Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol 1000 mg Effervescent Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each effervescent tablet contains 1000mg of Paracetamol.

Excipients: Sodium content approximately 657 mg/tablet
Sorbitol (E420) 45 mg/tablet.

For a full list of excipient see section 6.1

3 PHARMACEUTICAL FORM

Effervescent Tablet

White to off white, round, flat faced, bevelled edged tablets plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For adults and adolescents only:
Treatment of mild to moderate pain and/or fever.

4.2 Posology and method of administration

This presentation is reserved for use in adults and in adolescents over 50kg of body weight aged 16 years and above.

Doses depend on body weight and age; a single dose ranges from 10 to 15 mg/kg body weight (= b.w.) to a maximum of 60 mg/kg b.w. for total daily dose.

Adults and adolescents > 50 kg of body weight
Take one tablet (1000 mg) every four to six hours, upto a maximum of 3 tablets (3000 mg) in 24 hours.

Maximum daily dose:

- The maximum daily dose of Paracetamol must not exceed 3000 mg.
- Maximum single dose is 1000 mg (1 effervescent tablet).

Paracetamol 1000 mg Effervescent Tablets are for oral administration. The tablets should be placed in a full tumbler of water immediately before use and allowed to dissolve completely before swallowing.

Frequency of administration:

Doses of Paracetamol 1000 mg Effervescent Tablets should not be given more frequently than every 6 hours, and not more than 3 doses should be given in any 24 hour period.

Renal insufficiency:
In case of renal insufficiency 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

Paracetamol 1000 mg Tablets are not suitable for patients with renal and hepatic insufficiency when reduced dose is required. More appropriate pharmaceutical forms are available in the market for use.

Hepatic insufficiency:
In patients with impaired hepatic or Gilbert's syndrome, the dose must be reduced or the dosing interval prolonged.

The daily effective dose should not exceed 60 mg/kg/day (upto maximum 2000 mg /day) in the following situations:
- Adults weighing less than 50 kg
- Mild to moderate hepatic insufficiency, Gilbert's syndrome (familial non-haemolytic jaundice)
- Dehydration
- Chronic malnutrition
- Chronic alcoholism

Intake of paracetamol with food and drink does not affect the efficacy of the medicinal product.

4.3 Contraindications

- Hypersensitivity to Paracetamol, or any of the excipients.

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 children treated with 60mg/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 insufficiency, mild to moderate hepatocellular insufficiency (including Gilbert's syndrome), severe hepatic insufficiency (***Child-Pugh >9***), acute hepatitis, concomitant treatment with medicinal products affecting hepatic functions, glucose-6-phosphatedehydrogenase deficiency, haemolytic anaemia, dehydration, alcohol abuse and chronic malnutrition (see section 4.2).

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 2000 mg in such case. Alcohol should not be used during the treatment with Paracetamol.

"Caution is advised in asthmatic patients sensitive to aspirin, because light reaction bronchospasm with paracetamol (cross-reaction) has been reported in less than 5% of the patients tested"

Abrupt discontinuation of long-term use of high-dosed analgesics, taken not as directed, may cause headache, tiredness, muscular pain, nervousness and vegetative symptoms. The withdrawal symptoms subside within a few days. Patients should be advised to consult their doctor if headaches become persistent.

Paracetamol Effervescent Tablets should not be administered in children and adolescents below 16 years of age and under 50 kg body weight.

This medicinal product contains 657 mg of sodium per tablet. To be taken into consideration by patients on a controlled sodium diet**.**

This medicinal product contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Do not exceed the stated dose.

If symptoms persist consult a doctor.

Treatment with an antidote is advised if an overdose is suspected.

4.5 Interaction with other medicinal products and other forms of interaction

Hepatotoxic substances may increase the possibility of Paracetamol accumulation and overdose. The metabolization of paracetamol is increased in patients taking enzyme-inducing drugs such as rifampicin and some antiepileptics (carbamazepine, phenytoin, phenobarbital, primidone). Isolated reports describe unexpected hepatotoxicity in patients taking enzyme-inducing drugs and alcohol.

- Probenecid causes an almost 2-fold reduction in clearance of Paracetamol by inhibiting its conjugation with glucuronid acid. A reduction of the Paracetamol dose should be considered for concomitant treatment with probenecid.
- Salicylamide may prolong the elimination t1/2 of Paracetamol.
- Metoclopramide and domperidone accelerate absorption of Paracetamol. However, concurrent use need not be avoided.
- Cholestyramine reduces absorption of Paracetamol and therefore should not be administered within an hour following Paracetamol administration.
- Concomitant use of Paracetamol (4000 mg per day for at least 4 days) with oral anticoagulants may lead to slight variations of INR values. In this case, increased monitoring of INR values should be done during the duration of the combination and after its discontinuation.
- Isoniazid : Reduction of paracetamol clearance, with possible potentiation of its action and/ or toxicity, by inhibiting its metabolism in the liver.
- Lamotrigine: decrease in the bioavailability of lamotrigine, with possible reduction of its effect, due to possible induction of liver metabolism.
- Chloramphenicol: Increased plasma concentration of chloramphenicol

Interference with laboratory tests:
Paracetamol may affect uric acid tests by wolframato phosphoric acid, and blood sugar tests by glucose-oxidase-peroxidase.

4.6 Fertility, pregnancy and lactation

Epidemiological data on the oral administration of therapeutic doses of Paracetamol indicate no adverse reactions on pregnancy or on the health of the fetus/newborn child. Prospective data on overdose during pregnancy showed no increased risk of malformations. Reproduction studies investigating oral administration did not indicate any signs of malformation or fetotoxicity (see section 5.3).

Paracetamol is considered to be safe in normal therapeutic doses for short-term use as a minor analgesic/antipyretic, but patients should seek the advice of their doctor regarding its use.

Lactation:
Following oral administration, Paracetamol is excreted into breast milk in small quantities. To date, no adverse reactions or undesirable effects are known in association with lactation. Therapeutic doses of Paracetamol can be administered during breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The frequency using the following convention should be: 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). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Frequency	System	Symptoms
Rare >1/10000 - < 1/1000	Blood and lymphatic system disorders	Platelet disorders, stem cell disorders, agranulocytosis, leucopenia, thrombocytopenia, haemolytic anaemia, pancytopenia, methaemoglobenaemia
	Immune system disorders	Allergies (excluding angioedema).
	Psychiatric disorders	Depression NOS, confusion, hallucinations.
	Nervous system disorders	Tremor NOS, headache NOS.
	Eye disorders	Abnormal vision.
	Cardiac disorders	Oedema.
	Gastrointestinal disorders	Haemorrhage NOS, abdominal pain NOS, diarrhoea NOS, nausea, vomiting.
	Hepato-biliary disorders	Abnormal Hepatic function, hepatic failure, hepatic necrosis, jaundice.
	Skin and subcutaneous tissue disorders	Pruritus, rash, sweating, purpura, angioedema, urticaria
	General disorders and administration site conditions	Dizziness (excluding vertigo), malaise, pyrexia, sedation, drug interaction NOS.
	Injury, poisoning and procedural complications	Overdose and poisoning
Very Rare (< 10,000)	Respiratory, thoracic and mediastinal disorders	Bronchospasm
	Hepato-biliary disorders	hepatotoxicity
	General disorders and administration site conditions	hypersensitivity reaction (requiring discontinuation of treatment)
	Metabolism and nutrition disorders	Hypoglycemia
	Renal and urinary disorders	Sterile pyuria (cloudy urine) and renal side effects

Interstitial nephritis has been reported incidentally after prolonged use of high doses. Some cases of epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme, edema of the larynx, anaphylactic shock, anemia, liver alteration and hepatitis, renal alteration (severe renal impairment, haematuria, anuresis), gastro intestinal effects and vertigo have been reported.

4.9 Overdose

There is a risk of poisoning, particularly in elderly subjects, in young children, in patients with liver disease, in cases of chronic alcoholism and in patients with chronic malnutrition. Overdose of Paracetamol is potentially fatal in all populations. 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, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.

Or

b) Regularly consumes ethanol in excess of recommended amounts.

Or

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

Symptoms 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.

- Overdose, 10g or more of Paracetamol in adults or 150 mg/kg of body weight, causes 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.

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.

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: *other analgesics and antipyretics; anilides*
ATC code: N02BE01

5.2 Pharmacokinetic properties

Absorption

The absorption of paracetamol by the oral route is rapid and complete. Maximum plasma concentrations are reached 30 to 60 minutes following ingestion.

Distribution
Paracetamol is distributed rapidly throughout all tissues. Concentrations are comparable in blood, saliva and plasma. Protein binding is low.

Metabolism
Paracetamol is metabolized mainly in the liver following two major metabolic pathways: glucuronic acid and sulfuric acid 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 cysteine and mercaptopuric acid. Conversely, when massive intoxication occurs, the quantity of this toxic metabolite is increased.

Elimination
Elimination is essentially through the urine. 90% of the ingested dose is eliminated via the kidneys within 24 hours, principally as glucuronide (60 to 80%) and sulphate conjugates (20 to 30%). Less than 5% is eliminated in unchanged form.
Elimination half life is about 2 hours.

Special patient groups
Renal Insufficiency: In cases of severe renal insufficiency (creatinine clearance lower than 10 ml/min) the elimination of paracetamol and its metabolites is delayed.
Elderly Subjects. The capacity for conjugation is not modified.

5.3 Preclinical safety data

In animal studies investigating the acute, subchronic and chronic toxicity of paracetamol in the rat and mouse, 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. The metabolites that is probably responsible for the toxic effects and the corresponding organic changes have also been found in humans. Moreover, during long term use (i.e. 1 year) very rare cases of reversible chronic aggressive hepatitis have been described in the range of maximum therapeutic doses. At subtoxic doses, symptoms of intoxication can occur following a 3-week intake period. Paracetamol should therefore not be administered over a long period of time or at high doses.

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 and clinical experience to date have not indicated any teratogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous Citric acid
Sorbitol E420
Sodium Carbonate, Anhydrous
Sodium Bicarbonate
Povidone K 25 (E1201)
Simeticone emulsion (30%)
Docusate sodium
Saccharin Sodium
Macrogol 6000
Monosodium Glycine carbonate
Sodium Benzoate

Qualitative composition of Simeticone emulsion (30%):
Water
Polydimethylsiloxane
Polyethylene glycol stearate
Polyethylene glycol
Glycerides, C14-18, mono- and di
Polyethylene glycol distearate
Polyethylene glycol palmitate
Octamethylcyclotetrasiloxane

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

For Polypropylene tube:
Do not use the product after 1 month from the date of first opening.

6.4 Special precautions for storage

For Polypropylene Tube:
Store below 25°C. Keep the polypropylene tube tightly closed. Store in the original container to protect from moisture and light.

For Alu-Alu Strip Pack:
Store below 25°C. Store in the original package in order to protect from moisture and light.

6.5 Nature and contents of container

Paracetamol 1000 mg Effervescent Tablets are packed in Alu-Alu Strip packs and Polypropylene tubes.
Alu-Alu Strip pack:
Strip packs are made of two plain aluminium strip foils laminated with LDPE film. Each strip has 4 or 10 tablets. The strips are packed in a carton having 4 tablets (4x1), 8 tablets (4x2), 20 tablets (4x5), 40 tablets (4x10), or 10 tablets (1 x 10) and packed with a patient information leaflet.

Polypropylene Tubes:
White opaque plain polypropylene tube and white opaque tamper evident polyethylene caps with inbuilt desiccant. Each tube contains 10 or 12 tablets.
Pack size: 36 (3 x 12) tablets per carton, 10 (1 x 10) tablets per carton and 20 (2 x 10) tablets per carton. Each carton has a patient leaflet for each polypropylene tube.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited,
Sage House, 319 Pinner Road,
North Harrow, HA1 4 HF,
Middlesex,
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 1390/16/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th June 2011

10 DATE OF REVISION OF THE TEXT

May 2012