Paracetamol 500 mg Tablets

PL 36760/0002

UKPAR

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LAY SUMMARY

PARACETAMOL 500 MG TABLETS
(paracetamol)

This is a summary of the Public Assessment Report (PAR) for Paracetamol 500 mg Tablets (PL 36760/0002). It explains how the application for Paracetamol 500 mg Tablets was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Paracetamol 500 mg Tablets.

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

What are Paracetamol 500 mg Tablets and what are they used for?
Paracetamol 500 mg Tablets are a medicine with ‘well-established use’. This means that the medicinal use of the active substance of Paracetamol 500 mg Tablets is well established in the European Union for at least ten years, with recognised efficacy and an acceptable level of safety.

Paracetamol 500 mg Tablets are used in adults and children 12 years and older for the relief of headache, migraine, rheumatic and sharp nerve pain (neuralgia), toothache and period pain. Paracetamol 500 mg Tablets also relieve fever, sore throat, aches and pains of colds and flu.

How do Paracetamol 500 mg Tablets work?
Paracetamol 500 mg Tablets contain the active ingredient paracetamol. Paracetamol belongs to a group of medicines called analgesics and antipyretics, which act to relieve pain and reduce fever.

How are Paracetamol 500 mg Tablets used?
Paracetamol 500 mg Tablets are taken by mouth and must be swallowed whole with water.

This medicine should always be taken exactly as described in the package leaflet or as instructed by the patient’s doctor or pharmacist. The patient should check with the doctor or pharmacist if he/she is not sure.

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

Paracetamol 500 mg Tablets can be obtained without a prescription, at pharmacies, supermarkets and other retail outlets without the supervision of a pharmacist.

What benefits of Paracetamol 500 mg Tablets have been shown in studies?
As paracetamol is a well-known substance and its use in the licensed indications is well established, the applicant presented data from the scientific literature. The literature confirmed the efficacy and safety of paracetamol in the licensed indications.

What are the possible side effects from Paracetamol 500 mg Tablets?
Like all medicines, Paracetamol 500 mg Tablets can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Paracetamol 500 mg Tablets, see section 4 of the package leaflet available on the MHRA website.
Also, for the full list of restrictions, see the package leaflet.

**Why are Paracetamol 500 mg Tablets approved?**
The MHRA concluded that, in accordance with EU requirements, the benefits of Paracetamol 500 mg Tablets outweigh the identified risks and recommended that the product be approved for use.

**What measures are being taken to ensure the safe and effective use of Paracetamol 500 mg Tablets?**
Safety information has been included in the Summary of Product Characteristics and the package leaflet for Paracetamol 500 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/reviewed continuously as well.

**Other information about Paracetamol 500 mg Tablets.**
A Marketing Authorisation was granted in the UK on 20 November 2014.

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

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

This summary was last updated in February 2015.
Paracetamol 500 mg Tablets

PL 36760/0002

SCIENTIFIC DISCUSSION

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Scientific discussion

I INTRODUCTION

On 20 November 2014, the MHRA granted a Marketing Authorisation for the medicinal product Paracetamol 500 mg Tablets (PL 36760/0002) to Beximco Pharma UK Limited. The product is a General Sales Licence (GSL) medicine and is indicated in adults and children 12 years and over for the symptomatic treatment of fever and mild to moderate pain including headache, migraine, neuralgia, toothache, sore throat, period pain, relief of rheumatic pain and of pain associated with colds/influenza.

The application was submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance of well-established use.

Paracetamol 500 mg Tablets contain the active ingredient, paracetamol, which has analgesic and antipyretic effects. Paracetamol is thought to produce analgesia by inhibiting prostaglandin synthesis centrally and elevating the pain threshold. Paracetamol reduces fever by blocking the formation and release of prostaglandins in the central nervous system and inhibiting the action of endogenous pyrogens at the hypothalamic thermoregulatory centers.

Paracetamol is widely used in clinical indications like mild to moderate pain, including instances of tension headache, migraine headache, muscular aches, neuralgia, backache, joint pain, rheumatic pain, general pain, toothache, teething pain, for the pain of menstrual cramps and for the reduction of fever. Bibliographic literature data on the active ingredients have been submitted to support this application. As the application is based upon published literature it is not possible to comment on the GLP status of the studies.

No new non-clinical or clinical studies were conducted for this application, which is acceptable given that this is a bibliographic application for a product containing an active ingredient of well-established use.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Paracetamol 500 mg Tablets outweigh the risks and a Marketing Authorisation was granted.
II QUALITY ASPECTS

II.1 Introduction
The application is submitted in accordance with Article 10a (well established use application) of Directive 2001/83/EC, as amended.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is available as tablets. Each tablet contains 500 mg of paracetamol. The other ingredients consist of the pharmaceutical excipients pregelatinized starch, sodium starch glycolate, stearic acid, magnesium stearate and colloidal anhydrous silica.

The finished product is supplied in polyvinylchloride-polyvinylchloride/adhesive/aluminium blisters, in a pack size of 16 tablets.

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

II.2 Drug Substance

Paracetamol
INN: Paracetamol
Chemical name: N-(4-hydroxyphenyl)acetamide
Structure:

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\begin{align*}
\text{H}_3\text{C} & \text{N} \\
& \text{O} \\
& \text{OH}
\end{align*}
\]

Molecular formula: $C_8H_9NO_2$
Mr: 151.2
Appearance: A white or almost white crystalline powder
Solubility: Sparingly soluble in water, freely soluble in alcohol and 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.

II.3 Medicinal Product

Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious, stable, tablet containing 500 mg of paracetamol. Suitable pharmaceutical development data have been provided for this application.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.
None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Manufacturing Process**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. The manufacturing process has been validated at production scale and has shown satisfactory results.

**Control of Finished Product**
The finished product specification is acceptable. Test methods have been described that have been validated adequately. Batch data have been provided that comply with the release specifications. 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. Based on the results, a shelf-life of 2 years has been approved, with the special storage conditions ‘Do not store above 25°C.’

Suitable post approval stability commitments have been provided.

**Bioequivalence/Bioavailability**
A bioequivalence study was not necessary for an application of this type.

**II.4 Conclusion**
It is recommended that a Marketing Authorisation is granted for this application for Paracetamol 500 mg Tablets.

**II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**
The SmPC, PIL and labelling 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 current labelling is presented below:
Paracetamol 500 mg Tablets

Each tablet contains: Paracetamol 500 mg

FOR RELIEF FROM

✓ Cold and flu symptoms
✓ Fever
✓ Headache
✓ Toothache
✓ Period pain
✓ Rheumatic pain
✓ Muscle pain
✓ Swelling

Contains paracetamol

STORAGE: Do not store above 25°C.

DO NOT TAKE IF:

You are suffering from liver or heart disease.
You are allergic to paracetamol or any of the ingredients listed on the enclosed leaflet.

WARNINGS:

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 TABLETS
III  NON-CLINICAL ASPECTS

III.1  Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of paracetamol are well known and are adequately described in the applicant’s non-clinical overview. No new non-clinical data were submitted and none are required for this bibliographic application.

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2  Pharmacodynamics
The pharmacodynamic properties of paracetamol are well known and are adequately described in the applicant’s non-clinical overview.

III.3  Pharmacokinetics
The pharmacokinetic properties of paracetamol are well known and are adequately described in the applicant’s non-clinical overview.
III.4 Toxicology
The toxicological properties of paracetamol are well known and are adequately described in the applicant’s non-clinical overview.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)
As the introduction of Paracetamol 500 mg Tablets is likely to be balanced by a reduction in the use of other similar products, no increase in the environmental exposure to paracetamol is anticipated following approval of the Marketing Authorisation for the product. An Environmental Risk Assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
It is recommended that a Marketing Authorisation is granted for Paracetamol 500 mg Tablets, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction
This is a national application for a Marketing Authorisation for Paracetamol 500 mg Tablets. The legal basis of this application is a well-established medicinal use application according to Article 10a of Directive 2001/83/EC as amended, supported by bibliographic literature.

The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
No new clinical pharmacokinetic data have been submitted and none are required for an application of this type. The pharmacokinetic profile of paracetamol is well-known. Bibliographic pharmacokinetic data have been provided to support the application. An adequate summary of the pharmacokinetic profile of paracetamol has been provided.

IV.3 Pharmacodynamics
The clinical pharmacology of paracetamol is well-known. An adequate summary of the pharmacodynamic profile of paracetamol has been presented in the clinical overview.

IV.4 Clinical Efficacy
No new efficacy data have been submitted and none are required for this type of application. The clinical efficacy of paracetamol is well-established. Efficacy is adequately reviewed in the clinical overview.

IV.5 Clinical Safety
No new safety data were supplied or required for this bibliographic application. The safety profile of paracetamol is well-known. The safety profile of paracetamol has been adequately summarised by the Applicant in the clinical overview. No new or unexpected safety issues arose from the submitted safety data.

IV.6 Risk Management Plan
No Risk Management Plan has been submitted and none was required. This application was received prior to 21 July 2012, the date from which pharmacovigilance regulations in accordance with Directive 2010/84/EU came into force. Paracetamol has been in use for many years and its safety profile is
well-established. Routine pharmacovigilance activities and safety information that has been included in the Summary of Product Characteristics and the package leaflet for Paracetamol 500 mg Tablets, including the appropriate precautions to be followed by healthcare professionals and patients, are considered adequate.

**Conclusion**

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

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, as amended. The language used for the purpose of user testing the pack leaflet 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 AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**

**QUALITY**
The important quality characteristics of Paracetamol 500 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 an application of this type as the pharmacokinetics, pharmacodynamics and toxicology of paracetamol are well-known.

**EFFICACY**
No new clinical data were submitted and none were required for this type of application.

The published literature supports the efficacy of the product in the proposed indications and posology. The efficacy of paracetamol is well-known. The presented evidence for well-established use of the active substance is sufficient.

**SAFETY**
The safety profile of paracetamol is well-known. The literature review identified no new or unexpected safety issues or concerns.

**BENEFIT/RISK ASSESSMENT**
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Paracetamol is a well-known active substance. Extensive clinical experience with paracetamol is considered to have demonstrated the therapeutic value of the compound. The benefit/risk assessment is, therefore, considered to be positive.

**RECOMMENDATION**
The grant of a Marketing Authorisation is recommended.
Paracetamol 500 mg Tablets

PL 36760/0002

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation application on 16 March 2012.
2 Following standard checks and communication with the applicant the MHRA considered the application valid on 08 June 2012.
3 Following assessment of the application, the MHRA requested further information relating to the dossier on 13 September 2012, 19 April 2013, 03 February 2014 and 16 July 2014.
4 The applicant responded to the MHRA’s requests, providing further information on the dossier on 08 January 2013, 05 September 2013, 14 November 2013, 02 May 2014 and 19 September 2014.
5 The application was granted on 20 November 2014.
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