Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

DICYCLOVERINE HYDROCHLORIDE 10MG/5ML ORAL SOLUTION
DICYCLOVERINE HYDROCHLORIDE 10 MG TABLETS
DICYCLOVERINE HYDROCHLORIDE 20 MG TABLETS
(dicycloverine hydrochloride)

UK Licence No: PL 20117/0255-0257

Morningside Healthcare Limited

Medicines and Healthcare Products Regulatory Agency

LAY SUMMARY

Dicycloverine Hydrochloride 10mg/5ml Oral Solution
Dicycloverine Hydrochloride 10 mg Tablets
Dicycloverine Hydrochloride 20 mg Tablets
(dicycloverine hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Dicycloverine Hydrochloride 10mg/5ml Oral Solution (PL 20117/0255), Dicycloverine Hydrochloride 10 mg Tablets (PL 20117/0256) and Dicycloverine Hydrochloride 20 mg Tablets (PL 20117/0257). It explains how the applications for Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets were assessed and their authorisation recommended as well as their conditions of use. It is not intended to provide practical advice on how to use Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets.

For practical information about using Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets and what are they used for?
Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets are 'generic medicines'. This means that Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets are similar to 'reference medicines' already authorised in the European Union (EU) called Merbentyl Syrup 10mg/5ml, Merbentyl 10 mg tablets and Merbentyl 20 mg tablets.

Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets are used to treat cramps, pain in the stomach or gut (intestine), and stomach or gut (intestine) problems such as irritable bowel.

How do Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets work?
These medicines contain the active ingredient dicycloverine hydrochloride. This is an antispasmodic, and it relieves, prevents, or lowers the number of muscle spasms that occur. Dicyloverine works by relaxing the muscles in your stomach and gut (intestine). It stops sudden muscle contractions (spasms). In doing this, it relieves cramps, pain, bloating, wind and discomfort.

How are Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets used?
These medicines can only be obtained with a prescription.

Dicycloverine Hydrochloride 10mg/5ml Oral Solution can be taken before or after meals.

The usual dose in adults is 5 ml to 10 ml (10 mg – 20mg) three times each day. The usual dose in children aged 2 to 12 years is 5 ml (10 mg) three times each day. The usual dose in children aged 6 months to 2 years is 2.5 ml to 5 ml (5 mg – 10 mg) three or four times each day. In this age group the solution should be given 15 minutes before feeds and no more than 20 ml (40 mg) should be given in a 24 hour period.

Dicycloverine Hydrochloride 10 mg and 20 mg Tablets should be swallowed with a glass of water and can be taken before or after meals.

The usual dose in adults and children 12 years of age or older is one 10 mg tablet or one 20 mg tablet, three times each day. The usual dose in children aged 2 to 12 years of age is one 10 mg tablet three times each day. For children at the younger end of the age range, a tablet is not a suitable dosage form, and Dicycloverine Hydrochloride 10mg/5ml Oral Solution is more appropriate.

What benefits of Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets have been shown in studies?
The company provided data from the published literature on the active substance.

No additional studies were needed for Dicycloverine Hydrochloride 10mg/5ml Oral Solution as this product is a generic medicine that is given as an oral solution and contains the same active substance as the reference medicine, Merbentyl Syrup 10mg/5ml.

Because Dicycloverine Hydrochloride 10 mg and 20 mg Tablets are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicines, Merbentyl 10 mg tablets and Merbentyl 20 mg tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets?
Because Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets are generic medicines, their possible side effects are taken as being the same as those of the reference medicines, Merbentyl Syrup 10mg/5ml, Merbentyl 10 mg tablets and Merbentyl 20 mg tablets.
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For the full list of all side effects reported with Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why were Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets approved?
It was concluded that, in accordance with EU requirements, Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets have been shown to have comparable quality and to be comparable to Merbentyl Syrup 10mg/5ml, Merbentyl 10 mg tablets and Merbentyl 20 mg tablets. Therefore, the MHRA decided that, as for Merbentyl Syrup 10mg/5ml, Merbentyl 10 mg tablets and Merbentyl 20 mg tablets, the benefits outweigh the identified risks and recommended that Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets can be approved for use.

What measures are being taken to ensure the safe and effective use of Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets?
A risk management plan (RMP) has been developed to ensure that Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflets for Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets

Marketing Authorisations were granted in the UK on 14 July 2016.

The full PAR for Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets follows this summary. For more information about treatment with Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in September 2016.

SCIENTIFIC DISCUSSION

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Morningside Healthcare Limited Marketing Authorisations for the medicinal products Dicycloverine Hydrochloride 10mg/5ml Oral Solution (PL 20117/0255), Dicycloverine Hydrochloride 10 mg Tablets (PL 20117/0256) and Dicycloverine Hydrochloride 20 mg Tablets (PL 20117/0257) on 14 July 2016.

These products are prescription only medicines (legal classification POM).

These were applications made under the National Procedure, according to Article 10(1) of Directive 2001/83/EC, as amended. The reference product for Dicycloverine Hydrochloride 10mg/5ml Oral Solution is Merbentyl Syrup 10mg/5ml (PL 04425/0047), which was granted a Marketing Authorisation to Merrell Pharmaceuticals Ltd on 13 July 1983. The reference product is currently marketed by Winthrop Pharmaceuticals UK Limited (PL 17780/0564) following a change of ownership on 19 April 2011. The reference products for Dicycloverine Hydrochloride 10 mg and 20 mg Tablets are Merbentyl 10 mg and 20 mg Tablets (PL 04425/0035 and PL 04425/0081), which were granted Marketing Authorisations to Merrell Pharmaceuticals Ltd and Merrell Dow Pharmaceuticals Limited on 27 September 1982 and 13 February 1986, respectively. The reference products are currently marketed as Dicycloverine hydrochloride 10 mg Tablets (PL 17780/0565) and Dicycloverine hydrochloride 20 mg Tablets (PL 17780/0566) by Winthrop Pharmaceuticals UK Limited, following a change of ownership on 19 April 2011.

Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets are primarily indicated for treatment of functional conditions involving smooth muscle spasm of the gastrointestinal tract.

These products contain the active substance dicycloverine hydrochloride. Dicycloverine hydrochloride relieves smooth muscle spasm of the gastrointestinal tract.
Animal studies indicate that this action is achieved via a dual mechanism;

- a specific anticholinergic effect (antimuscarinic at the ACh-receptor sites), and;
- a direct effect upon smooth muscle (musculotropic).

With the exception of the bioequivalence study, no new clinical or non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

A bioequivalence study was performed, which compared the pharmacokinetics of the test product Dicycloverine Hydrochloride 20 mg Tablets to those of the reference product Dicycloverine hydrochloride 20 mg Tablets (PL 17780/0566; Winthrop Pharmaceuticals UK Limited). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice are in place for these product types at all sites responsible for the manufacture, assembly and batch release of the products.

A summary of the pharmacovigilance system and a detailed Risk Management Plan (RMP) have been provided with these applications and these are satisfactory.

II QUALITY ASPECTS

II.1 Introduction

Dicycloverine Hydrochloride 10mg/5ml Oral Solution is a clear to pale yellow coloured liquid, with a characteristic odour and taste. Each 5 ml contains 10 mg of the active ingredient dicycloverine hydrochloride.

Other ingredients consist of the pharmaceutical excipients, namely invert syrup, citric acid monohydrate (E 330), sodium benzoate (E 211), cherry flavour (contains acetic acid (E 260), propylene glycol (E 1520) and triethyl citrate (E 1505), vanilla flavour (contains propylene glycol (E 1520), blackcurrant flavour (contains propylene glycol (E 1520), raspberry flavour (contains acetic acid (E 260), propylene glycol (E 1520), triacetin (E 1518)) and purified water.

The finished product is packaged in the following container/closure systems:

- Amber, type III glass bottles each fitted with a white opaque high molecular high density polyethylene roll on pilfer proof child resistant closure with a low density polyethylene wad.
- Amber polyethylene terephthalate bottles each fitted with a white opaque high molecular high density polyethylene roll on pilfer proof child resistant closure with a low density polyethylene wad.

The product is presented in pack sizes of 100 ml, 120 ml and 150 ml, with a dosing pipette.Not all pack sizes may be marketed.

Dicycloverine Hydrochloride 10 mg Tablets are white to off-white, flat, bevelled-edged, round, 6.5mm diameter tablets with “D1” debossed on one side. Each tablet contains 10 mg of the active ingredient dicycloverine hydrochloride.

Dicycloverine Hydrochloride 20 mg Tablets are white to off-white flat, bevelled-edged, round, 8.5mm diameter tablets with “D2” debossed on one side. Each tablet contains 20 mg of the active ingredient dicycloverine hydrochloride.

Other ingredients consist of the pharmaceutical excipients, namely lactose monohydrate, cellulose microcrystalline (E 460), pregelatinised maize starch and magnesium stearate (E 470b).

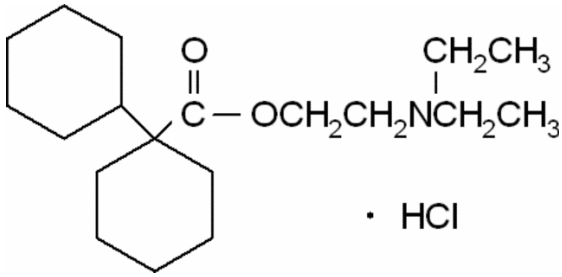
The finished product is packaged in opaque, white, 250 micron polyvinyl chloride blisters, with 20 micron aluminium lidding foil. The blisters contain either 7 or 10 tablets and are presented in packs of 50, 84, 90, 100, 168, or 180 tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug substance

Ph. Eur.:	Dicycloverine hydrochloride
INN:	Dicycloverine
Chemical name:	1,1-Bicyclohexyl]-1-carboxylic acid 2-(diethylamino)ethyl esterhydrochloride 2-(Diethylamino)ethyl 1-cyclohexylcyclohexane-1-carboxylatehydrochloride

Structure:



Molecular formula: $C_{19}H_{35}NO_2 \cdot HCl$
Molecular weight: 345.95
Appearance: White or almost white crystalline powder.
Solubility: Soluble in water, freely soluble in alcohol and in methylene chloride

All aspects of the manufacture and control of the active substance dicycloverine hydrochloride are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability (CEP).

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate globally acceptable and stable products that could be considered generic medicinal products of the reference products Merbentyl Syrup 10mg/5ml, Merbentyl 10 mg tablets and Merbentyl 20 mg tablets.

A satisfactory account of the pharmaceutical development has been provided.

For Dicycloverine Hydrochloride 10 mg and 20 mg Tablets comparative *in vitro* dissolution profiles have been provided for the applicant's products versus the reference products.

For the oral solution, the invert syrup is controlled according to its British Pharmacopoeia monograph. The flavourings (cherry, vanilla, blackcurrant and raspberry) are controlled according to in-house specifications. All other excipients comply with their respective European Pharmacopoeia monographs. None of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

For Dicycloverine Hydrochloride 10 mg and 20 mg Tablets, all the excipients comply with their respective European Pharmacopoeia monographs. None of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate description of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished products. Process validation has been carried out on three commercial scale batches of each strength/form of finished product. The results are satisfactory.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification for each product. Certificates of Analysis have been provided for all working standards used.

Stability of the product
Stability studies were performed, in accordance with current guidelines, on batches of finished product in the packaging proposed for marketing.

For Dicycloverine Hydrochloride 10mg/5ml Oral Solution, the results from these studies support a shelf-life of 2 years for the unopened pack, with the special storage conditions of "Keep the bottle in the outer carton". The contents of the bottle should be discarded 6 months after first opening.
For Dicycloverine Hydrochloride 10 mg and 20 mg Tablets, the results from these studies support a shelf-life of 3 years with no special storage conditions.

II.4 Discussion on chemical, pharmaceutical and biological aspects

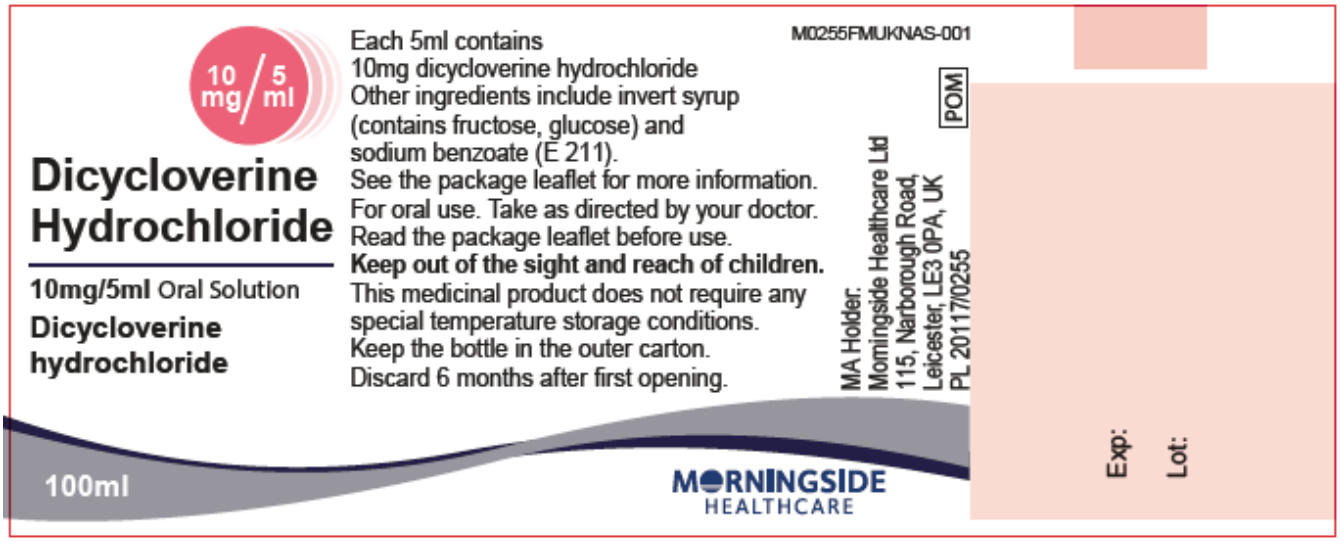
It is recommended that Marketing Authorisations are granted for Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

The SmPCs, PILs and labels are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website.

The approved labelling is shown below:




FPO
100ml
10mg/5ml Oral Solution
Dicycloverine
hydrochloride
Dicycloverine Hydrochloride
10 mg/5 ml
Dicycloverine Hydrochloride
10mg/5ml Oral Solution
Dicycloverine hydrochloride
Affix dispensing label here
Each 5ml contains
10mg dicycloverine hydrochloride
Other ingredients include invert syrup (contains fructose, glucose) and sodium benzoate (E 211).
See the package leaflet for more information.
For oral use.
Take as directed by your doctor.
Read the package leaflet before use.
Keep out of the sight and reach of children.
This medicinal product does not require any special temperature storage conditions.
Keep the bottle in the outer carton.
Discard 6 months after first opening.
POM
MA Holder:
Morningside Healthcare Ltd
115, Narborough Road,
Leicester, LE3 0PA, UK
PL 20117/0255
5 055132 715709
10 mg/5 ml
Dicycloverine Hydrochloride
10mg/5ml Oral Solution
Dicycloverine hydrochloride
100ml
MORNINGSIDE HEALTHCARE
M0255CAMUK100S-001
10 mg/5 ml
Dicycloverine Hydrochloride
10mg/5ml Oral Solution
Dicycloverine hydrochloride
100ml
MORNINGSIDE HEALTHCARE
Lot:
Exp:
FPO


Dicycloverine Hydrochloride 10mg Tablets
Dicycloverine hydrochloride
Affix dispensing label here
Each tablet contains
10mg dicycloverine hydrochloride
Contains lactose.
Read the package leaflet
for further information.
For oral use. Take as directed by your doctor.
Read the package leaflet before use.
Keep out of the sight and
reach of children.
This medicinal product does not require any
special storage conditions.
POM
Lot:
Exp:
FPO
MA Holder:
Morningside Healthcare Ltd
115, Narborough Road,
Leicester, LE3 0PA, UK
PL 20117/0256
5 055132 715716
M0256CAMUK100S-001
Dicycloverine Hydrochloride
10mg Tablets
Dicycloverine hydrochloride
100 Tablets
10 mg
MORNINGSIDE HEALTHCARE


Exp:
Dicycloverine Hydrochloride
10mg Tablets
Dicycloverine hydrochloride
Morningside Healthcare Ltd
Lot:
M0256FMUKNAS-001


MA Holder:
Morningside Healthcare Ltd
115, Narborough Road,
Leicester, LE3 0PA, UK
PL 20117/0257
5 055132 115723 1
Exp:
Lot:
FPO
Dicycloverine Hydrochloride
20 mg
20mg Tablets
Dicycloverine hydrochloride
84 Tablets
MORNINGSIDE HEALTHCARE
Dicycloverine Hydrochloride
20 mg
20mg Tablets
Dicycloverine hydrochloride
84 Tablets
Dicycloverine Hydrochloride 20mg Tablets
Dicycloverine hydrochloride
Affix dispensing label here
Each tablet contains
20mg dicycloverine hydrochloride
Contains lactose.
Read the package leaflet
for further information.
For oral use. Take as
directed by your doctor.
Read the package leaflet before use.
Keep out of the sight
and reach of children.
This medicinal product does not
require any special storage conditions.
POM
M0257CAMUK84S-001


Exp:
Dicycloverine Hydrochloride
20mg Tablets
Dicycloverine hydrochloride
Dicycloverine Hydrochloride
20mg Tablets
Dicycloverine hydrochloride
Dicycloverine Hydrochloride
20mg Tablets
Dicycloverine hydrochloride
Morningside Healthcare Ltd
Lot:
M0257FMUKNAS-001
Exp:
Dicycloverine Hydrochloride
20mg Tablets
Dicycloverine hydrochloride
Dicycloverine Hydrochloride
20mg Tablets
Dicycloverine hydrochloride
Dicycloverine Hydrochloride
20mg Tablets
Dicycloverine hydrochloride
Morningside Healthcare Ltd
Lot:
M0257FMUKNAS-001
Lot:
M0257FMUKNAS-001
Dicycloverine Hydrochloride
20mg Tablets
Dicycloverine hydrochloride
Dicycloverine Hydrochloride
20mg Tablets
Dicycloverine hydrochloride
Dicycloverine Hydrochloride
20mg Tablets
Dicycloverine hydrochloride
Morningside Healthcare Ltd
Exp:

III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of dicycloverine hydrochloride are well known. No new non-clinical data have been submitted for these applications and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology.

III.2 Pharmacology

No new pharmacology data are required for these applications and none have been submitted.

III.3 Pharmacokinetics

No new pharmacokinetic data are required for these applications and none have been submitted.

III.4 Toxicology

No new toxicology data are required for these applications and none have been submitted.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)

As these products are intended for generic substitution of products that are already marketed, no increase in environmental exposure to dicycloverine hydrochloride is anticipated. Thus the absence of an ERA is accepted.

III.6 Discussion of the non-clinical aspects

It is recommended that Marketing Authorisations are granted for Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets.

IV. CLINICAL ASPECTS

IV.1 Introduction

A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of the active substance. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

With the exception of the bioequivalence study detailed below, no new clinical studies have been performed and none are required for these types of application. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

For Dicycloverine Hydrochloride 10mg/5ml Oral Solution a bioequivalence study was not submitted as the product meets the criteria regarding oral solutions specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). The test product is an aqueous oral solution at the time of administration and contains active substances in the same concentration as the reference product.

In support of the applications for Dicycloverine Hydrochloride 10 mg and 20 mg Tablets, the applicant submitted results from the following bioequivalence study:

Study 1:

An open label, randomised, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study comparing the pharmacokinetics of the test product, Dicycloverine Hydrochloride 20 mg Tablets to those of the reference product Dicycloverine hydrochloride 20 mg Tablets (PL 17780/0566; Winthrop Pharmaceuticals UK Limited), in healthy, adult, male, human

subjects, under fasting conditions.

Volunteers were given each treatment after an overnight fast of at least 8 hours. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 24 hours post dose. Each treatment was separated by a washout period of 7 days.

A summary of the main pharmacokinetic results is presented in the tables below:

Summary of pharmacokinetic data for dicycloverine

Pharmacokinetic parameter	Test product		Reference product	
	Arithmetic mean ± SD[1]	CV (%)[2]	Arithmetic mean ± SD	CV (%)
C_{max} (ng/ mL)	67.453 ± 22.383	33.183	64.738 ± 20.826	32.169
AUC_t (ng.hr/ mL)	282.548 ± 97.371	34.462	281.216 ± 99.069	35.229
AUC_i (ng.hr/ mL)	333.106 ± 129.006	38.728	334.217 ± 137.676	41.194

[1] Standard deviation
[2] Coefficient of variation

Test and reference geometric mean and ratio for dicycloverine

Pharmacokinetic parameter	Geometric mean		Ratio (%)
	Test product	Reference product	
C_{max} (ng/ mL)	64.166	61.946	103.58
AUC_t (ng.hr/ mL)	267.666	265.159	100.95
AUC_i (ng.hr/ mL)	311.869	309.985	100.61

90% confidence intervals, intra-subject confidence intervals [CV (%)] and power for dicycloverine

Pharmacokinetic parameter	Geometric mean		Ratio (%)
	Test product	Reference product	
C_{max} (ng/ mL)	(97.96%;109.53%)	11.290	1.0000
AUC_t (ng.hr/ mL)	(95.46%;106.74%)	11.299	1.0000
AUC_i (ng.hr/ mL)	(94.96%;106.59%)	11.699	1.0000

Compared with the reference product, the 90 % confidence intervals for dicycloverine for the test product are within 80.00-125.00 % for Cmax and AUC. Dicycloverine Hydrochloride 20 mg Tablets can therefore be considered bioequivalent to Dicycloverine hydrochloride 20 mg tablets (PL 17780/0566).

As these products meet the bio-waiver criteria specified in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*), the results and conclusions of the bioequivalence study on the 20 mg strength can be extrapolated to the 10 mg strength tablets.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none are required for applications of this type.

IV.4 Clinical efficacy

No new data on efficacy have been submitted and none are required for applications of this type.

IV.5 Clinical Safety

No new data on safety have been submitted and none are required for applications of this type.
No new or unexpected safety concerns arose from these applications.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has submitted a RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

For all products:

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks		
Hypersensitivity to the active substance or to any of the excipients	The risks of hypersensitivity to the active substance or to any of the excipients associated with the use of the drug product are described in the SPC Sections 4.3 and 4.8 and PIL Sections 2 and 4 and appropriate advice is provided to the prescriber to minimise these risks.	None
Important Potential Risks		
Glaucoma and raised intraocular pressure	The risk of glaucoma and raised intraocular pressure associated with use of the drug product in patients with or suspected of	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	having glaucoma are described in the SPC Section 4.4 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise these risks.	
Urinary retention	The risk of urinary retention associated with use of the drug product in patients with or suspected of having prostatic hypertrophy are described in the SPC Section 4.4 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise these risks.	None
Aggravation of hiatus hernia	The risk of aggravation of hiatus hernia are described in the SPC Section 4.4 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise these risks.	None
Worsening of obstructive disease of the gastrointestinal tract	MAH will collect, process and report applicable events of worsening of obstructive disease of the gastrointestinal tract with dicycloverine to regulatory authority(ies), as per applicable guidelines.	None
Concomitant use of antiarrhythmic drugs and other drugs with antimuscarinic effects	MAH will collect, process and report applicable events associated with concomitant use of dicycloverine with antiarrhythmic drugs and other drugs with antimuscarinic effects to regulatory authority(ies), as per applicable guidelines.	None
Missing Information		
Use during pregnancy and lactation	The risks associated with use of the drug product during pregnancy and lactation are described in the SPC Sections 4.6 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise these risks.	None

For the 10 and 20 mg Tablets:

Safety Concern	**Routine Risk Minimisation Measures**	**Additional Risk Minimisation Measures**
Important Identified Risks		
Use in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption	The risks associated with use of the drug product in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption are described in the SPC Section 4.4 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise these risks.	None
Important Potential Risks		
None		
Missing Information		
None		

For the oral solution:

Safety Concern	**Routine Risk Minimisation Measures**	**Additional Risk Minimisation Measures**
Important Identified Risks		
Use in patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase – isomaltase insufficiency	The risks associated with use of the drug product in patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase – isomaltase insufficiency are described in the SPC Section 4.4 and PIL Section 2 and appropriate advice is provided to the prescriber to	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	minimise these risks.	
Important Potential Risks		
Medication error	The risk of medication error associated with use of the drug product is described in the SPC Section 4.2 and PIL Section 3 and appropriate advice is provided to the prescriber to minimise this risk.	None
Missing Information		
Use in infants younger than 6 months of age	The risks associated with use of the drug product in infants younger than 6 months of age are described in the SPC Sections 4.2, 4.3 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise these risks.	None

IV.7 Discussion of the clinical aspects

It is recommended that Marketing Authorisations are granted for Dicycloverine Hydrochloride 10mg/5ml Oral Solution and Dicycloverine Hydrochloride 10 mg and 20 mg Tablets.

V. USER CONSULTATION

The package leaflets have been evaluated in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results indicate that the package leaflets are well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to act upon the information that it contains.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied support the claim that the applicant's products and the reference products are interchangeable. Extensive clinical experience with dicycloverine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is therefore considered to be positive.

Annex 1 Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)