Public Assessment Report

Decentralised Procedure

Paracetamol Adult 500mg/5ml Oral Suspension

UK/H/2489/001/DC
UK licence number: PL 00427/0160

Rosemont Pharmaceuticals Ltd
LAY SUMMARY

On 27 March 2012, the MHRA granted Rosemont Pharmaceuticals Ltd a Marketing Authorisation (licence) for the medicinal product, Paracetamol Adult 500mg/5ml Oral Suspension (PL 00427/0160). This is a prescription-only medicine (POM).

Paracetamol belongs to a group of medicines called painkillers and analgesics. This medicine is a higher strength paracetamol oral suspension. It is used for mild to moderate pain when you cannot take other paracetamol formulations such as lower strength liquid paracetamol, effervescent tablets or tablets.

No new or unexpected safety concerns arose from this application. It was judged that the benefits of Paracetamol Adult 500mg/5ml Oral Suspension outweigh the risks; hence a Marketing Authorisation has been granted.
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Module 1

Information about Initial Procedure

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<td>MA Holder</td>
<td>Rosemont Pharmaceuticals Ltd&lt;br&gt;Rosemont House&lt;br&gt;Yorkdale Industrial Park&lt;br&gt;Braithwaite Street&lt;br&gt;Leeds&lt;br&gt;LS11 9XE&lt;br&gt;UK</td>
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Module 2
Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPC) for Paracetamol Adult 500mg/5ml Oral Suspension (PL 00427/0160) is as follows:

1 NAME OF THE MEDICINAL PRODUCT
Paracetamol Adult 500mg/5ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 5ml contains 500mg Paracetamol

Excipients:
Methyl parahydroxybenzoate – 6mg/5ml
Propyl parahydroxybenzoate – 1.5mg/5ml
Liquid maltitol – 2.05g/5ml

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Oral suspension
An opaque, pink/brown suspension

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
For the treatment of mild to moderate pain in patients who are unable to receive other paracetamol formulations such as lower strength liquid preparations, effervescent tablets or tablets.

4.2 Posology and method of administration
For oral administration only

Adults and adolescents over 16 years: 500mg (5ml) or 1000mg (10ml) up to three to four times a day, as required. Maximum daily dose should not exceed 4g (40ml).

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

4.3 Contraindications
Hypersensitivity to paracetamol and/or other constituents.
Patients with severe hepatic dysfunction.

Do not use this medicine in children and adolescents under 16 years.

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

Do not take with any other paracetamol-containing products.

Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed serious or irreversible liver damage.

Do not exceed the recommended dose.
Keep out of the reach and sight of children.
Excipient warnings:
This product contains the following excipients:
Parahydroxybenzoates: these may cause allergic reactions (possibly delayed).
Liquid maltitol: patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
The hepatotoxicity of Paracetamol, particularly after overdosage, may be increased by drugs which
induce liver microsomal enzymes such as barbiturates, tricyclic antidepressants and alcohol.

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

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

Antivirals: Regular use of Paracetamol possibly reduces metabolism of Zidovudine (increased risk of
neutropenia).

4.6 Fertility, Pregnancy and lactation
Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the
recommended dosage, but patients should follow the advice of their doctor regarding its use.
Paracetamol is excreted in breast milk, but not in clinically significant quantities. Available published
data do not contraindicate breast feeding.

4.7 Effects on ability to drive and use machines
None

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

Cases of acute pancreatitis have been reported. Paracetamol has been widely used and reports of
adverse reactions are rare, and are generally associated with overdosage.

Allergic reactions occur occasionally.
Nephrotoxic effects are uncommon and have not been reported in association with therapeutic doses,
except after prolonged administration.

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

Risk factors
If the patient

a) Is on long term treatment with carbamazepine, phenobarbital, 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 depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation,
cachexia.
Symptoms
Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

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

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours 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 24 hours from ingestion should be discussed with the NPIIS or a liver unit.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Analgesics and antipyretics, Anilides
ATC Code: N02 BE01

The mechanism of analgesic action has not been fully determined. Paracetamol may act predominantly by inhibiting prostaglandin synthesis in the central nervous system (CNS) and, to a lesser extent, through a peripheral action by blocking pain impulse generation. The peripheral action may also be due to inhibition of prostaglandin synthesis or to inhibition of the synthesis or actions of other substances that sensitize pain receptors to mechanical or chemical stimulation.

Paracetamol probably produces antipyresis by acting centrally on the hypothalamic heat regulating centre to produce peripheral vaso-dilation resulting in increased blood flow through the skin, sweating and heat loss. The central action probably involves inhibition of prostaglandin synthesis in the hypothalamus.

5.2 Pharmacokinetic properties
Oral absorption is rapid and almost complete, it may be decreased if paracetamol is taken following a high carbohydrate meal.

There is no significant protein binding with doses producing plasma concentrations below 60mcg (µg)/ml, but may reach moderate levels with high or toxic doses.

Approximately 90 - 95% of a dose is metabolised in the liver, primarily by conjugation with glucuronic acid, sulphuric acid and cysteine. An intermediate metabolite, which may accumulate in overdosage after primary metabolic pathways become saturated, is hepatotoxic and possibly nephrotoxic.

Half life is 1 to 4 hours; does not change with renal failure but may be prolonged in acute overdosage, in some forms of hepatic disease, in the elderly, and in the neonate; may be somewhat shortened in children.

Time to peak concentration, 0.5 - 2 hours; peak plasma concentrations, 5 - 20mcg (µg)/ml (with doses up to 650mg); time to peak effect, 1 - 3 hours; duration of action, 3 - 4 hours.
Elimination is by the renal route, as metabolites, primarily conjugates, 3% of a dose may be excreted unchanged.

Peak concentrations of 10 - 15mcg (µg)/ml have been measured in breast milk, 1 - 2 hours following maternal ingestion of a single 650mg dose. Half life in breast milk is 1.35 - 3.5 hours.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Propylene glycol (E1520)
- Methyl parahydroxybenzoate (E218)
- Propyl parahydroxybenzoate (E216)
- Liquid maltitol (E965)
- Saccharin sodium
- Acesulfame potassium (E950)
- Sodium dihydrogen phosphate dihydrate
- Disodium hydrogen phosphate dihydrate
- Magnesium aluminium silicate
- Masking flavour (containing propylene glycol (E1520))
- Strawberry flavour (C9987) (containing propylene glycol (E1520))
- Purified water

6.2 Incompatibilities

In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

- 24 months
- 1 month once open

6.4 Special precautions for storage

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

6.5 Nature and contents of container

- Bottle: Amber (Type III) glass with capacity of 150ml.
- Closure: HDPE, EPE wadded, tamper evident, child resistant closure
- Syringe: Polypropylene body and plunger with a capacity of 5ml.
- Bottle adaptor: Low Density Polyethylene.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Rosemont Pharmaceuticals Ltd
Rosemont House
Yorkdale Industrial Park
Braithwaite Street
Leeds
LS11 9XE
UK
8 MARKETING AUTHORISATION NUMBER(S)
   PL 00427/0160

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   27/03/2012

10 DATE OF REVISION OF THE TEXT
    27/03/2012
Module 3

Patient Information Leaflet

Paracetamol Adult 500mg/5ml Oral Suspension

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again
- If you have any further questions, ask your doctor or pharmacist
- This medicine has been prescribed only for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours
- If any of these side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet
1. What Paracetamol Oral Suspension is and what it is used for
2. Before you take Paracetamol Oral Suspension
3. How to take Paracetamol Oral Suspension
4. Possible side effects
5. How to store Paracetamol Oral Suspension
6. Further information

1. What Paracetamol Oral Suspension is and what it is used for
Paracetamol belongs to a group of medicines called pain-killers or analgesics. This medicine is a higher strength Paracetamol Oral Suspension. It is used for mild to moderate pain when you cannot take other paracetamol formulations such as lower strength liquid paracetamol, effervescent tablets or tablets.

2. Before you take Paracetamol Oral Suspension
Do not take this medicine if you have:
- had an allergic reaction to paracetamol or any of the ingredients listed in section 6. An allergic reaction can include a rash, itching or shortness of breath
- a liver disorder.

This medicine should not be given to children or adolescents under the age of 16 years.

Do not take paracetamol if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking paracetamol.

Take special care with this medicine if you have:
- kidney problems
- liver problems, including those due to drinking too much alcohol.

You may be more at risk of the side effects of paracetamol. Speak to your doctor or pharmacist if any of these apply to you.

Taking other medicines
You must not take any other medicines that contain paracetamol while you are taking this medicine.
Tell your doctor if you are taking any of these medicines:
- barbiturates (sleeping tablets)
- tricyclic antidepressants (such as amitriptyline)
- celecoxib (used to treat high cholesterol)
- warfarin (used to thin the blood and prevent clotting)
- zidovudine (used in HIV infections and AIDS)
- domperidone and metoclopramide (used to treat nausea and vomiting).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Paracetamol Oral Suspension with food and drink
Do not drink alcohol while taking paracetamol. This is because taking alcohol and paracetamol together can increase the risk of liver damage.

Pregnancy and breastfeeding
If you are pregnant, planning to become pregnant or are breast-feeding, talk to your doctor or pharmacist before taking this medicine.

Driving and using machines
This medicine should not affect your ability to drive or use machines.

Important information about some of the ingredients of Paracetamol Oral Suspension
This medicine contains:
- Methyl and propyl parahydroxybenzoates – some people are allergic to these (the allergy may happen some time after starting the medicine).
- Liquid maltitol (2.05g per 5ml dose). If your doctor has told you that you cannot tolerate some sugars, talk to your doctor before taking this medicine.

3. How to take Paracetamol Oral Suspension
Take this medicine as your doctor or pharmacist has told you. Look on the label and ask your doctor or pharmacist if you are not sure.

How to take
- This medicine contains 500mg of paracetamol in one 5ml dose.
- Take this medicine by mouth only.
- Shake the bottle for at least 10 seconds before use.
- Always use the syringe supplied with the pack.

Measuring your dose:
1. Open the bottle; press the cap and turn it anticlockwise (figure 1).
2. Insert the syringe adaptor into the bottle neck (figure 2).
3. Take the syringe and put it in the adaptor opening (figure 2).
4. Turn the bottle upside down (figure 3).
5. Fill the syringe with a small amount of solution by pulling the piston down (figure 4 A). Then push the piston upward in order to remove any possible bubbles (figure 4 B). Finally, pull the piston down to the graduation mark corresponding to the quantity in millilitres (ml) prescribed by your doctor (figure 4 C).

6. Turn the bottle the right way up.

7. Remove the syringe from the adaptor. Put the end of the syringe into your mouth and push the piston slowly back in to take the medicine.

8. Wash the syringe with water and let it dry before you use it again.

9. Close the bottle with the plastic screw cap.

How much to take
- Adults and adolescents over 16:
  500mg (5ml) to 1000mg (10ml) up to three to four times a day, as required. Maximum daily intake should not exceed 4g (40ml).

How often to take
- Take a dose of this medicine every 4 to 6 hours when needed.
- Do not take more than 4 doses in 24 hours.
- Do not exceed the stated dose.

If you take more paracetamol than you should (overdose):
-Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage. Phone your doctor or go to your nearest accident and emergency department straight away.
-There may be no symptoms during the first 24 hours although paleness, nausea (feeling sick), vomiting (being sick) and abdominal pain may occur.

If you forget to take this medicine:
Take the next dose when needed. Do not take a double dose to make up for a forgotten dose.

Possible side effects
Like all medicines, paracetamol can cause side effects, although not everybody gets them. The side effects below may sometimes happen.

If you have an allergic reaction to this medicine see a doctor straight away.
An allergic reaction may include:
- skin rash, itching skin, boils, sore lips and mouth, swelling of the face, fever
- sudden wheezing, fluttering or tightness of the chest or collapse.

If you get any of the following side effects, stop taking this medicine and see your doctor as soon as possible:
- bruising more easily, sore throat or other signs of infection (these may be signs of a blood disorder)
- severe pain in the abdomen and back, with fever (high temperature), loss of appetite, nausea and vomiting (these may be signs of pancreas inflammation).
Tell your doctor if you get any of these side effects:
- skin rash

If paracetamol is taken for a long time, it may lead to liver and kidney problems.
If any of the side effects gets serious, or if you notice any side effects not mentioned in this leaflet, please tell your doctor or pharmacist.

5. How to store Paracetamol Oral Suspension
- Keep out of the reach and sight of children.
- Do not store above 25°C. Do not refrigerate or freeze. Store in the original package.
- Do not use 1 month after you first open it. Take it back to the pharmacy.
- Do not use after the expiry date (month, year) on the label. The expiry date refers to the last day of that month.
- If it is out of date or you no longer want it, take it back to the pharmacy.
- Do not use Paracetamol Oral Suspension if you notice anything wrong with the medicine. Talk to your pharmacist.

6. Further information

What Paracetamol Oral Suspension contains
The active substance is paracetamol. Each 5ml contains 500mg paracetamol.
The other ingredients are methyl and propy parahydroxybenzoate (E218 and E216), propylene glycol (E1520), liquid maltitol (E965), saccharin sodium, acesulfame potassium (E950), sodium dihydrogen phosphate dihydrate, disodium hydrogen phosphate dihydrate, magnesium aluminium silicate, masking flavour, strawberry flavour and purified water.

What Paracetamol Oral Suspension looks like and contents of the pack
Paracetamol Oral Suspension is a pink-brown liquid which smells of strawberry.
It comes in a brown glass bottle holding 150ml of oral suspension with a 5ml purple syringe and an adaptor.

The Marketing Authorisation Holder and Manufacturer is
Rosemont Pharmaceuticals Ltd, Yorkdale Industrial Park, Braithwaite Street, Leeds, LS11 9XE, UK. Tel: + 44 (0) 113 244 1409

This medicinal product is authorised in the Member States of the EEA under the following names:
UK: Paracetamol Adult 500mg/5ml Oral Suspension
Eire: Paracetamol Adult 500mg/5ml Oral Suspension

This leaflet was last revised in 12/2011
Module 4

Labelling

Carton with Braille
Carton outline showing Braille
Each 5ml contains 500mg Paracetamol.
The product also includes methyl and propyl parahydroxybenzoate (E218 and E216) and liquid maltitol (E965).
See leaflet for further information.
Administration:
For oral use. Shake the bottle for at least 10 seconds before use.
Always use the syringe supplied with the pack.
Read the package leaflet before use.

**DO NOT TAKE WITH ANY OTHER PARACETAMOL-CONTAINING PRODUCTS. IMMEDIATE MEDICAL ADVICE SHOULD BE SOUGHT IN THE EVENT OF AN OVERDOSE, EVEN IF YOU FEEL WELL, BECAUSE OF THE RISK OF DELAYED, SERIOUS OR IRREVERSIBLE LIVER DAMAGE.**

**DO NOT EXCEED THE STATED DOSE**

**FOR ADULT USE ONLY**
Do not use this medicine in children and adolescents under 16 years.

Storage:
Do not store above 30°C.
Do not refrigerate or freeze.
Store in the original package.
Discard 1 month after first opening.

Date opened:
Keep out of the reach and sight of children.
Manufactured by the MA Holder:
Rosemont Pharmaceuticals Ltd., Leeds, LS11 9KE, UK.
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Rosemont Pharmaceuticals Ltd a Marketing Authorisation (MA) for the medicinal product, Paracetamol Adult 500mg/5ml Oral Suspension (PL 00427/0160; UK/H/2489/001/DC), on 27 March 2012. The product is a prescription-only medicine.

This is an abridged, bibliographic application for Paracetamol Adult 500mg/5ml Oral Suspension, submitted under Article 10a (well-established use) of Directive 2001/83 EC, as amended. The proposed product is a paracetamol suspension containing 500 mg of the active substance in 5 ml. Currently a number of paracetamol products are available in various pharmaceutical forms, including liquid formulations at lower strengths. In the UK, the applicant markets Paracetamol 120mg/5ml (2.4%w/v) Oral Suspension, and 250mg/5ml (5%w/v) Oral Suspension. The low strength product is normally used for children. For the 250 mg/5 ml and the proposed 500 mg/5 ml products, the adult posology is the same – i.e. 500 mg-1 g every 4-6 hours, with a maximum daily dose of 4 g. The applicant claims that this higher strength is an alternative to paracetamol 500 mg tablets for people with swallowing difficulties or lactose intolerance.

With the UK as the Reference Member State (RMS) in this Decentralised procedure, Rosemont Pharmaceuticals Ltd applied for a Marketing Authorisation for Paracetamol Adult 500mg/5ml Oral Suspension in Ireland.

Paracetamol Adult 500mg/5ml Oral Suspension is indicated for the treatment of mild to moderate pain in patients who are unable to receive other paracetamol formulations such as lower strength liquid preparations, effervescent tablets or tablets.

Paracetamol is an effective analgesic and antipyretic agent. The drug has no effect on the cardiovascular and respiratory systems, and it does not cause gastric irritation or bleeding like salicylates. The mechanism of analgesic action has not been fully determined. Paracetamol may act predominantly by inhibiting prostaglandin synthesis in the central nervous system (CNS) and, to a lesser extent, through a peripheral action by blocking pain impulse generation. The peripheral action may also be due to inhibition of prostaglandin synthesis or to inhibition of the synthesis or actions of other substances that sensitise pain receptors to mechanical or chemical stimulation.

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

The 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 this product. 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 MAH has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). This was an application for a generic product and there is no reason to conclude that marketing of this product will change the overall use pattern of the existing market. It contains the same active ingredient in the same amount and has the same route of administration as the tablets on the market. There are no environmental concerns associated with the method of manufacture or formulation of the product.

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 application included an adequate Risk Management Plan (RMP). The strength of the product is higher than other paracetamol liquid products currently authorised. The risk of unintentional overdose is thus increased and a number of measures are considered necessary to maximise the benefit-risk balance of the product. These include restriction to use in adults only, restriction to Prescription Only Medicine (POM), use of a dosing syringe and clear packaging and labelling. The MAH proposes appropriate risk-minimisation measures, in addition to routine pharmacovigilance activities, in order to minimise the identified risks.
II. ABOUT THE PRODUCT

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III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

Paracetamol

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

Structure:

\[
\begin{array}{c}
\text{O} \\
\text{H}_3\text{C} \\
\text{N} \\
\text{OH} \\
\end{array}
\]

Molecular formula: C₈H₉NO₂
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 this medicinal product.
MEDICINAL PRODUCT

Description and Composition

Paracetamol Adult 500mg/5ml Oral Suspension is presented as an opaque, pink/brown suspension. Each 5 ml of suspension contains 500 mg of the active ingredient, paracetamol.

Other ingredients consist of pharmaceutical excipients, namely propylene glycol (E1520), methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), liquid maltitol (E965), saccharin sodium, acetussulfame potassium (E950), sodium dihydrogen phosphate dihydrate, disodium hydrogen phosphate dihydrate, magnesium aluminium silicate, masking flavour (containing propylene glycol (E1520)), strawberry flavour (C9987) (containing propylene glycol (E1520)) and purified water. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs, with the exception of sodium dihydrogen phosphate dihydrate 10% w/v solution, disodium hydrogen phosphate dihydrate 10% w/v solution, masking flavour and strawberry flavour, which are controlled to 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.

Pharmaceutical development

Details of the pharmaceutical development of the medicinal product have been supplied and are satisfactory. The objective was to develop a stable, oral suspension formulation containing the active substance paracetamol in a concentration of 500 mg/5 ml.

Although the application has been submitted under Article 10(a), the applicant was required to provide some bridging data between the proposed product and the bibliographic data. Comparative dissolution data were provided for batches of the test product and an appropriate paracetamol 500 mg tablets reference product formulation. 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 product and the method of manufacture. Process validation studies were conducted and the results were satisfactory. The validation data demonstrated consistency of the manufacturing process.

Finished product specification

Finished product specifications are provided for 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 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
Paracetamol Adult 500mg/5ml Oral Suspension are licensed for marketing in amber (type III) glass bottles of 150 ml capacity. The bottles are closed with high-density polyethylene (HDPE), expanded polyethylene (EPE), tamper-evident closures. The bottles are packaged with a 5 ml syringe, a low-density polyethylene (LDPE) bottle adaptor and the Patient Information Leaflet (PIL) into cardboard outer cartons. The adaptor will be placed in the bottle on initial opening and will allow only the syringe tip to be inserted via its aperture into the bottle. Once the syringe is inserted, the bottle can then be inverted and an accurate dose be withdrawn from the syringe.

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. These data support the applied shelf-life of 24 months for the unopened bottle and 1 month once the bottle is opened.
Storage instructions are ‘Do not store above 25°C. Do not refrigerate or freeze. Store in the original package’.

Quality Overall Summary
A satisfactory quality overall summary is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Product Information
The approved Summary of Product Characteristics (SmPC), 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 is in line with the SmPC and is satisfactory. PIL user-testing has been accepted based on bridging to the successful user-testing of the ‘parent’ PIL for Paldesic 120mg/5ml Oral Suspension (Rosemont Pharmaceuticals Ltd). The text, content and layout of the proposed PIL are considered to be sufficiently similar to the approved PIL for the stated product. The bridging is accepted.

Conclusion
All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. There are no objections to approval of Paracetamol Adult 500mg/5ml Oral Suspension from a pharmaceutical point of view.
III.2 NON-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable considering that this is a bibliographic application for an active of well-established use. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic, and toxicological properties of paracetamol, a well-known active substance. The CV of the non-clinical expert has been supplied.

Paracetamol has both analgesic and antipyretic activity, which are mediated through inhibition of prostaglandin synthesis within the central nervous system. The proposed product is a higher strength than other paracetamol oral suspensions on the UK market (250 mg/5 ml). However, no non-clinical safety concerns are raised as the maximum daily dose of the proposed product is the same as for those products already licensed. Consequently, patients will be receiving the same dose only in a smaller volume.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA).

There are no objections to approval of Paracetamol Adult 500mg/5ml Oral Suspension from a non-clinical point of view.

III.3 CLINICAL ASPECTS

INTRODUCTION

Paracetamol is a well-established medicinal product that has been widely used for decades for symptomatic relief of mild to moderate pain and pyrexia.

INDICATIONS

Paracetamol Adult 500mg/5ml Oral Suspension is indicated for the treatment of mild to moderate pain in patients who are unable to receive other paracetamol formulations such as lower strength liquid preparations, effervescent tablets or tablets.

The indications are consistent with existing paracetamol formulations and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

The posology in adults and adolescents over 16 years is 500 mg (5 ml) or 1 g (10 ml) every 4-6 hours, with a maximum daily dose of 4 g (40 ml). Full details concerning the posology are provided in the SmPC. The posology is consistent with that for existing paracetamol formulations and is satisfactory.

CLINICAL PHARMACOLOGY

The clinical pharmacology of paracetamol is well-known. No new pharmacodynamic or pharmacokinetic data are supplied and none are required for this application.

Pharmacokinetics

*Distribution* - Paracetamol is rapidly and relatively uniformly distributed in the tissues. The ratio of concentrations in red blood cells and plasma is about 1.2:1 and binding to plasma proteins is insignificant. The apparent volume of distribution (Vd) of paracetamol in man is about 0.9 L/kg. Protein binding is approximately 20% (Prescott, 1980).
**Elimination** - The metabolites of paracetamol are predominantly excreted in the urine as glucuronide (60–80%) and sulphide (20–30%) conjugates, with less than 5% of the drug excreted unchanged. This ratio is similar between oral and intravenous formulations (Clements et al, 1984). Less than 1% of a paracetamol dose is recovered in the bile (Jayasinghe et al, 1986). The elimination half-life ($t_{1/2}$) of paracetamol 1 g is 2.7 hours and its rate of systemic clearance is 17.9 L/h. Paracetamol has a plasma half-life of around two hours. Paracetamol is dialysable.

**Metabolism** - Paracetamol has a plasma half-life of around two hours. Metabolism of the drug is primarily in the liver, via conjugation with glucuronic (60%) and sulphuric (35%) acids, or cysteine (3%) (Prescott, 1980). A small amount of drug undergoes cytochrome P-450 mediated N-hydroxylation to form N-acetyl-p-aminobenzoquinoneimine (NAPQI). The most important isoform of P-450 responsible for this oxidative pathway is CYP2E1, but forms CYP3A4 and CYP1A2 are also involved. Under normal circumstances, the NAPQI combines with sulfhydryl groups in hepatic glutathione, and is neutralised. Following the ingestion of large amounts of paracetamol, hepatic glutathione is depleted, and the NAPQI reacts instead with sulfhydryl groups on hepatic proteins. This can lead to sub-acute hepatic necrosis, and in severe cases to hepatic failure.

**Special populations**

**Impaired renal function** - The renal clearance of unchanged (but not conjugated) paracetamol was related to the urine flow rate. However, forced diuresis is of no practical value and is contraindicated on clinical grounds. There was no correlation between urine pH and clearance of unchanged or conjugated drug (Prescott & Wright, 1973).

**Impaired hepatic function** - Paracetamol metabolism was impaired in the patients with liver damage. The plasma half-life of the unchanged drug was significantly prolonged, and the ratio of the plasma concentrations of unchanged to conjugated paracetamol was significantly higher than in the patients without liver damage (Prescott & Wright, 1973).

**Elderly** - Thirty-two healthy men and women, 23 to 78 yr old, received single 650 mg intravenous doses of paracetamol and the drug's kinetics were determined from multiple plasma samples drawn over the next 8 to 12 hr (Divoll et al, 1982). Paracetamol elimination half-life averaged 2.7 hr (range, 1.9 to 4.3 hr) and was not related to age or sex. Volume of distribution (Vd, corrected for weight) was larger in men than in women (0.99 and 0.86 l/kg) and declined with age in both sexes. This probably reflects increased fat per kilogram body weight in women and in the elderly, together with incomplete distribution of this nonlipophilic drug into body fat. Paracetamol clearance tended to decline with age in both sexes, but differences were of borderline significance. On the basis of kinetics data alone, adjustment of paracetamol dosage for the elderly is generally not necessary.

**Children** - Paracetamol absorption may occur at a somewhat greater rate in children if the syrup form is utilized. The overall plasma elimination of paracetamol is somewhat slow in the neonate, but is comparable to that of adults in both children and adolescents, as judged by half-life determinations. This would suggest that the frequency of paracetamol administration in children should be similar to the schedule recommended for adults and that a dosing interval of four hours should not result in drug accumulation. The question of a toxic quantity of paracetamol for young children must remain open until adequate metabolic or retrospective toxicological data become known. Since the volumes of distribution (Vd) appear to be the same in both adults and children, the same dose should apply in both groups; currently, 10 mg/kg is considered to be both safe and effective for antipyresis (Peterson & Rumack, 1978).
Assessor’s comments on pharmacokinetics
The pharmacokinetic profile of paracetamol is well-established and no additional studies are required.

Pharmacodynamics
Paracetamol is thought to have a central mode of action for both antipyresis and analgesia. Studies measuring plasma and cerebrospinal fluid (CSF) paracetamol concentrations have shown that maximal analgesic and antipyretic activity occur 1-2 hours after peak plasma levels. Initially, CSF levels of paracetamol lag behind those seen in plasma, with an equilibration half-time of 0.72 hours (CV 117%). In the later stages of the study, CSF paracetamol levels rose higher than those found in plasma. The CSF to plasma partition coefficient has been estimated at 1.18 (CV 8%), a figure in keeping with a drug known to be distributed in plasma water without binding to plasma proteins. Calculations based upon pharmacodynamic models of the plasma-CSF-effector site system suggest that concentrations found in the CSF do not directly reflect those found at the effector site, i.e. further period of time is required to allow the drug to reach its receptors. The antipyretic effects of paracetamol have been related to drug concentration using a sigmoidal $E_{\text{max}}$ model with a low Hill coefficient. This model fits the observed pharmacodynamic data, and also predicts a maximum effect ($E_{\text{max}}$) which cannot be exceeded despite further increases in drug concentration. For antipyresis a paracetamol concentration of 10-20 μg/ml has been shown to be effective, and $E_{\text{max}}$ is estimated as 3°C. The situation is more complex for analgesia, as pain is more difficult to quantify than temperature. A similar sigmoidal $E_{\text{max}}$ model has been proposed, and a plasma paracetamol concentration of 10 μg/ml has been estimated to provide satisfactory analgesia for 50% of children undergoing tonsillectomy (Ward & Alexander-Williams, 1999).

Assessor’s comments on pharmacodynamics
The pharmacodynamic profile of paracetamol is well-established and no additional studies are required.

CLINICAL EFFICACY
No new data have been submitted and none are required. The efficacy of paracetamol is well-established from its extensive use in clinical practice. Efficacy is reviewed in the clinical overview. The clinical expert presents an overview of the efficacy of paracetamol in various indications from published studies. The use of paracetamol for the treatment of mild to moderate pain and reduction of fever is well-established and a significant number of studies provide evidence of efficacy of paracetamol in acute and chronic pain and pyrexia. Results of some meta-analyses are discussed below.

Acute pain
A meta-analysis was performed in order to assess the analgesia obtained from single oral doses of paracetamol alone and in combination with codeine in postoperative pain. Moore et al (1997) conducted a systematic review of randomised controlled trials. They found 31 trials of paracetamol against placebo with 2515 patients, 19 trials of paracetamol plus codeine against placebo with 1204 patients and 13 trials of paracetamol plus codeine against the same dose of paracetamol with 874 patients. Pain relief information was extracted, and converted into dichotomous information (number of patients with at least 50% pain relief). Wide variations in responses to placebo (0–72%) and active drug (3–89%) were observed. In postoperative pain states, paracetamol 1000 mg alone against placebo had a number-needed-
to-treat (NNT) of 3.6 (3.0–4.4) and paracetamol 600/650 mg alone an NNT of 5.0 (4.1–6.9). Paracetamol 600/650 mg plus codeine 60 mg against placebo had a better NNT of 3.1 (2.6–3.8), with no overlap of 95% confidence intervals with paracetamol 600/650 mg alone. In direct comparisons of paracetamol plus codeine with paracetamol alone the additional analgesic effect of 60 mg of codeine added to paracetamol was 12 extra patients in every 100 achieving at least 50% pain relief. In indirect comparisons of each with placebo it was 14 extra patients per 100. This was an NNT for adding codeine 60 mg of 9.1 (5.8–24). The results confirm that paracetamol is an effective analgesic, and that codeine 60 mg added to paracetamol produces worthwhile additional pain relief even in single oral doses.

A more recent meta-analysis assessed the efficacy of single dose oral paracetamol for the treatment of acute postoperative pain (Toms et al, 2008). They searched The Cochrane Library, MEDLINE, EMBASE, the Oxford Pain Relief Database and reference lists of articles to update an existing version of the review in July 2008. Randomised, double-blind, placebo-controlled clinical trials of paracetamol for acute postoperative pain in adults were selected. Two review authors independently assessed trial quality and extracted data. Area under the “pain relief versus time” curve was used to derive the proportion of participants with paracetamol or placebo experiencing at least 50% pain relief over four to six hours, using validated equations. NNT-benefit was calculated, with 95% confidence intervals (CI). The proportion of participants using rescue analgesia over a specified time period, and time to use, were sought as measures of duration of analgesia. Information on adverse events and withdrawals was also collected. Fifty-one studies, with 5762 participants, were included: 3277 participants were treated with a single oral dose of paracetamol and 2425 with placebo. About half of participants treated with paracetamol at standard doses achieved at least 50% pain relief over four to six hours, compared with about 20% treated with placebo. NNTs for at least 50% pain relief over four to six hours following a single dose of paracetamol were as follows: 500 mg NNT 3.5 (2.7 to 4.8); 600 to 650 mg NNT 4.6 (3.9 to 5.5); 975 to 1000 mg NNT 3.6 (3.4 to 4.0). There was no dose response. Sensitivity analysis showed no significant effect of trial size or quality on this outcome. About half of participants needed additional analgesia over four to six hours, compared with about 70% with placebo. Five people would need to be treated with 1000 mg paracetamol, the most commonly used dose, to prevent one needing rescue medication over four to six hours, who would have needed it with placebo. Reported adverse events were mainly mild and transient, and occurred at similar rates with 1000 mg paracetamol and placebo. No serious adverse events were reported. Withdrawals due to adverse events were uncommon and occurred in both paracetamol and placebo treatment arms. The authors conclude that a single dose of paracetamol provides effective analgesia for about half of patients with acute postoperative pain, for a period of about four hours, and is associated with few, mainly mild, adverse events.

Chronic pain

Osteoarthritis pain - Lee et al (2004) performed a meta-analysis comparing the efficacy and safety of recommended dosages of NSAIDs, including COX 2 inhibitors, versus paracetamol in the treatment of symptomatic hip and knee osteoarthritis. Medline and EMBASE searches were performed for original clinical trials directly comparing NSAIDs with paracetamol. Seven articles met inclusion criteria with sufficient data for analysis. Test of heterogeneity was not significant for either rest (P = 0.73) or walking (P = 0.76) pain. The scores for overall pain at rest (WMD –6.33 mm on a 100-mm visual analogue scale (VAS), 95% CI –9.24, –3.41) and walking pain (WMD –5.76 mm on a 100-mm VAS, 95% CI –8.99, –2.52) favoured the NSAID-treated group. Although NSAIDs elevated the risk of withdrawals due to AEs, the difference was not statistically significant (OR 1.45, 95% CI 0.93, 2.27). The authors conclude that NSAIDs are statistically superior in reducing rest and walking pain compared
with paracetamol for symptomatic osteoarthritis. Safety, measured by discontinuation due to AEs, was not statistically different between NSAID- and paracetamol-treated groups.

In a more recent meta-analysis Towheed et al (2006) assessed the efficacy and safety of paracetamol versus placebo and versus NSAIDs (ibuprofen, diclofenac, arthrotec, celecoxib, naproxen, rofecoxib) for treating OA. They searched MEDLINE (up to July 2005), EMBASE (2002-July 2005), Cochrane Central Register of Controlled Trials (CENTRAL), ACP Journal Club, DARE and the Cochrane Database of Systematic Reviews (all from 1994 to July 2005). Selection criteria were: published randomized controlled trials (RCTs) evaluating the efficacy and safety of paracetamol alone in OA. Pain, physical function and global assessment outcomes were reported. Continuous outcome measures were expressed as standardized mean differences (SMD). Dichotomous outcome measures were pooled using relative risk (RR) and the NNT was calculated. Fifteen RCTs involving 5986 participants were included in this review. Seven RCTs compared paracetamol to placebo and ten RCTs compared paracetamol to NSAIDs. In the placebo-controlled RCTs, paracetamol was superior to placebo in five of the seven RCTs and had a similar safety profile. Compared to placebo, a pooled analysis of five trials of overall pain using multiple methods demonstrated a statistically significant reduction in pain (SMD -0.13, 95% CI -0.22 to -0.04), which is of questionable clinical significance. The relative percent improvement from baseline was 5% with an absolute change of 4 points on a 0 to 100 scale. The NNT to achieve an improvement in pain ranged from 4 to 16. In the comparator-controlled RCTs, paracetamol was less effective overall than NSAIDs in terms of pain reduction, global assessments and in terms of improvements in functional status. No significant difference was found overall between the safety of paracetamol and NSAIDs, although patients taking traditional NSAIDS were more likely to experience an adverse GI event (RR 1.47, (95% CI 1.08 to 2.00)). 19% of patients in the traditional NSAID group versus 13% in the paracetamol group experienced an adverse GI event. The evidence to date suggests that NSAIDs are superior to paracetamol for improving knee and hip pain in people with OA. The size of the treatment effect was modest, and the median trial duration was only six weeks, therefore, additional considerations need to be factored in when making the decision between using paracetamol or NSAIDs. In OA subjects with moderate-to-severe levels of pain, NSAIDs appear to be more effective than paracetamol.

Rheumatoid Arthritis Pain - NSAIDs are usually preferred for simple analgesics such as paracetamol for rheumatoid arthritis. It is not clear, however, whether the trade-offs between benefits and harms of NSAIDs are preferable to those of paracetamol. The objective of the meta-analysis performed by Wienecke et al (2004) was to compare the benefits and harms of paracetamol with NSAIDs in patients with rheumatoid arthritis. PubMed and EMBASE databases were searched up until August 2007. Reference lists of identified articles were also searched. Selection criteria were: randomised double-blind studies comparing paracetamol with an NSAID. Four cross-over studies, published between 1968 and 1982, involving 121 patients, and four different NSAIDs were included. The NSAIDs were preferred more often than paracetamol by the patients or the investigator. In the largest trial, 20 out of 54 patients (37%) preferred ibuprofen and 7 out of 54 (13%) paracetamol. Investigators preference (as established by joint tenderness, grip strength and joint circumference) was 17 out of 35 for diclofenac versus 5 out of 35 for paracetamol in another trial. However, because of the weaknesses in the trials, no firm conclusion can be drawn. The authors conclude that when considering the trade off between the benefits and harms of NSAIDs and paracetamol, it is not known whether one is better than the other for rheumatoid arthritis. But people with rheumatoid arthritis and the researchers in the study did prefer non-steroidal anti-inflammatory drugs more than paracetamol.
Fever - A meta-analysis summarized the studies testing the efficacy and safety of single-dose paracetamol and ibuprofen for treating children’s pain or fever (Perrott et al, 2004). Reports were gathered by searching computerized databases and registries, relevant journals, and bibliographies of key articles. Seventeen blinded, randomized controlled trials with children (<18 years) receiving either drug to treat fever or moderate to severe pain. Under a fixed-effects model data were extracted by outcome measures, for an initial single dose of ibuprofen vs. paracetamol, of the risk ratio for achieving more than 50% of maximum pain relief, effect size for febrile temperature reduction, and risk ratio for minor and major harm. Ibuprofen (4-10 mg/kg) and paracetamol (7-15 mg/kg) showed comparable efficacy (3 pain relief trials; 186 children). The risk ratio point- estimates were 1.14 (95% CI, 0.82-1.58) at 2 hours after receiving the dose, and 1.11 (95% CI, 0.89-1.38) at 4 hours. Ibuprofen (5-10 mg/kg) reduced temperature more than paracetamol (10-15 mg/kg) at 2, 4, and 6 hours after treatment (respective weighted-effect sizes: 0.19 [95% CI, 0.05-0.33], 0.31 [95% CI, 0.19-0.44], and 0.33 [95% CI, 0.19-0.47]) (9 fever trials; 1078 children). For ibuprofen 10 mg/kg (paracetamol, 10-15 mg/kg), corresponding effect sizes were 0.34 (95% CI, 0.12-0.56), 0.81 (95% CI, 0.56-1.03), and 0.66 (95% CI, 0.44-0.87). There was no evidence the drugs differed from each other (or placebo) in incidence of minor or major harm (17 safety trials; 1820 children). The authors conclude that in children, single doses of ibuprofen (4-10 mg/kg) and paracetamol (7-15 mg/kg) have similar efficacy for relieving moderate to severe pain, and similar safety as analgesics or antipyretics. Ibuprofen (5-10 mg/kg) was a more effective antipyretic than paracetamol (10-15 mg/kg) at 2, 4, and 6 hours post treatment.

Assessor’s comments on efficacy
Paracetamol is a well establish product with a well recognised efficacy profile.

CLINICAL SAFETY
No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview. The safety profile of paracetamol is well-known.

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. Overdosage with paracetamol can result in severe liver damage and sometimes acute renal tubular necrosis.

The safety of paracetamol has been reviewed by Graham et al (2005). The major problem in the use of paracetamol is its hepatotoxicity after an overdose. Hepatotoxicity has also been reported after therapeutic doses, but critical analysis indicates that most patients with alleged toxicity from therapeutic doses have taken overdoses. Importantly, prospective studies indicate that therapeutic doses of paracetamol are an unlikely cause of hepatotoxicity in patients who ingest moderate to large amounts of alcohol. Controlled clinical trials have found that paracetamol is very well tolerated by the gastrointestinal tract. While variable results have been found in case control studies, most studies have shown no change or a small increase in the relative risk of perforations, ulcer or bleeding in the upper gastrointestinal tract.
With the potential for intentional or unintentional overdosage in mind, the applicant has adopted the following risk minimisation measures:

- including an adaptor to slow the flow of liquid from the bottle to try to put off ready use of the product unless necessary.

- providing a 5ml syringe to highlight to the patient that accurately measuring the dose is important with this product and again it prevents ready use of the product unless necessary.

- the product is presented with a child resistant closure. It is much easier for a child to open a carton and consume tablets from a blister strip or a polypropylene tube.

- highlighting in the product name that it is an adult formulation and in the product texts that the product should not be used in children under 16 years of age.

- a small volume pack of 150 ml capacity is being marketed.

- the medicine is restricted to POM legal classification

Adverse Effects according to organ systems:

*Blood and lymphatic system disorders* - There have been reports of blood dyscrasias including thrombocytopenia purpura, methaemoglobinemia and agranulocytosis, but these were not necessarily causality related to paracetamol.

*Immune system disorders* - Allergic reactions to paracetamol have been rarely reported, ranging from rashes (Morgan & Dorman, 2004) to bronchospasm and anaphylactic shock.

*Respiratory, thoracic and mediastinal disorders* - Frequent use of paracetamol may contribute to asthma morbidity and (allergic) rhinitis in adults (Shaheen et al, 2000).

*Gastrointestinal disorders* - Cases of acute pancreatitis have been reported. Paracetamol has been widely used and reports of adverse reactions are rare, and are generally associated with overdosage.

*Hepatobiliary disorders* - In usual dosage, paracetamol exerts no hepatotoxic effects. Hepatotoxicity is the most serious AE of acute overdose or poisoning manifesting itself in a dose-dependent, potentially fatal hepatic necrosis. In adults, hepatotoxicity may occur after ingestion of a single dose of 10 to 15 g (200 to 250 mg/kg) of paracetamol. A dose of 25 g or more is potentially fatal.

*Renal and urinary disorders* - Nephrotoxic effects are uncommon and have not been reported in association with therapeutic doses, except after prolonged administration.

**Assessor’s comments on efficacy**

The safety profile of paracetamol is well recognised.

**CLINICAL OVERVIEW**

A satisfactory clinical overview is provided and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.
PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)
The approved SmPC is consistent with that for existing paracetamol formulations and is acceptable.

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

Labelling
The labelling is satisfactory.

CONCLUSIONS
Sufficient clinical information has been submitted to support this application. The risk-benefit of the product is considered favourable from a clinical perspective. The grant of a Marketing Authorisation was, therefore, recommended.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Paracetamol Adult 500mg/5ml Oral Suspension 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.

CLINICAL
Medicinal products containing paracetamol have been available in the UK for many decades. Its use is well-established with recognised efficacy and acceptable safety.

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The approved SmPC is consistent with that for existing paracetamol formulations and is satisfactory.

The PIL is in line with the SmPC and is satisfactory. PIL user-testing has been accepted based on bridging to the successful user-testing of the PIL for Paldesic 120mg/5ml Oral Suspension (Rosemont Pharmaceuticals Ltd). The results show that the 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.

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 and sufficient space has been included for a standard UK pharmacy dispensing label.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with paracetamol is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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