Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol Rx 500 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg paracetamol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Capsule-shaped, white film-coated tablet, 17.0 mm x 7.2 mm, with break-line on one side and engraved with "PINEX 500" on the unscored side and "A" and "L" on the break-line side.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Symptomatic treatment of mild to moderate pain and/or fever.

4.2 Posology and method of administration

Paracetamol Rx 500 mg film-coated tablets are not intended for children weighing less than 26 kg.

Posology

Adults and adolescents (weighing more than 50 kg)

The usual dose is 500 mg to 1,000 mg every 4 to 6 hours as needed, to a maximum of 3 g daily. Maximum single dose is 1,000 mg.

Maximal daily dose should not be exceeded due to risk of serious hepatic damage (see sections 4.4 and 4.9).

Paediatric population (weighing 20–50 kg)

The recommended total daily dose of paracetamol is approximately 60 mg/kg divided in 4 or 6 separate doses, or approximately 15 mg/kg every 6 hours or 10 mg/kg every 4 hours. Maximal daily dose should not be exceeded due to risk of serious hepatic damage (see sections 4.4 and 4.9).

Paediatric dosage should be based on body weight and suitable dosage form used. Information on the age of children within each weight group given below is for guidance only.

Regular administration minimizes pain and fever oscillation. In children administration should be regular, including nighttimes, preferably at 6 hours intervals, otherwise at intervals of minimum 4 hours.

Children and adolescents weighing 43-50 kg (about 12-15 years)

The usual dose is 500 mg every 4 hours as needed, to a maximum of 2.5 g daily.

Children weighing 34-43 kg (about 11-12 years)

The usual dose is 500 mg every 6 hours as needed, to a maximum of 2 g daily.

Children weighing 26-34 kg (about 8-11 years)

The usual dose is 250 mg every 4 hours or 500 mg every 6 hours as needed, to a maximum of 1.5 g daily.

Renal insufficiency
Paracetamol should be used with caution in the presence of renal insufficiency and increased interval between doses is recommended in case of severe renal insufficiency. When creatinine clearance is lower than 10 ml/min. the minimum interval between two administrations should be 8 hours.

Hepatic insufficiency
Paracetamol should be used with caution in the presence of hepatic insufficiency or Gilbert's syndrome. The dose should be reduced or the dosing interval prolonged.

Elderly patients
Dose adjustment is not required in the elderly.

Chronic alcoholism
Chronic alcohol consumption may lower the paracetamol toxicity threshold. In these patients, the length of time between two doses should be a minimum of 8 hours. 2 g paracetamol per day should not be exceeded.

Method of administration
For oral use.
The tablet should be swallowed with a glass of water.

In case of high fever or signs of infection after more than 3 days of treatment or if pain persists after more than 5 days of treatment, the patient should be advised to contact a doctor.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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 unconsciousness does not occur. However, medical assistance should be sought immediately. Prolonged use except under medical supervision may be harmful. In adolescents treated with 60 mg/kg daily of paracetamol, the combination with another antipyretic is not justified except in the case of ineffectiveness.

Caution is advised in the administration of paracetamol to patients with moderate and severe renal impairment, mild to moderate hepatic impairment (including Gilbert's syndrome), severe hepatic impairment (Child-Pugh>9), acute hepatitis, concomitant treatment with medicinal products affecting hepatic functions, glucose-6-phosphatedehydrogenase deficiency, haemolytic anaemia, alcohol abuse dehydration and chronic malnutrition.

In patients with depleted glutathione status such as sepsis, malnourishment, alcohol abuse, renal and hepatic disorders, the use of paracetamol can increase the risk of liver failure and/or metabolic acidosis (see section 4.9).

The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease. Caution should be exercised in cases of chronic alcoholism. The daily dose should not exceed 2 grams in such case. Alcohol should not be used during the treatment with paracetamol.

In case of high fever or signs of infection after more than 3 days of treatment or if pain persists after more than 5 days of treatment, the patient should be advised to contact a doctor.

After long term treatment (> 3 months) of analgesics with use every second day or more frequently, headache may develop or aggravate. Headache caused by overuse of analgesics (MOH - medication-overuse headache) should not be treated by increasing the dose. In such cases the use of analgesics should be discontinued in consultation with a doctor.

Abrupt discontinuation following long-term, high-dose, incorrect use of analgesics may lead to headaches, fatigue, muscle pain, nervousness and autonomic symptoms. These withdrawal symptoms resolve within a few days. Until this time, further intake of analgesics should be avoided and not restarted without medical advice.

Caution is advised in asthmatic patient sensitive to acetylsalicylic acid, because light reaction bronchospasm with paracetamol (cross-reaction) has been reported.

Immediate medical advice should be sought in the event of overdosage even if the patient feels well because of the risk of irreversible liver damage (see section 4.9).

4.5 Interaction with other medicinal products and other forms of interactions

Paracetamol is extensively metabolised in the liver, and therefore it may interact with other medicinal products that use the same metabolic pathways or which are capable of inhibiting or inducing such pathways. Enzyme inducers have been observed to reduce the plasma concentrations of paracetamol by up to 60%.

Chronic alcohol intake or use of substances that induce liver enzymes, such as barbiturates, carbamazepine, phenytoin, rifampicin, isoniazid and St John's wort (*Hypericum perforatum*) can increase the hepatotoxicity of paracetamol due to increased and more rapid formation of toxic metabolites. Therefore, caution should be taken in case of concomitant use of enzyme inducing substances (see section 4.9).

In concomitant treatment with probenecid a dose reduction should be considered, because probenecid almost decreases by half the paracetamol clearance, by inhibiting the conjugation with glucuronic acid.

Salicylamide may prolong the elimination half-life of paracetamol.

Paracetamol can decrease the bioavailability of lamotrigine, with possible reduction of its effects, due to possible induction of its metabolism in the liver.

Paracetamol can significantly increase the elimination half-time of chloramphenicol. Monitoring of chloramphenicol plasma levels is recommended if combining paracetamol with chloramphenicol injection treatment.

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine. Intake of cholestyramine and paracetamol should be separated by one hour to obtain maximum effect. Concurrent intake of medicinal products that slow gastric emptying can delay the absorption and onset of effect of paracetamol.

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding.The effect may occur already at daily doses of 1.5-2 g paracetamol for 5-7 days. Occasional doses have no significant effect.

Interference with laboratory tests
Paracetamol may affect phosphotungstate uric acid tests and blood sugar tests by glucose-oxydase-peroxydase.

4.6 Fertility, 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.

Breastfeeding

Following oral administration, paracetamol is excreted into breast milk in small quantities. No undesirable effects on infants have been reported. Paracetamol may be used by breastfeeding women as long as the recommended dosage is not exceeded. In case of long term use caution should be exercised.

4.7 Effects on ability to drive and use machines

Paracetamol has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

At therapeutic doses few undesirable effects occur.

The frequency of undesirable effects is classified as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

System organ class	**Frequency**	**Undesirable effects**
Blood and lymphatic system disorders	Rare:	Platelet disorders, stem cell disorders.
	Very rare:	Trombocytopenia, leucopenia, neutropenia and haemolytic anaemia.
Immune system disorders	Rare:	Hypersensitivity (excluding angioedema).
Metabolism and nutrition disorders	Very rare:	Hypoglycaemia
Psychiatric disorders	Rare:	Depression NOS, confusion, hallucinations.
Nervous system disorders	Rare:	Tremor NOS, headache NOS.
Eye disorders	Rare:	Abnormal vision.
Cardiac disorders	Rare:	Oedema.
Gastrointestinal disorders	Rare:	Haemorrhage NOS, abdominal pain NOS, diarrhoea NOS, nausea, vomiting.
Hepatobiliary disorders	Rare:	Hepatic function abnormal, hepatic failure, hepatic necrosis, jaundice.
	Very rare:	Hepatotoxicity
Skin and subcutaneous tissue disorders	Rare:	Pruritus, rash, sweating, purpura, angioedema, urticaria.
Renal and urinary disorders	Very rare:	Sterile pyuria (cloudy urine) and renal side effects
General disorders and administration site conditions	Rare:	Dizziness (excluding vertigo), malaise, pyrexia, sedation, drug interaction NOS.
	Very rare:	Hypersensitivity reaction (requiring discontinuation of treatment)
Injury, poisoning and procedural complications	Rare:	Overdose and poisoning

NOS= Not otherwise specified.

Very rare cases of serious skin reactions have been reported.

Some cases of erythema multiforme, oedema of the larynx, anaphylactic shock, anaemia, liver alteration and hepatitis, renal alteration (severe renal impairment, nephrite interstitial, haematuria, anuresis), gastrointestinal effects and vertigo have been reported.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie

4.9 Overdose

For paracetamol there is a risk of intoxication, especially for elderly, small children, patients with liver diseases, in cases of chronic alcoholism, patients with chronic malnutrition and patients that use enzyme inducing substances. Overdosage may be fatal.

Symptoms
The symptoms of paracetamol intoxication are nausea, vomiting, anorexia, paleness and abdominal pain and these symptoms usually occur within 24 hours after intake. An overdosage paracetamol of 7.5 gram or more as a single administration in adults, or 140 mg/kg bodyweight as a single administration in children, causes hepatic cytolysis that may lead to complete and irreversible necrosis resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy that may lead to coma or death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin have been observed, together with lowered prothrombin levels that may occur 12 to 48 hours after administration. Clinical signs of liver damage usually occur for the first time after two days and reach a maximum after 4 to 6 days. Even in the absence of serious hepatic damage, acute renal failure with renal tubular necrosis may occur. Other non-liver symptoms after overdose with paracetamol may be myocardial abnormalities and pancreatitis.

Emergency treatment
- Immediate hospitalisation.
- After overdosage a blood sample should be drawn to determine the paracetamol level as soon as possible, before the start of treatment.
- Rapid evacuation of the ingested product by means of gastric lavage, followed by administration of activated charcoal (adsorbens) and sodium sulphate (laxans).
- Dialysis may lower plasma concentration of paracetamol.
- Treatment consists of administration of the antidote N-acetylcystein (NAC), intravenously or orally, if possible before the tenth hour after intake. NAC may even offer protection after 10 hours but in such cases a prolonged treatment is given.
- Symptomatic treatment.
- Liver tests should be performed at the start of treatment and should be repeated every 24 hours. In most cases, the hepatic transaminases will return to normal within one to two weeks, with full recovery of liver function. However, in very rare cases a liver transplantation may be indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other analgesics and antipyretics, anilides; ATC code: N02BE01

Paracetamol has both analgesic and antipyretic effects. However, it does not have an anti-inflammatory effect. The mechanism of analgesic action has not been fully determined. The main action of paracetamol is the inhibition of cyclo-oxygenase, an enzyme which is important for the prostaglandin synthesis. Central nervous system cyclo-oxygenase is more sensitive for paracetamol than peripheral cyclo-oxygenase and this explains why paracetamol has an antipyretic and analgesic efficacy. Paracetamol probably produces antipyresis by acting centrally on the hypothalamic heat regulating centre.

5.2 Pharmacokinetic properties

Absorption
After oral administration paracetamol is rapidly and almost completely absorbed. Peak plasma concentrations are reached after 30 minutes to 2 hours.

Distribution
Paracetamol is distributed rapidly throughout all tissues. Concentrations are comparable in blood, saliva and plasma. The volume of distribution of paracetamol is approximately 1 l/kg bodyweight. At therapeutic doses protein binding is negligible.

Biotransformation
In adults paracetamol is metabolized in the liver following two major metabolic pathways: glucuronic acid (~60%) and sulphuric acid (~35%) conjugates. The latter route is rapidly saturated at doses higher than the therapeutic dose. A minor route, catalyzed by the cytochrome P450, results in the formation of an intermediate reagent (N-acetyl-p-benzoquinoneimine) which under normal conditions of use is rapidly detoxified by glutathione and eliminated in the urine, after conjugation with cystein (~3%) and mercaptopuric acid. In neonates and children <12 years sulphate conjugation is the main elimination route and glucuronidation is lower than in adults. Total elimination in children is comparable to that in adults, due to an increased capacity for sulphate conjugation.

Elimination
Elimination of paracetamol is essentially through the urine. 90% of the ingested dose is eliminated via the kidneys within 24 hours, predominantly as the glucuronide (60 to 80%) and the sulphate (20 to 30%) conjugates. Less than 5% is eliminated in unchanged form. The elimination half life is about 2 hours.
In cases of renal or hepatic insufficiency, after overdose, and in neonates the elimination half life of paracetamol is delayed. The maximum effect is equivalent with plasma concentrations.

In cases of severe renal insufficiency (creatinine clearance lower than 10 ml/min) the elimination of paracetamol and its metabolites is delayed.

For elderly patients, the capacity for conjugation is not modified.

5.3 Preclinical safety data

In animal studies investigating the acute, sub-chronic and chronic toxicity of paracetamol in rats and mice, gastrointestinal lesions, blood count changes, degeneration of the hepatic and renal parenchyma, and necrosis were observed. These changes are, on the one hand, attributed to the mechanism of action and, on the other, to the metabolism of paracetamol.

Extensive investigations showed no evidence of any relevant genotoxic risk of paracetamol in the therapeutic, i.e. non-toxic, dose range.

Long-term studies in rats and mice yielded no evidence on relevant carcinogenic effects at non-hepatotoxic dosages of paracetamol.

Paracetamol crosses the placental barrier.
Animal studies yield no evidence on reproductive toxicity.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Pregelatinised maize starch
Hydroxypropylcellulose
Talc
Magnesium stearate

Film-coating:
Polyvinyl alcohol
Macrogol 3350
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

PVC/Aluminium blisters: Do not store above 25°C.

Polyethylene containers: This medicinal product does not require any special temperature storage conditions.

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Blisters (PVC/Aluminium)
Tablet container (HDPE) with cap (PE)

Pack sizes:
Blister: 10, 20, 30, 50 and 100 tablets
Tablet container: 100, 200, 250, 300 and 500 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/009/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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