SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Paracetamol Sandoz 500 mg, tabletten

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, biconvex, round shaped tablets with PA debossed on one side with 11.0 ± 0.5 mm of diameter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of mild to moderate pain and/or fever.

[Nationally completed name] is indicated for adults, adolescents and children aged 9 years and older.

4.2 Posology and method of administration

Posology
The lowest effective dose should be used.

Adults and adolescents aged 15 years and older (above 55 kg body weight)
Start with 1 tablet (500 mg of paracetamol), if necessary 2 tablets (1000 mg) at a time, up to a maximum of 6 tablets (3000 mg of paracetamol) per 24 hours.

Paediatric population
Adolescents between 12-15 years (40-55 kg of body weight)
1 tablet at a time, maximum of 4-6 tablets per 24 hours (total dose 2000-3000 mg).

Children between 9-12 years (30-40 kg of body weight)
1 tablet at a time, maximum of 3-4 tablets per 24 hours (total does 1500-2000 mg).

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

[Nationally completed name] is not recommended for children below 9 years.

Directions for use

- Use the drug for the shortest time possible.
- Depending on recurring symptoms, repeat administration is allowed.
- The minimum dose interval should be 4 hours.
- Do not exceed the recommended dose because of the risk of serious liver damage (see sections 4.4 and 4.9)
- Do not use in combination with other products containing paracetamol.

Special population

Renal impairment
In case of renal insufficiency, the dose should be reduced:

Glomerular filtration rate	Dose in mg of paracetamol/minimum dose interval
10 - 50 ml/min	500 mg/6 hours
< 10 ml/min	500 mg/8 hours

Hepatic impairment
In patients with impaired hepatic function or Gilbert's syndrome, the dose should be reduced or the dose interval prolonged.

Other
The daily dose should not exceed 60 mg paracetamol/kg body weight/day (up to 2 g of paracetamol/day) in the following situations:

- adults weighing less than 50 kg
- mild to severe hepatic impairment
- Gilbert's syndrome (familial non-haemolytic jaundice)
- chronic alcoholism
- dehydration
- chronic malnutrition

High doses of paracetamol should be avoided for prolonged periods of time as the risk of liver damage is increased.

If pain persists for more than 5 days or if fever persists for more than 3 days, or if symptoms worsen, treatment should be stopped and a physician should be consulted.

Method of administration
Oral use.

The tablets should be swallowed with a sufficient amount of water or dissolved in a sufficient amount of water, stirred well and drunk up.

Taking paracetamol with food and drink does not affect the effectiveness of the medicine.

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 recommended dose should not be exceeded.

- Long-term or frequent use is discouraged.
- Patients should be advised not to use other products simultaneously that also contain paracetamol.
- In case of high fever, signs of secondary infection or persistence of symptoms, treatment should be reconsidered.
- Taking multiple daily doses at once may cause severe liver damage; unconsciousness does not occur in such cases. However, medical attention should be sought immediately, even when the patient feels well, because of the risk of irreversible damage to the liver (see section 4.9). Prolonged use may lead to damage and should only take place under medical supervision.
- Caution should be exercised when administering paracetamol to patients with moderate to severe renal insufficiency, mild to severe hepatic insufficiency (including Gilbert's Syndrome), severe hepatic insufficiency (Child-Pugh>9), acute hepatitis, concomitant administration of drugs affecting hepatic function, glucose-6- phosphate dehydrogenase deficiency, hemolytic anemia, alcohol abuse, dehydration and chronic malnutrition.
- The danger of overdose is greater in patients with non-cirrhotic alcoholic liver disease. In cases of chronic alcoholism, caution is required. The daily dose should then not exceed 2 grams. Alcohol should not be consumed during treatment with paracetamol.
- Caution should be exercised in asthmatic patients sensitive to acetylsalicylic acid, as mild bronchospasm has been reported as a cross-reaction after use of paracetamol.
- In young people treated with 60 mg/kg/day paracetamol, combination with another antipyretic is not permitted, except for lack of efficacy.
- After long-term use (> 3 months) of analgesics with intake every other day or more frequently, headache may develop or worsen. Headache caused by overuse of analgesics (substance-dependent headache) should not be treated by increasing the dose. In such cases, the use of analgesics should be discontinued in consultation with a physician.
- In patients with a state of glutathione depletion such as in sepsis, the use of paracetamol may increase the risk of metabolic acidosis (see section 4.9).

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

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%). Therefore it may interact with other active substances that follow the same metabolic pathways or which are capable of inhibiting or inducing such pathways.

The hepatotoxicity of paracetamol may be potentiated by chronic or excessive intake of alcohol or concomitant administration of medicinal products that affect the liver (see section 4.4).
Liver enzyme inducers, such as rifampicin, barbiturates and tricyclic antidepressants, may cause an increase in severity of paracetamol overdose due to the increased and accelerated formation of toxic metabolites. Rifampicin and some antiepileptic drugs (phenytoin, phenobarbital, carbamazepine, primidone) have been shown to decrease the AUC of paracetamol in plasma by 60% and may worsen the hepatotoxicity of paracetamol overdose due to increased and more rapid formation of toxic metabolites. Caution should be observed in case of simultaneous intake with enzyme inducers (see section 4.9).

In case of concomitant treatment with probenecid, the dose of paracetamol should be reduced, because probenecid reduces the clearance of paracetamol by 50% by preventing the conjugation of paracetamol with glucuronic acid.
Salicylamide may prolong the half-life of paracetamol.
Isoniazid decreases the clearance of paracetamol, possibly enhancing the action and/or toxicity of paracetamol, by preventing metabolism in the liver.
Simultaneous ingestion of drugs that delay gastric emptying may delay the absorption and onset of the effect of paracetamol.
The absorption rate of paracetamol can be increased by metoclopramide or domperidone.

Effect of paracetamol on other drugs
With concurrent, chronic use of paracetamol and zidovudine, neutropenia is more common, presumably due to decreased metabolism of zidovudine as a result of competitive inhibition of conjugation. Concomitant intake of paracetamol and zidovudine should therefore occur only on medical advice.
Concomitant ingestion of paracetamol with lamotrigine causes a decrease in the bioavailability of lamotrigine, possibly reducing its efficacy due to possible induction of metabolism in the liver.
The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol, with increased risk of bleeding. Occasional use of a paracetamol dose has no significant effect.

Disruption of laboratory tests:
Paracetamol can affect the uric acid test with tung tic phosphoric acid, as well as the blood sugar test with glucose oxidase-peroxidase.

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.

Breast-feeding

Paracetamol is excreted in breast milk in small amounts. No effects have been reported in breast-fed infants. Paracetamol can be used during breast-feeding as long as the recommended doses are not exceeded.

Fertility
There are no known harmful effects on fertility with normal use of Paracetamol 500 mg tablets.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Few adverse reactions occur with therapeutic doses. Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as: 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).

System Organ Class	Rare	Very rare	Frequency not known
Blood and lymphatic system disorders	Agranulocytosis (after long-term use), thrombocytopenia, thrombocytopenic purpura, leukopenia, haemolytic anaemia	Pancytopenia	
Immune system disorders	Allergic reactions (excluding angioedema)	Hypersensitivity (including angioedema, difficulty breathing, sweating, nausea, hypotension, shock, anaphylaxis)	
Metabolism and nutrition disorders		Hypoglycaemia	
Psychiatric disorders	Depression, confusion, hallucinations		
Nervous system disorders	Tremor, headache		
Eye disorders	Visual disorders		
Cardiac disorders	Oedema		
Respiratory, thoracic and mediastinal disorders		Bronchospasm*	

System Organ Class	Rare	Very rare	Frequency not known
Gastrointestinal disorders	Bleeding, abdominal pain, diarrhoea, nausea, vomiting		
Hepatobiliary disorders	Abnormal liver function/ hepatic enzyme increased, hepatic failure, hepatic necrosis, jaundice	Hepatotoxicity**	
Skin and subcutaneous tissue disorders	Rash, pruritus, erythema, urticaria, hyperhidrosis	Serious skin reactions, exanthema	Acute generalized exanthematous pustulosis (AGEP), toxic epidermal necrolysis (TEN), drug-induced dermatosis, Stevens-Johnson syndrome
Renal and urinary disorders		Sterile pyuria (cloudy urine), severe renal impairment, interstitial nephritis, hematuria, anuria	
General disorders and administration site conditions	Dizziness (excluding vertigo), malaise, pyrexia, sedation		

* Bronchospasm in patients who are sensitive to acetylsalicylic acid or other NSAIDs (analgesic asthma).
** Hepatobiliary disorders: Liver damage is possible in children who have taken 150 mg/kg or more of paracetamol once. In adults, liver damage has been reported after chronic use of 3-4 grams of paracetamol per day (see section 4.9).

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

Paracetamol may cause poisoning, particularly in elderly patients, small children, patients with liver disease, in cases of chronic alcoholism, patients with chronic malnutrition, in patients with a state of glutathione depletion (see section 4.4) and patients using enzyme inducers.
An overdose of paracetamol can cause liver failure, which may necessitate liver transplantation or lead to death. Acute pancreatitis has been observed, mostly in association with hepatic impairment and liver toxicity (see also section 5.2).
Liver damage is possible in adults or children who have taken 150 mg/kg or more of paracetamol once. In patients with risk factor(s) - such as patients with liver disease, chronic alcoholism, malnutrition, the use of enzyme-inducing agents - liver damage is possible with a single intake of paracetamol from 100 mg/kg. Liver damage after chronic use of 3-4 grams of paracetamol per day has been reported.

Symptoms
Symptoms of paracetamol overdose are nausea, vomiting, anorexia, pallor and abdominal pain and usually occur within 24 hours after ingestion. Even if other symptoms are absent or improve, abdominal pain may indicate liver damage. A single ingestion of 140 mg/kg of paracetamol or more may cause moderate hepatic cytolysis. Ingestion of 200 mg/kg or more may lead to full and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy, which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin have been reported together with decreased levels of pro-thrombin, possibly appearing 12 to 48 hours after ingestion. Clinical symptoms of liver damage usually become apparent after 2 days and reach a maximum after 4 to 6 days.
Even in the absence of serious liver damage, acute renal failure with acute tubular necrosis can occur.

Management
Immediate hospitalization even if no symptoms of overdose are present
Before treating overdose a blood sample should be taken immediately to measure the plasma paracetamol concentration. The paracetamol concentration in the blood is indicative of the degree of intoxication from 4 hours after exposure. Before then, blood samples are only useful to confirm exposure.
In the event of a major overdose, possibly leading to severe intoxication, absorption-reducing therapy may be applied: gastric lavage if feasible within 1 hour after ingestion, and administration of activated charcoal.
Treatment includes administration of the antidote N-acetylcysteine (NAC) or methionine, intravenously or orally (then do not administer activated charcoal), if possible before 6-8 hours after ingestion. However, NAC may even improve the prognosis up to 36 hours after intake if the paracetamol concentrations are still detectable.
Further treatment is symptomatic.
Liver tests should be performed at the start of the treatment and repeated every 24 hours. In most cases, hepatic transaminase levels will return to normal within 1 to 2 weeks with full recovery of liver function. However, liver transplantation will be necessary in very rare cases.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: analgesics, other analgesics and antipyretics, anilides, ATC code: N02BE01

Paracetamol has both analgesic and antipyretic effects, but it has no anti-inflammatory properties. The mechanism of action of paracetamol has not been fully clarified. The effect seems to be based on inhibition of the enzyme prostaglandin synthetase, but this does not explain the lack of anti-inflammatory actions. Distribution of paracetamol throughout the body and thus the location of the inhibition of prostaglandin synthetase may also be of importance. The benefit of paracetamol lies in the fact that some of the adverse reactions characteristic of NSAIDs are completely or largely absent.

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 doses.
The concentration in saliva and breast milk is related to plasm concentration.

Biotransformation
In adults, paracetamol is conjugated in the liver with glucuronic acid (approx. 60%), sulphate (approx. 35%) and cysteine (approx. 3%). Small quantities are converted to a toxic metabolite via cytochrome P450, which is normally rapidly inactivated by conjugation with glutathione. Overdose can deplete glutathione and thus lead to acute liver damage.
In neonates and children below 12 years of age 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 primarily excreted in the urine (90% of the oral dose within 24 hours), mainly as the glucuronide (60-80%) and sulphate conjugates (20-30%). About 5% is excreted unchanged. The elimination half-life varies from 1 to 4 hours.

Special populations

Renal insufficiency
In patients suffering from renal disease, no changes in kinetics were found for paracetamol. Severe kidney disease does lead to an accumulation of pharmacologically inactive paracetamol conjugates. In case of insufficient kidney function (renal insufficiency), the dose should be reduced (see 4.2).

Liver failure
No changes in kinetics were found in patients suffering from liver diseases, except in patients suffering from severe liver diseases. With impaired liver function, total body clearance decreases, suggesting that metabolic clearance is approximately 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.

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

Other special populations
No changes in kinetics were found in patients suffering from thyroid and gastrointestinal disorders. In the elderly, conjugation capacity is unchanged.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

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

Pregelatinized starch (maize)
Povidone K-30 (E 1201)
Stearic acid (E 570)
Crospovidone (E 1202)
Sodium starch glycolate (type A)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

8, 16 (8x2), 10, 50 (10x5) tablets in a transparent PVC/PVDC-Aluminium blister pack.

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. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Sandoz B.V.
Veluwezoom 22
1327 AH Almere
Nederland

8. NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

RVG 128911

9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING

Datum van eerste verlening van de vergunning: 4 maart 2024

10. DATUM VAN HERZIENING VAN DE TEKST