SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Paracetamol Accord 500 mg effervescent tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg paracetamol.

Excipients with known effect:
Each 500 mg tablet contains 418.5 mg sodium and 100 mg sorbitol (E420).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Effervescent tablet.

White to off-white, round, flat, beveled edges tablets, plain on both sides with odour of lemon.
Diameter: 25.4 mm approximately

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

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

Adults and adolescents over 50 kg bodyweight (>15 years):
1 - 2 tablets (500 mg – 1 g) every 4 to 6 hours as required.
It is generally not required to exceed 3 g of paracetamol per day (6 tablets per 24 hours).
The maximum daily dose is 4 g (8 tablets per 24 hours).

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

The recommended dose for children is 10-15 mg/kg body weight every 4-6 hours, 3 to 4 times per 24 hours. The maximum dose for children is 60 mg/kg/24 hours divided into 4 doses.

Children over 40 kg bodyweight (>12 years):
1 tablet (500 mg) every 4-6 hours. The maximum daily dose is 2.5 g (5 tablets per 24 hours).

The dose interval should always be at least 4 hours.

Method of administration

For oral administration. The tablets should be placed in a glas of water and allowed to dissolve completely before swallowing.

Special groups of patients:
Impaired liver function, chronic alcohol consumption:
In patients with impaired hepatic function or Gilbert's syndrome, the dose must be reduced or the dosing interval prolonged (see section 4.4).

Impaired kidney function:
In patients with 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

Elderly patients:
Dose adjustment is not required in the elderly.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

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.

Do not combine with other analgesics containing paracetamol (e.g. combination medications).

Higher doses than recommended lead to a risk of very severe liver damage.

Clinical signs of liver damage generally only start after a few days and climax after 4-6 days as a rule. An antidote should be administered as soon as possible. See also section 4.9 Overdose.

In the event of high fever, signs of secondary infection or if symptoms last longer than 3 days, treatment must be reassessed.

Caution should be exercised in patients with asthma who are sensitive to acetylsalicylic acid, as mild reactions of bronchospasm have been reported with paracetamol (cross-reaction).

The risks of overdose are greater in those with non-cirrhotic alcoholic liver disease due to alcohol intake. Caution should be exercised in patients with chronic alcoholism. In such cases, the dose should not exceed 2 g daily. Alcohol should not be used during treatment with paracetamol.

Caution in patients with glutathione depleted states such as sepsis; the use of paracetamol may increase the risk of metabolic acidosis.

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 and 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.

This medicinal product contains 418.5 mg sodium per effervescent tablet, equivalent to 20.9% of the WHO recommended maximum daily intake of 2 g sodium for an adult and is considered to represent ‘high’ sodium..

The maximum daily dose of this product is equivalent to 167.4% of the WHO recommended maximum daily intake of 2 g sodium for adults and is considered to represent ‘high’ sodium.

[Product name] is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

This medicine contains 100 mg sorbitol (E420) in each effervescent tablet Sorbitol is a source of fructose. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.
Effect on laboratory tests
Paracetamol may affect uric acid tests in serum through the phosphotungstic acid and blood sugar tests by glucose-oxidase-peroxidase.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Studies have shown that the effect of *warfarin* may be enhanced in treatment with paracetamol. The effect appears to increase with the dose of paracetamol but can occur at doses of just 1.5-2.0 g paracetamol a day for at least 5-7 days. Single doses of paracetamol at normal dosage are not deemed to have any effect.

Pharmacokinetic interactions

Effects of other medicinal products on the pharmacokinetics of paracetamol
In pharmacokinetic studies, enzyme-inducing medicinal products such as certain anti-epileptic drugs (*phenytoin, phenobarbital, carbamazepine*) have been shown to reduce the plasma AUC of paracetamol to approx. 60%. Other substances with enzyme-inducing properties, e.g. rifampicin and St. John's wort (hypericum) are also suspected of producing lower concentrations of paracetamol. In addition, there may be a greater risk of liver damage from treatment with the maximum recommended dose of paracetamol in patients who are on enzyme-inducing medicinal products.

Probenecid immediately halves clearance of paracetamol by inhibiting its conjugation with glucuronic acid. This should mean that the dose of paracetamol can be halved in simultaneous treatment with probenecid.

The absorption rate of paracetamol may be increased by *metoclopramide*, but the substances can be given together. The absorption of paracetamol is reduced by *cholestyramine*. Cholestyramine should not be given within an hour if the maximum analgesic effect is to be achieved.

Zidovudine may affect paracetamol metabolism and vice versa, which may add to the toxicity of both.

Effects of <Invented Name> on the pharmacokinetics of other medicinal products
Paracetamol can affect the pharmacokinetics of *chloramphenicol*. Analysis of plasma chloramphenicol is therefore recommended with combination therapy.

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 Fertility, pregnancy and lactation

Pregnancy
A large amount of data on pregnant women indicates 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
Low levels of paracetamol are excreted in human milk. No undesirable effects on breastfed infants have been reported. Paracetamol can be used during breast-feeding as long as the recommended dosage is not exceeded. In case of long-term use, caution should be exercised.

Fertility
There are no concerns about effects on fertility due to paracetamol treatment.

4.7 Effects on ability to drive and use machines

No effects have been observed.

4.8 Undesirable effects

Side effects caused by <Invented Name> are generally rare. The most common side effects are skin reactions and elevated liver transaminase:

Adverse reactions frequency is specified 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 available data)

System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Rare	Platelet disorders, stem cell disorders, agranulocytosis, thrombocytopenia, neutropenia, leukopenia, haemolytic anaemia, pancytopenia
Immune system disorders	Rare	Allergies (excluding angioedema)
	Very rare	Anaphylactic shock, hypersensitivity reaction (requiring discontinuation of treatment)
Metabolism and nutrition disorders	Very rare	Hypoglycaemia
	Not Known	High anion gap metabolic acidosis
Psychiatric disorders	Rare	Depression, confusion, hallucination
Nervous system disorders	Rare	Tremor, headache
Eye disorders	Rare	Abnormal vision
Respiratory, thoracic and mediastinal disorders	Very rare	Bronchospasm
Gastrointestinal disorders	Rare	Haemorrhage, abdominal pain, diarrhoea, nausea, vomiting
Hepatobiliary disorders	Rare	Elevated liver transaminase, abnormal hepatic function, hepatic failure, hepatic necrosis, jaundice
	Very rare	liver damage
Skin and subcutaneous tissue disorders	Rare	Rash, urticaria, angioedema, Allergic dermatitis
	Very rare	Serious skin reactions have been reported

	Not known	Stevens-Johnson syndrome, toxic epidermal necrolysis
Renal and urinary system	Very rare	Sterile pyuria (cloudy urine), renal side effects

Description of selected adverse reactions

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.

Liver damage with paracetamol has occurred in conjunction with alcohol abuse. The risk of kidney damage cannot be entirely ruled out with long-term use.

Interstitial nephritis has been reported incidentally after prolonged use of high doses. Some cases of *erythema multiforme*, oedema of the larynx, anaemia, liver alteration and hepatitis, renal alteration (severe renal impairment, haematuria, anuresis) 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 the national reporting system listed in Appendix V.

4.9 Overdose

At excess doses the conjugation capacity in the liver may be reduced after which a large part of the dose is metabolised by oxidation. If stores of glutathione are depleted the reactive intermediate metabolites bind irreversibly to liver macromolecules. Clinical symptoms of liver damage generally only appear after a few days. It is therefore crucial to start treatment with an antidote as soon as possible in order to prevent or minimise liver damage after toxic doses.

Toxicity:
See below under Treatment for information on toxic plasma concentrations. 5 g over 24 hours for up to 3½ year-olds, 15-20 g for adults, 10 g to an alcoholic produced lethal intoxication. A toxic dose for adults is generally 140 mg/kg and a toxic dose for children approx. 175 mg/kg. Starvation, dehydration, medication with enzyme-inducing agents (antiepileptic's, promethazine etc.) and chronic high alcohol consumption are risk factors and can cause pronounced liver damage even in small doses. Even sub-acute "therapeutic" overdose has led to serious intoxication with doses varying from 6 g/day for a week, 20 g for 2 or 3 days, etc.

Symptoms:
For a few hours following ingestion and for the first 1-2 days there may be abdominal pains, nausea and vomiting. After 2-3 days there may be signs of liver damage with elevated transaminase levels, falling prothrombin values, coagulopathy, icterus, malaise, hypoglycaemia, hypokaliemia, hypophosphataemia, metabolic acidosis, disseminated intravasal coagulation. Manifest liver failure and hepatic coma. Liver damage generally peaks after 4-6 days. Kidney damage may be secondary to liver damage or as the sole or main toxic manifestation within 24-72 hours of the overdose. Pancreatitis and toxic myocardial damage with arrhythmia and heart failure have been reported. At extremely high concentrations there have been reports of loss of consciousness combined with acidosis and hyperglycaemia. Pancytopaenia.

Treatment:
If necessary, gastric irrigation and activated charcoal. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion. Acute response. False lows may be measured if acetylcysteine has already been administered. If an antidiarrhoeal has been taken a new sample should

be taken 2 hours after the first (delayed peak concentration). Treatment with acetylcysteine initiated within 8-10 hours provides complete protection from liver damage, after which the effect diminishes. Acetylcysteine is used if the paracetamol concentration is above the following levels at respective points: 1000 micromol/l at 4 hours, 700 micromol/l at 6 hours and 450 micromol/l at 9 hours after exposure. In cases of concomitant alcoholism, starvation, dehydration, impaired liver function or medication with enzyme-inducing drugs there may be grounds for setting the threshold for antidote therapy at about ¾ the listed levels. The method of administration is adapted to the circumstances (level of consciousness, tendency to vomiting etc.). However, intravenously administered acetylcysteine is deemed more effective and safer. Dosage of acetylcysteine: *Intravenously* initially 150 mg/kg in 200-300 ml isotonic infusion solution over 15 minutes, then 50 mg/kg in 500 ml 50 mg/ml glucose over 4 hours and then 6.25 mg/kg/hour over 16 hours (75 mg/kg dissolved in 500 ml isotonic glucose solution and administered over 12 hours). Fluid volumes can be reduced, if necessary. Contact the National (local) Poisons Information Centre for information.) for a specific schedule. (In exceptional circumstances, acetylcysteine may be administered orally if the intravenous route is not available. Contact the National (local) Poisons Information Centre for information. Acetylcysteine may provide some protection even after 10 hours, but in such cases prolonged treatment should be administered. Acetylcysteine also reduces mortality in the event of manifest paracetamol-induced liver failure (please discuss with the Poisons Information Centre). Close monitoring of hepatic and renal function, coagulation status, fluid and electrolyte status. Liver and kidney failure therapy is often required in cases where the deadline for effective antidote treatment has passed and there are toxic concentrations present. Haemoperfusion may be indicated in special circumstances. In extreme cases a liver transplant may be required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: analgesic and antipyretic, ATC code: N02BE01

Paracetamol is an aniline derivative with analgesic and antipyretic actions similar to those of acetylsalicylic acid.

The antipyretic effect is probably achieved through action on the hypothalamic heat-regulation centre, whereby heat dissipation is increased. Central action is probably related to the inhibition of prostaglandin synthesis in the hypothalamus.

The latency period for the analgesic effect is approx. ½ hour. The peak effect is achieved within 1-2 hours and lasts for 4-5 hours. The course of the antipyretic effect is somewhat slower. Thus the latency period is approx. ½-1 hour, maximum reduction in fever is recorded after 2-3 hours and the effect lasts for about 8 hours.

5.2 Pharmacokinetic properties

Absorption
Paracetamol is absorbed well when administered orally. Peak plasma concentration of paracetamol is achieved within ½-1 hour.

Distribution
Paracetamol is distributed rapidly into all tissues. Blood, plasma and saliva concentrations are comparable. Protien binding is low with recommended doses.

Biotransformation
The plasma half-life is approx. 2 hours. Paracetamol is primarily metabolised in the liver by conjugation to glucuronide and sulphate. A small amount (about 3-10% of a therapeutic dose) is

metabolised by oxidation by cytochrome P450 and the reactive intermediate metabolite thus formed is bound preferentially to the liver glutathione and excreted as cysteine and mercapturic acid conjugates.

Elimination
Excretion occurs via the kidneys. Approx. 2-3% of a therapeutic dose is excreted unchanged, approx. 80-90% as glucuronide and sulphate and a smaller amount as cysteine and mercapturic acid derivatives.

Renal insufficiency
In patients with severe renal insufficiency (creatinine clearance < 10 ml/min), elimination of paracetamol and its metabolites is delayed.

Elderly patients
Conjugation is unchanged in this patient group.

Paediatric population
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. In children the formation of the toxic intermediate product is reduced compared with adults. Additionally, neonates have an increased ability to replete liver glutathione. Therefore, severe liver damage caused by paracetamol would seem to be rarer in children than in adults. The elimination half-life of paracetamol is 2–2.5 hours in children.

5.3 Preclinical safety data

There is no pre-clinical data of relevance to the safety assessment beyond what has already been covered in the Summary of Product Characteristics.

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

Anhydrous citric acid (E330)
Sodium hydrogen carbonate
Sorbitol (E420)
Sodium carbonate anhydrous
Povidone
Simethicone
Saccharin sodium
Macrogol
Powdarome lemon premium (Flavouring preparations, flavouring substances, natural flavouring substances, maize maltodextrin, acacia gum, alpha-tocopherol)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C
Tube: Keep the tube tightly closed to protect from moisture,
Strip: Store in the original primary container to protect from moisture.

6.5 Nature and contents of container

Perforated unit dose Strip [4 layer-Paper/PE/Alu/ Surlyn (co-polymer of Ethylene/Methacrylic acid/Zinc material)] containing 6, 10, 12, 16, 20, 24, 30, 40, 60, 90, 100 and 500 tablets.

Tablet container and white opaque tamper evident polyethylene cap with inbuilt desiccant (dry granules or beads of silica gel and molecular sieve) containing 6, 10, 12, 16, 20, 24, 30, 40, 60, 90, 100 and 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7. MARKETING AUTHORISATION HOLDER

<To be completed nationally>

8. MARKETING AUTHORISATION NUMBER(S)

<To be completed nationally>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

5 December 2018
<To be completed nationally>

10. DATE OF REVISION OF THE TEXT

2025-01-23