Public Assessment Report

UKPAR

Paracetamol 500 mg capsules, soft (paracetamol)

UK licence Number: PL 14338/0010

Patheon Softgels B.V.
Paracetamol 500 mg capsules, soft

LAY SUMMARY

Paracetamol 500 mg capsules, soft
(paracetamol)

This is a summary of the Public Assessment Report (PAR) for Paracetamol 500 mg capsules, soft (PL 14338/0010). It explains how Paracetamol 500 mg capsules, soft were assessed and their authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use this product. The product will be referred to as Paracetamol capsules for the remainder of this lay summary, for ease of reading.

For practical information about using Paracetamol capsules, patients should read the package leaflet available on the MHRA website or contact their doctor or pharmacist.

What are Paracetamol 500 mg capsules and what are they used for?
Paracetamol 500 mg capsules are a ‘generic medicine’. This means that Paracetamol 500 mg capsules are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Panadol original tablets, which is currently granted a Marketing Authorisation to SmithKline Beecham (SWG) Limited.

Paracetamol 500 mg capsules are used for the relief of headache, tension headache, migraine, backache, rheumatic and muscular pain, toothache and period pain. Paracetamol also relieves sore throat and the fever, aches and pains of colds and flu and are recommended for the relief of pain due to mild arthritis.

How do Paracetamol 500 mg capsules work?
The active ingredient in Paracetamol 500 mg capsules is paracetamol, which is a painkiller and also brings down high temperatures (reducing fever).

How are Paracetamol 500 mg capsules used?
The pharmaceutical form of this medicine is a soft capsule and the route of administration is oral.

This medicine should be taken exactly as advised by the patient’s doctor or pharmacist. The patient should check with their doctor or pharmacist if they are not sure.

The recommended dose in adults, elderly, and children aged 16 years and over is 1 to 2 capsules every 4 to 6 hours as needed. The patient must not take more than 8 capsules in 24 hours.

The recommended dose in children aged 10 to 15 years is 1 capsule every 4 to 6 hours as needed. The child must not take more than 4 capsules in 24 hours.

Please read Section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

This medicine can be obtained without a prescription.
What benefits of Paracetamol 500 mg capsules have been shown in studies?
Because Paracetamol 500 mg capsules are a generic medicine, studies in people have been limited to tests to determine that the medicines are bioequivalent to the reference product Panadol original tablets (Smithkline Beecham (SWG) Limited). Two medicines are bioequivalent when they produce similar levels of active substance in the body.

What are the possible side effects of Paracetamol 500 mg capsules?
Because Paracetamol 500 mg capsules are a generic medicine, their possible side effects are taken as being the same as those of the reference product, Panadol original tablets (SmithKline Beecham (SWG) Limited).

For the full list of all side effects reported with Paracetamol 500 mg capsules, see Section 4 of the package leaflet available on the MHRA website.

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

Why are Paracetamol 500 mg capsules approved?
It was concluded that, in accordance with EU requirements, Paracetamol 500 mg capsules have been shown to have comparable quality and to be bioequivalent to Panadol original tablets. Therefore, the MHRA decided that, as for the reference medicine, Panadol original tablets, the benefits are greater than the risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Paracetamol 500 mg capsules?
A Risk Management Plan (RMP) has been developed to ensure that Paracetamol 500 mg capsules 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 of Paracetamol 500 mg capsules, including the appropriate precautions to be followed by patients.

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

Other information about Paracetamol 500 mg capsules
The UK granted a Marketing Authorisation for Paracetamol 500 mg capsules on 27 December 2017.

The full PAR for Paracetamol 500 mg capsules follows this summary.

For more information about treatment with Paracetamol 500 mg capsules, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in February 2018.
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I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA considered that the application for Paracetamol 500 mg capsules, soft (PL 14338/0010) could be approved.

The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference product cited for the determination of expiry of data exclusivity is Panadol 500 mg, comprimé pelliculé sécable authorised in France to GlaxoSmithKline santé grand public in 1996. This reference product was also used to determine bioequivalence. The equivalent UK reference product is Panadol Original Tablets (PL 00071/5074R; SmithKline Beecham (SWG) Limited) licensed in May 1984 which was subject to a change of ownership application in May 2016 to the current Marketing Authorisation Holder GlaxoSmithKline Consumer Healthcare (UK) Trading Limited (PL 44673/0081).

Paracetamol 500 mg capsules, soft are available on the ‘general sales list’ (legal status “GSL”) and can be purchased at pharmacies, supermarkets and other retail outlets without the supervision of a pharmacist.

Paracetamol is a mild analgesic and antipyretic, and is recommended for the treatment of most painful and febrile conditions, for example, headache including migraine and tension headaches, toothache, backache, rheumatic and muscle pains, dysmenorrhoea, sore throat, and for relieving the fever, aches and pains of colds and flu. The product is also recommended for the symptomatic relief of pain due to non-serious arthritis.

The mechanism by which paracetamol reduces fever and pain is still not fully understood. Paracetamol reduces the production of prostaglandins, although it has little anti-inflammatory activity. It appears to act via at least two pathways, possibly involving the inhibition of the enzyme cyclooxygenase (COX), modulation of the endogenous cannabinoid system, and acting centrally to reduce temperature.

A single bioequivalence study was performed, which compared the pharmacokinetics of the test product Paracetamol 500 mg capsules, soft to those of the reference product Panadol 500 mg scored film-coated tablets (GlaxoSmithKline Santé Grande Public). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, 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 reference product that has been licensed for over 10 years.

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

A satisfactory summary of the pharmacovigilance system and a detailed Risk Management Plan (RMP) has been provided with the application.

A Marketing Authorisation was granted in the UK on 27 December 2017.
II QUALITY ASPECTS

II.1 Introduction
Paracetamol 500 mg capsules, soft, contain 500 mg of the active ingredient paracetamol.

Other ingredients consist of the following pharmaceutical excipients:

*Body*
- macrogol, purified water, propylene glycol, povidone, silica, colloidal anhydrous

*Capsule shell*
- Gelatin, sorbitol, liquid, partially dehydrated (E420), purified water, glycerol, titanium dioxide (E171)

*Capsule printing*
- Black iron oxide (E172), propylene glycol, hypromellose

The finished product is packed into polyvinylidene chloride / polyvinyl chloride / aluminium / polyethylene terephthalate blisters in cartons in pack sizes of 2, 4, 6, 8, 10, 12, 14 or 16 capsules.

Not all pack sizes may be marketed. However, the company have agreed to provide mock-ups of any pack size to the licensing authority before marketing.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation, Regulation (EU) No 10/2011 (as amended), and are suitable for contact with foodstuffs.

II.2. Drug Substance

**INN:** paracetamol
**Chemical name:** N-(4-hydroxyphenyl)acetamide

![Structural formula](image)

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

All aspects of the manufacture and control of the active substance, paracetamol, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.
II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious and stable liquid-filled capsule formulation, which would be comparable to the reference product Panadol 500 mg scored film-coated tablets. A satisfactory account of the pharmaceutical development has been provided.

Comparable in vitro dissolution profiles have been provided for the test and reference products.

The printing ink Opacode WB black NS-78-17821 is controlled by means of a suitable in-house specification. All other excipients comply with their respective European Pharmacopoeia (Ph. Eur.) monographs.

With the exception of gelatin, none of the excipients contain materials of animal or human origin. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines and Healthcare (EDQM) to show that they are manufactured in line with current European guidelines concerning minimising the risk of transmission of Bovine Spongiform Encephalopathy / Transmissible Spongiform Encephalopathies (BSE/TSE).

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
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 at the commercial scale and shown satisfactory results.

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

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf life of 18 months, with the storage conditions “Do not store above 25°C” and “Store in the original package in order to protect from moisture”.

Suitable post approval stability commitments have been provided to continue stability testing on batches of the finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of the product from a pharmaceutical perspective.
Paracetamol 500 mg capsules, soft

III  NON-CLINICAL ASPECTS

III.1  Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of paracetamol are well-known. No new non-clinical data have been submitted for this application 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 the application and none have been submitted.

III.3  Pharmacokinetics
No new pharmacokinetic data are required for the application and none have been submitted.

III.4  Toxicology
No new toxicology data are required for the application and none have been submitted.

III.5  Ecotoxicity/environmental risk assessment (ERA)
As the product is intended for generic substitution with other products already on the market, no increase in environmental exposure is anticipated. An ERA is, therefore, not deemed necessary.

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

IV  CLINICAL ASPECTS

IV.1  Introduction
The clinical pharmacology of paracetamol is well-known. With the exception of the bioequivalence study detailed below, no new clinical studies have been performed and none are required for this type of application. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2  Pharmacokinetics
In support of the application, the Marketing Authorisation Holder has submitted results from the following bioequivalence study:

A single centre, open, randomized, single dose, two-period, two-treatment, two-sequence, crossover study, comparing the pharmacokinetics of the test product Paracetamol 500 mg capsules, soft (Patheon Softgels B.V.) versus the reference product, Panadol 500 mg scored film-coated tablets (GlaxoSmithKline Sante Grande Public), under fasting conditions, in healthy male and female volunteers.

After an overnight fast, each subject received a single oral dose (1 x 500 mg) of the test formulation or a single oral dose (1 x 500 mg) of the reference formulation administered with 200 mL of water.
Blood samples were collected for plasma levels before dosing and up to and including 12 hours after each administration. The washout period between the treatment phases was 5 days.

Summary statistics for pharmacokinetic parameters for paracetamol for the test and reference product are shown below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Geometric Mean Ratio T/R</th>
<th>Lower Confidence Limit</th>
<th>Upper Confidence Limit</th>
<th>Level of Confidence</th>
<th>Intra-subject CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀₋₅₀</td>
<td>0.9893</td>
<td>0.9525</td>
<td>1.0166</td>
<td>0.9000</td>
<td>6.4</td>
</tr>
<tr>
<td>Cₘₐₓ</td>
<td>1.0088</td>
<td>0.9261</td>
<td>1.0988</td>
<td>0.9000</td>
<td>20.4</td>
</tr>
</tbody>
</table>

**Conclusion**

The 90% confidence intervals of the test/reference ratio for AUC and $C_{max}$ values for paracetamol lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Based on the data provided the applicant’s test product, Paracetamol 500 mg capsules, soft can be considered bioequivalent to the reference product, Panadol 500 mg scored film-coated tablets (GlaxoSmithKline Sante Grande Public).

**IV.3 Pharmacodynamics**

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

**IV.4 Clinical efficacy**

No new efficacy data were submitted and none were required for this type of application.

**IV.5 Clinical safety**

With the exception of the safety data collected during the bioequivalence study, no new data on safety have been submitted and none are required for an application of this type. No new or unexpected adverse events were observed during the bioequivalence study.
IV.6 Risk Management Plan (RMP)
The Marketing Authorisation Holder (MAH) has submitted a Risk Management Plan (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 the product.

A summary of safety concerns, as approved in the RMP is provided below:

<table>
<thead>
<tr>
<th>Important identified risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity reactions</td>
</tr>
<tr>
<td>Hepatotoxicity/ abnormal liver function (Patients with pre-existing liver disease, chronic alcoholism, malnutrition, dehydration, underweight adults)</td>
</tr>
<tr>
<td>Overdose (non-intentinal and intentional)</td>
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<tr>
<td>Use in patients with severe renal impairment</td>
</tr>
<tr>
<td>Use in patients with hepatic impairment</td>
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<tr>
<td>Drug interaction with anticoagulants</td>
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<tr>
<td>Drug interaction with enzyme Inducers</td>
</tr>
<tr>
<td>Blood disorders (including thrombocytopenia and agranulocytosis)</td>
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<tr>
<td>Bronchospasm, including risk in asthmatic patients sensitive to aspirin or NSAIDs</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Important potential risks</th>
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</thead>
<tbody>
<tr>
<td>Drug-induced Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalised exanthematous pustulosis (AGEP)</td>
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</table>

<table>
<thead>
<tr>
<th>Missing information</th>
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</thead>
<tbody>
<tr>
<td>Medication errors</td>
</tr>
<tr>
<td>Use in children &lt; 12 years</td>
</tr>
</tbody>
</table>

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects
There are no objections to the approval of the product from a clinical perspective.

V User consultation
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English. The results show that the package leaflet meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI Overall conclusion, benefit/risk assessment and recommendation
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with paracetamol is considered to have demonstrated the therapeutic value of the compound. The product is considered to be bioequivalent to the marketed reference product and their benefits and risks are considered similar. The benefit/risk balance is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The following text is the approved label text for this medicine, no label mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained:
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Paracetamol 500 mg capsules, soft

Paracetamol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 500 mg paracetamol.

3. LIST OF EXCIPIENTS

Contains sorbitol, propylene glycol, glycerol, and soya lecithin. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

2 capsules, soft
4 capsules, soft
6 capsules, soft
8 capsules, soft
10 capsules, soft
12 capsules, soft
14 capsules, soft
16 capsules, soft

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Paracetamol is used for the relief of headache, tension headache, migraine, backache, rheumatic and muscular pain, toothache and period pain. Paracetamol also relieves sore throat and the fever, aches and pains of colds and flu and are recommended for the relief of pain due to mild arthritis. The active ingredient is paracetamol which is a painkiller and also reduces your temperature when you have a fever.

Adults, elderly, and children aged 16 years and over:
- Swallow 1-2 capsules every 4 hours as needed.
- Do not take more than 8 capsules in 24 hours.

Children aged 10 to 15 years:
- Give 1 capsule every 4 to 6 hours as needed.
- Do not give more than 4 capsules in 24 hours.

Do not give to children under 10 years.

Children should not be given Paracetamol for more than 3 days without consulting a doctor.

Do not take more frequently than every 4 hours.
Do not take more than the recommended dose.
Do not take Paracetamol if you have ever had an allergic reaction to paracetamol, to peanut or soya, or to any of the other ingredients of this medicine. See leaflet for further information. For oral use. Read the package leaflet 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

EXP: (month/year)

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture. Do not store above 25°C.

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

Patheon Softgels B.V.
De Posthoornstraat 7
5048 AS Tilburg
The Netherlands

12. MARKETING AUTHORITY NUMBER(S)

PL 14338/0010

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

GSL

15. INSTRUCTIONS ON USE

UK requirement (blue box):

GSL

Do not take more medicine than the label tells you to. If you do not get better, talk to your doctor.

Do not take anything else containing paracetamol while taking this medicine.
Do not take Paracetamol if you have ever had an allergic reaction to paracetamol, to peanut or soya, or to any of the other ingredients of this medicine. See leaflet for further information.

For oral use.

Read the package leaflet 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**

EXP. (month/year)

9. **SPECIAL STORAGE CONDITIONS**

Store in the original package in order to protect from moisture.
Do not store above 25°C.

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**

Pathoet Softgels B.V.
De Posthoornstraat 7
5048 AS Tilburg
The Netherlands

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 14377/0010

13. **BATCH NUMBER**

Lot:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

GSL

15. **INSTRUCTIONS ON USE**

UK requirement (blue box):

GSL

Do not take more medicine than the label tells you to. If you do not get better, talk to your doctor.
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.

16. INFORMATION IN BRAILLE

Paracetamol 500 capsules
Table of content of the PAR update
Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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