Public Assessment Report

Decentralised Procedure

Paracetamol / Caffeine 500 mg/65 mg Tablets

(paracetamol and caffeine)

Procedure No: UK/H/5505/001/DC

UK Licence No: PL 17907/0305

Bristol Laboratories Limited
This is a summary of the public assessment report (PAR) for Paracetamol / Caffeine 500 mg/65 mg Tablets (PL 17907/0305; UK/H/5505/001/DC). It explains how Paracetamol / 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 / Caffeine 500 mg/65 mg Tablets.

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

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

Paracetamol / Caffeine 500 mg/65 mg Tablets is a ‘generic medicine’. This means that Paracetamol / Caffeine 500 mg/65 mg Tablets are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Panadol Extra 500 mg/65 mg Tablets (Glaxo Smithkline Consumer (Ireland) Ltd).

Paracetamol / Caffeine 500 mg/65 mg Tablets are for the symptomatic treatment of mild to moderate pain and/or fever in conditions such as headache, toothache and period pains.

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

Paracetamol / Caffeine 500 mg/65 mg Tablets are taken by mouth. This medicine should be taken exactly as described in the leaflet or as described by a doctor or pharmacist.

The recommended dose in adults (16 years and over) is two tablets up to four times daily. No more than 8 tablets should be taken in any 24 hour period and the tablets should not be taken more often than every 4 hours.

Paracetamol and Caffeine 500 mg/65 mg Tablets should not be given to children under 16 years of age.

This medicine is available in a pharmacy, without a prescription.

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

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

Paracetamol / Caffeine 500 mg/65 mg Tablets contain the active ingredients paracetamol and caffeine. Paracetamol is a pain reliever (analgesic) and helps reduce temperature when patients have a fever, and caffeine helps to increase the pain relief from paracetamol and helps patients to become more alert.

**How have Paracetamol / Caffeine 500 mg/65 mg Tablets been studied?**

Because Paracetamol / Caffeine 500 mg/65 mg Tablets is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Panadol Extra 500 mg/65 mg Tablets (Glaxo Smithkline Consumer (Ireland) Ltd). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the benefits and risks of Paracetamol / Caffeine 500 mg/65 mg Tablets?**

As Paracetamol / Caffeine 500 mg/65 mg Tablets is a generic medicine that is bioequivalent to Panadol Extra 500 mg/65 mg Tablets (Glaxo Smithkline Consumer (Ireland) Ltd), its benefits and risks are taken as being the same as those for Panadol Extra 500 mg/65 mg Tablets (Glaxo Smithkline Consumer (Ireland) Ltd).

**Why are Paracetamol / Caffeine 500 mg/65 mg Tablets approved?**
It was concluded that, in accordance with EU requirements, Paracetamol / Caffeine 500 mg/65 mg Tablets have been shown to have comparable quality and to be bioequivalent to Panadol Extra 500 mg/65 mg Tablets (Glaxo Smithkline Consumer (Ireland) Ltd). Therefore, the view was that, as for Panadol Extra 500 mg/65 mg Tablets (Glaxo Smithkline Consumer (Ireland) Ltd) the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of Paracetamol / Caffeine 500 mg/65 mg Tablets?
A risk management plan has been developed to ensure that Paracetamol / Caffeine 500 mg/65 mg Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Paracetamol / Caffeine 500 mg/65 mg Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Paracetamol / Caffeine 500 mg/65 mg Tablets
The Republic of Ireland and the UK agreed to grant a Marketing Authorisation for Paracetamol / Caffeine 500 mg/65 mg Tablets on 20th November 2014. A Marketing Authorisation was granted in the UK on 21st January 2015.

The full PAR for Paracetamol / Caffeine 500 mg/65 mg Tablets follows this summary. For more information about treatment with Paracetamol / Caffeine 500 mg/65 mg Tablets, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in March 2015.
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I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Paracetamol and Caffeine, 500 mg/65 mg Tablets (PL 17907/0305; UK/H/5505/001/DC), indicated for the symptomatic treatment of mild to moderate pain and/or fever in adults and children aged 16 years or over, is approvable. This product is supplied through a pharmacy (P).

This application was submitted under the Decentralised Procedure (DCP) according to Article 10(1) of Directive 2001/83/EC, as amended. The applicant has cross referred to Panadol Extra 500 mg/65 mg Tablets, which was originally granted to Glaxo Smithkline Consumer (Ireland) Ltd on 14th June 1994.

With the UK as the RMS in this Decentralised Procedure, Bristol Laboratories Limited applied for a Marketing Authorisation for Paracetamol and Caffeine, 500 mg/65 mg Tablets in the Republic of Ireland.

Paracetamol has antipyretic and mild analgesic properties together with some anti-inflammatory activity. It may act predominantly by inhibiting prostaglandin synthesis in the central nervous system (CNS) and to a lesser extent through a peripheral action by blocking pain-impulse generation. It probably produces antipyresis by acting centrally on the hypothalamic heat-regulating centre to produce peripheral vasodilatation, resulting in increased blood flow through the skin, sweating and heat loss. Caffeine is widely used as a central nervous system (CNS) stimulant and is also considered to act as an adjunct to analgesics. It constricts cerebral vasculature and decreases cerebral blood flow and oxygen tension in the brain. It is believed that caffeine helps to relieve headache by providing a more rapid onset of action and/or enhanced pain relief with lower doses of analgesic.

No new clinical or non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

No bioequivalence or bioavailability studies have been performed in support of this application. A biowaiver for not performing bioequivalence studies was submitted and is considered acceptable.

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

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

All involved Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 210 – 20th November 2014). After a subsequent national phase, the UK granted a Marketing Authorisation (PL 17907/0305) for this product on 21st January 2015.
II QUALITY ASPECTS

II.1 Introduction

This product is a capsule shaped tablet and contains 500 mg paracetamol and 65 mg caffeine as active ingredients. The excipients present are povidone K-30 (E1201), povidone K-90 (E1201), potato starch, pregelatinised starch, purified talc, croscarmellose sodium, stearic acid (E570) and magnesium stearate.

All excipients used comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for these excipients.

The only excipient used that contains material of animal or human origin is stearic acid. Satisfactory documentation has been provided by the stearic acid suppliers stating that the stearic acid they provide complies with the criteria described in the current version of the monograph ‘Products with risk of transmitting agents of animal spongiform encephalopathies’. Confirmation has also been given that the magnesium stearate used in the tablet is of vegetable origin.

The finished product is packaged in opaque polyvinylchloride (PVC)/polyvinylidenechloride (PVdC) blisters with backing foil. The pack sizes are 4, 6, 12, 24, 30, 32, 48, 60 and 90 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.

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Paracetamol

Chemical name(s): N-(4-hydroxyphenyl)ethanamide

Structure:

Molecular formula: C₈H₉NO₂
Molecular weight: 151.17 g/mol
Appearance: White or almost white crystalline powder or colourless crystals.
Solubility: Sparingly soluble in water, freely soluble in alcohol, very slightly soluble in methylene chloride.

Paracetamol is the subject of a European Pharmacopoeia monograph.

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.

INN: Caffeine

Chemical name(s): 1,3,7-trimethyl-1H-purine-2,6(3H,7H)-dione

Structure:
Molecular formula: $C_8H_{10}N_4O_2$
Molecular weight: 151.17 g/mol
Appearance: White or almost white crystalline powder or silky white or almost white crystals.
Solubility: Sparingly soluble in water, freely soluble in boiling water, slightly soluble in ethanol (96%).

Caffeine is the subject of a European Pharmacopoeia monograph.

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.

II.3 Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate a globally acceptable, stable product that could be considered a generic medicinal product of Panadol Extra 500 mg/65 mg Tablets (Glaxo Smithkline Consumer (Ireland) Ltd).

A satisfactory account of the pharmaceutical development has been provided.

Comparative dissolution and impurity profiles have been presented for the proposed product and its respective reference product.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. The applicant has committed to perform validation on the first three full scale commercial batches.

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 specification. Certificates of Analysis have been provided for any working standards used.

Stability of the product
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 18 months with no special storage conditions has been set. This is satisfactory.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisation is recommended.
III NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of paracetamol and caffeine are well-known, no further non-clinical studies are required and none have been provided.

The applicant has not provided additional studies and further studies are not required for this type of application. An overview based on literature review is, thus, appropriate. The non-clinical overview has been written by an appropriately qualified person.

III.2 Pharmacology
No new data have been submitted and none are required for applications of this type.

III.3 Pharmacokinetics
No new data have been submitted and none are required for applications of this type.

III.4 Toxicology
No new data have been submitted and none are required for applications of this type.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Paracetamol and Caffeine 500 mg/65 mg Tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this product from a non-clinical point of view.

IV CLINICAL ASPECTS

IV.1 Introduction
The combination of paracetamol and caffeine is a well-established analgesic combination. The applicant has not provided any new pharmacodynamic or pharmacokinetic data and none are required for this type of application.

A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of paracetamol and caffeine.

IV.2 Pharmacokinetics
No bioequivalence or bioavailability studies have been performed in support of this application. A biowaiver for not performing bioequivalence studies was submitted that is considered acceptable. The active substances, paracetamol and caffeine, are highly soluble, with linear dose-dependent kinetics, and the comparative dissolution curves are consistently equivalent over the appropriate pH range.

IV.3 Pharmacodynamics
No new efficacy data have been submitted and none are required for this type of application.

IV.4 Clinical efficacy
No new efficacy data have been submitted and none are required for this type of application.

IV.5 Clinical safety
No new safety data were submitted and none are required.

IV.6 Risk Management Plan (RMP)
The MAH has submitted a risk management plan, 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 Paracetamol / Caffeine 500 mg/65 mg Tablets.

### Summary of the safety concerns

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
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</tr>
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</table>
| Important identified risks| ● Allergic reactions  
                           | ● Hepatic impairment  
                           | ● Renal impairment  
                           | ● Concomitant use with other paracetamol-containing drug products  
                           | ● Overdose |
| Important potential risks | ● Central nervous system related effects due to concomitant use of caffeine in excessive amounts (by dietary intake)  
                          | ● Persistent headaches  
                          | ● Thrombocytopenia  
                          | ● Use in pregnancy and lactation |
| Missing information       | ● Use in children under 12 years of age |
Summary table of Risk Minimisation Measures

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Important identified risks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>The risks of allergic reactions associated with the use of the drug product are described in the SPC Section 4.3, 4.8, and PIL Section 4 and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Hepatic impairment</td>
<td>The risks of hepatic impairment associated with the use of the drug are described in the SPC Section 4.4, 4.8, and PIL Section 2, 4 and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>The risks of renal impairment associated with the use of the drug product are described in the SPC Section 4.4, and PIL Section 2 and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Concomitant use with other paracetamol-containing drug products</td>
<td>The risks associated with the concomitant use of the drug product with other paracetamol-containing products are described in the SPC Section 4.2, 4.4, and PIL Section 2 and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Overdose</td>
<td>The risks associated with the overdose of the drug product are described in the SPC Section 4.2, 4.4, 4.9, and PIL Section 3 and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------</td>
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<td>---------------------------------------</td>
</tr>
<tr>
<td>Central nervous system related effects due to concomitant use of caffeine in excessive amounts (by dietary intake)</td>
<td>The risks of CNS-related effects due to concomitant use of caffeine in excessive amounts (by dietary intake) with the drug product are described in the SPC Section 4.4, 4.8, and PIL Section 3 and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Persistent headaches</td>
<td>The risk of persistent headaches associated with the use of the drug product is described in the SPC Section 4.4, and PIL Section 3, and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>The risks of thrombocytopenia and related bleeding events are described in the SPC Section 4.5, 4.8, and PIL Section 4 and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Use in pregnancy and lactation</td>
<td>The SPC Section 4.6 and PIL Section 2 states that the drug product should not be used during pregnancy due to the possible increased risk of lower birth weight and spontaneous abortion associated with caffeine consumption. Also, the drug product should not be used during lactation as caffeine in breast milk may potentially have a stimulating effect on breastfed infants.</td>
<td>None</td>
</tr>
<tr>
<td>Missing information</td>
<td></td>
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<tr>
<td>Use in children under 12 years of age</td>
<td>The SPC Section 4.2, 4.4, and PIL Section 3, 5 states that the drug product is not recommended for children under 12 years of age.</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
IV.7 Discussion on the clinical aspects
The grant of a Marketing Authorisation is recommended.

V USER CONSULTATION
For Paracetamol / Caffeine 500 mg/65 mg Tablets a user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Co-Codamol Tablets (PL 11311/0153). The bridging report submitted by the applicant is acceptable.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
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.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

The Marketing Authorisation for this product was granted on the basis of text versions of the labelling and leaflet. The applicant has provided a commitment to submit colour mock-ups for approval before marketing.

| PARTICULARS TO APPEAR ON THE OUTER Packaging |
| Carton |

1. NAME OF THE MEDICINAL PRODUCT

Paracetamol / Caffeine 500mg/65mg Tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each Tablet contains 500 mg Paracetamol and 65mg Caffeine

3. LIST OF EXCIPIENTS

see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets
4 Tablets
6 Tablets
12 Tablets
24 Tablets
30 Tablets
32 Tablets
48 Tablets
60 Tablets
90 Tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use. Read the package insert before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

-

8. EXPIRY DATE
9. SPECIAL STORAGE CONDITIONS

No special storage conditions required.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

-

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol Laboratories Ltd, Unit 3, Canalside, Northbridge Road, Berkhamsted, Herts HP4 1EG, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 17907/0305

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Pharmacy only (UK)
General Sales (IE)

15. INSTRUCTIONS ON USE

For oral use

16. INFORMATION IN BRAILLE

Paracetamol / Caffeine 500mg/65mg Tablets

17. Special requirements for GSL/P pack

Do not take anything else containing paracetamol while taking this medicine. Do not take more medicine than the label tells you to. If you do not get better, talk to your doctor. Talk to a doctor at once if you take too much of this medicine even if you feel well.
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

#### Blister

<table>
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<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<table>
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<tr>
<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
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<tr>
<th>4. BATCH NUMBER</th>
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Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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