Public Assessment Report

Paracetamol Tablets BP 500mg

PL 17907/0049

Bristol Laboratories Limited

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Lay Summary

The MHRA granted Bristol Laboratories Limited a Marketing Authorisation (licence) for the medicinal products Paracetamol 500mg Tablets on 16th February 2006. Paracetamol is used to relieve pain (analgesic) and to reduce an increased body temperature (anti-pyretic) and is available without prescription. This formulation is for the treatment of mild to moderate pain including headache, migraine, neuralgia, toothache, sore throat, period pain, aches and pains.

The application was made under 2001/83/EC Article 10.c as amended, an informed consent application referring to Paracetamol tablets authorised to Bristol Laboratories (PL 17907/0001).

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Paracetamol 500mg Tablets outweigh the risks, hence a Marketing Authorisation was granted.

SCIENTIFIC DISCUSSION

Introduction

This Public Assessment Report is based on the Assessment Report produced in response to a National simple abridged application for an oral tablet formulation for the treatment of mild to moderate pain including headache, migraine, neuralgia, toothache, sore throat, period pain, aches and pains.. These applications were made under Article 10.c, an informed consent application, referring to Paracetamol 500mg Tablets authorised to Bristol Laboratories in the UK (PL 17907/0001). A letter of access has been provided by Bristol Laboratories Limited authorising the MHRA to refer to PL 17907/0001 in relation to this application.

PHARMACEUTICAL ASSESSMENT

Strength, pharmaceutical form, route of administration, container and pack sizes

The product contains 500mg of paracetamol in tablet form for oral administration, the product is available without prescription. In accordance with the reference product the finished product will be available in packs of 8, 12, 16 tablets packed in aluminium/PVC blister strips.

Drug Substance

The manufacturers of the Active Ingredient have provided satisfactory Certificates of Suitability for the production of paracetamol. Paracetamol complies with the BP/EP monograph and a satisfactory specification for Paracetamol applied by finished product manufacturer has been provided. The specification is identical to that applied to the reference product and the proposed suppliers are identical to that of the reference product.

Finished Product

The qualitative composition of the tablets is paracetamol, pregelatinised maize starch, sodium metabisulphite, magnesium stearate and water. The formula used is identical to that of the reference product. The finished product specification is identical to that of the reference product.

No animal products are used in the formulation of this product and the product complies with the EU guidelines Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products..

Manufacture

The manufacturing process and in-process controls and validated batch sizes are as described for the reference product. No bioequivalence data have been submitted with this application. The product is manufactured to the same formulae and by the same process as the reference product. Analytical methods used are identical to that of the reference product.

Shelf-life

The shelf-life of the product is 5 years in the original packaging with the direction “do not store above 25 °C” and is the same as the reference product.

Summary of Product Characteristics

The SPC is satisfactory after necessary amendments.

Expert Reports

Satisfactory expert reports were provided and it was confirmed that the dossier for this product is identical to that of the reference product.

Patient Information Leaflet

The Patient Information Leaflet was amended and is now satisfactory.

Conclusion

Marketing Authorisations for this product was granted.

PRE-CLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for an application of this type

CLINICAL ASSESSMENT

This application is an informed consent application and the clinical data is identical to that of PL 17907/001and therefore no further clinical assessment is necessary.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The data for this application is the same as that previously assessed for the reference product.

PRECLINICAL

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

EFFICACY

Paracetamol is a well-known drug and no new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's products are identical to the reference product. Extensive clinical experience with paracetamol is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

STEPS TAKEN DURING ASSESSMENT

1	Applications received on the 24/06/2003
2	Additional information regarding Pharmaceutical Assessment requested on the 08/10/2003, 19/05/2005, 29/07/2005. Additional information on the Medical Assessment requested on the 0/10/2003.
3	Additional information regarding the Pharmaceutical Assessment received on 07/05/2004, 19/05/2005 and 08/06/2005. Additional information regarding the Medical Assessment was received on the 07/05/2004.
4	The Applications were determined on the 16/02/2006

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Paracetamol 500 mg Tablets BP.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Paracetamol 500 mg.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablet

White, capsule shaped tablet with a break-line on one face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of mild to moderate pain including headache, migraine, neuralgia, toothache, sore throat, period pain, aches and pains.
Symptomatic relief of rheumatic aches and pains.
Symptomatic relief of influenza, feverishness, feverish colds.

4.2 Posology and method of administration

For oral administration.

Adults, the elderly and children over 12 years: One or two tablets to be taken up to four times daily. Maximum dose of 8 tablets in 24 hours.

Children 6 to 12 years of age: Half a tablet to be taken up to four times a day.

Children under 6 years of age: Not recommended.

The dose should not be repeated more frequently than every 4 hours, and not more than 4 doses should be taken in any 24 hour period.

4.3 Contraindications

Hypersensitivity to paracetamol or any of the other ingredients.

4.4 Special warnings and special precautions for use

Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

Do not exceed the stated dose.
Immediate medical advice should be sought in the event of an overdose even if you feel well, because of the risk of delayed serious liver damage.
Do not take with any other paracetamol-containing products.
If symptoms persist consult your doctor.
Keep out of the reach and sight of children.

4.5 Interactions with other medicinal products and other forms of interaction

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine.

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

4.6 Pregnancy and lactation

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage, but patients should follow the advice of their doctor regarding its use.

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding.

4.7 Effects on ability to drive and use machines

No or negligible influence.

4.8 Undesirable effects

Adverse effects are rare but hypersensitivity including skin rash may occur.
There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.

4.9 Overdose

Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

Risk Factors:
If the patient

a, Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
Or
b, Regularly consumes ethanol in excess of recommended amounts.
Or
c, Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea,

vomiting, anorexia and abdominal pain. Liver damage may become apparent 12

to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic

acidosis may occur. In severe poisoning, hepatic failure may progress to

encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death.

Acute renal failure with acute tubular necrosis, strongly suggested by loin pain,

haematuriaand proteinuria, may develop even in the absence of severe liver

damage.

Cardiac arrhythmias and pancreatitis have been reported.

Management

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to Hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage.
Management should be in accordance with established treatment guidelines, see BNF overdose section.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours postingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. Management of patients who present with serious hepatic dysfunction beyond 24 h from ingestion should be discussed with the NPIS or a liver unit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Paracetamol is an effective analgesic and antipyretic agent but has only weak anti-inflammatory properties. Its mechanism of action is not fully understood, as it is only a weak inhibitor of prostaglandin bio-synthesis, but it has been suggested that it is more effective against enzymes in the CNS than those in the periphery. The drug has no effect on the cardiovascular and respiratory systems, and it does not cause gastric irritation or bleeding like salicylates.

5.2 Pharmacokinetic properties

Paracetamol is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring 30 minutes to 2 hours after ingestion. It is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted unchanged as paracetamol. The elimination half life varies from about 1 to 4 hours. Plasma protein binding is negligible at usual therapeutic concentrations but increases with increasing concentration.

A minor hydroxylated metabolite which is usually produced in very small amounts by mixed function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione, may accumulate following paracetamol overdosage and cause liver damage.

5.3 Preclinical safety data

No data of relevance which is additional to that included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinised Maize Starch
Sodium Metabisulphite
Magnesium Stearate

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Al/PVC child resistant blisters comprised of 20µm hard aluminium foil laminated to 15µm rigid PVC, and 250µm PVC enclosed in an outer carton.

Pack sizes: 8, 12, 16 tablets.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling <and disposal>

None applicable.

7. MARKETING AUTHORISATION HOLDER

Bristol Laboratories Ltd
Unit 3, Canalside,
Northbridge Road,
Berkhamsted
Hertfordshire
HP4 1EG

8. MARKETING AUTHORISATION NUMBER(S)

PL 17907/0049

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Labels and Leaflets

PARACETAMOL
TABLETS BP 500 mg
PL Holder:
Bristol Laboratories Ltd.

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TABLETS BP 500mg

Please read all this leaflet carefully before you start taking this medicine.
Keep the leaflet, you may need to read it again.
If you have any further questions, please ask your doctor or pharmacist.

The name of this medicine is
PARACETAMOL 500 MG TABLETS BP

Each tablet contains Paracetamol BP 500 mg as the active substance.
Other ingredients are Pregelatinised Maize Starch, Sodium Metabisulphite and Magnesium Stearate.

Product Licence holder and Manufacturer:
Bristol Laboratories Ltd., Unit 3, Canalside, Northbridge Road, Berkhamsted, Herts, HP4 1EG

What the tablets are and what they are used for

The tablets are white capsule shaped with a breakline on one side.
Paracetamol is an analgesic and an antipyretic which means it relieves pain and lowers temperature. The tablets are available in cartons containing 8, 12 or 16 tablets (not all packs may be marketed).
Paracetamol Tablets are used for the relief of mild to moderate pain including headache, migraine, neuralgia, toothache, sore throat, period pains, rheumatic aches and pains.
Also for the relief of symptoms of influenza, feverishness and feverish colds.

Before you take Paracetamol Tablets

Do not take if you are allergic to paracetamol or any of the other ingredients.
The ingredient Sodium Metabisulphite contained in the tablets may rarely cause severe hypersensitivity reactions and bronchospasm (breathing difficulties).

Do not take with any other paracetamol-containing products.

Take special care if:
- You suffer from any liver or kidney problems.
- You suffer from alcohol dependence.
- You are taking any other medicines especially any of the following: anticoagulants to thin the blood e.g. Warfarin; the drugs Colestyramine, Metoclopramide or Domperidone.

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Please speak to your doctor or pharmacist before taking these tablets if any of the statements under "Take special care if" applies to you.
Pregnancy and Breastfeeding- Check with your doctor before taking these tablets.

How to take

The tablets should be swallowed with a drink of water.

Adults, the elderly and children over 12 years: Take one or two tablets up to 4 times a day or as instructed by your doctor.

Children 6 to 12 years of age: Take half a tablet up to 4 times a day.
Not recommended for children under 6 years of age.

The dose should not be repeated more frequently than every 4 hours and not more than 4 doses should be taken in any 24 hour period.

DO NOT EXCEED THE STATED DOSE. If symptoms persist consult your doctor.

If you take more Paracetamol Tablets than you should:
Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed serious liver damage.

If you forget to take a dose of Paracetamol Tablets:
Do not take a double dose to make up for the missed dose.

Possible Side Effects

Like all medicines, paracetamol may sometimes cause side effects, and those which may occur occasionally are allergic reactions including skin rash and changes in blood, which may lead to bruising or bleeding gums. If you do notice any side effects, including any not mentioned in this leaflet, please inform your doctor or pharmacist.

Storing the tablets

Keep out of the reach and sight of children. Do not store above 25°C.
Store in the original package, in order to protect the tablets from moisture.
Do not use the tablets after the expiry date shown on the label or carton.
This leaflet was revised August 2005.

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