SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Paracetamol Kappler 500 mg, tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg paracetamol.

3. PHARMACEUTICAL FORM

Tablet.

White to off-white, caplet-shaped tablets having a break-line on one side and plain on the other side, with a length of approximately 17 mm and a width of approximately 7 mm.
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.

<Product name> 500 mg tablets are indicated in adults, adolescents and children 6 years and older, weighing at least 22 kg.

4.2 Posology and method of administration

Posology

The dosage interval depends on the symptoms and the maximum total daily dose.

If symptoms persist for more than 3 days, a doctor should be consulted.

The lowest possible dose that is required to be effective for the shortest time possible, should be used.

The maximum daily dose must not be exceeded.

Adults and adolescents from 15 years of age (≥ 55 kg)
500 mg to 1 000 mg at a time, 3-4 times a day. A maximum daily dose of 3 000 mg per 24 hours must not be exceeded.
Minimum dosing interval: 4 hours.
The lowest possible dose that is required to be effective for the shortest time possible, should be used.

Paediatric population
Children from 6-15 years of age
The dosage is based on the information in the table below. Paracetamol is dosed according to body weight (age is given as a guidance), usually at 10 to 15 mg/kg body weight as a single dose, up to a maximum of 60 mg/kg body weight as a total daily dose.

Dosage table children from 6-15 years of age:

Body weight	Age	Dose	Max. number of doses per day	Max. daily dose
22-30 kg	6-9 years	250 mg	4-6 times a day	1 000-1 500 mg
30-40 kg	9-12 years	500 mg	3-4 times a day	1 500-2 000 mg
40-55 kg	12-15 years	500 mg	4-6 times a day	2 000-3 000 mg

The lower dosage frequency is intended for children in the lower end of the relevant weight and/or age category.

Children < 6 years of age
This medicinal product does not allow appropriate dosing these patients (and should not be used). Other pharmaceutical forms are available for this patient group.

Children < 9 years of age
This medicinal product does not allow appropriate dosing these patients (and should not be used). Other pharmaceutical forms are available for this patient group.

Special populations
Renal impairment
In patients with kidney dysfunction, the dose must be reduced or the dose interval extended.
A daily dose of 2 g should not be exceeded without medical advice.

Severe renal impairment
In patients with severe renal impairment (creatinine clearance < 10 ml/min), a dose interval of at least 8 hours must be observed.

Unless otherwise prescribed, a dose reduction is recommended for patients with renal insufficiency, and a minimum dosing interval of 6 hours, see table:

Adults:

Glomerular filtration rate	Paracetamol dose
10-50 ml/min	500 mg every 6 hours
< 10 ml/min	500 mg every 8 hours

Hepatic impairment
In patients with liver dysfunction and Gilbert's syndrome, the dose must be reduced or the dose interval extended.
A daily dose of 2 g should not be exceeded without medical advice.

The maximum daily dose of 60 mg/kg body weight (up to a maximum of 2 g paracetamol per day) should not be exceeded without medical advice in the following cases:
- a body weight below 50 kg
- chronic alcoholism
- water deprivation
- chronic malnutrition

For people with impaired liver and kidney function, see section 4.4.

Elderly patients
Experience has shown that no special dose adjustment is necessary.
However, a dose reduction or prolongation of the dosing interval may be necessary in debilitated, immobilised elderly patients with impaired liver/renal function, a reduction in dose or prolongation of the dosing interval may be necessary.

Method of administration

The tablet is for oral use and should be swallowed with sufficient liquid and may be taken with a meal, but this is not necessary.

Taking paracetamol with food delays absorption because food decreases gastrointestinal motility and transit time. For faster pain relief, the tablets should be taken on an empty stomach, especially if the meal is high in carbohydrates.

Tablets have a break-line, allowing them to be divided in equal doses and to be taken as half or a whole (see section 3).

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

The patient should be advised to avoid the simultaneous use of this medicine with other medicinal products containing paracetamol, such as flu/cold medicines. If another medicine containing paracetamol is administered, the maximum paracetamol dose of 3 g per day in adults should not be exceeded, taking into account the content of all the medicines used by the patient.

Paracetamol overdose can lead to liver failure that may require liver transplantation or death. Paracetamol toxicity can occur from a single overdose or after multiple excessive doses.

Administration of paracetamol doses higher than recommended carries a risk of very serious liver damage. Clinical symptoms of liver damage are usually first observed 1 to 2 days after an overdose. The most severe symptoms of liver damage are generally observed after 3 to 4 days. In case of suspected overdose, seek medical attention immediately. Treatment with antidote should be given as soon as possible (see section 4.9).

Paracetamol should be used with particular caution in the following cases:
- hepatocellular insufficiency
- chronic alcohol abuse
- severe renal insufficiency (creatinine clearance < 50 ml/min (see section 4.2))
- Gilbert's syndrome (Meulengracht disease)
- concomitant use of drugs that impair liver function (see section 4.5)
- glucose-6-phosphate dehydrogenase deficiency (favism)
- haemolytic anaemia
- glutathione deficiency
- dehydration
- chronic malnutrition
- body weight below 50 kg
- elderly patients

In case of high fever, signs of secondary infection or persistent symptoms beyond 3 days, treatment should be re-evaluated.

Caution is advised in asthmatic patients sensitive to acetylsalicylic acid, as mild bronchospasms have been reported as a cross-reaction after the use of paracetamol.

With prolonged use of any type of pain-relieving headache medication, headaches can become worse and more frequent (medication overuse headache). If this condition develops

or is suspected, headache treatment should be discontinued in consultation with a doctor. Medication overuse headache should be suspected in patients with frequent or daily headache attacks despite (or because of) regular use of painkillers.

In general, continuous use of analgesics, especially in combination with other analgesic drugs, can lead to persistent kidney damage with a risk of kidney failure (analgesic nephropathy).

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.

Effects on laboratory values
The use of paracetamol may influence the determination of uric acid using phosphotungstic acid and the determination of blood sugar using glucose oxidase peroxidase.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions
The anticoagulant effect of warfarin and other coumarins may be increased by prolonged regular daily intake of paracetamol. This leads to an increased risk of bleeding; occasional intake has no significant effect.

Pharmacokinetic interactions
In cases of chronic alcohol abuse, an overdose with paracetamol may be more severe due to increased and accelerated formation of toxic metabolites.

Effect of other medicinal products on paracetamol
Paracetamol is metabolised in the liver by the conjugation enzymes UGT1A1, SULT1A1, and NAT, and to a limited extent by Cytochrome P450 (CYP) 2E1 and 2D6 (~5 %). Consequently, paracetamol may interact with other medicinal products that follow the same metabolic pathway or that may inhibit or induce that pathway. When using substances that induce liver enzymes, such as rifampicin, barbiturates, tricyclic antidepressants, and St. John's wort, an overdose with paracetamol may be more severe due to increased and accelerated formation of toxic metabolites. With rifampicin and some antiepileptics (phenytoin, phenobarbital, carbamazepine, primidone), it has been shown that the plasma AUC of paracetamol decreases by 60 % and the hepatotoxicity of a paracetamol overdose may worsen as a result of increased and accelerated formation of toxic metabolites.
Caution should be exercised when taken concomitantly with enzyme-inducing agents (see section 4.9). In the event of concomitant treatment with probenecid, the dose of paracetamol should be reduced, as probenecid reduces the clearance of paracetamol by 50 % by inhibiting the conjugation of paracetamol with glucuronic acid. Salicylamide can prolong the half-life of paracetamol. Isoniazid causes a decrease in the clearance of paracetamol, which may enhance the effect and/or toxicity of paracetamol by inhibiting metabolism in the liver. Concomitant intake of drugs that slow gastric emptying may delay the absorption and onset of effect of paracetamol. Concomitant use of medicines that accelerate gastric emptying, such as metoclopramide and domperidone, accelerates the absorption and onset of action of paracetamol.
Colestyramine decreases the absorption of paracetamol. Paracetamol should be administered at least 1 hour before or 4-6 hours after colestyramine.

Effect of paracetamol on other medicinal products

The simultaneous use of paracetamol and zidovudine (AZT) increases the likelihood of developing neutropenia, presumably due to reduced metabolism of zidovudine as a result of competitive inhibition of conjugation. Paracetamol should therefore only be used simultaneously with zidovudine on medical advice. Concomitant administration of paracetamol with lamotrigine reduces the bioavailability of lamotrigine, potentially reducing its effectiveness due to possible induction of hepatic metabolism. Caution should be exercised 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 malformations, nor foetal/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.

During pregnancy, paracetamol should not be used for prolonged periods, in high doses or in combination with other medicines, as its safety in these cases has not been established.

Breast-feeding
Paracetamol is eliminated in the maternal milk. No adverse effects have been reported in children who are breast-fed. Paracetamol can be used in therapeutic doses by women who breast-feed.

Fertility
There are no available data on the effect of paracetamol on fertility.

4.7 Effects on ability to drive and use machines

As far as is known, this medicinal product does not have any influence on the ability to drive or the ability to use machines.

4.8 Undesirable effects

Side effects are generally rare. The most common side effects are urticaria and increased liver transaminase (frequency: very common, 1/10 treated patients).

The following are found in spontaneous reports.
In this section, frequencies of undesirable effects are defined 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) and not known (cannot be estimated from the available data).

System Organ Class	**Rare**	**Very rare**	**Not known**
Investigations	Blood creatinine increased.		
Blood and lymphatic system disorders		Thrombocytopenia, agranulocytosis, leukopenia, haemolytic anaemia.	

System Organ Class	Rare	Very rare	Not known
Immune system disorders		Anaphylactic reaction.	
Respiratory, thoracic and mediastinal disorders		Bronchospasm (NSAID exacerbated respiratory disease) in patients sensitive to acetylsalicylic acid and NSAIDs.	
Renal and urinary disorders		In long-term treatment, the possibility of kidney damage cannot be excluded (see section 4.4).	
Skin and subcutaneous tissue disorders	Urticaria.	Angioedema, dermatitis allergic (hypersensitivity including skin rash), Stevens-Johnson syndrome, toxic epidermal necrolysis, severe cutaneous adverse reaction.	
Hepatobiliary disorders	Transaminases increased.	Hepatic dysfunction.	
Metabolism and nutrition disorders			High anion gap metabolic acidosis.

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.

The frequency, type and severity of side effects in children are expected to be the same as in adults.

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

There is a risk of intoxication with paracetamol, particularly in the elderly, young children and patients with hepatic disorders, in cases of chronic alcoholism, in patients with chronic malnutrition and in patients who use enzyme-inducing drugs.

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

Symptoms
Overdose experience indicates that clinical signs of liver damage usually occur 24-48 hours after ingestion and peak within 4-6 days.
The symptoms of paracetamol overdose in the first 24 hours are pallor, nausea, vomiting and anorexia. Abdominal pain can be the first symptom of liver damage, which is usually not seen for 24 to 48 hours and can sometimes be delayed up to 4 to 6 days after ingestion. 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 may develop even in the absence of severe liver injury. Cardiac arrhythmia has been reported.

Management
Immediate treatment according to current clinical guidelines is essential for paracetamol overdose.
If an overdose is suspected or recognised, seek immediate help from the Poison Help Line at <to be completed nationally> and send the patient to the nearest emergency department for treatment. This should be done even if the patient has no symptoms or signs of overdose due to the risk of delayed liver damage.
Rapid administration of intravenous N-acetylcysteine as an antidote to paracetamol should be initiated immediately, without delaying blood tests, if more than the recommended daily dose is ingested or suspected, Methionine can be used as an antidote when treatment with intravenous N-acetylcysteine is not possible, e.g. in cases of allergy.
The antidote should be dosed according to the recommendations of the Poison Control Centre (tel: <to be completed nationally>) and national clinical guidelines.

Ventricular emptying is recommended if there is a short interval from ingestion (< 1 hour).
Administration of activated charcoal is recommended if the interval from ingestion is less than 4 hours.
Breathing and circulation should be monitored in severe poisonings. In case of convulsions, diazepam can be administered.
In all cases of suspected or recognised paracetamol overdose, it is important to check liver parameters, coagulation parameters, renal parameters, electrolytes, haematology, acid-base status and cardiac ECG. Repetition of these tests should follow current guidelines and according to the patient's history and clinical status.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: analgesics, anilides
ATC code: N02BE01

Paracetamol has probably both peripheral and central analgesic effect as well as antipyretic effect on the thermoregulatory centre in the hypothalamus. Does not affect haemostasis and does not irritate the gastrointestinal mucosa.

5.2 Pharmacokinetic properties

Absorption

After oral administration, paracetamol is rapidly and almost completely absorbed. The maximum concentration is reached after 30 minutes to 2 hours, depending on the formulation and nutritional status (paracetamol may be taken independently of food). The average bioavailability after oral administration is approximately 80 % due to first-stage hepatic passage, independent of the dose.

Distribution
The volume of distribution of paracetamol is approximately 1 l/kg body weight. At therapeutic doses, plasma protein binding is negligible. The concentration in saliva and breast milk is related to the concentration in plasma.

Biotransformation
Metabolism is virtually the only route by which paracetamol is excreted.
In adults, paracetamol is conjugated in the liver with glucuronic acid by uridine 5'-diphospho-glucuronosyltransferase (UGT) 1A1 (approx. 60 %), sulphate (approx. 35 %) by sulfotransferase (SULT) 1A1, and cysteine by N-acetylcysteine transferase (NAT) (approx. 3 %). A small portion (~5 %) of paracetamol is converted in the body with the help of cytochrome P450 (CYP) 2E1 and 2D6 into a highly reactive metabolite (N-acetyl-p benzoquinone) which is normally rapidly inactivated by conjugation with glutathione via glutathione-S-transferase (GST). Overdosing can deplete glutathione stores and thus lead to acute liver damage.

Elimination
Paracetamol is mainly excreted in the urine. 90 % of the ingested dose is excreted via the kidneys within 24 hours, mainly in the form of the glucuronide (60-80 %) and the sulphate conjugate (20-30 %), and approx. 5 % unchanged. The elimination half-life varies from 1 to 4 hours with an average of 2.3 hours in healthy volunteers. Total body clearance is 5 ml/min/kg body weight. The renal clearance of paracetamol is approximately 10 ml/min.

Special populations

Renal insufficiency
In patients suffering from renal disorders, no changes in kinetics for paracetamol were found. Severe renal disorders do, however, lead to an accumulation of pharmacologically inactive paracetamol conjugates. In case of insufficient renal function (renal insufficiency), the dose should be reduced or the dose interval extended (see section 4.2).

Hepatic insufficiency
In patients suffering from liver disorders, no changes in kinetics were found, except in patients suffering from severe liver disorders. With impaired liver function, total body clearance decreases, suggesting that metabolic clearance is virtually equal to total body clearance. For patients with insufficient liver function (hepatic insufficiency) or Gilbert's syndrome, the dose should be reduced or the administration interval extended.

Paediatric population
In neonates and children up to 12 years of age, sulphate conjugation is the predominant elimination route and glucuronidation occurs to a lesser extent than is the case in adults. However, due to an increased sulphation capacity, the total elimination capacity in children is broadly comparable to that of adults.

Other special populations
- In patients suffering from thyroid and gastrointestinal disorders, no changes in kinetics were found.
- In the elderly, the conjugation capacity remains 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

Pregelatinised starch (Starch 1500)
Maize starch
Povidone K30
Talc (E553b)
Stearic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The tablets are packed in blisters or unit-dose blisters manufactured of opaque PVC foil sealed with an aluminium foil or packed in HDPE bottles sealed with a liner and closed with a cap.

Pack sizes:
<Product name> 500 mg tablets are available in packs containing 10, 10x1, 12, 12x1, 16, 16x1, 20, 20x1, 24, 24x1, 30, 30x1, 40, 40x1, 50, 50x1 and 100 tablets.

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

Kappler Pharma Consult GmbH
Fonyoder Str. 18
89340 Leipheim
Duitsland

8. MARKETING AUTHORISATION NUMBER

RVG 135241

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 22 oktober 2026

10. DATE OF REVISION OF THE TEXT