SUMMARY OF PRODUCT CHARACTERISTICS

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
Propylene Glycol

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

Posology

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.

Special Populations

Renal impairment:

When a 500 mg administration is possible:

It is recommended, when giving paracetamol to patients with renal impairment, to reduce the dose and to increase the minimum interval between each administration to at least 6 hours unless directed otherwise by a physician. See Table below:

Adults:

Glomerular filtration rate	Dose
10-50 ml/min	500mg every 6 hours
<10ml/min	500mg every 8 hours

Hepatic impairment:

In patients with hepatic impairment or Gilbert's Syndrome, the dose should be reduced or the dosing interval prolonged.

The daily dose should not exceed 2g/day unless directed by a physician.

The elderly:

Experience has indicated that normal adult dosage is usually appropriate. However in frail, immobile, elderly subjects or in elderly patients with renal or hepatic impairment, a reduction in the amount or frequency of dosing may be appropriate.

The maximum daily dose should not exceed 60mg/kg/day (up to a maximum of 2g per day) in the following situations, unless directed by a physician:

- Weight less than 50kg
- Chronic alcoholism
- Dehydration
- Chronic malnutrition

Method of administration
For oral administration only

4.3 Contraindications

Hypersensitivity to paracetamol or to any of the excipients listed in section 6.1.
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

Paracetamol should be administered with caution under the following circumstances (see section 4.2 where relevant):

- Hepatic impairment
- Renal impairment (GFR≤50ml/min)
- Gilbert's Syndrome (familial non-haemolytic jaundice)
- Concomitant treatment with medicinal products affecting hepatic function
- Glucose-6-phosphate dehydrogenase deficiency (may lead to methaemoglobinaemia and haemolytic anaemia)
- Haemolytic anaemia
- Elderly

Cases of hepatic dysfunction/ failure have been reported in patients with depleted glutathione levels, such as those who are severely malnourished, anorexic, have a low body mass index, dehydrated, are chronic heavy users of alcohol or have sepsis. In patients with glutathione-depleted states the use of paracetamol may increase the risk of metabolic acidosis.

In general, medicinal products containing paracetamol should be taken for only a few days without the advice of a physician or dentist and not at high doses.

If high fever or signs of secondary infection occur or if symptoms persist for longer than 3 days, a physician should be consulted.

Prolonged or frequent use is discouraged. Patients should be advised not to take other paracetamol containing products concurrently. Taking multiple daily doses in one administration can severely damage the liver; in such case medical assistance should be sought immediately.

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.

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal impairment and sepsis, or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

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.

Patients should be advised that paracetamol may cause severe skin reactions. If a skin reaction such as skin reddening, blisters, or rash occurs, they should stop use and seek medical assistance right away.

Do not exceed the recommended dose.
Keep out of the sight and reach of children.

Excipient warnings:

This product contains the following excipients:

- Methyl and propyl parahydroxybenzoates: These may cause allergic reactions (possibly delayed).
- Liquid maltitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.
- Propylene Glycol. This medicine contains 112.2mg propylene glycol per 5ml dose. Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce adverse effects in children less than 5 years old.
  While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or lactating patients should be considered on a case by case basis.
  Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction.
- Sodium. This medicine contains less than 1mmol sodium per ml, that is to say essentially ‘sodium-free’.

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, however, concurrent use need not be avoided.
Absorption is reduced by colestyramine. Therefore, the cholestyramine should not be taken within one hour if maximal analgesia is required.

Chloramphenicol: Increased plasma concentration of chloramphenicol.

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).

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy
A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Breast-feeding
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

The following convention has been utilised for the classification of the frequency of adverse reactions: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1000), very rare (<1/10,000), not known (cannot be estimated from available data).

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

Very rare: Thrombocytopaenia.

Very rare cases of serious skin reactions have been reported.

Very rare: Cutaneous hypersensitivity reactions including, among others, skin rashes, angioedema, Stevens Johnson syndrome and Toxic Epidermal Necrolysis.

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.

Very rare: Anaphylaxis.

Very rare: Bronchospasm in patients sensitive to aspirin and other NSAIDs.

Very rare: Hepatic dysfunction.

Uncommon: Nephrotoxic effects have not been reported in association with therapeutic doses, except after prolonged administration.
High Anion Gap Metabolic Acidosis (HAGMA) may occur with an unknown frequency.

Not known: High anion gap metabolic acidosis: Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme.
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Paracetamol overdose can result in liver damage which may be fatal.
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).

Overdose of paracetamol can cause liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death.
Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 48 hours after administration.
Liver damage is likely in patients who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of toxic metabolite become irreversibly bound to liver tissue.
Some patients may be at increased risk of liver damage from paracetamol toxicity:

Risk factors

If the patient

a) Patients with liver disease
b) Elderly patients
c) Young children
d) Is on long term treatment with carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, St. John's Wort or other drugs that induce liver enzymes
   or
e) Regularly consumes ethanol in excess of recommended amounts.
   or
f) Is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms

Symptoms of paracetamol overdosage generally appear within the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain or patients may be asymptomatic. 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. Overdose may also result in disseminated intravascular coagulation.

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 NPIS 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 sensitise 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

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

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 HDPE 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

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