff, Part 9 of the Scottish Drug Tariff).

The Drug Tariffs can be accessed online at: National Health Service Drug Tariff for England and Wales: www.ppa.org.uk/ppa/edt_intro.htm
Health and Personal Social Services for Northern Ireland Drug Tariff: www.dhispsni.gov.uk/pas-tariff
Scottish Drug Tariff: www.isdscotland.org/HealthTopics/Prescribing-and-Medicines/Scottish-Drug-Tariff/

Details of NPF preparations
Preparations on the Nurse Prescribers' Formulary which are not included in the BP or BPC are described as follows in the Nurse Prescribers' Formulary. Although brand names have sometimes been included for identification purposes, it is recommended that non-proprietary names should be used for prescribing medicinal preparations in the NPF except where a non-proprietary name is not available.

Arachis Oil Enema
arachis oil 100%

Catheter Maintenance Solution, Sodium Chloride (proprietary products: OptiFlo S; Uro-Tainer Sodium Chloride; Uriflex-S), sodium chloride 0.9%

Catheter Maintenance Solution, 'Solution G' (proprietary products: OptiFlo G; Uro-Tainer Saby G; Uriflex G), citric acid 3.23%, magnesium oxide 0.38%, sodium bicarbonate 0.7%, disodium edetate 0.01%

Catheter Maintenance Solution, 'Solution R' (proprietary products: OptiFlo R; Uro-Tainer Solution R; Uriflex R), citric acid 6%, gluconolactone 0.6%, magnesium carbonate 2.8%, disodium edetate 0.01%

Chlorhexidine gluconate alcoholic solutions (proprietary product: Unisept chlorhexidine gluconate in aqueous solution

Co-danthramer Capsules P (paracetamol 150 mg, co-danthramer 25/200 (dantron 25 mg, poloxamer '188' 200 mg)
Co-danthramer Capsules, Strong P (paracetamol 150 mg, co-danthramer 37.5/500 (dantron 37.5 mg, poloxamer '188' 500 mg)
Co-danthramer Oral Suspension P (paracetamol product: Codalax), co-danthramer 25/200 in 5 mL (dantron 25 mg, poloxamer '188' 200 mg/5 mL)
Co-danthramer Oral Suspension, Strong P (paracetamol product: Codalax Forte), co-danthramer 75/1000 in 5 mL (dantron 75 mg, poloxamer '188' 1 g/5 mL)
Co-danthrusate Oral Suspension P (paracetamol product: Normax), co-danthrusate 50/60 (dantron 50 mg, docusate sodium 60 mg/5 mL)

Dimeticone barrier creams (proprietary products: Conotran Cream, dimeticone '350' 22%, Sispel Barrier Cream, dimeticone '1000' 10%, dimeticone 10–22%)

Dimeticone Lotion (proprietary product: Hedrin), dimeticone 4%

Docusate Enema (proprietary product: Norgalax Micro-enema) docusate sodium 120 mg in 10 g

Liquid and White Soft Paraffin Ointment liquid paraffin 50%, white soft paraffin 50%

Macrogol Oral Liquid, Compound (proprietary product: Movicol Liquid), macrogol '3350' (polyethylene glycol '3350') 13.125 g, sodium bicarbonate 178.5 mg, sodium chloride 350.7 mg, potassium chloride 46.6 mg/25 mL

Macrogol Oral Powder, Compound (proprietary product: Laxido Orange, Molaxole, Movicol) macrogol '3350' (polyethylene glycol '3350') 13.125 g, sodium bicarbonate 178.5 mg, sodium chloride 350.7 mg, potassium chloride 46.6 mg/sachet

Note: Amount of potassium chloride varies according to flavour of Movicol® as follows: plain-flavour (sugar-free) = 50.2 mg/sachet; lime and lemon flavour = 46.6 mg/sachet; chocolate flavour = 31.7 mg/sachet. 1 sachet when reconstituted with 125 mL water provides K+ 5.4 mmol/litre

Macrogol Oral Powder, Compound, Half-strength (proprietary product: Movicol-Half), macrogol '3350' (polyethylene glycol '3350') 6.563 g, sodium bicarbonate 89.3 g, sodium chloride 175.4 mg, potassium chloride 23.3 mg/sachet
Malathion aqueous lotions
(proprietary products: Derbac-M Liquid), malathion 0.5% in
an aqueous basis

Mebendazole Oral Suspension (PrM)
(proprietary product: Vermox), mebendazole 100 mg/5 mL

Mebendazole Tablets (PrM)
(can be sold to the public if supplied for oral use in the
treatment of enterobiasis in adults and children over 2 years
provided its container or package is labelled to show a max.
single dose of 100 mg and it is supplied in a container or
package containing not more than 800 mg (proprietary
products: Oves, Vermox), mebendazole 100 mg

Mouthwash Solution-tablets
consist of tablets which may contain antimicrobial,
colouring and flavouring agents in a suitable soluble
effervescent basis to make a mouthwash

Nicotine Inhalation Cartridge for Oromucosal Use
(for use with inhalation mouthpiece; to be prescribed as
either a starter pack (6 cartridges with inhalator device and
holder) or refill pack (42 cartridges with inhalator device))
(proprietary products: NicAssist Inhalator, Nicorette
Inhalator), nicotine 10 mg or 15 mg

Nicotine Lozenge
nicotine (as bitartrate) 1 mg or 2 mg (proprietary product:
Nicorette Mint Lozenge, Nicotinell Mint Lozenge), or nicotine
(as resinate) 1.5 mg, 2 mg, or 4 mg (proprietary product:
NiQuitin Lozenges, NiQuitin Minis, NiQuitin Pre-quit)

Nicotine Medicated Chewing Gum
(proprietary products: NicAssist Gum, Nicorette Gum,
Nicotinell Gum, NiQuitin Gum), nicotine 2 mg or 4 mg

Nicotine Nasal Spray
(proprietary product: NicAssist Nasal Spray, Nicorette Nasal
Spray), nicotine 500 micrograms/metered spray

Nicotine Oral Spray
(proprietary product: Nicorette Quickmist), nicotine
1 mg/metered spray

Nicotine Sublingual Tablets
(to be prescribed as either a starter pack (2 × 15-tablet
discs with dispenser) or refill pack (7 × 15-tablet discs))
(proprietary product: NicAssist Microtab, Nicorette Microtab),
nicotine (as a cyclodextrin complex) 2 mg

Nicotine Transdermal Patches
(prescriber should specify the brand to be dispensed)
releasing in each 16 hours, nicotine approx. 5 mg, 10 mg, or
15 mg (proprietary products: Boots NicAssist Patch, Nicorette
Patch) or releasing in each 16 hours approx. 10 mg, 15 mg,
or 25 mg (proprietary products: NicAssist Transparent Patch,
Nicorette Invisi Patch), or releasing in each 24 hours nicotine
approx. 7 mg, 14 mg, or 21 mg (proprietary products:
Nicopatch, Nicotinell TTS, NiQuitin, NiQuitin Clear)

Permethrin Cream
(proprietary product: Lyclear Dermal Cream), permethrin 5%

Senna Oral Solution
(proprietary product: Senokot Syrup), sennosides
7.5 mg/5 mL

Senna and Ispaghula Granules
(proprietary product: Manevac Granules), senna fruit 12.4%,
ispaghula 54.2%

Sodium Citrate Compound Enema
(proprietary products: Micolette Micro-enema; Micralax
Micro-enema; Relaxit Micro-enema), sodium citrate 450 mg
with glycerol, sorbitol and an anionic surfactant

Sodium Picosulfate Capsules
(proprietary products: Dulcolax Perles), sodium picosulfate
2.5 mg

Sodium Picosulfate Elixir
(proprietary products: Dulcolax Liquid), sodium picosulfate
5 mg/5 mL

Sterculia Granules
(proprietary product: Normacol Granules), sterculia 62%
Non-medical prescribing

A range of non-medical healthcare professionals can prescribe medicines for patients as either Independent or Supplementary Prescribers.

Independent prescribers are practitioners responsible and accountable for the assessment of patients with previously undiagnosed or diagnosed conditions and for decisions about the clinical management required, including prescribing. They are recommended to prescribe generically, except where this would not be clinically appropriate or where there is no approved non-proprietary name.

Supplementary prescribing is a partnership between an independent prescriber (a doctor or a dentist) and a supplementary prescriber to implement an agreed Clinical Management Plan for an individual patient with that patient’s agreement.

Independent and Supplementary Prescribers are identified by an annotation next to their name in the relevant professional register.

Information and guidance on non-medical prescribing is available on the Department of Health website at www.dh.gov.uk/health/2012/04/prescribing-change.

For information on the mixing of medicines by Independent and Supplementary Prescribers, see Mixing of medicines prior to administration in clinical practice—responding to legislative changes, National Prescribing Centre, May 2010 (available at www.npc.nhs.uk/improving_safety/mixing_meds/resources/mixing_of_medicines.pdf).

For information on the supply and administration of medicines to groups of patients using Patient Group Directions see Guidance on prescribing p. 1.

**Nurses**

Nurse Independent Prescribers (formerly known as Extended Formulary Nurse Prescribers) are able to prescribe any medicine for any medical condition.

Nurse Independent Prescribers are able to prescribe, administer, and give directions for the administration of Schedule 2, 3, 4, and 5 Controlled Drugs. This extends to diamorphine, dipipanone, or cocaine for treating organic disease or injury, but not for treating addiction.

Nurse Independent Prescribers must work within their own level of professional competence and expertise.

The Nurse Prescribers’ Formulary p. 1322 for Community Practitioners provides information on prescribing.

**Pharmacists**

Pharmacist Independent Prescribers can prescribe any medicine for any medical condition.

They are also able to prescribe, administer, and give directions for the administration of Schedule 2, 3, 4, and 5 Controlled Drugs. This extends to diamorphine, dipipanone, or cocaine for treating organic disease or injury, but not for treating addiction.

Pharmacist Independent Prescribers must work within their own level of professional competence and expertise.

**Optometrists**

Optometrist Independent Prescribers can prescribe any licensed medicine for ocular conditions affecting the eye and the tissues surrounding the eye, except Controlled Drugs or medicines for parenteral administration.

Optometrist Independent Prescribers must work within their own level of professional competence and expertise.
Index of proprietary manufacturers

The following is an alphabetical list of manufacturers and other companies referenced in the BNF, with their medicines information or general contact details. For information on 'special-order' manufacturers and specialist importing companies see 'Special-order manufacturers'.

3M
3M Health Care Ltd
Tel: (01509) 611 611

Abbott
Abbott Healthcare
Abbott Healthcare Products Ltd
Tel: (01628) 773 355
medinfo.shl@abbott.com

AABB
AABB Ltd
Tel: 0800 124 411
customercontactuk@gsk.com

A1 Pharmaceuticals
A1 Pharmaceuticals Plc
Tel: (01708) 528 900
sales@a1plc.co.uk

Adienne Pharma and Biotech
Tel: 0039 8987 3333
advice@activahealthcare.co.uk

Agerion
Agerion Pharmaceuticals Ltd
Tel: 08000 2343 7466
medinfo.emea@agerion.com

Agema
Agema GmbH
Tel: (020) 3239 6241
uk@agepha.com

Aguettant
Aguettant Ltd
Tel: (01934) 835 694
info@aguettant.co.uk

Air Products
Air Products plc
Tel: 0800 373 580

Alan Pharmaceuticals
Alan Pharmaceuticals
Tel: 0800 376 7950

Alcon
Alcon Laboratories (UK) Ltd
Tel: 0345 266 9363
gbmedicaldepartment@alcon.com

Alexion
Alexion Pharma UK Ltd
Tel: (01932) 359 220
alexion.uk@alxn.com

Alimera
Alimera Sciences Limited
Tel: 0800 019 1253
medicalinformation@alimerasciences.com

Alissa
Alissa Healthcare
Tel: (01489) 80 759
enquiries@alissahcare.com

ALK-Abelló
ALK-Abelló (UK) Ltd
Tel: (0118) 903 7940
info@uk.alk-abelló.com

Alkopharma
Alkopharma Sarl
Tel: (0041) 277 206 969
regulatory@alkopharma.com

Allergan
Allergan Ltd
Tel: (01628) 494 026

Allergy
Allergy Therapeutics Ltd
Tel: (01903) 844 702

Alliance
Alliance Pharmaceuticals Ltd
Tel: (01249) 466 966
info@alliancepharma.co.uk

Almirall
Almirall Ltd
Tel: 0800 008 7399
medinfouk@almirall.com

Altacor
Altacor Ltd
Tel: (01223) 421 411
info@altacor-pharma.com

AMCo
Andipharm Mercury Company Ltd
Tel: 08700 70 30 33
medicalinformation@amcolimited.com

Amgen
Amgen Ltd
Tel: (01223) 420 305
gbinfo@amgen.com

AMO
Abbot Medical Optics
Tel: 0800 376 7950

Amed
Amed Healthcare Ltd
Tel: (0330) 333 0079
info@amedhealthcare.com

Apollo Medical
Apollo Medical Technologies Ltd
Tel: (01636) 831 201
supercheck2@btinternet.com

Archimed
Archimed
Tel: 0800 756 9951
enquiries@archimed.co.uk

Archimedes
Archimedes Pharma UK Ltd
Tel: (0118) 931 5094
medicalinformationuk@archimedespharma.com

Arctic Medical
Arctic Medical Ltd
Tel: (01303) 277 751
sales@arcticmedical.co.uk

Ardana
Ardana Bioscience Ltd
Tel: (0131) 226 8550

ARIAD
ARIAD Pharma UK Ltd
Tel: 0800 0002 7423
eumedinfop Ariad.com

Ark Therapeutics
Ark Therapeutics Group Plc
Tel: (020) 7388 7722
info@arktherapeutics.com

Aspen
Aspen
Tel: 0800 008 7392
aspenmedinfo@professionalinformation.co.uk

Aspen Medical
Aspen Medical Europe Ltd
Tel: (01527) 587 728
customers@aspenmedical-europe.com

AS Pharma
AS Pharma Ltd
Tel: 0870 066 4117
info@aspharma.co.uk
Index of proprietary manufacturers

Aspire
Aspire Pharma Ltd
Tel: (01730) 231 148
info@aspirepharma.co.uk

Astellas
Astellas Pharma Ltd
Tel: (020) 3379 8000
medinfo.gb@astellas.com

AstraZeneca
AstraZeneca UK Ltd
Tel: 0800 783 0033
medical.informationuk@astraZeneca.com

Auden Mckenzie
Auden Mckenzie (Pharma Division) Ltd
Tel: (01895) 627 420

Auxilium
Auxilium
Tel: 0845 017 2315
auxilium@pilglobal.com

Axcan
Axcan Pharma SA
Tel: (0033) 130 461 900

AYMES
AYMES International Ltd
Tel: 0845 6805 496
info@aymes.com

Ayrton Saunders
Ayrton Saunders Ltd
Tel: (0151) 709 2074
info@ayrtons.com

BAP
BAP Medical UK Ltd
Tel: 0844 879 7689

Bard
Bard Ltd
Tel: (01293) 527 888

Basilea
Basilea Pharmaceutica Ltd
Tel: (01483) 790 023
ukmedinfo@basilea.com

Bausch & Lomb
Bausch & Lomb UK Ltd
Tel: (01748) 828 864
medical.informationuk@bausch.com

Baxter
Baxter Healthcare Ltd
Tel: (01635) 206 345
surecall@baxter.com

Bayer
Bayer Healthcare Pharmaceuticals
Tel: (01635) 563 000
medical.information@bayer.co.uk

Bayer Consumer Care
Bayer Healthcare Pharmaceuticals
Tel: (01635) 563 000
medical.information@bayer.co.uk

Bayer Diabetes Care
Bayer Healthcare Pharmaceuticals
Tel: (01635) 563 000
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Index of proprietary manufacturers

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Unlicensed medicines are available from 'special-order' manufacturers and specialist-importing companies; the MHRA maintains a register of these companies at tinyurl.com/cdskhe.

Licensed hospital manufacturing units also manufacture 'special-order' products as unlicensed medicines, the principal NHS units are listed below. A database (Pro-File; www.pro-file.nhs.uk) provides information on medicines manufactured in the NHS; access is restricted to NHS pharmacy staff.

The Association of Pharmaceutical Specials Manufacturers may also be able to provide further information about commercial companies (www.apsm-uk.com).

The MHRA recommends that an unlicensed medicine should only be used when a patient has special requirements that cannot be met by use of a licensed medicine.

As well as being available direct from the hospital manufacturer(s) concerned, many NHS-manufactured Specials may be bought from the Oxford Pharmacy Store, owned and operated by Oxford Health NHS Foundation Trust.

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REPORT OF SUSPECTED ADVERSE DRUG REACTIONS

If you suspect an adverse reaction may be related to one or more drugs/vaccines/complementary remedies, please complete this Yellow Card. See 'Adverse reactions to drugs' section in BNF or www.mhra.gov.uk/yellowcard for guidance. Do not be put off reporting because some details are not known.

**PATIENT DETAILS**

Patient Initials: ___________  Sex: M / F  Is the patient pregnant? Y / N  Ethnicity: ___________
Age (at time of reaction): ___________  Weight (kg): ___________  Identification number (e.g. Practice or Hospital Ref): ___________

**SUSPECTED DRUG(S)/VACCINE(S)**

<table>
<thead>
<tr>
<th>Drug/Vaccine (Brand if known)</th>
<th>Batch</th>
<th>Route</th>
<th>Dosage</th>
<th>Date started</th>
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**SUSPECTED REACTION(S)** Please describe the reaction(s) and any treatment given. (Please attach additional pages if necessary):

Date reaction(s) started: ___________  Date reaction(s) stopped: ___________

Do you consider the reactions to be serious?  Yes / No

If yes, please indicate why the reaction is considered to be serious (please tick all that apply):

- Patient died due to reaction
- Life threatening
- Congenital abnormality
- Involved or prolonged inpatient hospitalisation
- Involved persistent or significant disability or incapacity
- Medically significant; please give details: ___________

If the reactions were not serious according to the categories above, how bad was the suspected reaction?

- Mild
- Unpleasant, but did not affect everyday activities
- Bad enough to affect everyday activities
It’s easy to report online: www.mhra.gov.uk/yellowcard

**OTHER DRUG(S) (including self-medication and complementary remedies)**

Did the patient take any other medicines/vaccines/complementary remedies in the last 3 months prior to the reaction? Yes / No

If yes, please give the following information if known:

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**Additional relevant information** e.g. medical history, test results, known allergies, rechallenge (if performed). For reactions relating to use of a medicine during pregnancy please state all other drugs taken during pregnancy, the last menstrual period, information on previous pregnancies, ultrasound scans, any delivery complications, birth defects or developmental concerns.

Please list any medicines obtained from the internet:

**REPORTER DETAILS**

Name and Professional Address:

Postcode:  
Tel No:  
Email:  
Speciality:  
Signature:  
Date:  

**CLINICIAN (if not the reporter)**

Name and Professional Address:

Postcode:  
Tel No:  
Email:  
Speciality:  
Date:  

Information on adverse drug reactions received by the MHRA can be downloaded at www.mhra.gov.uk/daps

Stay up-to-date on the latest advice for the safe use of medicines with our monthly bulletin Drug Safety Update at: www.mhra.gov.uk/drugsafetyupdate

Please attach additional pages if necessary. Send to: FREEPOST YELLOW CARD (no other address details required)
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Additional relevant information e.g. medical history, test results, known allergies, rechallenge (if performed). For reactions relating to use of a medicine during pregnancy please state all other drugs taken during pregnancy, the last menstrual period, information on previous pregnancies, ultrasound scans, any delivery complications, birth defects or developmental concerns.

Please list any medicines obtained from the internet:

REPORTER DETAILS
Name and Professional Address:

Postcode: Tel No:
Email:
Speciality:
Signature: Date:

CLINICIAN (if not the reporter)
Name and Professional Address:

Postcode: Tel No:
Email:
Speciality:
Date:

Information on adverse drug reactions received by the MHRA can be downloaded at www.mhra.gov.uk/daps
Stay up-to-date on the latest advice for the safe use of medicines with our monthly bulletin Drug Safety Update at: www.mhra.gov.uk/drugsafetyupdate

Please attach additional pages if necessary. Send to: FREEPOST YELLOW CARD (no other address details required)
Adult Advanced Life Support Algorithm

Unresponsive?
Not breathing or only occasional gasps

Call Resuscitation Team

CPR 30:2
Attach defibrillator/monitor
Minimise interruptions

Assess rhythm

Shockable
(VF/pulseless VT)

Non-shockable
(PEA/Asystole)

Return of spontaneous circulation

1 Shock
Immediately resume CPR for 2 mins
Minimise interruptions

Immediate post cardiac arrest treatment
- Use ABCDE approach
- Controlled oxygenation and ventilation
- 12-lead ECG
- Treat precipitating cause
- Temperature control / therapeutic hypothermia

During CPR
- Ensure high-quality CPR: rate, depth, recoil
- Plan actions before interrupting CPR
- Give oxygen
- Consider advance airway and capnography
- Continuous chest compressions when advanced airway in place
- Vascular access (intravenous, intraosseous)
- Give adrenaline every 3-5 min
- Correct reversible causes

Reversible causes
- Hypoxia
- Hypovolaemia
- Hypo- / hyperkalaemia / metabolic
- Hypothermia
- Thrombosis – coronary or pulmonary
- Tamponade – cardiac
- Toxins
- Tension pneumothorax

Adapted with the kind permission of the Resuscitation Council (UK) from Resuscitation Guidelines, October 2010
Medical emergencies in the community

Drug treatment outlined below is intended for use by appropriately qualified healthcare professionals. Only drugs that are used for immediate relief are shown, advice on supporting care is not given. Where the patient’s condition requires investigation and further treatment, the patient should be transferred to hospital promptly.

Acute coronary syndromes

- ANGINA: UNSTABLE
  - ASPIRIN dispersible tablets p. 104 (75 mg, 300 mg)
    - BY MOUTH (DISPERSED IN WATER OR CHEWED)
      - Adult: 300 mg
  - PLUS
    - EITHER Glyceryl trinitrate aerosol spray p. 190 (400 micrograms/metered dose)
      - SUBLINGUALLY
        - Adult: 1–2 sprays, repeated as required
    - OR Glyceryl trinitrate tablets p. 190 (300 micrograms, 500 micrograms, 600 micrograms)
      - SUBLINGUALLY
        - Adult: 0.3–1 mg, repeated as required

- MYOCARDIAL INFARCTION: NON-ST-SEGMENT ELEVATION
  Treat as for Angina: unstable

- MYOCARDIAL INFARCTION: ST-SEGMENT ELEVATION
  - ASPIRIN dispersible tablets p. 104 (75 mg, 300 mg)
    - BY MOUTH (DISPERSED IN WATER OR CHEWED)
      - Adult: 300 mg
  - Glyceryl trinitrate aerosol spray p. 190 (400 micrograms/metered dose)
    - SUBLINGUALLY
      - Adult: 1–2 sprays, repeated as required
  - OR Glyceryl trinitrate tablets p. 190 (300 micrograms, 500 micrograms, 600 micrograms)
    - SUBLINGUALLY
      - Adult: 0.3–1 mg, repeated as required
  - Metoclopramide hydrochloride injection p. 347 (5 mg/mL)
    - BY INTRAVENOUS INJECTION
      - Adult (under 60 kg) 18-19 years: 5 mg
      - Adult over 60 kg 18-19 years: 10 mg
      - Adult over 19 years: 10 mg
  - Diamorphine hydrochloride injection p. 361 (5 mg powder for reconstitution)
    - BY SLOW INTRAVENOUS INJECTION (1-2 mg/minute)
      - Adult: 5 mg followed by a further 2.5–5 mg if necessary
        - Elderly or frail patients: reduce dose by half
    - OR Morphine sulphate injection p. 367 (10 mg/mL)
      - BY SLOW INTRAVENOUS INJECTION (1-2 mg/minute)
        - Adult: 5–10 mg followed by a further 5–10 mg if necessary
        - Elderly or frail patients: reduce dose by half
  - Oxygen, if appropriate

Airways disease, obstructive

- ASTHMA: ACUTE
  Regard each emergency consultation as being for severe acute asthma until shown otherwise; failure to respond adequately at any time requires immediate transfer to hospital

- EITHER Salbutamol aerosol inhaler p. 222
  (100 micrograms/metered inhalation)
    - BY AEROSOL INHALATION VIA LARGE-VOLUME SPACER (AND A CLOSE-FITTING FACE MASK IF CHILD UNDER 3 YEARS)
      - Adult and child: 2–10 puffs each inhaled separately, repeated every 10–20 minutes or as necessary
  - OR Salbutamol nebuliser solution p. 222 (1 mg/mL, 2 mg/mL)
    - BY INHALATION OF NEBULISED SOLUTION (VIA OXYGEN-DRIVEN NEBULISER IF AVAILABLE)
      - Child 4 years and below: 2.5 mg every 20–30 minutes or as necessary
      - Child 5-11 years: 2.5–5 mg every 20–30 minutes or as necessary
      - Child 12-17 years: 5 mg every 20–30 minutes or as necessary
      - Adult: 5 mg every 20–30 minutes or as necessary
  - OR Terbutaline sulfate nebuliser solution p. 225 (2.5 mg/mL)
    - BY INHALATION OF NEBULISED SOLUTION (VIA OXYGEN-DRIVEN NEBULISER IF AVAILABLE)
      - Child 4 years and below: 5 mg every 20–30 minutes or as necessary
      - Child 5-11 years: 5–10 mg every 20–30 minutes or as necessary
      - Child 12-17 years: 10 mg every 20–30 minutes or as necessary
      - Adult: 10 mg every 20–30 minutes or as necessary
  - PLUS (in all cases)
    - EITHER Prednisolone tablets p. 585 (or prednisolone soluble tablets) (5 mg)
      - BY MOUTH
        - Child 11 years and below: 1–2 mg/kg (max. 40 mg) once daily for up to 3 days or longer if necessary; if child has been taking an oral corticosteroid for more than a few days, give prednisolone 2 mg/kg (max. 60 mg) once daily
        - Child 12-17 years: 40–50 mg once daily for at least 5 days
        - Adult: 40–50 mg once daily for at least 5 days
    - OR Hydrocortisone (preferably as sodium succinate) p. 583
      - BY INTRAVENOUS INJECTION
        - Child 17 years and below: 4 mg/kg (max. 100 mg) every 6 hours until conversion to oral prednisolone is possible; alternative dose if weight unavailable:
          - Child 1 year and below: 25 mg
          - Child 2-4 years: 50 mg
          - Child 5-17 years: 100 mg
          - Adult: 100 mg every 6 hours until conversion to oral prednisolone is possible
      - High-flow oxygen should be given if available (via face mask in children)
      - Monitor response 15 to 30 minutes after nebulisation; if any signs of acute asthma persist, arrange hospital admission. While awaiting ambulance, repeat nebulised beta, agonist (as above) and give with
        - Ipratropium bromide nebuliser solution p. 217
          (250 micrograms/mL)
          - BY INHALATION OF NEBULISED SOLUTION (VIA OXYGEN-DRIVEN NEBULISER IF AVAILABLE)
            - Child 11 years and below: 250 micrograms, repeated every 20–30 minutes for the first 2 hours, then every 4–6 hours as necessary
            - Child 12-17 years: 500 micrograms every 4–6 hours as necessary
            - Adult: 500 micrograms every 4–6 hours as necessary
Anaphylaxis

**ANAPHYLAXIS**

**Adrenaline/epinephrine injection p. 196 (1 mg/mL (1 in 1000))**

- **Child 5 years and below:** 150 micrograms (0.15 mL), repeated every 5 minutes if necessary
- **Child 6-11 years:** 300 micrograms (0.3 mL), repeated every 5 minutes if necessary
- **Child 12-17 years:** 500 micrograms (0.5 mL), repeated every 5 minutes if necessary
- **Adult:** 500 micrograms (0.5 mL), repeated every 5 minutes if necessary

High-flow oxygen and intravenous fluids should be given as soon as available.

**Chlorphenamine maleate injection p. 245**

- **BY INTRAMUSCULAR OR INTRAVENOUS INJECTION** may help counter histamine-mediated vasodilation and bronchoconstriction.

**Hydrocortisone (preferably as sodium succinate) p. 583**

BY INTRAVENOUS INJECTION has delayed action but should be given to severely affected patients to prevent further deterioration.

Bacterial infection

**MENINGOCOCCAL DISEASE**

**Benzy1penicillin sodium injection p. 480 (600 mg, 1.2 g)**

- **Neonate:** 300 mg
- **Child 1 month-11 months:** 300 mg
- **Child 1-9 years:** 600 mg
- **Child 10-17 years:** 1.2 g
- **Adult:** 1.2 g

*Note* A single dose should be given before urgent transfer to hospital, so long as this does not delay the transfer.

**OR** if history of allergy to penicillin

**Cefotaxime injection p. 457 (1 g)**

- **Neonate:** 50 mg/kg
- **Child 1 month-11 years:** 50 mg/kg (max. 1 g)
- **Child 12-17 years:** 1 g
- **Adult:** 1 g

*Note* A single dose can be given before urgent transfer to hospital, so long as this does not delay the transfer.

**OR** if history of immediate hypersensitivity reaction (including anaphylaxis, angioedema, urticaria, or rash immediately after administration) to penicillin or to cephalosporins

**Chloramphenicol injection p. 452 (1 g)**

- **Neonate:** 50 mg/kg
- **Child 1 month-11 years:** 50 mg/kg
- **Child 12-17 years:** 1 g
- **Adult:** 1.2 g

*Note* A single dose can be given before urgent transfer to hospital, so long as this does not delay the transfer.

Seizures

**CONVULSIVE (INCLUDING FEBRILE) SEIZURES LASTING LONGER THAN 5 MINUTES**

**OR** Diazepam rectal solution p. 267 (2 mg/mL, 4 mg/mL)

- **EITHER** by rectum
  - **Neonate:** 1.25–2.5 mg, repeated once after 10–15 minutes if necessary
  - **Child 1 month-11 years:** 5 mg, repeated once after 10–15 minutes if necessary
  - **Child 12-17 years:** 10–20 mg, repeated once after 10–15 minutes if necessary
  - **Adult:** 10–20 mg, repeated once after 10–15 minutes if necessary
  - **Elderly 65 years and over:** 10 mg, repeated once after 10–15 minutes if necessary

**OR** Midazolam oromucosal solution p. 414

- **BY BUCAL ADMINISTRATION, REPEATED ONCE AFTER 10 MINUTES IF NECESSARY**
  - **Neonate:** 300 micrograms/kg [unlicensed]
  - **Child 1-2 months:** 300 micrograms/kg (max. 2.5 mg) [unlicensed]
  - **Child 3 months-11 months:** 2.5 mg
  - **Child 1-4 years:** 5 mg
  - **Child 5-9 years:** 7.5 mg
  - **Child 10-17 years:** 10 mg
  - **Adult:** 10 mg [unlicensed]
Approximate Conversions and Units

Conversion of pounds to kilograms

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Conversion of stones to kilograms

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Conversion from millilitres to fluid ounces

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Recommended wording of cautionary and advisory labels

For details please see p. 1291

1. Warning: This medicine may make you sleepy
2. Warning: This medicine may make you sleepy. If this happens, do not drive or use tools or machines. Do not drink alcohol
3. Warning: This medicine may make you sleepy. If this happens, do not drive or use tools or machines
4. Warning: Do not drink alcohol
5. Do not take indigestion remedies 2 hours before or after you take this medicine
6. Do not take indigestion remedies, or medicines containing iron or zinc, 2 hours before or after you take this medicine
7. Do not take milk, indigestion remedies, or medicines containing iron or zinc, 2 hours before or after you take this medicine
8. Warning: Do not stop taking this medicine unless your doctor tells you to stop
9. Space the doses evenly throughout the day. Keep taking this medicine until the course is finished, unless you are told to stop
10. Warning: Read the additional information given with this medicine
11. Protect your skin from sunlight—even on a bright but cloudy day. Do not use sunbeds
12. Do not take anything containing aspirin while taking this medicine
13. Dissolve or mix with water before taking
14. This medicine may colour your urine. This is harmless
15. Caution: flammable. Keep your body away from fire or flames after you have put on the medicine
16. Dissolve the tablet under your tongue—do not swallow.
   Store the tablets in this bottle with the cap tightly closed.
   Get a new supply 8 weeks after opening
17. Do not take more than... in 24 hours
18. Do not take more than... in 24 hours. Also, do not take more than... in any one week
19. Warning: This medicine makes you sleepy. If you still feel sleepy the next day, do not drive or use tools or machines. Do not drink alcohol
20. Take with or just after food, or a meal
21. Take 30 to 60 minutes before food
22. Take this medicine when your stomach is empty. This means an hour before food or 2 hours after food
23. Suck or chew this medicine
24. Swallow this medicine whole. Do not chew or crush
25. Dissolve this medicine under your tongue
26. Take with a full glass of water
27. Spread thinly on the affected skin only
28. Do not take more than 2 at any one time. Do not take more than 8 in 24 hours
29. Contains paracetamol. Do not take anything else containing paracetamol while taking this medicine. Talk to a doctor at once if you take too much of this medicine, even if you feel well
30. Contains aspirin. Do not take anything else containing aspirin while taking this medicine
Abbreviations and Symbols

Internationally recognised units and symbols are used in the BNF publications where possible.

ACBS Advisory Committee on Borderline Substances, see Borderline Substances

ACE Angiotensin-converting enzyme

ADHD Attention deficit hyperactivity disorder

AIDS Acquired immunodeficiency syndrome

approx. approximately

AV atrioventricular

BAN British Approved Name

BMI body mass index

BP British Pharmacopoeia 2013, unless otherwise stated

BPC British Pharmaceutical Codex

CAPD Continuous ambulatory peritoneal dialysis

CDs preparation in Schedule 1 of the Misuse of Drugs Regulations 2001 (and subsequent amendments). For regulations see Controlled drugs and drug dependence p. 7.

CDs preparation in Schedule 2 of the Misuse of Drugs Regulations 2001 (and subsequent amendments). For regulations see Controlled drugs and drug dependence p. 7.

CDs preparation in Schedule 3 of the Misuse of Drugs Regulations 2001 (and subsequent amendments). For regulations see Controlled drugs and drug dependence p. 7.

CDs preparation in Schedule 4 (Part I) of the Misuse of Drugs Regulations 2001 (and subsequent amendments). For regulations see Controlled drugs and drug dependence p. 7.

CDs preparation in Schedule 4 (Part II) of the Misuse of Drugs Regulations 2001 (and subsequent amendments). For regulations see Controlled drugs and drug dependence p. 7.

CHM Commission on Human Medicines

CHMP Committee for Medicinal Products for Human Use

CNS central nervous system

CSM Committee on Safety of Medicines (now subsumed under Commission on Human Medicines)

d. c. direct current

d. m. modified-release

DMARD Disease-modifying antirheumatic drug

d. c. direct current

d. m. modified-release

DPF Dental Practitioners’ Formulary

e.c enteric-coated (termed gastro-resistant in BP)

eeg electro-encephalogram

eGFR estimated glomerular filtration rate, see Prescribing in renal impairment p. 17

f.c film-coated

g6pd glucose-6-phosphate dehydrogenase

HIV Human immunodeficiency virus

HRT Hormone replacement therapy

i/m intramuscular

i/v intravenous

INR international normalised ratio

MAOI Monoamine-oxidase inhibitor

max. maximum

MHRA Medicines and Healthcare products Regulatory Agency

m/r modified-release

NCL no cautionary labels, see Guidance for cautionary and advisory labels Appendix 3

NHS National Health Service

npd not prescribable under National Health Service (NHS) Regulations 2001 (and subsequent amendments). For regulations see Controlled drugs and drug dependence p. 7.

NICE National Institute for Health and Care Excellence

NPF Nurse Prescribers’ Formulary

NSAID Non-steroidal anti-inflammatory drug

NSTEMI non-ST-segment elevation myocardial infarction

PGD patient group direction

PHE Public Health England (formerly Health Protection Agency (HPA))

PGM prescription-only medicine, see Fig. 1 How to use BNF publications p. xi

® trade mark

rINN Recommended International Non-proprietary Name

RSV respiratory syncytial virus

s/c sugar-coated

SLS Selected List Scheme

SMC Scottish Medicines Consortium

SPC Summary of Product Characteristics

sp. species

SSRI Selective serotonin reuptake inhibitor

STEMI ST-segment elevation myocardial infarction

UK United Kingdom

Units for SI units see Prescription writing p. 4

WHO World Health Organization

limited experience of the use of this product and the MHRA requests that all suspected adverse reactions should be reported, see Adverse reactions to drugs p. 11

general sales list

p. pharmacy only medicine

Latin abbreviations

Directions should be in English without abbreviation. However, Latin abbreviations have been used when prescribing.

The following is a list of appropriate abbreviations. It should be noted that the English version is not always an exact translation.

a. c. = ante cibum (before food)

b. d. = bis die (twice daily)

o. d. = omni die (every day)

o. m. = omni mane (every morning)

o. n. = omni nocte (every night)

p. c. = post cibum (after food)

p. r. n. = pro re nata (when required)

q. d. s. = quater die sumendum (to be taken four times daily)

q. q. h. = quarta quaque hora (every four hours)

stat = immediately

t. d. s. = ter die sumendum (to be taken three times daily)

t. i. d. = ter in die (three times daily)

E numbers

The following is a list of common E numbers and the inactive ingredients to which they correspond.

| E102  | Tartrazine                     |
| E211  | Sodium Benzoate               |
| E104  | Quinoline Yellow              |
| E223  | Sodium Metabisulphite         |
| E110  | Sunset Yellow FCF             |
| E320  | Butylated Hydroxyanisole      |
| E123  | Amaranth                      |
| E321  | Butylated Hydroxytoluene      |
| E124  | Ponceau 4R                    |
| E322  | Lecithins                     |
| E127  | Erythrosine BS                |
| E420  | Sorbitol                      |
| E132  | Indigo Carmine                |
| E421  | Mannitol                      |
| E142  | Green S                       |
| E422  | Glycerol                      |
| E171  | Titanium Dioxide              |
| E901  | Beeswax (white and yellow)    |
| E172  | Iron oxides, iron hydroxides  |
| E1520 | Propylene Glycol              |
| E200  | Sorbic Acid                   |