Public Assessment Report

Decentralised Procedure

Paracetamol 250mg Suppositories
Paracetamol 500mg Suppositories

UK/H/3781/01-02/DC
UK licence numbers: PL 35104/0001-2

Phoenix Labs
LAY SUMMARY

On 15th November 2010, the MHRA granted Phoenix Labs Marketing Authorisations (licences) for the medicinal products Paracetamol 250mg and 500mg Suppositories (PL 35104/0001-2). These are P licensed medicines available only from pharmacies, under the supervision of a pharmacist.

Paracetamol Suppositories contain a medicine called paracetamol, one of a group of medicines called pain-killers (analgesics). A suppository is a small, torpedo-shaped medicine which is inserted into the back passage (rectum). Paracetamol Suppositories are used to treat pain and high temperature (fever) in children from the age of 6 years. They are used by children who find it difficult to take paracetamol as tablets or syrup.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of Paracetamol 250mg and 500mg Suppositories outweigh the risks; hence Marketing Authorisations have been granted.
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# Module 1

## Information about Initial Procedure

| Product Name                      | Paracetamol 250mg Suppositories  
<table>
<thead>
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<th>Paracetamol 500mg Suppositories</th>
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<tbody>
<tr>
<td>Type of Application</td>
<td>Well-established use, Article 10a</td>
</tr>
<tr>
<td>Active Substance</td>
<td>Paracetamol</td>
</tr>
<tr>
<td>Form</td>
<td>Suppositories</td>
</tr>
<tr>
<td>Strength</td>
<td>250mg and 500mg</td>
</tr>
</tbody>
</table>
| MA Holder                        | Phoenix Labs  
|                                  | Pharmapark  
|                                  | Cahill May Roberts  
|                                  | Chapelizod  
|                                  | Dublin 20  
|                                  | Ireland                           |
| Reference Member State (RMS)     | UK                               |
| Concerned Member States (CMS)    | Ireland                          |
| Procedure Number                 | UK/H/3781/01-02/DC                |
| Timetable                        | End of Procedure: Day 210 – 17th October 2010 |
Module 2

Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPC) for Paracetamol 250mg and 500mg Suppositories (PL 35104/0001-2) is as follows. Differences between the individual SmPCs are highlighted:

1 NAME OF THE MEDICINAL PRODUCT
Paracetamol 250mg Suppositories
Paracetamol 500mg Suppositories

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each suppository contains 250mg / 500mg Paracetamol
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Suppository
White, torpedo shaped, suppository

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
For the treatment of mild to moderate pain and fever in children from the age of 6 years.
Paracetamol suppositories may be especially useful in patients unable to take oral forms of paracetamol e.g. Post-operative patients or patients with nausea and/or vomiting.

4.2 Posology and method of administration
For rectal use only

250mg Suppository
Children aged 6-9 years (20 – 30kg): 1 suppository
Children aged 10-12 years (30 – 40kg): 1-2 suppositories

500mg Suppository
Children aged 10-12 years (30 – 40kg): 1 suppository
12 years and over: 1-2 suppositories.

The dosage should be based on the child’s age and weight. These doses may be repeated up to a maximum of 4 times in 24 hours. The dose should not be repeated more frequently than every 4 hours. The recommended dose should not be exceeded. The product should not be used for more than 3 days, except on the advice of a doctor. Higher doses do not produce any increase in analgesic effect. Only whole suppositories should be administered – do not break the suppository before administration.

4.3 Contraindications
Patients who are hypersensitive to paracetamol or any of the other constituents.

4.4 Special warnings and precautions for use
Paracetamol suppositories should not be combined with other analgesic medications that contain paracetamol.
Paracetamol suppositories should be administered with care to patients with impaired kidney or liver function. The hazards of overdose are greater in those with non-cirrhotic liver disease.
Label and leaflet should state the following warnings:

**Label**
- Do not exceed the stated dose.
- If symptoms persist consult your doctor.
- Keep out of the reach and sight of children.
- Leave at least 4 hours between doses.
- Immediate medical advice should be sought in the case of an overdose, even if the child seems well.
- Do not give with other Paracetamol containing products.

**Leaflet**
- Immediate medical advice should be sought in the event of an overdose, even if the child seems well, because of the risk of delayed, serious liver damage.

4.5 **Interaction with other medicinal products and other forms of interaction**

The anti-coagulant 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.

Drugs which induce hepatic microsomal enzymes such as alcohol, barbiturates and other anticonvulsants, may increase the hepatotoxicity of paracetamol, particularly after over-dosage. In addition, the risk of liver damage during treatment with maximum recommended doses of paracetamol will be higher in patients being treated with enzyme-inducing agents.

4.6 **Pregnancy and lactation**

Pregnancy: Paracetamol Suppositories can be used during pregnancy if clinically needed.

Lactation: Paracetamol Suppositories can be used during breast feeding.

4.7 **Effects on ability to drive and use machines**

None known

4.8 **Undesirable effects**

Paracetamol is usually well tolerated in normal use.

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

Cases of liver damage have been reported rarely. Hepatic necrosis may occur after paracetamol overdose (see Section 4.9).

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

- Is on long term treatment with carabamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John’s Wort or other drugs that induce liver enzymes.

Or

- Regularly consumes ethanol in excess of recommended amounts.

Or

- 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 and clinical symptoms generally culminate after 4-6 days. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, coma and death. Acute renal failure with acute tubular necrosis 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 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 the NPIS or a liver unit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic Group: Anilides, ATC Code: N02 BE01
Paracetamol is an aniline derivative with analgesic and antipyretic actions similar to those of aspirin but with no demonstrable anti-inflammatory activity. It does not affect thrombocyte aggregation or bleeding time. Paracetamol is generally well tolerated by patients hypersensitive to acetylsalicylic acid. It produces analgesia by elevation of the pain threshold and antipyresis through action on the hypothalamic heat-regulation center.

5.2 Pharmacokinetic properties
Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. Peak plasma concentrations occur about 2 to 3 hours after rectal administration. Usual analgesic doses produce total serum concentrations of 5 to 20mcg/ml. 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.

Paracetamol is excreted in the urine mostly as metabolites; 2-4% is excreted unchanged. The average elimination half life is 1 to 4 hours; half life is slightly prolonged in neonates (2.2 to 5 hours) and in cirrhotics.

The overall elimination rate constant for paracetamol in children, from birth to 12 years of age, is the same as for adults but neonates have diminished capacity to form glucuronide conjugates of paracetamol.

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Hard fat
Macrogol cetostearyl ether
Glyceryl ricinoleate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 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
Ten suppositories packed in white/opaque PVC/PE film.
Each suppository is packed separately. Due to the perforations of the welds an individual suppository can be torn out.
Two strips, each containing five suppositories, are packed into a cardboard carton.

6.6 Special precautions for disposal
The suppository should only be removed from the blister packaging immediately before use.

7 MARKETING AUTHORISATION HOLDER
Phoenix Labs
Pharmapark
Cahill May Roberts
Chapelizod
Dublin 20
Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 35104/0001
PL 35104/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
15/11/2010

10 DATE OF REVISION OF THE TEXT
15/11/2010
Module 3
Patient Information Leaflet

Information for the user

FOR RECTAL ADMINISTRATION ONLY

Paracetamol 250mg Suppositories
Paracetamol 500mg Suppositories

Read all of this leaflet carefully because it contains important information for you and your child. This medicine is available without prescription. However, you still need to use it carefully to get the best results from it.

• Keep this leaflet. You may need to read it again.
• Ask your pharmacist if you need more information or advice.
• You must contact your child’s doctor if your child’s symptoms get worse or do not improve.
• If your child gets any side effects after being given this medicine, please tell a doctor or pharmacist.

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

1. What Paracetamol Suppositories are and what they are used for
Paracetamol Suppositories contain a medicine called paracetamol. Paracetamol is one of a group of medicines called painkillers (analgesics). A suppository is a small, torpedo-shaped medicine which is inserted into the back passage (rectum). Paracetamol Suppositories are used to treat pain and high temperature (fever) in children from the age of 6 years. They are used by children who find it difficult to take paracetamol as tablets or syrup.

2. Before you give Paracetamol Suppositories to your child
Do not give your child these suppositories if:
• They are allergic to paracetamol or the other main ingredient which is called “hard fat”.

Take special care with Paracetamol Suppositories
Check with your doctor or pharmacist before using these suppositories if:
• Your child has liver or kidney problems

Taking other medicines
Please tell your child’s doctor or pharmacist if your child is taking, or has recently taken, any other medicines. This includes medicines that you buy without a prescription and herbal medicines. This is because the suppositories can affect the way some medicines work and some medicines can have an effect on Paracetamol Suppositories. In particular, tell your child’s doctor or pharmacist if your child is taking any of the following:
• Other medicines that contain paracetamol—do not give your child Paracetamol Suppositories at the same time
• Barbiturates (a type of sedative)
• Medicines for epilepsy or fits (also called “anti-convulsants”)
• Medicines such as warfarin for treating blood clots
Do not give your child alcohol, or any medicines containing alcohol whilst they are being given these suppositories.

3. How to administer Paracetamol Suppositories to your child
This medicine is for rectal use only. If your child’s doctor or pharmacist has told you how to use this medicine, do exactly as they have told you. Otherwise follow the instructions below. If you do not understand the instructions, or are not sure, ask the doctor or pharmacist.

How many Paracetamol Suppositories to give your child
Paracetamol 250 mg Suppositories
Children aged 6 to 8 years (20 – 30 kg) — one 250 mg suppository
Children aged 9 to 12 years (30 – 40 kg) — one to two 250 mg suppositories
Paracetamol 500mg Suppositories
Children aged 10 to 12 years (30–40kg) – one 500 mg suppository
Children aged 12 years and older – one to two 500 mg suppositories
The dosage should be based on your child’s age and weight.
These doses may be repeated up to a maximum of 4 times in 24 hours.
Suppositories should not be given more often than every 4 hours.
If you are not sure how many suppositories to give your child, don’t guess, ask your child’s doctor or a pharmacist.
Do not give your child this medicine for more than 3 days, without speaking to your child’s doctor.
Do not give your child more suppositories than stated above.

How to use Paracetamol Suppositories
1. Your child’s bowels need to be empty when you give them this medicine. If your child needs to go to the toilet, make sure they do so before you give them the suppository.
2. You may find it easier to give your child the suppository if they are lying on their front or side. Do whichever is more comfortable for your child.
3. Wash your hands. Then peel the wrapping apart to remove the suppository. Do not break the suppository before use.
4. Gently push the suppository into your child’s back passage, pointed end first. Then wash your hands.
5. Try to keep your child still for a minute or two.
6. If your child needs to be given another suppository remove another one from the wrapper. Then insert it into your child’s back passage as before. Once again you should try to keep your child still for a minute or two. Then wash your hands.

If you forget to give Paracetamol Suppositories to your child
• Give them as soon as you remember, then go on as before.
• However, if it is almost time for the next dose, skip the missed dose.
• Do not give your child a double dose (two doses at the same time) next time, to make up for a forgotten dose.

If you give too many Paracetamol Suppositories to your child
• Do not give your child more suppositories than stated in the section called “How many Paracetamol Suppositories to give your child”.
• Immediate medical advice should be sought in the event of an overdose, even if the child seems well, because of the risk of delayed, serious liver damage

4. Possible side effects
Like all medicines, Paracetamol Suppositories can cause side effects, although not everybody gets them.
The following side effects can happen with this medicine.
• Redness or soreness in or around the back passage are common.
• Allergic reactions.
• Skin problems, such as a rash or itching.
• Blood problems. If these happen, your child may bruise or bleed more easily, get infection more easily, or get a high temperature (fever) and ulcers in the mouth and throat.
• Liver problems.
If your child gets any of the side effects mentioned above, or gets any side effects not mentioned in this leaflet, talk to your child’s doctor or pharmacist.

5. How to store Paracetamol Suppositories
• Keep this medicine out of the reach and sight of children.
• Do not store above 25°C and keep the blister strips in the outer carton.
• Do not use this medicine after the expiry date which is stated on the carton and blister. The expiry date refers to the last day of that month.
• Return any unused suppositories to the pharmacist, unless your child’s doctor has told you to keep them.

6. Further Information
What Paracetamol Suppositories contain - The active substance is paracetamol. The other ingredients are hard fat, mctigrol oleate, lecithin and glycerol monostearate.
What Paracetamol Suppositories look like and the contents of the pack – A suppository is a small, torpedo shaped medicine which is inserted into the back passage (rectum). Each pack contains 10 white suppositories, each containing either 250mg or 500mg paracetamol.

Marketing Authorisation Holder and Manufacturer
The Marketing Authorisation is held by Phoenix Labs, Cahill May Roberts, Phamapark, Chapelizod, Dublin 20, Ireland.
Paracetamol Suppositories are manufactured by RBF hasoox S.A., 51-131 Wodow, Poland.
This medicinal product is authorized in the member states of the EEA under the following names:
UK Paracetamol 250mg Suppositories / Paracetamol 500mg Suppositories
Ireland Paracetamol 250mg Suppositories / Paracetamol 500mg Suppositories
Leaflet Prepared: October 2010
© Phoenix Labs
Module 4
Labelling

Paracetamol 250mg Suppositories - PL 35104/0001

Carton and suppository blister
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Phoenix Labs Marketing Authorisations for the medicinal products Paracetamol 250mg and 500mg Suppositories (PL 35104/0001-2; UK/H/3781/01-02/DC) on 15th November 2010. The products are P licensed medicines.

The applications were submitted as abridged, bibliographic applications, for an active of well-established use, according to Article 10(a) of Directive 2001/83/EC, as amended.

Paracetamol 250mg and 500mg Suppositories are indicated for the treatment of mild to moderate pain and fever in children from the age of 6 years. Paracetamol suppositories may be especially useful in patients unable to take oral forms of paracetamol e.g. post-operative patients or patients with nausea and/or vomiting.

Paracetamol is an aniline derivative (ATC code: N02B E01) with analgesic and antipyretic actions similar to those of aspirin but with no demonstrable anti-inflammatory activity. It does not affect thrombocyte aggregation or bleeding time. Paracetamol is generally well-tolerated by patients hypersensitive to acetylsalicylic acid. It produces analgesia by elevation of the pain threshold and antipyresis through action on the hypothalamic heat-regulation centre.

No new non-clinical or clinical efficacy studies were conducted for these applications, which is acceptable given that these were bibliographic applications for products containing an active of well-established use.

The Reference Member State (RMS) has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP). The risk management for paracetamol is adequately controlled by the product information and through the pharmacovigilance activities detailed in the PhVS. There are no ongoing safety concerns with this well-established active that require additional risk-management activities.

The Marketing Authorisation Holder has provided adequate justification for not submitting a detailed Environmental Risk Assessment (ERA). It is not considered that these medicinal products represent any risk to the environment. There are no environmental concerns associated with the method of manufacture or formulation of the products.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Paracetamol 250mg Suppositories  
Paracetamol 500mg Suppositories |
<table>
<thead>
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<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Paracetamol</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Anilides (N02B E01)</td>
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<td>Pharmaceutical form and strength(s)</td>
<td>Suppositories 250mg and 500mg</td>
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<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/3781/01-01/DC</td>
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<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Ireland</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 35104/0001-2</td>
</tr>
</tbody>
</table>
| Name and address of the authorisation holder      | Phoenix Labs  
Pharmapark  
Cahill May Roberts  
Chapelizod  
Dublin 20  
Ireland |
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

ACTIVE SUBSTANCE

Paracetamol

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

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H3C              OH
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Molecular formula:  C$_8$H$_9$NO$_2$
Molecular weight:  151.2 g/mol
CAS No:  103-90-2
Physical form:  A white or almost white, crystalline powder
Solubility:  Sparingly soluble in water, freely soluble in alcohol and very slightly soluble in methylene chloride

The active substance, paracetamol, is the subject of a European Pharmacopeia (Ph. Eur.) monograph.

All aspects of the manufacture and control of paracetamol are supported by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability (CEP). The certificate is accepted as confirmation of the suitability of paracetamol for inclusion in these medicinal products.

The Certificate of Suitability specifies that the retest period of the active substance is 5 years if stored in a polyethylene liner placed inside a fibre drum.
PARACETAMOL 250mg and 500mg Suppositories

MEDICINAL PRODUCT

Description and Composition
Paracetamol 250mg and 500mg Suppositories are presented as white, torpedo-shaped suppositories containing 250mg or 500mg of the active ingredient, paracetamol.

Other ingredients consist of pharmaceutical excipients, namely hard fat, macrogol cetostearyl ether and glyceryl ricinoleate. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs, with the exception of glyceryl ricinoleate, which complies with satisfactory in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed products. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used and no overages.

Pharmaceutical development
Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The objective was to obtain a simple paracetamol suppository formulation using minimum excipients whilst ensuring that the products met their specifications both at release and shelf life.

Comparative dissolution data were provided for batches of the test products and appropriate reference originator products. The dissolution profiles were satisfactory.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies were conducted and validation data provided for both the 250mg and 500mg strength products and the results were satisfactory.

Finished product specification
The finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided for both strengths of the medicinal product, and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System
The medicinal products are licensed for marketing in pack sizes of 10 suppositories packed in white / opaque PVC / PE film blisters. Each suppository is packed separately. Due to the perforations of the welds, an individual suppository can be torn out. Two strips, each containing five suppositories, are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons.
Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. Storage instructions are ‘Do not store above 25°C. Store in the original package’. The suppository should only be removed from the blister packaging immediately before use.

**Bioequivalence Study**


**Quality Overall Summary**

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

**Product Information**

The approved Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL), and labelling are satisfactory. Mock-ups of the PIL and labelling have been provided. The labelling fulfils the statutory requirements for Braille. The PIL user testing report has been evaluated and is accepted.

**Conclusion**

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. There are no objections to approval of Paracetamol 250mg and 500mg Suppositories from a pharmaceutical point of view.
III.2 NON-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable considering that these were bibliographic applications for products containing an active of well-established use. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic, and toxicological properties of paracetamol, a widely used and well-known active substance. The overview, dated August 2009, cites approximately 114 references from the published literature dated up to 2009. The CV of the non-clinical expert has been supplied.

There are no objections to approval of Paracetamol 250mg and 500mg Suppositories from a non-clinical point of view.

III.3 CLINICAL ASPECTS

BACKGROUND

Paracetamol, a para-aminophenol derivative is a non-opiate analgesic. Its mechanism of action is not completely understood, but it is known that it inhibits synthesis of prostaglandins in the central nervous system. Its primary target is enzyme cyclooxygenase.

Paracetamol has analgesic and antipyretic properties but only a weak anti-inflammatory activity. It does not affect thromboocyte aggregation and bleeding time.

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 10 to 60 minutes after oral doses. Paracetamol is distributed into most body tissues. It crosses the placenta and can be found in breast milk. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations. Paracetamol is metabolised mainly in the liver and excreted in the urine mainly as the glucuronide and sulfate conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life of paracetamol varies from about 1 to 3 hours.

Paracetamol is given orally or as a rectal suppository for mild to moderate pain and for fever. It may also be given by intravenous infusion for the short-term treatment of moderate pain, particularly after surgery, and of fever. Being less irritant to the stomach than aspirin, paracetamol is often the analgesic or antipyretic of choice, especially in the elderly and in patients in whom salicylates or other Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are contra-indicated.

The usual oral dose is 0.5 to 1 g every 4 to 6 hours up to a maximum of 4 g daily. Paracetamol may be given as suppositories in a rectal dose of 0.5 to 1 g every 4 to 6 hours, up to 4 times daily. Paracetamol is also given by intravenous infusion over 15 minutes: patients weighing over 50 kg - single doses of 1 g every 4 or more hours, to a maximum of 4 g daily; from 33 to 50 kg - single doses of 15 mg/kg every 4 or more hours, to a maximum of 60 mg/kg or 3 g daily (whichever is less).

Adverse effects of paracetamol are rare and usually mild, although haematological reactions including thrombocytopenia, leucopenia, pancytopenia, neutropenia, and agranulocytosis have been reported. Skin rashes and other hypersensitivity reactions occur occasionally. Hypotension has been reported rarely with parenteral use.

Overdose with paracetamol can result in severe liver damage and sometimes acute renal tubular necrosis. Prompt treatment with acetylcysteine or methionine is essential.
Pharmacokinetic studies in 12 nursing mothers given a single dose of paracetamol showed that peak paracetamol concentrations in breast milk of 10 to 15 micrograms/ml were achieved in 1 to 2 hours. No adverse effects have been seen in breast-fed infants whose mothers were receiving paracetamol, and the American Academy of Paediatrics considers that it is compatible with breast feeding. The BNF also considers that the amount of paracetamol distributed into breast milk is too small to be harmful to a breast-fed infant.

INDICATIONS
Paracetamol 250mg and 500mg Suppositories are indicated for the treatment of mild to moderate pain and fever in children from the age of 6 years. Paracetamol suppositories may be especially useful in patients unable to take oral forms of paracetamol e.g. post-operative patients or patients with nausea and/or vomiting.

The indications are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION
The proposed doses (section 4.2 of the SmPCs) are:

For 250mg suppository:
Children aged 6-9 years (20 – 30kg): 1 suppository
Children aged 10-12 years (30 – 40kg): 1-2 suppositories

For 500mg suppository:
Children aged 10-12 years (30 – 40kg): 1 suppository
12 years and over: 1-2 suppositories

The SmPCs also instruct that these doses may be repeated up to a maximum of 4 times in 24 hours and that the dose should not be repeated more frequently than every 4 hours. The products should not be used for more than 3 days, except on the advice of a doctor.

The indications and posology, as proposed in the SmPCs, are in line with other similar products on the UK market and are fully supported by the submitted bibliographic evidence.

TOXICOLOGY
The toxicology of paracetamol is well-known. No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY
Pharmacodynamics
The pharmacodynamics of paracetamol are well-characterised and have been adequately reviewed. No new pharmacodynamic data have been supplied and none are required for this type of application.

Pharmacokinetics
These are bibliographic applications and several references to published literature citing the well-established use of paracetamol and pharmacokinetic studies using paracetamol suppositories have been presented. Original non-clinical and clinical trial studies have not been carried out with the proposed products. Bioequivalence studies are not necessary to support these bibliographic applications.
While most of the pharmacokinetics of paracetamol is well-known, of particular interest for these applications is absorption and bioequivalence of the suppositories compared to the wider used oral preparations as well as the dose equivalence between two preparations. The applicant provided the following statements in that respect. The names of the publications which they quoted as evidence to the statements are enclosed in the square brackets:

In an open study involving 18 healthy volunteers carried out at the Central Laboratory of German Pharmacists (Zentrallaboratorium Deutscher Apotheker) in Germany, Blume et al. found that relative bioavailability of paracetamol suppositories (Benuron suppositories 125 mg and 250 mg) in comparison to tablets (Benuron tablets 500 mg) is 102% and 93% for 125 mg and 250 mg suppositories, respectively. Mean maximum paracetamol serum concentrations were determined as 2.1 μg/ml, 2.0 μg/ml and 3.5 μg/ml after administration of 125 mg suppository, 250 mg suppository and 500 mg cut-in-half tablet, respectively [Blume H, Ali SL, Elze M, Krämer J, Scholtz ME. The relative bioavailability of paracetamol in suppositories in comparison to tablets. Arzneimittelforschung. 1996; 46, 975-80].

In an open study involving 10 healthy volunteers, Kollöffel et al. (1996) compared bioavailability of paracetamol suspension and rectal suppositories at the dose of 1000 mg. It was found that the absorption of the oral suspension is better because Tmax is shorter, Cmax is higher and area under the curve is larger. [Kollöffel WJ, Driessen FG, Goldhoorn PB. Plasma concentration profiles after preoperative rectal administration of a solution of paracetamol in children. Pharm World Sci. 1996; 18: 105-8].

A study by Feldman determined relative bioavailability of paracetamol from three suppository formulations compared to oral tablets. The author revealed that bioavailability of paracetamol from suppositories is highly variable. [Feldman S. Bioavailability of acetaminophen suppositories. Am J Hospital Society. 1975; 32: 1173-5].


Studies performed in adults show that, after rectal administration, bioavailability of the drug is not dose-dependent and is lower in comparison to oral administration. It is about 30 to 40%. [Eandi M, Viano I, Ricci Gamalero S. Absolute bioavailability of paracetamol after oral or rectal administration in healthy volunteers. Arzneimittelforschung. 1984; 34(8): 903-7].

The approximate absorption half-life after rectal administration is about 35 min in children. It is deemed that the total bioavailability of paracetamol in rectal suppositories ranges from 30-40% which is the equivalent of about 0.54 oral dose but serum concentrations can be very variable and unpredictable, even in the same patient [Anderson BJ, Holford NH, Woollard GA, Kanagasundaram S, Mahadevan M. Perioperative pharmacodynamics of acetaminophen analgesia in children. Anesthesiology. 1999; 90: 411-21].

In a study by Montgomery, 10 children who underwent minor surgery received a single 650 mg paracetamol suppository. It was established that the absorption is erratic and delayed. [Montgomery CJ, McCormack JP, Reichert CC, Marsland CP. Plasma concentrations after high-dose (45 mg kg-1) rectal acetaminophen in children. Can J Anaesth. 1995; 42: 982-6].

Paracetamol is well-absorbed after rectal administration and reaches the maximum plasma concentration about 2-3 hours after administration [Ibáñez Y, Rodríguez JM, Luján M, Grattan TJ, Martin AJ, Burnett I. A pharmacokinetic study investigating the rate of absorption of a 500 mg dose of a rapidly absorbed paracetamol tablet and a standard paracetamol tablet. Curr Med Res Opin. 2006 Oct; 22(10): 1893-7].


In children, the time to reach the maximum plasma concentration of the drug after rectal administration is similar to the maximum time observed in adults [Dordoni B, Willson RA, Thompson RP, Williams R. Reduction of absorption of paracetamol by activated charcoal and cholestyramine: a possible therapeutic measure. Br Med J. 1973; 3: 86-7].

It is suggested that the maximum serum concentration of paracetamol is the main determinant of the efficacy (a concentration of 10 μg/ml is required for analgesia). The maximum serum concentrations after oral, rectal and intravenous administration are reached within 60 min, 180 min and 40 min, respectively [Livingstone HL, Marcus RJ. Which preparation of paracetamol? An audit of usage and costs. Paediatr Anaesth. 2007 Oct; 17(10): 1009-10].


In adults, the maximum serum concentration of paracetamol administered at doses of 25, 35 and 45 mg/kg bw were 12.5, 16.5 and 20 μg/ml, respectively [Chandrasekharan et al., 2002].

Mean paracetamol concentrations of 5.5, 8.8 and 14.2 μg/ml in children were reached after rectal administration of doses of 10, 20 and 30 mg/kg, respectively [Eguia L, Materson BJ. Acetaminophen-related acute renal failure without fulminant liver failure. Pharmacotherapy. 1997 Mar-Apr; 17(2): 363-70].

After enema with 20 mg/kg acetaminophen in children, plasma concentration of the drug was 11 μg/ml [Dargan PI, Jones AL. Management of paracetamol poisoning. Trends Pharmacol Sci. 2003; 24: 154-7].
In a randomized study by Birmingham et al., after induction of anaesthesia children received a single rectal dose of paracetamol: 10, 20 or 30 mg/kg. Paracetamol concentration in venous blood was determined every 30 min in order to define its pharmacokinetic properties. The authors recommend that the rectal dose of paracetamol should be 40 mg/kg [Birmingham PK, Tobin MJ, Henthorn TK, Fisher DM, Berkelhamer MC, Smith FA, Fanta KB, Coté CJ. Twenty-four-hour pharmacokinetics of rectal acetaminophen in children: an old drug with new recommendations. Anesthesiology. 1997; 87: 244-52].

Pharmacokinetic conclusions
Overall, the evidence from these publications can be accepted as sufficient. The quoted publications demonstrate that paracetamol is less bioavailable when given as suppository than as an oral preparation. There is evidence of higher variability in absorption of suppositories compared to the oral preparations. Several quoted papers deal with the equivalence of the dose between oral and rectal preparations. Possible differences in pharmacokinetics in adults and children are also addressed (e.g. Hansen at al. 1999). The applicant has taken these into consideration when proposing posology for the products.

The products do not contain any unusual excipients and the quoted references can be regarded as relevant for the pharmacokinetics of the products. The information provided and related discussion is, therefore, appropriate and sufficient.

CLINICAL EFFICACY & SAFETY
No new data have been submitted and none are required for applications of this type. The safety and efficacy of paracetamol is well-known including the safety and efficacy in the target population and the applicant quotes a number of publications to support their claims. The provided information on safety and efficacy of the products is appropriate and sufficient. No new or unexpected safety concerns arise from these applications.

PRODUCT INFORMATION:
Summary of Product Characteristics (SmPC)
The approved SmPCs are satisfactory.

Patient Information Leaflet
The final PIL is in line with the approved SmPCs and is satisfactory.

Labelling
The labelling is satisfactory.

Clinical overview
To support the application, the company has presented and discussed in their clinical overview 174 publications relating to the use of paracetamol and paracetamol suppositories. A number of submitted papers also address the use of paracetamol in children as well as use of paracetamol suppositories in children.

The clinical overview is satisfactory and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

CONCLUSIONS
Sufficient clinical information has been submitted to support these applications. The risk-benefit of the products is considered favourable from a clinical perspective. The grant of Marketing Authorisations was therefore recommended on medical grounds.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Paracetamol 250mg and 500mg 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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type. A non-clinical overview has been provided by an appropriately qualified person, and consists of a review of the published literature.

EFFICACY
No new data are submitted and none are required for this type of application.

The published literature supports the efficacy of these products in the proposed indications. The safety and efficacy of paracetamol is well-known, including the safety and efficacy in the target population. The presented evidence for well-established use of the active substance and its use in the product formulation, as well as its use in the target population, is sufficient.

The literature review identifies no new safety issues or concerns. The safety profile of paracetamol is well-known.

PRODUCT LITERATURE
The approved SmPCs are satisfactory.

The PIL is in line with the SmPCs and is satisfactory. 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 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.

Mock-ups of the labelling have been provided. The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Paracetamol is an active substance of well-known safety and efficacy. It has been used for a number of decades in the EU. Paracetamol has also been used in suppositories in the target population in the EU for a number of decades. The benefit: risk balance for these products is, therefore, comparable to that of the similar products which are already available on the market.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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