Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol Krka 500 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg paracetamol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, caplet-shaped tablet, debossed with "500" on one side and plain on other side (17.5 mm long x 7.3 mm x 5.7 mm thick).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of mild to moderate pain and fever.

4.2 Posology and method of administration

Posology

Paracetamol should be used at the lowest effective dose for the shortest possible time. The maximum daily dose must not be exceeded.

Adults and adolescents aged 16 years and older (≥ 55 kg of body weight)
500-1000 mg 3-4 times a day, but not more than 4 g per day. In individual cases, 500 mg 3-4 times a day may be sufficient.
Minimum dosing interval between doses should be at least 4 hours.

Paediatric population
Children between 9-12 years (30-40 kg of body weight) 500 mg up to 3 times a day.
Children between 12-15 years (40-55 kg of body weight) 500 mg up to 4 times a day.
Doses depend on body weight and age. Recommended single dose is 15 mg/kg of body weight. The maximal daily dose for patients weighing less than 50 kg is 60 mg/kg of body weight/day.
Minimum dosing interval between doses should be at least 4 hours.

Paracetamol Krka is not suitable for children under 9 years of age.

Patients with renal insufficiency
The drug should be used with caution in patients with renal insufficiency.
In case of moderate and severe renal insufficiency the dose should be adjusted:

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

Patients with hepatic impairment
The drug should be used with caution in patients with hepatic dysfunction (see section 4.4). In patients with impaired liver function, the dose should be reduced or the dosing interval extended.
The daily dose should not exceed 2 g in the following situations:

- liver insufficiency,
- Gilbert's syndrome (familial non-hemolytic jaundice),
- chronic alcohol consumption.

Elderly
No dosage adjustment is required in the elderly.

Method of administration
For oral use. Swallow the tablets with a sufficient amount of water.

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

Patients should be advised not to take other paracetamol containing products concurrently. Concomitant use with other products containing paracetamol may lead to overdose.

Overdose with paracetamol can lead to liver failure that may result in liver transplantation or death. Treatment with antidote should be given as soon as possible (see section 4.9).

An underlying liver disease may increase the risk of paracetamol-related liver damage. Patients diagnosed with hepatic or renal insufficiency should seek medical attention before using paracetamol, and the benefits and risks should be carefully considered.

Cases of hepatic impairment/liver failure at maximum therapeutic doses of paracetamol have been reported in patients with glutathione deficiency, such as in patients who are severely malnourished, have anorexia, low BMI, are chronic alcohol abusers or have sepsis. In these patients, continuous use and maximum doses are not recommended because of a risk of toxic liver reactions and paracetamol should be used at the lowest effective dose.

In patients with glutathione deficiency, the use of paracetamol may increase the risk of metabolic acidosis.

If high fever or signs of secondary infection occur or if symptoms persist for longer than 3 days, the treatment should be re-evaluated.

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 or 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.

With prolonged use of any type of analgesic headache medication, headaches can become worse and more frequent (medicine overuse headache). If this condition develops or is suspected, the headache treatment should be discontinued in consultation with a physician. Medication overuse headaches should be suspected in patients with frequent or daily headache attacks despite (or due to) regular use of analgesics.

Generally, sustained use of analgesics, especially in combination with other analgesic drugs, can lead to persistent renal damage with risk of renal failure (analgesic nephropathy).

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Metoclopramide and domperidone may increase the rate of absorption of paracetamol.

Cholestyramine reduces the absorption of paracetamol. Paracetamol should be administered at least 1 hour before or 4-6 hours after colestyramine.

Drugs with enzyme inducing effect (eg. phenytoin, carbamazepine, rifampicin, phenobarbital, St Johns wort) decrease the bioavailability of paracetamol through an increased glucoronidation, and the risk of hepatic toxicity is increased.

Probenecid reduces the clearance of paracetamol by almost 50%. Thus, the paracetamol dose may be halved during concomitant treatment.

Paracetamol may affect the plasma concentrations of chloramphenicol. Monitoring of chloramphenicol plasma levels is recommended if combining paracetamol with chloramphenicol injection treatment.

The anticoagulant effect of warfarin and other coumarins may increase by prolonged regular daily intake of paracetamol. This leads to an increased risk of bleeding. Occasional intake has no significant effect.

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

Fertility
A harmful effect on fertility has not been established.

Pregnancy
Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. Paracetamol may be used during pregnancy, if clinically necessary, but should be used at the lowest effective dose for the shortest possible time and at the lowest possible dosage frequency. In case of doubt, a doctor should be consulted.

Breast-feeding
Therapeutic doses of this medicinal product may be used during breast-feeding. Paracetamol is excreted in breast milk, but not in clinically significant amounts at recommended doses. According to available published data, breast-feeding is not contraindicated.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Side effects are generally rare. The most frequent side effects are urticaria and increased liver transaminase, seen in 0.01% - 0.1% of treated patients.

Undesirable effects that may occur during treatment with paracetamol are classified into the following groups in order of frequency:
•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

Very rare: agranulocytosis, thrombocytopenia, leukopenia, haemolytic anaemia

Immune system disorders

Very rare: anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis

Metabolism and nutrition disorders
Not known: high anion gap metabolic acidosis

Respiratory, thoracic and mediastinal disorders

Very rare: bronchospasm (analgesic asthma) in patients sensitive to aspirin and NSAIDs

Renal and urinary disorders

Very rare: During long-term treatment, the possibility of renal damage cannot be excluded (see section 4.4).

Skin and subcutaneous tissue disorders

Rare: urticaria

Very rare: angioedema, allergic dermatitis (hypersensitivity reactions including skin rash)

Very rare cases of severe skin reactions have been reported.

Hepatobiliary disorders

Rare: increased liver transaminases

Very rare: hepatic dysfunction

Laboratory test

Rare: increased serum creatinine

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.

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, Website: www.hpra.ie

4.9 Overdose

There is a risk of poisoning, especially in elderly patients, small children, patients with liver disease, cases of chronic alcoholism, patients with chronic malnutrition, in patients with glutathione depletion as in sepsis and patients using enzyme-inducing drugs.

An overdose of > 6 g of paracetamol as a single dose in adults or > 125 mg/kg body weight as a single dose in children paracetamol can cause liver failure, that may require liver transplantation or can lead to death. Similarly, an overdose of paracetamol can cause irreversible hepatic failure because of high total dose levels over a period of time. Acute pancreatitis has been observed, usually in association with liver dysfunction and liver toxicity.

Symptoms
Experience with overdose indicates that clinical signs of liver damage usually occur 24-48 hours after ingestion and reach maximum after 4-6 days.
Symptoms of paracetamol overdose are nausea, vomiting, anorexia, pallor and abdominal pain and usually occur within 24 hours after ingestion. Abdominal pain may be the first symptom of liver injury, which is usually not seen until after 24 to 48 hours, and may sometimes be delayed up to 4 to 6 days after ingestion. The liver damage is generally maximal 72 to 96 hours after ingestion, but may continue if adequate treatment is not initiated (see below). Abnormal glucose metabolism and metabolic acidosis may occur. Acute renal failure with acute tubular necrosis can develop even in the absence of severe liver damage. Cardiac arrhythmia has been reported.

Management:
- immediate hospitalization;
- before treating overdose a blood sample should be taken immediately to measure the plasma paracetamol concentration;
- rapid removal of the ingested product by gastric lavage, followed by administration of activated charcoal (adsorbant) and sodium sulphate (laxative);
- treatment includes administration of the antidote N-acetylcysteine (NAC), intravenously or orally, if possible before 10 hours after ingestion. NAC may provide a certain protective effect even after 10 hours, but in these cases a prolonged treatment is given;
- symptomatic treatment.

Breathing and circulation must be monitored by more severe poisoning. In case of seizures, diazepam may be administered.

In all cases of presumed or recognized overdose with paracetamol, it is important to monitor liver parameters, coagulation parameters, renal parameters, electrolytes, hematology, acid-base status and cardiogram (ECG). Repeating these studies should follow current guidelines and otherwise according to the patient's anamnestic information and clinical status.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: analgesics, anilides, ATC code: N02BE01.

Paracetamol is an antipyretic and analgesic. Paracetamol produces antipyresis through action on the hypothalamic heat-regulation centre and analgesia by elevation of the pain threshold. Paracetamol has analgesic and antipyretic actions similar to aspirin, but it has no useful anti-inflammatory properties.

Paracetamol produces its analgesic effect from the inhibition of prostaglandin synthesis. Prostaglandins appear to sensitise pain receptors to mechanical stimulation or to other chemical mediators. Paracetamol lowers the body temperature in patients with fever but rarely lowers normal body temperature. This is again due to the inhibition of synthesis and release of prostaglandins. The drug also acts on the hypothalamus to produce antipyresis; heat dissipation is increased as a result of vasodilation and increased peripheral blood flow.

Paracetamol is generally well tolerated by patients hypersensitive to acetylsalicylic acid.

5.2 Pharmacokinetic properties

Absorption
Paracetamol is rapidly and almost completely absorbed after oral administration. Plasma concentration reaches a peak in 30 minutes to 2 hours.

Distribution
The volume of distribution of paracetamol measures approximately 1 L/kg body weight. Plasma protein binding is negligible with therapeutic dosages.

Biotransformation
In adults, paracetamol is conjugated in the liver with glucuronic acid (approx. 60%), sulphate (approx. 35%) and cysteine (approx. 3%). 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
Paracetamol is excreted in the urine, mainly as the glucuronide (60 to 80%) and sulphate conjugates (20 to 30%). About 5% is excreted unchanged. The elimination half-life varies from 1 to 4 hours. In case of serious renal insufficiency (creatine clearance less than 10 ml / min) is the elimination of paracetamol and its metabolites delayed. The conjugation capacity in the elderly is unchanged.

5.3 Preclinical safety data

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

Sodium starch glycolate (type A)
Povidone
Partially pregelatinised maize starch
Stearic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister (clear, transparent PVC/Alu foil): 10, 12, 20, 30, 50, 60, 100, 105 and 120 tablets, in a box.
Blister (white, opaque PVC/Alu foil): 10, 12, 20, 30, 50, 60, 100, 105 and 120 tablets, in a box.
White, opaque HDPE bottle with a child-resistant white PP closure: 100 and 105 tablets, in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

8 MARKETING AUTHORISATION NUMBER

PA1347/095/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th May 2020
Date of last renewal: 20th September 2024

10 DATE OF REVISION OF THE TEXT

April 2025