Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol 500mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Paracetamol 500.0 mg.

Excipients(s):
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
White, uncoated capsule shape tablet marked with "B score T" on one side and plain on the other side.

Note: Length, width and thickness of the tablet is 16.50±0.20 mm, 8.20±0.20 mm and 5.10±0.30 mm respectively.
The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology:

For oral use only.

Adults and adolescents15 years (> 55 kg body weight)
1 to 2 tablets (500-1000 mg) at a time, up to 6 tablets (3000 mg) per 24 hours.

Children and young people up to 15 years
6-9 years: ½ tablet at a time, up to 4-6 times per 24 hours
9-12 years: 1 tablet at a time, up to 3-4 times in 24 hours
12-15 years: 1 tablet at time, up to 4-6 times per 24 hours

Direction for use:
- Paracetamol tablet is not suitable for children below 6 years.
- The dosing interval should be at least 4 hours.
- Do not use in combination with other paracetamol-containing products.
- The indicated dose should not be exceeded due to risk of serious damage to the liver (see section 4.4 and 4.9).
- The lower frequency of administration is intended for children in the lower limit of the relevant age group.
- Depending on the onset of symptoms (fever and pain) repeated administration is allowed.
- If pain for more than 5 days or fever for more than 3 days exists or get worse, or if any other symptom occur, treatment should be discontinued and a physician should be consulted.
- The ingestion of paracetamol with food and drink does not affect the efficacy of the medicinal product.
- In case of renal insufficiency (renal failure), the dose should be reduced:

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

- In patients with impaired hepatic or Gilberts syndrome, the dose must be reduced or the dosing interval prolonged.
- The daily effective dose should not exceed 60 mg/kg/day. In the following situations the daily dose should not exceed 2 g/day:
- Adults weighing less than 50 kg
- Mild to moderate hepatic insufficiency, Gilbert's syndrome (familial non-haemolytic jaundice)
- Dehydration
- Chronic malnutrition

Method of administration
The tablet should be swallowed with a large amount of water or, if desired, left to dissolve in plenty of water, which should be stirred well before drinking.

4.3 Contraindications

Hypersensitivity to the paracetamol or to any of the excipients listed in section 6.1.
Use in children under 6 years of age.

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.

Multiple daily doses or in the event of overdosage may cause severe damage to the liver; in such cases, immediate medical advice should be sought even if the patient feels well because of the risk of irreversible liver damage (see section 4.9). In young subjects 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 severe renal or severe hepatic impairment (child-Pugh> 9), mild to moderate hepatic impairment (incl. Syndrome Gilbert),acute hepatitis, concomitant administration of drugs that affect the liver function, glucose -6-phosphatedehyrogenase deficiency, haemolytic anaemia, alcohol abuse, chronic dehydration and malnutrition.

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

In cases of high fever, signs of a secondary infection, or persistence of the symptoms for more than three days, medical advice should be sought.

After prolonged use (> 3 months) of analgesics intake every day or more often, headaches may occur or worsen. Headaches caused by overuse of analgesics (mean-tested headache) should not be handled by increasing the dose. In those cases, the use of analgesics should be taken after consulting a doctor.

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

Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

4.5 Interaction with other medicinal products and other forms of interaction

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine. The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged daily use of paracetamol with increased risk of bleeding. Occasional doses have no significant effect.

Paracetamol is extensively metabolized in the liver and can therefore interact with medicinal products with the same metabolic pathway or induce/inhibit the same metabolic pathway. Chronic use of alcohol or medicinal products which induce liver enzymes like rifampicin, barbiturates, some anti-epileptic drugs (e.g. carbamazepine, phenytoin, phenobarbital, pirimidone) and St. John's Wort can increase the hepatotoxicity of paracetamol as a result of an increased and fast formation of toxic metabolites. Caution is therefore necessary with concomitant use of enzyme-inducing drugs.

Probenecide blocks the binding of paracetamol to glucuronic acid reducing paracetamol clearance by a factor of about 2. If probenecide is taken concurrently the paracetamol dose should be reduced.

Paracetamol can increase the plasma concentration of chloramphenicol.

With chronic concomitant use of paracetamol and zidovudine, neutropenia often occurs and is probably due to the reduced metabolism of zidovudine.

Salicylamide may prolong the elimination t1/2 of paracetamol.

Isoniazid reduces the paracetamol clearance, with possible potentiation of its action and/or toxicity, by inhibition of its metabolism in the liver.

Paracetamol may decrease the bioavailability of lamotrigine, with possible reduction of its effect, due to a possible induction of its metabolism in the liver.

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

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.

Breast feeding:
Paracetamol is excreted in breast milk but not in a clinically significant amount. No negative 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.

Fertility:
No detrimental effects on fertility upon normal use of paracetamol are known.

4.7 Effects on ability to drive and use machines

Paracetamol 500mg Tablets 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	Agranulocytosis (long-term use), thrombocytopenia, thrombocytopenic purpura, leucopenia, haemolytic anaemia, Platelet disorders, stem cell disorders.
	Very rare	Pancytopenia
Immune system disorders	Rare	Hypersensitivity (excluding angioedema).
	Very rare	Hypersensitivity (angioedema,ventilation difficult, hyperhidrosis, nausea, hypotension, shock, anaphylactic reaction), requiring discontinuation of treatment
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.
Respiratory, thoracic and mediastinal disorders	Very rare	Bronchospasm in patients sensitive to aspirin and other NSAIDS
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.
	Administration of 6 grams of paracetamol may already lead to hepatic damage (in children: more than 140 mg/kg); higher doses cause irreversible hepatic necrosis.	
Skin and subcutaneous	Rare	Pruritus, rash, sweating, purpura,

tissue disorders		angioedema, urticaria.
	Very rare	Serious skin reactions have been reported
	Unknown	Acute generalised exanthemateus pustulosis, toxic necrolysis, drug-induced dermatosis, Stevens-Johnson-syndrome
Renal and urinary disorders	Very rare	Sterile pyuria (cloudy urine) and renal side effects (severe renal impairment, nephrite interstitial, haematuria, anuresis)
General disorders and administration site conditions	Rare	Dizziness (excluding vertigo), malaise, pyrexia, sedation, drug interaction NOS.
Injury, poisoning and procedural complications	Rare	Overdose and poisoning

NOS= Not otherwise specified.

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

Paracetamol can result in poisoning, particularly in elderly subjects, young children, patients with liver diseases, in cases of chronic alcoholism, in patients suffering from chronic malnutrition and patients using liver enzyme inducing agents. Overdose may be fatal in these cases.

Liver damage is possible in adults who have taken 6 g or more of paracetamol, especially if the patient has risk factors (see below).

Risk Factors:

If the patient

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

Or

- Regularly consumes ethanol in excess of recommended amounts.

Or

- Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms:

Acute paracetamol intoxication can progress in several phases.

The symptoms of paracetamol over dosage in the first two days are nausea, vomiting, anorexia, pallor and abdominal pain. Slight intoxication is limited to these symptoms.

When intoxication is more severe, subclinical symptoms as increased liver enzymes appear. From 2 to 4 days after exposure, clinical symptoms of liver damage are manifest, such as painful hepatomegaly, jaundice, encephalopathy, coma and disturbed blood clotting, all secondary to liver insufficiency.

Insufficient kidney functioning (tubule necrosis) is rare. Severe intoxication may result in metabolic acidosis may occur.

Treatment:

Local treatment guidelines for paracetamol overdose should be followed.

Directly after intake of a paracetamol overdose, possibly leading to severe intoxication, absorption – decreasing therapy can be applied such as gastric lavage within one hour of intake or administration of activated charcoal.

N-acetylcysteine (NAC) can be administered as antidote. For administration of NAC and further treatment, the concentration of paracetamol in blood should be determined. In general, intravenous administration of NAC is preferred and should be continued until paracetamol is no longer detectable. It is important to realize that intake of NAC up to 36 hours after intake can improve prognosis. Oral administration of NAC should not be combined with oral activated charcoal.

Liver tests have to be performed at the start of treatment and need to be repeated each 24 hours after treatment. In most cases, hepatic transaminases will return to normal levels within two weeks after intake of overdose with complete recovery of liver function. In rare cases, liver transplantation may be required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other analgesics and antipyretics, Anilides

ATC code: N02BE01

Paracetamol is an effective antipyretic and analgesic agent. However, it has no antiinflammatory effect.

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 without a conspicuous peripheral anti-inflammatory activity.

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.

Metabolism
In adults paracetamol is conjugated in the liver with glucuronic acid (~60%), sulphate (~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. For elderly patients, the capacity for conjugation is not modified.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Animal studies have not indicated any teratogenic potential.

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

Maize starch
Gelatin (E441)
Silica, colloidal anhydrous (E551)
Talc (E553B)
Sodium starch glycolate (Type A)(E468)
Magnesium stearate (E572)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Paracetamol 500mg Tablets is packed in PVC-ALU blister packs of 8, 10, 12, 16, 20, 24, 30, 32, 50, 56, 60, 100 & 300 tablets. Not all pack sizes may be marketed.

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

PA2315/065/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th July 2015
Date of last renewal: 24th April 2020

10 DATE OF REVISION OF THE TEXT

November 2022