Paracetamol 60mg and 1000mg Suppositories  
PL 00156/0098-9

UKPAR

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Paracetamol 60mg and 1000mg Suppositories
PL 00156/0098-9

LAY SUMMARY

On 29\textsuperscript{th} June 2009, the MHRA granted Martindale Pharmaceuticals Limited Marketing Authorisations (licences) for Paracetamol 60mg and 1000mg Suppositories (PL 00156/0098-9).

This product contains paracetamol, which belongs to a group of medicines called analgesics. An analgesic is a medicine that relieves pain.

Paracetamol 60mg and 1000mg Suppositories BP are used in the treatment of mild to moderate pain or fever. The 60mg suppositories are for children aged 1 to 2 years.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Paracetamol 60mg and 1000mg Suppositories outweigh the risks; hence Marketing Authorisations have been granted.
SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Paracetamol 60mg and 1000mg Suppositories (PL 00156/0098-9) to Martindale Pharmaceuticals Limited on 29th June 2009. These products are dispensed in pharmacies for the treatment of mild to moderate pain and pyrexia.

These applications for Paracetamol 60mg and 1000mg Suppositories are submitted as abridged standard applications according to Article 10.1(a) of Directive 2001/83/EC.

The product contains the active substance paracetamol, a widely used general purpose mild analgesic and antipyretic. It is similar in efficacy to aspirin, but with no demonstrable anti-inflammatory activity.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
Paracetamol
INN: Paracetamol
Chemical name: Acetaminophen, N-Acetyl-p-aminophenol, Paracetamolum, 4’-hydroxyacetanilide, N-(4-hydroxyphenyl)aceta
Structure:

Physical form: A white crystalline powder
Solubility: Sparsely soluble in water, freely soluble in alcohol and very slightly soluble in methylene chloride. Solubility in water increases as the pH increases
Molecular formula: C₉H₉NO₂
Molecular weight: 151.2

An appropriate specification based on the European Pharmacopoeia has been provided.

All aspects of the manufacture of the active substance paracetamol from its starting materials are controlled by a Certificate of Suitability.

An appropriate retest period has been proposed based on stability data submitted for the active substance paracetamol.

An appropriate specification is provided for the active substance, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specification.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

DRUG PRODUCT
Other ingredients
Other ingredients consist of pharmaceutical excipients polyoxyl 40 stearate and hard fat.

Statements have been provided by the excipient manufacturers confirming the animal-free origins of both excipients.

**Product development**
The objective of the development programme was to produce products that could be considered generic medicinal products of Paracetamol 500mg Suppositories (Rice Steel and Company Limited, February 1995).

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative dissolution and impurity profiles have been provided for the finished products versus the reference products Paracetamol 500mg Suppositories (Rice Steel and Company Limited, February 1995).

**Manufacture**
A description and flow-chart of the manufacturing method has 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 finished product and the results appear satisfactory. The applicant has committed to perform process validation on the first three full production-scale batches.

**Finished product specification**
The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis for all working standards used have been provided and are satisfactory.

**Container-Closure System**
The product is packaged in Strips of opaque white suppository moulds composed of polyvinyl chloride (PVC) and polyethylene (PE) with a polyurethane adhesive. Each strip contains 6 suppositories. These strips are then packed into outer cartons. The product is packed in sizes of 12 suppositories.

Specifications and certificates of analysis have been provided. 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. Based on the results, a shelf life of 2 years has been set, which is satisfactory.

Storage conditions are ‘Do not store above 25°C’ and ‘Keep the blister strips in the outer carton.’

**ADMINISTRATIVE**

**Expert Report**
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.
Summary of Product Characteristics (SPC)
These are pharmaceutically satisfactory.

Labelling
These are pharmaceutically satisfactory.

Patient Information Leaflet (PIL)
This is pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Form
These are pharmaceutically satisfactory.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.
PRECLINICAL ASSESSMENT

These applications for Paracetamol 60mg and 1000mg Suppositories are submitted as abridged standard applications according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal products of Paracetamol 500mg Suppositories, first authorised to Rice Steel and Company Limited in February 1995.

No new preclinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
To support the applications, the marketing authorisation holder has included a single bioequivalence study:

A single-dose randomized, 2-way, crossover bioequivalence study comparing the pharmacokinetics of Paracetamol 1000mg Suppository (Test) versus 2x 500mg Paracetamol Suppositories (Reference) under fasted conditions.

All subjects had an overnight fast of before dosing. Blood sampling was performed pre-drug administration, during the study and up to 72 hours post dose in each treatment period. There was a washout period of 7 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as log-transformed values:

<table>
<thead>
<tr>
<th>Paracetamol</th>
<th>AUC\text{0-t} (ng/ml/h)</th>
<th>AUC\text{0-}\infty (ng/ml/h)</th>
<th>C\text{max} (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>49162±1.37</td>
<td>50620±1.38</td>
<td>7418±1.33</td>
</tr>
<tr>
<td>Reference</td>
<td>48701±1.46</td>
<td>50202±1.47</td>
<td>7072±1.41</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>95.9-106</td>
<td>95.8-106</td>
<td>97.9-112</td>
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</table>

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC\text{0-t} and C\text{max} for paracetamol lie within 80-125% boundaries. Thus, bioequivalence has been shown between the test and reference products in this study.

EFFICACY
No new data has been provided.

SAFETY
No new data has been provided.

EXPERT REPORTS
The clinical expert report has been written by a suitably qualified person and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
This is consistent with that for the reference product and is satisfactory.

LABELLING
These are satisfactory.

APPLICATION FORMS (MAA)
These are satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
These are consistent with those for the reference products and are satisfactory.
DISCUSSION
The applicant has satisfactorily demonstrated bioequivalence between the test and reference products.

MEDICAL CONCLUSION
The bioequivalence study submitted has shown that Paracetamol 60mg and 1000mg Suppositories can be considered as generic medicinal products to the originator products Paracetamol 500mg Suppositories (Rice Steel and Company Limited).

The grant of marketing authorisations is recommended for these applications.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Paracetamol 60mg and 1000mg Suppositories 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.

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

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Paracetamol 60mg and 1000mg Suppositories and the reference products. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 1000mg capsule can be extrapolated to the other strengths of 60mg.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference products.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the reference products are interchangeable. Extensive clinical experience with paracetamol is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
**STEPS TAKEN FOR ASSESMENT**

<table>
<thead>
<tr>
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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 18&lt;sup&gt;th&lt;/sup&gt; June 2001.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 30&lt;sup&gt;th&lt;/sup&gt; March 2007.</td>
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<td>3</td>
<td>Following assessment of the applications, the MHRA requested further information on the quality sections of the dossier on 4&lt;sup&gt;th&lt;/sup&gt; April 2007, 30&lt;sup&gt;th&lt;/sup&gt; June 2008 and 24&lt;sup&gt;th&lt;/sup&gt; March 2009.</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality sections of the dossier on 24&lt;sup&gt;th&lt;/sup&gt; October 2007, 6&lt;sup&gt;th&lt;/sup&gt; August 2008 and 24&lt;sup&gt;th&lt;/sup&gt; March 2009.</td>
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<td>5</td>
<td>The applications were determined on 26&lt;sup&gt;th&lt;/sup&gt; June 2009.</td>
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Paracetamol 60mg and 1000mg Suppositories
PL 00156/0098-9

**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

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<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Paracetamol 60 mg Suppositories BP

2 Qualitative and Quantitative Composition
Each Suppository contains 60 mg Paracetamol
For a full list of excipients see section 6.1.

3 Pharmaceutical Form
Suppository
Clean white to off-white conical or torpedo shaped suppositories

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Paracetamol 60mg Suppositories are indicated for the treatment of mild to moderate pain and pyrexia in children.

4.2 Posology and Method of Administration
For rectal administration.
Children:
1-2 years (8 – 11 kg) 2 suppositories.
Dose may be repeated every 4 – 6 hours up to a maximum of 4 doses in 24 hours. Dose should be based on age and weight.

4.3 Contra-indications
Hypersensitivity to paracetamol or any of the other constituents.

4.4 Special Warnings and Precautions for Use
Use with caution in the presence of renal or hepatic dysfunction. The hazards of overdose are that much greater in those with non-cirrhotic alcoholic liver disease. Do not exceed the recommended dose.
Paracetamol should be used with caution in patients with anaemia or an infection.
Patients should be advised not to take other paracetamol containing products concurrently. If symptoms persist, medical opinion should be sought.
Keep out of the reach and sight of children.

4.5 INTERACTION 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 cholestyramine.
The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.
Drugs that induce hepatic microsomal enzymes such as barbiturates and other anticonvulsants, may increase the hepatotoxic potential of paracetamol particularly after overdosage. Alcohol abuse increases the risk for paracetamol toxicity.
Rifampicin can interact to reduce the effectiveness of paracetamol.

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
None Known
4.8 Undesirable Effects
Adverse effects at therapeutic doses are rare, but hypersensitivity including skin rash may occur. There have been a few reports of blood dyscrasias, including thrombocytopenia and agranulocytosis, but these were not necessarily causality related to paracetamol. Redness of the mucous membrane of the rectum and minor vascular changes have been reported. Isolated cases of liver damage have also been rarely reported.

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). It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested) become irreversibly bound to liver tissue.

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 overdose 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, haematuria and proteinuria, may develop 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 post-ingestion. 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 24h from ingestion should be discussed with NPIS or a liver unit.

Pharmacological Properties
5.1 PHARMACODYNAMIC PROPERTIES
ATC Code: N02BE01
Paracetamol is an aniline derivative with analgesic and antipyretic actions. Paracetamol produces its analgesic effect from the inhibition of prostaglandin synthesis. Prostaglandins appear to sensitise pain receptors to mechanical stimulation or to other chemical mediators. Paracetamol lowers the body temperature in patients with fever but rarely lowers normal body temperature. This is again due to the inhibition of synthesis and release of prostoglandins. The drug also acts on the hypothalamus to produce antipyresis; heat dissipation is increased as a result of vasodilation and increased peripheral blood flow.
Paracetamol is generally well tolerated by patients hypersensitive to acetylsalicylic acid.

5.2 Pharmacokinetic Properties
Paracetamol is well absorbed by both oral and rectal routes. Peak plasma concentrations occur about 2 to 3 hours after rectal administration. Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk. Plasma-protein binding is negligible at usual therapeutic concentrations. The plasma half life is about 2 hours. Paracetamol is primarily metabolised in the liver by conjugation to glucuronide and sulphate. A small amount (about 3 - 10% of a therapeutic dose) is metabolised by oxidation and the reactive intermediate metabolite thus formed is bound preferentially to the liver glutathione and excreted as cystein and mercapturic acid conjugates. Excretion occurs via the kidneys. 2 - 3% of a therapeutic dose is excreted unchanged; 80 - 90% as glucuronide and sulphate and a smaller amount as cystein and mercapturic acid derivatives.

5.3 Preclinical Safety Data
Paracetamol is a well established drug substance whose pre-clinical profile has been thoroughly investigated and is established.

Pharmaceutical Particulars

6.1 List of Excipients
Hard Fat
Polyoxyl 40 Stearate

6.2 Incompatibilities
None known

6.3 Shelf Life
24 months

6.4 Special Precautions for Storage
Do not store above 25°C. Keep the blister strips in the outer carton.

6.5 Nature and Contents of Container

6.6 Instruction for Use/Handling
Wash hands thoroughly before opening the individual packaging. The suppository is shaped for rectal insertion, ensure the tip of the suppository is inserted first. Do not open until immediately before use.

Administrative Data

7 Marketing Authorisation Holder
MARTINDALE PHARMACEUTICALS LTD
Bampton Road
Romford
Essex RM3 8UG

8 Marketing Authorisation Number
PL 00156/0099

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
29/06/2009

10 DATE OF REVISION OF THE TEXT
29/06/2009
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Paracetamol 1000 mg Suppositories BP

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Suppository contains 1000 mg Paracetamol
For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM
Suppository
Clean white to off-white conical or torpedo shaped suppositories.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Paracetamol 1000 mg Suppositories are indicated for the treatment of mild to moderate pain and pyrexia. The suppositories may be particularly useful in patients unable to take oral forms of Paracetamol e.g. post-operatively or with nausea and vomiting.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
For rectal administration.

Children:
Not recommended in children under the age of 12.

Adults and Adolescents:
1 suppository

The dose may be repeated every 4-6 hours up to a maximum dose of 4 doses in 24 hours. Dose should be based on age and weight.

4.3 CONTRAINDICATIONS
Hypersensitivity to paracetamol or any of the other constituents.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Use with caution in the presence of renal or hepatic dysfunction. The hazards of overdose are that much greater in those with non-cirrhotic alcoholic liver disease. Do not exceed the recommended dose.

Paracetamol should be used with caution in patients with anaemia or an infection. Patients should be advised not to take other paracetamol containing products concurrently. If symptoms persist, medical opinion should be sought. Keep out of the reach and sight of children.

4.5 INTERACTION 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 cholestyramine.

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

Drugs that induce hepatic microsomal enzymes such as barbiturates and other anticonvulsants, may increase the hepatotoxic potential of paracetamol particularly after overdosage. Alcohol abuse increases the risk for paracetamol toxicity.

Rifampicin can interact to reduce the effectiveness of paracetamol.
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
None known

4.8 UNDESIRABLE EFFECTS
Adverse effects at therapeutic doses are rare, but hypersensitivity including skin rash may occur. There have been a few reports of blood dyscrasias, including thrombocytopenia and agranulocytosis, but these were not necessarily causality related to paracetamol.

Redness of the mucous membrane of the rectum and minor vascular changes have been reported. Isolated cases of liver damage have also been rarely reported.

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).

It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested) become irreversibly bound to liver tissue.

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 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, haematuria and proteinuria, may develop 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 post-ingestion. 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 24h from ingestion should be discussed with NPIS or a liver unit.

5

5.1 PHARMACODYNAMIC PROPERTIES

ATC Code: N02BE01

Paracetamol is an antipyretic and analgesic. Paracetamol produces antipyresis through action on the hypothalamic heat-regulation centre and analgesia by elevation of the pain threshold. Paracetamol has analgesic and antipyretic actions similar to aspirin, but it has no useful anti-inflammatory properties.

Paracetamol produces its analgesic effect from the inhibition of prostaglandin synthesis. Prostaglandins appear to sensitize pain receptors to mechanical stimulation or to other chemical mediators. Paracetamol lowers the body temperature in patients with fever but rarely lowers normal body temperature. This is again due to the inhibition of synthesis and release of prostoglandins. The drug also acts on the hypothalamus to produce antipyresis; heat dissipation is increased as a result of vasodilatation and increased peripheral blood flow.

Paracetamol is generally well tolerated by patients hypersensitive to acetylsalicylic acid.

5.2 PHARMACOKINETIC PROPERTIES

Paracetamol is rapidly and almost completely absorbed from the alimentary tract. Peak plasma concentrations occur within 0.5 to 2 hours after rectal administration. Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk. Plasma-protein binding is negligible at usual therapeutic concentrations. The plasma half-life is about 2 hours. Paracetamol is primarily metabolised in the liver by conjugation to glucuronide and sulphate. A small amount (about 3-10% of a therapeutic dose) is metabolised by oxidation and the reactive intermediate metabolite thus formed is bound preferentially to the liver glutathione and excreted as cysteine and mercapturic acid conjugates. Excretion occurs via the kidneys. 2 - 4% of a therapeutic dose is excreted unchanged; 80 - 90% as glucuronide and sulphate and a smaller amount as cysteine and mercapturic acid derivatives. The average elimination half-life is 1 to 4 hours, although this is extended in neonates and cirrhotic patients.

5.3 PRECLINICAL SAFETY DATA

Paracetamol is a well established drug substance whose pre-clinical profile has been thoroughly investigated and is established.

6

6.1 LIST OF EXCIPIENTS

Hard Fat
Polyoxyl 40 stearate

6.2 INCOMPATIBILITIES

None known

6.3 SHELF LIFE

24 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C. Keep the blister strips in the outer carton.

6.5 NATURE AND CONTENTS OF CONTAINER

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Wash hands before opening individual packaging. The suppository is shaped for rectal insertion, ensure the tip of the suppository is inserted first.
Do not open until immediately before use.

7 MARKETING AUTHORISATION HOLDER
MARTINDALE PHARMACEUTICALS LTD
Bampton Road
Romford
Essex RM3 8UG

8 MARKETING AUTHORISATION NUMBER(S)
PL 00156/0098

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
29/06/2009

10 DATE OF REVISION OF THE TEXT
29/06/2009
PACKAGE LEAFLET: INFORMATION FOR THE USER

Paracetamol 60mg Suppositories BP

Paracetamol

Read all of this leaflet carefully before you or your child starts taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor, or pharmacist.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Paracetamol 60mg Suppositories BP are and what they are used for
2. Before you or your child use Paracetamol 60mg Suppositories BP
3. How to use Paracetamol 60mg Suppositories BP
4. Possible side effects
5. How to store Paracetamol 60mg Suppositories BP
6. Further information

If symptoms persist you should consult your doctor.

Do not exceed the recommended dose.

**Taking other medicines**
Please tell your doctor, nurse or pharmacist if you or your child are taking, or have recently taken, any other medicine including medicines obtained without prescription.
Please tell your doctor if you or your child are taking any of the following medicines:

- warfarin, a medicine used to thin the blood. Regular use of paracetamol and warfarin together may increase the risk of bleeding; occasional use has no effect
- metoclopramide (a medicine used to stop you feeling, or being, sick)
- domperidone (a medicine used to stop you feeling, or being, sick)
- cholestyramine (a medicine used to treat high cholesterol levels)
- medicines used to treat epilepsy or fits, such as phenobarbitone

Do not use Paracetamol 60mg Suppositories BP with other medicines that contain paracetamol.

If you have any doubts as to whether Paracetamol 60mg Suppositories BP are suitable for you or your child please consult your doctor.

**Pregnancy and breast-feeding**
If you are pregnant or breast-feeding you should ask your doctor for advice before taking Paracetamol 60mg Suppositories BP.

**Driving and using machines**
There are no known effects of taking Paracetamol 60mg Suppositories BP on driving or using machines.

Continued overleaf
3. How to use Paracetamol 60mg Suppositories BP
For rectal use only.
Always use Paracetamol 60mg Suppositories BP exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
- If you need to empty your bowels, this should be done before inserting the suppository
- Wash your hands
- Peel the wrapping apart and remove the suppository from its plastic wrapping by grasping the two halves of the wrapping at the tip of the suppository and pulling them gently apart.
- Moisten the suppository tip before insertion
- Push the suppository as high as possible into the rectum (back passage)
- If you are unsure about how to use the suppositories, please consult your doctor or pharmacist

How much to use
Children 1-2 years
The usual dose for children aged 1-2 years (body weight 8-11 kg) is 2 suppositories. The dose may be repeated every 4-6 hours up to a maximum of 4 doses in 24 hours. The dose will be based on age and weight. Your doctor or pharmacist will advise you of this.
You must not exceed the stated dose.

If you use more Paracetamol 60mg Suppositories BP than you should
Immediate medical advice should be sought in the event of an overdose, even if you or your child feel well, because of the risk of delayed, serious liver damage.

4. Possible Side Effects
Like all medicines Paracetamol 60mg Suppositories BP can cause side effects, although not everybody gets them.
Side effects that may occur include:
- a rash or itching initially
- soreness in or around the back passage

If any of these side effects gets serious, or you notice any other side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to Store Paracetamol 60mg Suppositories BP
Keep out of the reach and sight of children.
Do not store above 25°C. Keep the blister strip in the outer carton
Do not use Paracetamol Suppositories after the expiry date on the carton label. The expiry date refers to the last day of that month.
Do not use if the strip containing the suppositories is damaged.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further Information
What Paracetamol 60mg Suppositories BP contain
The active ingredient is paracetamol 60mg
The other ingredients are hard fat and Polyoxyx 40 Ester

What Paracetamol 60mg Suppositories BP look like and contents of the pack:
Paracetamol 60mg Suppositories BP are smooth, white suppositories supplied in a plastic cavity in strips of 6. Each pack contains 12 suppositories.

Marketing Authorisation Holder
Martindale Pharmaceuticals Ltd
Bampton Road, Romford, RM3 8UG

Manufacturer:
Macarthy's Laboratories Ltd
T/A Martindale Pharmaceuticals
Bampton Road, Romford, RM3 8UG

Product Licence Number:
PL 00156/0099

This leaflet was last approved in: March 2009
In this leaflet:
1. What Paracetamol 1000mg Suppositories BP are and what they are used for
2. Before you use Paracetamol 1000mg Suppositories BP
3. How to use Paracetamol 1000mg Suppositories BP
4. Possible side effects
5. How to store Paracetamol 1000mg Suppositories BP
6. Further information

1. What Paracetamol 1000mg Suppositories BP are and what they are used for
Paracetamol belongs to a group of medicines called analgesics. An analgesic is a medicine that relieves pain. Paracetamol 1000mg Suppositories BP are used in the treatment of mild to moderate pain or fever.

2. Before you use Paracetamol 1000mg Suppositories BP
You should not use Paracetamol 1000mg Suppositories BP if:
- you are allergic (hypersensitive) to paracetamol or to any of the ingredients listed in section 6 of this leaflet
If this applies to you please tell your doctor before using this medicine.
Take special care with Paracetamol 1000mg Suppositories BP if:
- you suffer from kidney problems
- you suffer from liver problems, including those caused by alcoholism
- you have an infection
If symptoms persist you should consult your doctor.

Do not exceed the recommended dose.

Taking other medicines
Please tell your doctor, nurse or pharmacist if you are taking, or have recently taken, any other medicine including medicines obtained without prescription.
Please tell your doctor if you are taking any of the following medicines:
- warfarin, a medicine used to thin the blood. Regular use of paracetamol and warfarin together may increase the risk of bleeding; occasional use has no effect
- metoclopramide (used to stop you feeling, or being, sick)
- domperidone (used to stop you feeling, or being, sick)
- cholestyramine (used to treat high cholesterol levels)
- medicines used to treat epilepsy or fits, such as phenobarbitone
Do not use Paracetamol 1000mg Suppositories BP with other medicines that contain paracetamol.
If you have any doubts as to whether Paracetamol 1000mg Suppositories BP are suitable for you please consult your doctor.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding you should ask your doctor for advice before taking Paracetamol 1000mg Suppositories BP.

Driving and using machines
There are no known effects of taking Paracetamol 1000mg Suppositories BP on driving or using machines.

Continued overleaf
3. How to use Paracetamol 1000mg Suppositories BP

For rectal use only.
Always use Paracetamol 1000mg Suppositories BP exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure:

- If you need to empty your bowels, this should be done before inserting the suppository.
- Wash your hands.
- Peel the wrapping apart and remove the suppository from its plastic wrapping by grasping the two halves of the wrapping at the tip of the suppository and pulling them gently apart.
- Moisten the suppository tip before insertion.
- Push the suppository as high as possible into the rectum (back passage).
- If you are unsure about how to use the suppositories, please consult your doctor or pharmacist.

How much to use

Adults and children over 12 years
The usual dose is one suppository every 4 - 6 hours up to a maximum of 4 doses in 24 hours. Dose should be based on age and weight.

Children under 12 years
Do not use in children under 12 years
You must not exceed the stated dose.

If you use more Paracetamol 1000mg Suppositories BP 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.

4. Possible Side Effects

Like all medicines Paracetamol 1000mg Suppositories BP can cause side effects, although not everybody gets them.
Side effects that may occur include:
- a rash or itching initially
- soreness in or around your back passage

If any of these side effects gets serious, or you notice any other side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to Store Paracetamol 1000mg Suppositories BP

Keep out of the reach and sight of children.
Do not store above 25°C. Keep the blister strip in the outer carton.
Do not use Paracetamol 1000mg Suppositories BP after the expiry date on the carton label.
The expiry date refers to the last day of that month.
Do not use if the strip containing the suppositories is damaged.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further Information

What Paracetamol 1000mg Suppositories BP contain
The active ingredient is paracetamol 1000mg. The other ingredients are hard fat and Polyoxyl 40 Ester

What Paracetamol 1000mg Suppositories BP look like and contents of the pack:
Paracetamol 1000mg Suppositories BP are smooth, white suppositories supplied in a plastic cavity in strips of 6. Each pack contains 12 suppositories.

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Product Licence Number:
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This leaflet was last approved in: March 2009
Paracetamol 60mg Suppositories BP

CONTAINS PARacetamol

For rectal administration only. Not to be taken orally.

Paracetamol 60mg Suppositories are recommended for children.
The recommended dose for children of 1-2 years (8-11 kg) is 2 suppositories.
Dose may be repeated every 4-6 hours. Up to a maximum of 4 doses in 24 hours.
Dose should be based on age and weight.
Do not exceed the stated dose. If symptoms persist consult your doctor.

Do not give with any other paracetamol-containing products. Immediate medical advice should be sought in the event of an overdose, even if your child seems well.

Each suppository contains Paracetamol Ph Eur 60mg, Polyoxy 40 Stearate and Hard Fat.
For instructions on use please refer to the patient information leaflet supplied.
Do not store above 25°C. Do not open until immediately before use.
Keep the blister strip in the outer carton. Keep out of the reach and sight of children.

PL00156/0099 MartinDale Pharmaceuticals, Romford, Essex RM3 8UG, UK.