Public Assessment Report

Decentralised Procedure

Paracetamol 80 mg Suppositories
Paracetamol 125 mg Suppositories

UK/H/4804/001-2/DC

UK licence no: PL 35104/0003-4

Applicant: Phoenix Labs
LAY SUMMARY

The MHRA granted Phoenix Labs Marketing Authorisations (licences) for the medicinal products Paracetamol 80 mg and 125 mg Suppositories (PL 35104/0003-4) on 17 January 2012. 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 80 mg and 125 mg Suppositories are used to treat mild to moderate pain and high temperature (fever) in babies (from the age of 3 months) and children from the age of 1 year respectively. 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 80 mg and 125 mg Suppositories outweigh the risks; hence Marketing Authorisations have been granted.
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Module 1

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<td>125 mg</td>
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<tr>
<td>MA Holder</td>
<td>Phoenix Labs, Pharmapark, Chapelizod, Dublin 20, Ireland</td>
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<tr>
<td>Reference Member</td>
<td>UK</td>
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<tr>
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<td>Procedure Number</td>
<td>UK/H/4804/001-2/DC</td>
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<tr>
<td>End of Procedure</td>
<td>14 December 2011</td>
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Module 2
Summary of Product Characteristics

The UK Summary of Product Characteristics (SPC) for Paracetamol 80 mg and 125 mg Suppositories (PL 35104/0003-4) is as follows:
Differences between the two SmPCs are highlighted in yellow.

1 NAME OF THE MEDICINAL PRODUCT
Paracetamol 80mg Suppositories
Paracetamol 125mg Suppositories

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each suppository contains 80mg/ 250 mg 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
Paracetamol 80mg Suppositories
For the treatment of mild to moderate pain and fever in babies and children from the age of 3 months.

Paracetamol 125mg Suppositories
For the treatment of mild to moderate pain and fever in babies and children from the age of one year.

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

Paracetamol 80mg Suppositories
Dosage should be based on the child’s weight, with a recommended dosage of 15mg/kg per administration. Ages presented below are provided as an accompanying guide only.

3 – 12 months (5kg): One suppository

Paracetamol 125mg Suppositories
Dosage should be based on the child’s weight, with a recommended dosage of 15mg/kg per administration. Ages and weight ranges presented below are provided as an accompanying guide only.

1 – 3 years (10kg): One suppository
4 – 6 years (15kg): Two suppositories

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.

Hepatic / renal dysfunction
Caution should be exercised when administering the product to patients with severe hepatic or renal impairment.

4.3 Contraindications
Hypersensitivity to paracetamol or to any of the excipients listed in section 6.1.
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 Fertility, pregnancy and lactation

Fertility: There are no data on the effects of paracetamol suppositories on human fertility. Fertility was unaffected following paracetamol treatment in animal studies (see section 5.3).

Pregnancy: 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.

Lactation: 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

<table>
<thead>
<tr>
<th>Common</th>
<th>≥1/100 to &lt;1/10</th>
<th>Miscellaneous</th>
<th>Redness or soreness of the rectal mucous membrane</th>
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<tr>
<td>Rare</td>
<td>≥1/10,000 to &lt;1/1,000</td>
<td>General</td>
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<tr>
<td></td>
<td></td>
<td>Skin</td>
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<td></td>
<td></td>
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There have been reports of blood dyscrasias including thromocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.
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
a. Is on long term treatment with carabamazepine, 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 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.

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.

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 and other handling
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 35104/0003
PL 35104/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
17/01/2012

10 DATE OF REVISION OF THE TEXT
17/01/2012
Module 3  
Patient Information Leaflet

Information for the user

FOR RECTAL ADMINISTRATION ONLY

Paracetamol 80mg 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 they are 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 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 babies and children from the age of 3 months. 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
3 to 12 months: One suppository
This dose 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.
Common (affects more than 1 in 100 people)
• Redness or soreness in or around the back passage.
Rare (affects less than 1 in 1,000 people)
• 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.
• Do not remove the suppositories from the blister until immediately before use.
• 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, macrogol cetostearyl ether and glyceryl ricinoleate.
• 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 80mg paracetamol.

Marketing Authorisation Holder and Manufacturer
This Marketing Authorisation is held by Phoenix Labs, Cahill May Roberts, Phasmepark, Chapelizod, Dublin 20, Ireland.
Paracetamol Suppositories are manufactured by PPF/Hexal-LEK S.A., 51-131 Wojska, Poland.
This medicinal product is authorised in the Member States of the EEA under the following names:
UK Paracetamol 80mg Suppositories
Ireland Paracetamol 80mg Suppositories

Leaflet Prepared: 12/2011
© Phoenix Labs
PAR-Paracetamol 80mg and 125mg Suppositories

PHOENIX LABS

Information for the user

FOR RECTAL ADMINISTRATION ONLY

Paracetamol 125mg 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 they are 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 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 babies and children from the age of 1 year. 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
1 to 3 years: One suppository
4 to 6 years: Two suppositories

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.
Common (affects more than 1 in 100 people)
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Rare (affects less than 1 in 1,000 people)
• 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.
• Do not remove the suppositories from the blister until immediately before use.
• 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, macrogol cetyl ester and glyceryl ricinoleate.
• 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 125mg paracetamol.
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
On 14 December 2011, Ireland and the UK agreed to grant Marketing Authorisations (MAs) to Phoenix Labs for the medicinal products Paracetamol 80 mg and 125 mg Suppositories. The MAs were granted via a Decentralised Procedure (DCP), with the UK as Reference Member State (RMS: UK/H/4804/001-2/DC). After the national phase, MAs were granted in the UK on 17 January 2012. These are pharmacy (P) licensed medicines available from pharmacies, under the supervision of a pharmacist.

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 80 mg and 125 mg are indicated for the treatment of mild to moderate pain and fever in babies and children from the age of 3 months and one year respectively. 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 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 necessary for these applications, which is acceptable given that these were bibliographic applications for products containing an active of well-established use. Bioequivalence studies are not necessary to support these bibliographic applications.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types 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.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person 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 Marketing Authorisation holder (MAH) has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional minimisation have not been identified, routine pharmacovigilance activities are proposed and
a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well-established.

The MAH has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). These applications have been submitted under well-established use; it is not expected that the environmental exposure to paracetamol will increase following the marketing approval of the proposed products.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Paracetamol 80 mg Suppositories  
| Paracetamol 125 mg Suppositories |
| Name(s) of the active substance(s) (INN) | Paracetamol |
| Pharmacothereapeutic classification (ATC code) | N02BE01 |
| Pharmaceutical form and strength(s) | Suppository 80 & 125 mg |
| Reference numbers for the Mutual Recognition Procedure | UK/H/4804/01-02/DC |
| Reference Member State | United Kingdom |
| Member States concerned | Ireland |
| Marketing Authorisation Number(s) | PL 35104/0003  
| PL 35104/0004 |
| Name and address of the authorisation holder | Phoenix Labs, Phimapark, Chapelizod, Dublin 20, Ireland |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

rINN name: Paracetamol

Chemical name: N-(4-hydroxyphenyl)ethanamide

Molecular formula: C₈H₉NO₂

Molecular weight: 151.2g/mol

Structure

![Structure of Paracetamol](image)

General properties

Description:
A white or almost white crystalline powder.

Solubility:
Sparingly soluble in water, freely soluble in alcohol, and very slightly soluble in methylene chloride.

Paracetamol is the subject of a European Pharmacopoeia (Eur Ph.) monograph.

Manufacture

All aspects of the manufacture and control of the active substance paracetamol are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

The active substance is stored in appropriate packaging. Satisfactory specifications have been provided for the packaging materials used. The primary packaging in direct contact with the active substance complies with relevant Ph.Eur. requirements and complies with Directive 2002/72/EC (as amended) and is suitable for contact with foodstuffs.

DRUG PRODUCT

Description and Composition

The drug products are presented as white, torpedo shaped suppositories. Each suppository contains 80 mg or 125 mg respectively for the different strengths of the product.

Other ingredients consist of pharmaceutical excipients, hard fat, macrogol cetostearyl ether and glyceryl ricinoleate. All the ingredients in the suppositories comply with their relevant Ph.Eur monograph, with the exception of glyceryl ricinoleate, which complies with satisfactory in-house specifications. Appropriate justification for the inclusion of each of the excipients has been provided. Satisfactory Certificates of Analysis for each of the excipients
have been presented. The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in the product, or used in the manufacturing process. Furthermore, no genetically modified organisms are used in the manufacture of the excipients.

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

**In vitro Dissolution Studies**
These are bibliographic applications and no clinical or non clinical data has been submitted. The dissolution test is used here to identify formulation factors that are influencing and may have a crucial effect on the bioavailability of the active ingredient in the drug product.

Reference is made to the dissolution method developed for 250 mg and 500 mg paracetamol. It is proposed to use it across the product range, from 80 mg to 500 mg.

The dissolution method developed for paracetamol suppositories 250 mg and 500 mg, was assessed as part of the pharmaceutical development of these dosages and it was considered acceptable.

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are accepted. The validation data demonstrated consistency of the manufacturing process.

**Finished Product Specification**
Finished product specifications are provided for both release and shelf-life, and are satisfactory; they provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and adequately validated, as appropriate. Satisfactory batch analysis data are provided 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 polyvinylchloride (PVC)/polyethylene (PE) blister strips. Each suppository is packed separately. Due to the perforations of the welds, an individual suppository can be torn out. Two blister strips, each containing five suppositories, are placed 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).
Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been approved. Storage conditions are “Do not store above 25°C”.

**Bioequivalence Study**

**Quality Overall Summary**
A satisfactory quality overall summary is provided and has been prepared by an appropriately qualified expert. The *curriculum vita* of the expert *has* been provided.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC, PIL and labelling are pharmaceutically acceptable. Colour mock-ups of the labelling and PIL have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test show that the patients/users are able to act upon the information that is contains.

**MAA Form**
The MAA forms are pharmaceutically satisfactory.

**Conclusion**
There are no objections to the approval of Paracetamol 80 mg and 125 mg Suppositories from a pharmaceutical point of view.

**III.2 NON-CLINICAL ASPECTS**
The pharmacodynamic, pharmacokinetic and toxicological properties of paracetamol are well-known. Therefore, no further studies are required and the applicant has provided none. An overview based on the literature is thus appropriate.

**ENVIRONMENTAL RISK ASSESSMENT (ERA)**
The applicant has provided a proper justification for not performing an environmental risk assessment in accordance with the guideline (CHMP/SWP/4447/00).

**NON-CLINICAL OVERVIEW**
The non-clinical overall summary was written by a suitably qualified person and is satisfactory. The *curriculum vita* of the expert has been provided.

**SUMMARY OF PRODUCT CHARACTERISTICS (SmPCs)**
Section 4.6 and 5.3 are satisfactory from a non-clinical viewpoint.

There are no objections to the approval of Paracetamol 80 mg and 125 mg Suppositories from a non-clinical point of view.

**III.3 CLINICAL ASPECTS**
These applications are based on Article 10a of Directive 2001/83/EC as amended, since paracetamol has a well-established use in the claimed indications.
No new biopharmaceutic or clinical pharmacology data has been presented by the applicant for the paediatric doses. Several recent publications concerning the safety and efficacy of paracetamol have been reviewed in the clinical overview, and are appraised in this report.

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 centre.

Paracetamol Suppositories are indicated for the treatment of mild to moderate pain and fever in children over 3 months old. They 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.

**CLINICAL PHARMACOLOGY**

**Biopharmaceutics**

Paracetamol suppositories have been available without prescription for a number of years in Europe and the USA.

After oral administration, paracetamol is rapidly absorbed from the small intestine and its bioavailability ranges from 60% (after the dose of 500 mg) to 90% (after 1 g). After rectal administration, bioavailability is usually lower, determined as 2/3 availability after oral administration. Moreover, in contrast with the oral route, bioavailability is higher after 500 mg than after 1 g. In an open study involving 18 healthy volunteers carried out at the Central Laboratory of German Pharmacists in Germany, Blume et al. found that relative bioavailability of paracetamol suppositories (125 mg and 250 mg) in comparison to tablets (500 mg) was 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. 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 T<sub>max</sub> is shorter, C<sub>max</sub> is higher and area under the curve is larger.

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. In a randomized study by Birmingham et al. an effective dose of paracetamol administered in rectal suppositories was determined. The study involved 28 children divided into 3 groups that received a single dose of 10, 20 or 30 mg/kg of paracetamol, respectively, in a suppository. It was established that the recommended dose of paracetamol administered rectally should be 40 mg/kg. 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.

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%. T<sub>1/2</sub> of absorption after p.r. administration is 35 min.

**Pharmacokinetics**

**Absorption**
Paracetamol is well absorbed after rectal administration and reaches the maximum plasma concentration about 2-3 hours after administration. Patients who do not tolerate oral paracetamol or small children can receive the drug rectally but higher doses of paracetamol are necessary to obtain comparable serum concentrations. 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. Clinical studies show that the absorption rates of paracetamol in rectal suppositories is variable. In a randomized study by Birmingham et al., after induction of anaesthesia children received a single rectal dose of PAR: 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. In a study by Andersen et al., the absorption t1/2 in children was 4.5 min after p.o. administration of liquid paracetamol. 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.

**Distribution**

Paracetamol is distributed to most body tissues. Protein binding of paracetamol is low. The degree of binding to blood proteins increases with increasing plasma concentrations of paracetamol.

Paracetamol is very slightly soluble in fats. Penetration into body fluids and internal organs is good, rapid and even. The volume of distribution of paracetamol is estimated at 59.9-71.8 l (about 1.0 l/kg). Plasma protein binding of paracetamol is low (about 25% at therapeutic concentrations), and is higher at higher doses. The maximum serum concentration of paracetamol is reached within 1-2 h after oral administration and within a wide range from 1 to 4 h after rectal administration. Serum half-life (T1/2) of paracetamol is 1-4 h (1-2.5 h in healthy adults). Bioavailability of paracetamol is from about 68% for the dose of 0.5 g, up to about 90% for 1.0-2.0 g. The volume of distribution in the body is 0.7 l/kg in children and 1 to 2 l/kg in adults.

**Metabolism**

Paracetamol is metabolized predominantly (about 95%) in the liver by conjugation with glucuronic acid and cysteine. Hepatotoxic intermediate metabolite N-acetyl-p-benzoquinone imine, which is produced in small amounts, rapidly undergoes conjugation with reduced glutathione and is excreted in the urine after conjugation with cysteine and mercapturic acid. After high doses of paracetamol the reserves of hepatic glutathione can become depleted. As a consequence, the toxic metabolite accumulates in the liver, which may result in hepatocyte damage or necrosis, and acute hepatic failure. Paracetamol is metabolised in the liver by multiple pathways, primarily to glucuronides (about 60%) and sulphates (about 35%). Paracetamol causes the induction of hepatic microsomal enzymes. A third pathway for hepatic transformation involves cytochrome P450-catalyzed formation of N-acetyl-p-benzoquinone imine, a reactive intermediate product that may be reduced back to paracetamol with the participation of NADPH or detoxified by conjugation with glutathione. The biotransformation process is similar in older children and in adults, while in newborns and infants, the insufficient conjugation with glucuronic acid is balanced by an increased binding to sulphuric acid.

**Excretion**
Paracetamol is excreted mainly in the urine as metabolites: glucuronates, sulphates and products of cysteine conjugation, with 85-100% of an ingested dose excreted in the urine within 24 hours, including less than 3-5% excreted as the parent compound. Large amounts of glucuronide and sulphhydryl metabolites are initially excreted in the urine, but glucuronates are hydrolysed to the parent compound and glutathione derivatives are transformed into 3-cysteinyl derivative by GGTP.

At therapeutic doses, about 45-55% of the total oral dose was excreted by healthy volunteers as glucuronates, 20-30% as sulphuric acid conjugates and 15-25% as mercapturic acid conjugates.

Biological half-life (t1/2) of paracetamol ranges from 1 to 4 hours and can be prolonged after toxic doses or in persons with hepatic failure, whereas renal failure does not change T1/2 of acetaminophen. Mean biological half-life of the drug in newborns between 28 and 32 weeks of age was 11 hours, and between 32 and 36 weeks of age was shorter, i.e. 4-5 hours. According to other authors, differences in biological half-life of paracetamol in newborns, children and adults were not observed.

**Pharmacodynamics**

The mechanism of action of paracetamol has not been fully identified. Most probably paracetamol inhibits specific cyclooxygenase isoenzyme in the central nervous system. The ability of paracetamol to inhibit prostaglandin biosynthesis in the central nervous system has been confirmed in many reports. Some authors attribute the action of paracetamol to a cyclooxygenase variant termed COX-3.

**Conclusions on Clinical Pharmacology**

The clinical overview contains an adequate summary of the clinical pharmacology of paracetamol suppositories. Rectally administered paracetamol has a lower bioavailability than oral paracetamol, and the variability within patients is wide. In addition Cmax is lower and Tmax is higher for rectal paracetamol than for oral formulations.

**CLINICAL EFFICACY**

The clinical studies presented in support of these applications have been previously assessed by the relevant authorities within the European Union where these products are approved. No new clinical data have been submitted.

**Antipyretic Action**

Antipyretic drugs, including paracetamol, have central effects. There is extensive evidence that increased body temperature does not have negative effects, and supports the immune system, which is a serious argument against clinically unjustified use of antipyretic drugs. The arguments for the use of the drugs include: no relationship between the type of fever and type of infection, no data on the effect of antipyretic drugs on the duration of disease and prevention of adverse consequences of prolonged fever, such as weakness or wasting. In practice fever is reduced to improve general condition of a patient and accelerate recovery. The next indication for use of antipyretics in children is prevention of febrile convulsions. There is no convincing evidence of the efficacy of the prevention of convulsions but this is a generally accepted procedure before preventive vaccination, recommended e.g. by the American Academy of Paediatrics. Antipyretic efficacy of paracetamol in children has been documented in more than 30 recent clinical studies (i.e. conducted after 1976), in the majority of cases performed as double-blind, placebo-controlled studies.

The therapeutic concentrations of paracetamol measured in the plasma in respect of the antipyretic effect ranges from 10 to 20 μg/ml [Brown et al., 1992], while the therapeutic concentration of the drug in respect of the analgesic effect has not been precisely defined. It
is considered that therapeutic range for analgesia coincides with the range for antipyresis [Chandrasekharan et al., 2002; EMEA, 1999]. Oral dose of 15 mg/kg, rectal dose of 15 mg/kg and high rectal dose of 35 mg/kg paracetamol show similar antipyretic effects.

**Analgesic Activity**
The analgesic effects of oral paracetamol are well recognised. Several studies have confirmed that rectal suppositories show similar efficacy in children (eg, Owczarzak et al., 2006). The target analgesic dose is considered to be 10-15 mg/kg.

**Conclusions on Clinical Efficacy**
No new data have been submitted. Paracetamol products have been used extensively in practice across the EU for over 60 years with accepted efficacy for the treatment of pain and fever. The efficacy of rectal paracetamol in adults and children is adequately summarised in the clinical overview.

**CLINICAL SAFETY**
The safety of paracetamol in the doses proposed has been adequately summarised in the clinical overview, and was reviewed as part of the initial approval for the 250 and 500 mg formulations. The applicant has submitted an addendum to the clinical overview detailing recent publications concerning the safety of paracetamol. Those relevant to the use of paracetamol in children are reviewed below.

**Increased risk of asthma and associated atopic conditions**
Paracetamol use has been associated with an increased risk of asthma and other allergic conditions such as eczema and rhinoconjunctivitis. This is based upon a number of observational studies which have suggested an association between paracetamol use and the development of allergic disease in early childhood and adolescence. However there is an obvious confounding effect of childhood infections, which are independently linked to an increased risk of asthma. Some studies have shown that the association between paracetamol use and risk of allergic disease disappears when adjustments are made for the incidence of childhood infections. The association is further weakened by the nature of the evidence, coming from observational studies only, and by the lack of a plausible mechanism.

Evidence for this possible association has been reviewed by the Commission on Human Medicines’ Pharmacovigilance Expert Advisory Group in October 2008, and was considered to be insufficient to support such an association.

**Effectiveness of oral versus rectal paracetamol**
A 2001 report by the American Academy of Pediatrics highlights the variable pharmacokinetics of rectal paracetamol and recommends avoidance of rectal paracetamol “unless specifically discussed with the health care provider and that directions be followed”. A meta-analysis by Goldstein et al. in 2008 demonstrated comparable effectiveness of oral and rectal paracetamol, however there are numerous limitations with this study, in particular the inclusion of only three paediatric studies assessing antipyresis and one study assessing analgesia. It is considered that the rectal dose level of 15 mg/kg has an acceptable safety profile in children, and that a rectal formulation is of use in children unable to use oral medication.

**Risk of unintentional overdose of paracetamol due to inadequate understanding of patients**
A cross-sectional study by Hornsby et al. in 2003 showed that only one third of responders could identify the correct maximum dose of paracetamol, and 7% were unsure whether a maximum dose existed. This problem is further compounded in the dosing of children by
parents, when recommended doses vary by weight and age. This highlights the need for clear product labelling.

Interaction of paracetamol with warfarin which may potentially increase the risk of haemorrhage
It is known that use of paracetamol may enhance the anti-coagulatory effect of warfarin. The product labelling mentions this.

Immunomodulatory effects of paracetamol
A number of studies published recently have highlighted an immunomodulatory affect of paracetamol. There is some evidence that prophylactic use of paracetamol for post-vaccination fever may attenuate the antibody response to the vaccination. However, this evidence is considered preliminary at this stage.

Risk of liver and kidney damage at doses within the recommended therapeutic range
Heard et al conducted a study of the effect on liver function of paracetamol at the maximum recommended dose for a 10 day period 40. Patients included in the study were healthy volunteers without risk factors for liver damage, notably they reported consuming less than one drink of alcohol per day for the preceding 30 days. 58% of the patients developed a serum ALT (alanine aminotransferase) above the maximum normal level but serum bilirubin and INR were unaffected. This study suggests that even at a recommended dose in healthy patients the use of regular paracetamol over a relatively short period produces a measurable effect on liver function, however the implications of this are unclear. In contrast another similar study by the same group showed that a period of 5 days of paracetamol at the maximum recommended dose in patients who drink alcohol excessively did not produce a demonstrable negative effect on measures of liver function 41. However, these patients were newly abstinent from alcohol on entering the study which may have had a positive effect which outweighed the negative effect of paracetamol.

Case reports have suggested that liver injury may occur in children taking recommended doses of paracetamol, however a recent systematic review of defined population based studies suggested that the incidence of even minor hepatic adverse events with therapeutic dosing of paracetamol was only 0.031% and no major adverse events were discovered. A study has shown that use of paracetamol at therapeutic doses in patients with chronic renal failure led to an increased risk of end stage renal failure. A warning is included in the product labelling.

Conclusions on Clinical Safety
Paracetamol has been used in children for a long time with an acceptable safety profile. The recent adapt presented do not significantly alter this safety profile.

BENEFIT RISK ASSESSMENT
These applications contain an adequate review of published clinical data on the clinical pharmacology, efficacy and safety of rectal paracetamol in children. There are no objections to the approval of Paracetamol 80 mg and 125 mg Suppositories from a clinical point of view.

Expert Report
To support the application, the company has presented and discussed in their clinical overview the use of paracetamol and paracetamol suppositories. A number of papers also address the use of paracetamol in children as well as use of paracetamol suppositories in
children.

The clinical overall is satisfactory and has been prepared by an appropriately qualified physician. The *curriculum vitae* of the expert has been provided.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**

The SmPCs and PIL are medically acceptable. The labelling is medically acceptable and in-line with current requirements.

**MAA form**

The MAA forms are medically satisfactory.

**Conclusion**

Sufficient clinical information has been submitted to support these applications. There are no objections to approval of Paracetamol 80 mg and 125 mg Suppositories from a clinical point of view.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT QUALITY
The important quality characteristics of Paracetamol 80 mg and 125 mg 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.

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

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

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

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The approved SmPCs are 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. 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 labeling have been provided. The approved labeling 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 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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