1. NAME OF THE MEDICINAL PRODUCT

Kruidvat Paracetamol 500 mg tablet, tabletten.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg of paracetamol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
(Almost) white, round tablet which is 13 mm in diameter with a score line on one side and the inscription “PARACETAMOL” on the other .

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

Adults and adolescents from 15 years (>50 kg body weight):
1 to 2 tablets (500-1000 mg) at a time, maximum 6 tablets (3000 mg) per 24 hours.

Children and adolescents under 15 years:
The recommended daily dose of paracetamol is about 60 mg/kg which is divided into 4 or 6 administrations daily, i.e. 15 mg/kg every 6 hours or 10 mg/kg every 4 hours.

Children from 12 to 15 years (43-50 kg):
1 tablet (500 mg) at a time, every 4 hours, if needed, with a maximum of 4 tablets per day.

Children from 11 to 12 years (34-43 kg):
1 tablet (500 mg) at a time, every 6 hours, if needed, with a maximum of 4 tablets per day.

Children from 8 to 11 years (26-34 kg):
½ tablet (250 mg) at a time every 4 hours, or 1 tablet (500 mg) every 6 hours, if needed, with a maximum of 3 tablets per day. Other pharmaceutical forms containing paracetamol (i.e. solutions) exist as an alternative for children who might have difficulties to swallow a tablet.

Indications for use:
- Not suitable for children below 8 years of age.
- The dosing interval must be at least 4 hours.
- Do not use in combination with other paracetamol-containing products.
- Do not exceed the stated dose on account of the risk of severe damage to the liver (see sections 4.4 and 4.9).
- Repeat administration is permitted, depending on the recurrence of the symptoms (fever and pain).
- If the pain lasts longer than 5 days or becomes worse or if the fever lasts longer than 3 days or becomes worse or if other symptoms appear, the treatment should be stopped and a doctor should be consulted.
- The taking of paracetamol with food and drink does not affect the efficacy of the medicine.
- The total daily dose may not be higher than 2 g/day in the following situations:
    - adults who weigh less than 50 kg
    - mild to moderate hepatic insufficiency, Gilbert syndrome (familial non-haemolytic jaundice)
    - dehydration
    - chronic malnutrition
    - chronic alcoholism

Renal insufficiency
In the case of unsatisfactory activity of the kidneys (renal insufficiency), the dose should be reduced.

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

Hepatic insufficiency
In the case of patients with unsatisfactory activity of the liver (hepatic insufficiency) or Gilbert syndrome, the dose should be reduced or the dosing interval should be prolonged.

Method of administration:
For oral use. Swallow tablet with sufficient water or, if desired, let it dissolve in a large quantity of water, stir well and drink.

4.3 Contraindications

Hypersensitivity to paracetamol or one of the excipients mentioned in section 6.1.

4.4 Special warnings and precautions for use

- Long-term or frequent use is discouraged.
- Caution is required with hepatic and renal impairment.
- The patients must be advised not to use other products which also contain paracetamol at the same time.
- The taking of several daily doses in one go can cause severe damage to the liver; a loss of consciousness does not occur in such cases. However, medical help should be sought

immediately, even if the patient feels well, because of the risk of irreversible damage to the liver (see section 4.9).
- Long-term use can result in damage except under medical supervision. In young people who are treated with 60 mg/kg/day of paracetamol, combination with another antipyretic is not permitted, except in case of lack of effectiveness.
- Caution is required with the administration of paracetamol to patients with moderate to severe renal insufficiency, mild to moderate hepatic insufficiency (incl. Gilbert syndrome), severe hepatic insufficiency (Child-Pugh > 9), acute hepatitis, the concomitant administration of medicinal products which influence hepatic function, glucose-6-phosphate dehydrogenase deficiency, haemolytic anaemia, alcohol abuse, dehydration and chronic malnutrition.
- The risk of an overdose is greater in patients with non-cirrhotic alcoholic hepatic conditions. In case of chronic alcoholism, caution is required. The daily dose may not exceed 2 grams. During treatment with paracetamol, no alcohol may be used.
- In the case of a high fever, symptoms of a secondary infection or the persistence of symptoms, treatment should be reconsidered.
- After long-term use (> 3 months) of analgesics with intake every other day or more often, headache can develop or become worse. Headache which has been caused by the excessive use of analgesics (medication-overuse headache) must not be treated by increasing the dose. In these cases, the use of analgesics should be stopped in consultation with a doctor.
- Caution is required in asthmatic patients who are sensitive to acetylsalicylic acid, as mild bronchospasms have been reported as a cross-reaction after the use of paracetamol.
- 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, sepsis, 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.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol is metabolised in the liver and can consequently interact with other medicinal products which follow the same metabolic route or which inhibit or induce this route. With chronic alcohol abuse and with the use of substances which induce hepatic enzymes such as barbiturates and tricyclic antidepressants, an overdose of paracetamol can have a more serious course as a result of the increased and more rapid formation of toxic metabolites.

- Enzyme-inducing agents: Caution is required with the concomitant intake of enzyme-inducing agents (see section 4.9 Overdose).
- Probenecid: In the case of concomitant treatment with probenecid, the dose of paracetamol should be decreased, as probenecid reduces the clearance of paracetamol by 50% because it prevents the conjugation of paracetamol with glucuronic acid.
- Chloramphenicol: Paracetamol can considerably increase the half-life of chloramphenicol.
- Metoclopramide or domperidone: The rate of absorption of paracetamol can be increased by metoclopramide or domperidone.
- Colestyramine: The rate of absorption of paracetamol can be reduced by colestyramine.

- Warfarine: The anticoagulatory effect of warfarin and other coumarins can be increased with the long-term, regular use of paracetamol, resulting in an increased risk of bleeding. In this case, regular INR tests are recommended. There is no significant effect if a dose is taken occasionally.
- Zidovudine: Neutropenia occurs more often with the concomitant, chronic use of paracetamol and zidovudine, presumably as a result of the reduced metabolism of zidovudine as a result of the competitive prevention of conjugation. The concomitant intake of paracetamol and zidovudine should, therefore, only take place subject to medical advice. In case of concomitant use of paracetamol and zidovudine, white blood cells and hepatic laboratory tests are recommended.
- Salicyclamide: Salicyclamide can increase the half-life of paracetamol.
- Isoniazid: Isoniazid reduces the clearance of paracetamol, which may increase the efficacy and/or toxicity of paracetamol by preventing hepatic metabolism.
- Lamotrigine: The concomitant intake of paracetamol with lamotrigine reduces the bioavailability of lamotrigine, which may result in reduced efficacy as a result of induction of hepatic metabolism.
- Effect on laboratory tests: paracetamol can influence the uric acid test using tungsten phosphoric acid as well as the blood glucose test using glucose oxidase-peroxidase
- 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 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."

Lactation:
Paracetamol is excreted in the maternal milk. No adverse effects have been reported in children who have been breastfed. When administered in therapeutic doses, paracetamol can be used by women who breastfeed.

4.7 Effects on ability to drive and use machines

As far as is known, this medicinal product does not have an effect on the ability to drive and use machines.

4.8 Undesirable effects

In therapeutic doses, few undesirable effects occur.

The following frequencies can be mentioned: Very common (≥ 1/10), common (≥1/100, <1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), and not known (cannot be determined with the available data).

Blood and lymphatic system disorders:

Rare: agranulocytosis (after long-term use), thrombocytopenia, thrombocytopenic purpura, leukopenia, haemolytic anaemia.
Very rare: pancytopenia.
Not known: anemia

Immune system disorders:
Rare: allergies (excluding angioedema)
Very rare: hypersensitivity reaction (angioedema, breathing difficulties, sweating, nausea, hypotension, shock, anaphylaxis), as a result of which the treatment must be stopped

Metabolism and nutrition disorders:
Very rare: hypoglycaemia
Unknown: High anion gap metabolic acidosis

Psychiatric disorders:
Rare: depression, confusion, hallucinations

Nervous system disorders:
Rare: tremor, headache

Eye disorders:
Rare: visual abnormalities

Cardiac disorders:
Rare: oedema

Respiratory, thoracic and mediastinal conditions:
Very rare: bronchospasms in patients who are sensitive to aspirin and other NSAIDs (analgesic asthma)

Gastrointestinal disorders:
Rare: bleeding, abdominal pain, diarrhoea, nausea, vomiting

Hepatobiliary disorders:
Rare: abnormal hepatic function, hepatic failure, hepatic necrosis, jaundice
Very rare: hepatotoxicity
Amounts of 6 grams of paracetamol can already cause hepatic damage (in children above 140 mg/kg); larger quantities cause irreversible hepatic necrosis. Hepatic damage after the chronic use of 3-4 grams of paracetamol a day has been reported.
Not known: hepatitis

Skin and subcutaneous tissue disorders:
Rare: pruritus, rash, sweating, purpura, urticaria
Very rare: exanthema, severe cutaneous reactions
Not known: acute generalised exanthematous pustulosis, toxic necrolysis, drug-induced dermatosis, Stevens-Johnson syndrome; angio-oedema

Renal and urinary disorders:

Very rare: sterile pyuria (cloudy urine) and renal side effects (severe renal impairment, interstitial nephritis, haematuria, anuresis)

General disorders and administration site conditions:
Rare: dizziness (excluding vertigo), malaise, pyrexia, sedation

Injury, poisoning and procedural complications:
Rare: overdose and intoxication

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 the national reporting system listed in Appendix V.

4.9 Overdose

In the case of overdose of paracetamol, there is a risk of acute liver toxicity, particularly in elderly people, young children, in case of hepatic or renal insufficiency, in cases of chronic alcoholism, chronic malnutrition, in patients with enzyme-inducing drug use and in adult patients whose weight is less than 50 kg. The hepatotoxicity occurs within 24 to 48 hours after ingestion. An overdose can be fatal. Also see section 5.2.

Symptoms:
The symptoms of paracetamol intoxication are nausea, vomiting, anorexia, pallor and abdominal pain and these symptoms usually occur within 24 hours after intake. After an overdose of paracetamol of 140 mg/kg, moderate hepatic damage can occur as result of hepatic cytolysis. From 200 mg/kg, severe hepatic damage can occur, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy, which can result in coma and death. At the same time, elevated levels of hepatic transaminases (AST and ALT), lactate dehydrogenase and bilirubin have been observed together with lowered prothrombin levels which can appear 12 to 48 hours after administration. Clinical symptoms of hepatic damage are usually visible for the first time after two days and reach a maximum after 4 to 6 days.

Emergency treatment:
- Immediate admission to hospital, even if no symptoms of overdose are present.
- After an overdose, a blood sample should be taken as quickly as possible before the start of the treatment in order to establish the paracetamol content.
- In case of a large overdose, possibly resulting in severe intoxication, absorption-reducing treatment can be applied: gastric lavage, if performed within 1 hour of intake, and the administration of activated charcoal.

- Treatment includes the administration of the antidote N-acetylcysteine (NAC) or methionine, intravenous or oral (if so, do not administer any activated charcoal!), where possible before 10 hours after intake. However, NAC can even improve the prognosis up to 36 hours after intake if the paracetamol concentration can still be detected. Further treatment is symptomatic.
- Liver tests should be performed at the start of the treatment and should be repeated every 24 hours. In most cases, the hepatic transaminases will return to normal within one to two weeks, with a complete restoration of the liver function. In very rare cases, however, a liver transplant can be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other analgesics and antipyretics, ATC code: N02BE01.
Paracetamol has both an analgesic and an antipyretic effect. However, it does not have any anti-inflammatory effect. The mechanism of action of paracetamol is still not fully understood. The effect appears to be based on the inhibition of the enzyme prostaglandin synthetase, but the lack of an anti-inflammatory effect cannot be explained by this. It is possible that the distribution of paracetamol throughout the body and thus the site where inhibition of prostaglandin synthetase takes place also plays a role. Paracetamol has the advantage that a number of the side effects which are characteristic of NSAIDs are completely or largely absent with paracetamol. Thus, paracetamol is a good alternative to NSAIDs for the purpose of combating pain and fever.

5.2 Pharmacokinetic properties

Absorption
After oral administration, paracetamol is quickly and almost completely absorbed. The maximum concentration is reached after 30 minutes to 2 hours.

Distribution
The distribution volume of paracetamol is around 1 l/kg of bodyweight. In therapeutic doses, there is negligible plasma protein binding. The concentration in saliva and maternal milk is related to the concentration in plasma.

Biotransformation
In adults, paracetamol is conjugated with glucuronic acid (around 60%), sulphate (around 35%) and cysteine (around 3%) in the liver. With the help of cytochrome P-450, a small proportion of the paracetamol in the body is converted into a very reactive metabolite which is normally quickly inactivated by conjugation with glutathione.
An overdose can exhaust glutathione stocks and thus result in acute liver damage. In neonates and children up to the age of 12 years, sulphate conjugation is the main elimination route and glucuronidation takes place to a lesser extent than in adults. However, the total elimination capacity in children is generally similar to that of adults because of the increased sulphation capacity.

Elimination
Paracetamol is mainly excreted in the urine. 90% of the dose taken is excreted via the kidneys within 24 hours, mainly in the form of the glucuronide (60-80%) and the sulphate conjugate (20-30%) and around 5% unchanged. The elimination half-life ranges from 1 to 4 hours. In case of severe renal

insufficiency (creatinine clearance of less than 10 ml/min), the elimination of paracetamol and its metabolites is slowed down. In elderly people, there is no change in the conjugation capacity.

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

- maize starch
- gelatine
- croscarmellose sodium
- magnesium stearate

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

Paracetamol tablets are available in blister packs of 4, 6, 10, 20, 30, 50, 90, 100, 250 and 500 tablets or in unit dose packs. The blister strip is made of white PVC foil and aluminium foil.

6.6 Special precautions for disposal

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Aurobindo Pharma BV
Baarnsche Dijk 1
3741 LN Baarn
Nederland

8. MARKETING AUTHORISATION NUMBER

RVG 114335

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 7 augustus 2014.

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft de rubrieken 4.4, 4.5 en 4.8: 12 maart 2025