SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Parakris-500 (Paracetamol Tablets BP 500mg)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:
Paracetamol BP ----------500mg.
Excipients----------Q.S

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Oral Tablet

White coloured, round shape uncoated tablet, one side score line and other side plain.

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

Adults (including elderly) and children 12 years and older (minimum 40kg):
Tablets 500 mg: 1-2 tablets every 4-6 hours,,
The maximum daily dose is 4g (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 each weight group given below is for guidance only.

50 mg /kg/day divided into 3 to 4 doses.
Maximum treatment time without consulting a doctor is 3 days for fever and 5 days for pain. Tablets

500 mg:

Weight	Age	Dose
17-25 kg	4 - 7 years	½ tablet every 4-6 hours, max. 4 times per 24 hours.
25-40 kg	7-12 years	½-1 tablet every 4-6 hours, max. 4 times per 24 hours.
>40 kg	>12 years	1-2 tablets every 4-6 hours, max. 8 tablets per 24 hours.

The dose interval should always be at least 4 hours.
Maximum daily dose should not be exeeeded due to risk of serious hepatic damage (see sections 4.4 and 4.9)

Method of administration For
oral administration.

Special groups of patients:
Impaired liver function:
In patients with impaired hepatic function or Gilbert's syndrome, the dose must be reduced or the dosing interval prolonged.

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 or any of the excipients listed in section 6.1.

Sever liver insufficiency.

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 under 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.

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 < to be completed nationally > on the pharmacokinetics of other medicinal products
Paracetamol can affect the pharmacokinetics of *chloramphenicol*. Analysis of plasma chloramphenicol is therefore recommended with combination therapy.

Effect on laboratory tests
Paracetamol may affect uric acid tests in serum through the phosphotungstic acid and blood sugar tests by glucose-oxidase-peroxidase.

4.6 Fertility, pregnancy and lactation

Pregnancy
A large amount of data on pregnant women indicates neither malformative, nor feto/neonatal toxicity. Paracetamol can be used during pregnancy if clinically needed 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 Adverse effects

Side effects caused by <product 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 the available data)

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

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 cases of 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

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 <to be completed nationally>.

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, antipyretic, ATC code: N02BE01

Paracetamol is an aniline derivative with analgesic and antipyretic actions similar to those of acetylsalicylic acid but paracetamol does not cause gastrointestinal irritation and is also well tolerated by patients with ulcers. Paracetamol does not affect thrombocyte aggregation or bleeding time. Paracetamol is generally well tolerated by patients who are hypersensitive to acetylsalicylic acid.

The antipyretic effect is achieved through action on the hypothalamic heat-regulation centre, whereby heat dissipation is increased.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize Starch, Citric acid, Dibasic Calcium Phosphate, Sodium Starch Glycolate, P.V.P.K 90, Methyl Paraben, Propyl Paraben, Magnesium Stearate, Purified Talc & Colloidal Silicon Dioxide (Aerosil).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister strip: 3 years

6.4 Special precautions for storage

Store in a cool, dry place below 30°C, away from sunlight.

6.5 Nature and contents of container

Blister made from opaque PVC with an aluminium /PVC lidding foil. Package Size: 10 x 10

Tablets.

6.6 Special precautions for disposal and other handling

No special requirements

7 Manufactured by:

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