

Paracetamol and Caffeine 500 mg/65 mg Tablets
(paracetamol and caffeine)

PL 00071/0659

UKPAR

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LAY SUMMARY

Paracetamol and Caffeine 500 mg/65 mg Tablets (paracetamol and caffeine)

This is a summary of the Public Assessment Report (PAR) for Paracetamol and Caffeine 500 mg/65 mg Tablets (PL 00071/0659). It explains how Paracetamol and Caffeine 500 mg/65 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 Paracetamol and Caffeine 500 mg/65 mg Tablets.

For practical information about using Paracetamol and Caffeine 500 mg/65 mg Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Paracetamol and Caffeine 500 mg/65 mg Tablets and what are they used for?

Paracetamol and Caffeine 500 mg/65 mg Tablets contain the active substances paracetamol and caffeine. Paracetamol and Caffeine 500 mg/65 mg Tablets are used for the relief of headache, migraine, backache, pain of osteoarthritis, toothache and period pain. They also relieve discomfort in colds, flu and sore throat and help reduce temperature.

How are Paracetamol and Caffeine 500 mg/65 mg Tablets used?

Paracetamol and Caffeine 500 mg/65 mg Tablets are taken orally. The recommended dose in adults and children aged 12 years and over is 2 tablets every 4 hours as needed. No more than 8 tablets should be taken in any 24 hour period. Patients are advised to avoid taking too much caffeine in drinks like coffee, tea and some canned drinks whilst they are taking this tablet.

Paracetamol and Caffeine 500 mg/65 mg Tablets can be obtained from a pharmacy.

For further information on how Paracetamol and Caffeine 500 mg/65 mg Tablets are used, please see the Summary of Product Characteristics or the package leaflet available on the MHRA website.

How do Paracetamol and Caffeine 500 mg/65 mg Tablets work?

Paracetamol and Caffeine 500 mg/65 mg Tablets contain the active ingredients paracetamol and caffeine. Paracetamol is a painkiller and reduces the temperature when a patient has a fever. Caffeine acts to further help the effectiveness of paracetamol.

What benefits of Paracetamol and Caffeine 500 mg/65 mg Tablets have been shown in studies?

The active ingredients paracetamol and caffeine have well-established use and have been available in the European Union for many years.

The company provided bibliographic data on the efficacy and safety for this well-established combination. These data have shown that Paracetamol and Caffeine 500 mg/65 mg Tablets are effective in treating the indications listed above.

What are the possible side effects from Paracetamol and Caffeine 500 mg/65 mg Tablets?

Like all medicines, Paracetamol and Caffeine 500 mg/65 mg Tablets can have side effects, but not everybody gets them.

For the full list of all side effects reported with Paracetamol and Caffeine 500 mg/65 mg Tablets, see section 4 of the package leaflet.

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

Why are Paracetamol and Caffeine 500 mg/65 mg Tablets approved?

No new or unexpected safety concerns arose from this application. It was, therefore, considered that the benefits of Paracetamol and Caffeine 500 mg/65 mg Tablets outweigh the identified risks; and the grant of a Marketing Authorisation was recommended.

What measures are being taken to ensure the safe and effective use of Paracetamol and Caffeine 500 mg/65 mg Tablets?

A satisfactory pharmacovigilance system has been provided to monitor the safety of this product.

Other information about Paracetamol and Caffeine 500 mg/65 mg Tablets

A Marketing Authorisation was granted in the UK on 19th May 2010.

For more information about taking Paracetamol and Caffeine 500 mg/65 mg Tablets, read the package leaflet, or contact your doctor or pharmacist.

The full PAR for Paracetamol and Caffeine 500 mg/65 mg Tablets follows this summary.

This summary was last updated in December 2014.

Paracetamol and Caffeine 500 mg / 65 mg Tablets

PL 00071/0659

SCIENTIFIC DISCUSSION

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INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation for the medicinal product Paracetamol and Caffeine 500 mg/65 mg Tablets to SmithKline Beecham (SWG) Limited (PL 00071/0659) on 19th May 2010.

This pharmacy (P) medicine is indicated for the symptomatic treatment of mild to moderate pain and relief of fever. The tablets are recommended for the treatment of most painful conditions including headache, migraine, backache, toothache, pain of osteoarthritis, and dysmenorrhoea, and for relieving the fever, aches and pains of colds and flu and sore throat.

This application was submitted as a national abridged application according to Article 8(3) of Directive 2001/83/EC, as amended. The aim of this application was to update the formulation of the currently marketed Panadol Extra Tablets (PL 00071/0306) changing the tablet shape, film-coat and incorporating printing ink on the tablet.

The product contains the active ingredients paracetamol and caffeine. The active ingredients exert their effect by unrelated pharmacological mechanisms. Paracetamol is a centrally acting analgesic (a pain killer that acts on pain centres on the brain), which is used to relieve mild to moderate pain in the body and also acts as an antipyretic to help reduce body temperature; caffeine is a mild stimulant.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of this product.

PHARMACEUTICAL ASSESSMENT

PHARMACEUTICAL ASSESSMENT

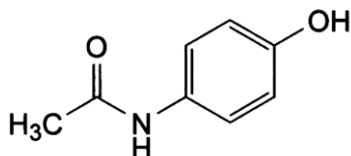
DRUG SUBSTANCE (1)

Paracetamol

INN/ BAN Paracetamol

Chemical name: N-(4-hydroxyphenyl)acetamide

Structure



Molecular formula: $C_8H_9NO_2$

Molecular weight: 151.2 g/mol

General Properties

Description: Paracetamol is a white, crystalline powder. It is sparingly soluble in water, free soluble in alcohol and very slightly soluble in dichloromethane.

Manufacture

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

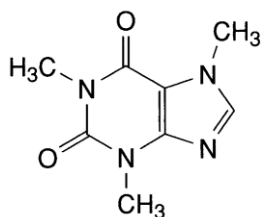
DRUG SUBSTANCE (2)

Caffeine

INN/ BAN Caffeine

Chemical name: 1,3,7-trimethyl-1,3-dihydro-1H-purine-2,5-dione, or 1,3,7-trimethylxanthine.

Structure



Molecular formula: $C_8H_{10}N_4O_2$

Molecular weight: 194.2 g/mol

General Properties

Caffeine is a white or almost white, crystalline powder. It is sparingly soluble in water, freely soluble in boiling water, and slightly soluble in ethanol.

Manufacture

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

DRUG PRODUCT**Other ingredients**

Other ingredients consist of pharmaceutical excipients, namely starch pregelatinised, maize starch, purified talc, croscarmellose sodium, stearic acid, povidone, potassium sorbate, hypromellose and triacetin. All the ingredients within the tablet comply with relevant Ph. Eur monographs.

The printing ink consists of: propylene glycol, shellac, brilliant blue FCF (E133), sodium lactate and dimethylpolysiloxane. The composition of the printing ink is from non-pharmacopoeial grade material; this is satisfactory considering that these ingredients are used in such small quantities.

Appropriate justification for the inclusion of each excipient has been provided. Satisfactory Certificates of Analysis have been provided for all the excipients.

None of the excipients used contains material of animal or human origin.

There were no novel excipients used and no overages.

Pharmaceutical Development

Suitable pharmaceutical development data have been provided for this application.

The pharmaceutical development was aimed at updating the current Panadol Extra Tablets (PL 00071/0306) changing the debossing of the tablet to printing onto the tablet.

Manufacture

A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results appear satisfactory.

Finished product specification

The finished product specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of analysis have been provided for any working standards used.

Container Closure System

The finished product is packed in a blister pack composed of polyvinylchloride/aluminium (PVC/Al) and then packed with the patient information leaflet (PIL) into an outer cardboard carton. Pack sizes are 4, 6, 8, 10, 12, 16, 20, 24, 30 and 32 tablets.

The Marketing Authorisation holder has stated that not all pack sizes may be marketed. The Marketing Authorisation Holder (MAH) has committed to submit mock-ups for all packaging for assessment before those pack sizes are commercially marketed.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 60 months has been set with the following storage precaution "Do not store above 25°C". These are satisfactory.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels

The SmPC, PIL and labelling are pharmaceutically acceptable.

Marketing Authorisation Application (MAA) form

The MAA form is pharmaceutically satisfactory.

Expert Report

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion

It is recommended that a Marketing Authorisation is granted for this application.

NON-CLINICAL ASSESSMENT

No new non-clinical data have been supplied with this application and none are required for an application of this type. A non-clinical expert report has been written by a suitably qualified person and is satisfactory.

The Marketing Authorisation holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA).

CLINICAL ASSESSMENT

INTRODUCTION

Clinical Background

Paracetamol has been widely available as an over-the-counter analgesic since the 1950s. Paracetamol tablets (500 mg) were first marketed in the UK in 1956. The maximum recommended adult dose is 1.0 g every 4-6 hours up to a maximum of 4 g in 24 hours.

The proposed product contains an established combination of paracetamol and caffeine, and this combination is widely available.

Caffeine acts as an analgesic adjuvant which enhances the clinical efficacy of paracetamol. GlaxoSmithKline data on file and published data support the efficacy and safety profile of products containing this combination.

The Clinical Overview has adequately reviewed all the relevant clinical documentation relevant to this application. In view of the widespread use of paracetamol and the nature of the paracetamol and caffeine formulation, the data presented here are considered adequate in support of this application.

Indications

Paracetamol and Caffeine 500 mg/65 mg Tablets are a mild to moderate analgesic and antipyretic. The tablets are recommended for the treatment of most painful and febrile conditions, for example, headache, including migraine, backache, toothache, pain of osteoarthritis, and dysmenorrhoea, and for relieving the fever, aches and pains of colds and flu, and sore throat.

Dose and Dose Regimen

Each tablet contains 500 mg paracetamol and 65 mg caffeine. The maximum recommended dose of paracetamol and caffeine is two tablets (500 mg paracetamol, 65 mg caffeine in each tablet) every 4-6 hours, up to a maximum of 8 tablets in 24 hours.

Legal Status

The proposed legal status is P – not subject to medical prescription; supply through pharmacies only. This type of combination tablet formulation has been available in the EU without prescription for many years.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Overview

A confirmatory pharmacokinetic study has demonstrated that paracetamol and caffeine is bioequivalent to PANADOL (also known as PANODIL Tablets) for the paracetamol component. Results from a supportive pharmacokinetic study are consistent confirmatory study. Data from the studies indicate that there is no pharmacokinetic interaction between paracetamol and caffeine. Further details regarding this study are contained in the Clinical overview.

The pharmacokinetics of both paracetamol and caffeine, alone and in combination, is well established and has been adequately reviewed by the Clinical Expert.

It has been established that no pharmacokinetic interaction occurs between paracetamol and caffeine.

Assessor's overall conclusions on pharmacokinetics

The pharmacokinetics of this combination is well-established and adequately reviewed in this dossier.

Bioequivalence

There are no important issues related to bioavailability that might affect efficacy or safety of Paracetamol and Caffeine 500 mg / 65 mg Tablets. A confirmatory pharmacokinetic study has demonstrated that paracetamol and caffeine is bioequivalent to PANADOL (also known as PANODIL Tablets) for the paracetamol component. Results from a supportive pharmacokinetic study are consistent with the confirmatory study. Data from the studies indicate that there is no pharmacokinetic interaction between paracetamol and caffeine. No new studies have been conducted with the proposed formulation and none are required for this type of application.

Pharmacodynamics

Pharmacodynamics and mechanism of action

The primary pharmacodynamics of paracetamol and caffeine alone and in combination is well described and has been adequately reviewed by the Clinical Expert.

CLINICAL EFFICACY

The superior analgesic efficacy of paracetamol 500 mg/caffeine 65 mg compared to the single actives and placebo has previously been demonstrated in clinical studies. This has been adequately reviewed in the Clinical Overview. Caffeine acts as an analgesic adjuvant which enhances the efficacy of paracetamol.

Paracetamol

The antipyretic activity of paracetamol is thought to be mediated by central prostaglandin synthetase inhibition. This may also play a role in the analgesic effect though the precise mechanism remains unclear. Paracetamol does not have an anti-inflammatory effect and, unlike NSAIDs, does not inhibit peripheral prostaglandin synthesis and serious gastro-intestinal adverse events are not associated with this active.

Caffeine

Caffeine is a methylxanthine and has a mild stimulant effect. The specific mechanism by which it acts as an analgesic adjuvant remains unclear, but may be mediated via adenosine antagonism (adenosine being one of the kinins released in association with pain), inhibition of COX-2 synthesis or by affecting the emotional response to pain.

CLINICAL SAFETY

The overall safety profile of products containing paracetamol and caffeine is well-established with extensive safety monitoring conducted on all currently marketed formulations. The safety profile of this combination has been adequately reviewed in the Clinical Overview. There are currently no safety concerns regarding this combination.

Pharmacovigilance & Risk Management Plans

An overview of GlaxoSmithKline's organisation and processes for conducting pharmacovigilance activities has been provided and is consistent with regulatory requirements. The MHRA agrees that a formal Risk-Management Plan is not required for this product.

EXPERT REPORTS

The Clinical Expert Report has been written by a suitably qualified person.

PRODUCT LITERATURE**SmPC**

This is satisfactory.

Patient Information Leaflet

This is satisfactory.

User Testing: A Bridging Report Summary is provided.

According to The Medicines (Marketing Authorisations and Miscellaneous Amendments) Regulations 2004 [SI 2004/3224] this report considers the legibility, clarity and ease of use of the Patient Information provided with Paracetamol and Caffeine 500 mg / 65 mg Tablets. By referring to the Patient Information provided with similar products which have been successfully user tested, it is appropriate to consider that the Patient Information provided with Paracetamol and Caffeine 500 mg / 65 mg Tablets is legible, clear and easy to use by consumers.

Assessor's comment: this approach is considered to be satisfactory, and no further user testing is required.

Label

This is considered to be satisfactory.

Application Form

This is satisfactory.

CONCLUSION

From a clinical perspective and the benefit/risk evaluation is considered to be favourable, and a Marketing Authorisation is recommended.

OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY

The important quality characteristics of Paracetamol and Caffeine 500 mg/65 mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY

The superior analgesic efficacy of paracetamol 500 mg/caffeine 65 mg compared to the single actives and placebo has previously been demonstrated in clinical studies. The use of this combination has been widely available for many years.

No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labelling are satisfactory and consistent with those for the innovator product.

BENEFIT RISK ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with paracetamol and caffeine is considered to have demonstrated the therapeutic value of the compound. The benefit risk is, therefore, considered to be positive.

Paracetamol and Caffeine 500 mg/65 mg Tablets**PL 00071/0659****STEPS TAKEN FOR ASSESMENT**

1	The MHRA received the Marketing Authorisation application on 20 th May 2009.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 9 th June 2009.
3	Following assessment of the application the MHRA requested further information relating to the quality dossiers on 24 th August 2009 and 17 th February 2010.
4	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 20 th October 2009 and 26 th April 2010.
5	The application was determined on 19 th May 2010.

Paracetamol and Caffeine 500 mg/65 mg Tablets**PL 00071/0659****STEPS TAKEN AFTER ASSESSMENT**

The following table lists some non-safety updates to the Marketing Authorisation for this product that has been approved by the MHRA since the product was first licensed. The table includes updates that are detailed in the annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

Date submitted	Application type	Scope	Outcome
20/08/2014	Type II	To update section 4.1 (Therapeutic indications) of the SmPC to bring in line with new clinical data	Variation granted 4/11/2014

ANNEX 1 – CLINICAL VARIATION ASSESSMENT REPORT

Reference:	PL 00071/0659 - 0014
Product:	Paracetamol and Caffeine Tablets 500 mg/65 mg
Marketing Authorisation Holder:	SmithKline Beecham (SWG) Limited
Active Ingredient(s):	Paracetamol and Caffeine

Reason:

To update section 4.1 (Therapeutic indications) of the SmPC and bring it in line with new clinical data.

Linked / Related Variation(s) or Case(s):

N/A

Supporting Evidence

A revised section 4.1 of the SmPC was proposed as follows:

Paracetamol and Caffeine 500 mg / 65 mg tablets are indicated for the treatment of mild to moderate pain and relief of fever. The tablets are recommended for the treatment of most painful conditions including headache, migraine, backache, toothache, pain of osteoarthritis, and dysmenorrhoea, and for relieving the fever, aches and pains of colds and flu and sore throat. Paracetamol and Caffeine 500 mg / 65 mg tablets have a dual action for pain relief as caffeine acts as an adjuvant to enhance the pain relief effect of Paracetamol.

Evaluation

The evidence below was presented in support of the sentence discussing the “adjuvant” effects of caffeine.

Dual Action: Role of Caffeine in a Paracetamol/ Caffeine Combination

The entire evidence base of the role of caffeine added to common analgesics was reviewed in 2012 by the Cochrane collaboration (Derry 2012) looking at studies that assessed the relative efficacy in acute pain of a single dose of any analgesic plus caffeine against the same dose of analgesic alone.

In this systematic review of 19 randomised controlled studies (7238 participants) the common analgesics paracetamol or ibuprofen were combined with 100 mg to 130 mg caffeine, and the most common pain conditions studied were postoperative dental pain, postpartum pain, and headache. There was a small but statistically significant benefit with caffeine used at doses of 100 mg or more, which was not dependent on the pain condition or type of analgesic. About 5% to 10% more participants achieve a good level of pain relief (at least 50% of the maximum) with the addition of caffeine, giving a number needed to treat (NNT) of about 15.

Most comparisons individually demonstrated numerical superiority with caffeine, but not statistical superiority. One serious adverse event was reported with caffeine, but was considered unrelated to any study medication.

The authors of the review concluded that the addition of caffeine (≥ 100 mg) to a standard dose of commonly used analgesics provides a small but important increase in the proportion of participants who experience a good level of pain relief.

Conclusion

The Agency ruled that whilst it is correct that the review does show a small increase in patients experiencing good pain relief, the specific wording added to the SmPC required redress.

Decision - Request for Further Information

POINTS RAISED

The Agency stated that inclusion in section 4.1 of the proposed wording was unacceptable on the grounds that the caffeine effect was inaccurately described – and could be considered promotional. The Agency advised that such data – appropriately worded – should be included within section 5.1 as supporting evidence.

1. The whole sentence added is not suitable to be included in 4.1. Such data should be in section 5.1 as supporting evidence.
2. The wording used is considered promotional and would not help the healthcare professional or patient in making an informed decision.
3. The wording is incorrect- there is no “dual action”, instead the caffeine acts adjunctively with the paracetamol to slightly enhance the analgesic effect.
4. It should be made explicitly clear that there is no evidence that this adjunctive effect is seen in fever.

The addition of this sentence is therefore unacceptable. An addition to section 5.1 summarising the reviews findings may be acceptable as long as it is performed factually and without the promotional wording.

The updates to the first part of the indication are acceptable as they are editorial. However, it should read “for the symptomatic treatment of...” as this is factually correct.

Assessment of RFI Response:

The applicant agreed with the Agency’s decision and removed the proposed statement concerning the role of caffeine in 4.1. The applicant elected not to add this information to 5.1 on the grounds that this would cause duplication within the section. The applicant made an editorial amendment to 4.1, as per the Agency’s request.

Assessor’s comments: The changes made are acceptable. Point resolved.

Section 4.1 of the SmPC was amended as follows:

Paracetamol and Caffeine 500 mg / 65 mg tablets are indicated for the symptomatic treatment of mild to moderate pain and relief of fever. The tablets are recommended for the treatment of most painful conditions including headache, migraine, backache, toothache, pain of osteoarthritis, and dysmenorrhoea, and for relieving the fever, aches and pains of colds and flu and sore throat.

Decision - Approved

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) Updated

Following approval of the variation on 4th November 2014 the SmPC was updated. In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.

PATIENT INFORMATION LEAFLET (PIL) Updated

Following approval of the variation on 4th November 2014 the PIL was updated. In accordance with Directive 2010/84/EU the Patient Information Leaflet (PIL) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.

