SUMMARY OF PRODUCT CHARACTERISTICS

1. NAAM VAN HET GENEESMIDDEL

Paracetamol Sandoz 500 mg, tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg paracetamol.
Excipient with known effect:
Each tablet contains up to 1.87 mg of sodium.

Each tablet contains 1000 mg paracetamol.
Excipient with known effect:
Each tablet contains up to 3.74 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

500 mg tablet:
Tablet.
White, caplet-shaped tablets, debossed “500” on one side and plain on the other side (17.5 mm x 7.3 mm).

1000 mg tablet:
Tablet.
White to off-white, caplet-shaped tablets, debossed with scoreline between “10” and “00” on one side and scoreline between “PA” and “RA” on the other side (21.4 mm x 9.0 mm).
The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

<[Nationally completed name] 500 mg, tablets>
Mild to moderate pain and fever.

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

<[Nationally completed name] 1000 mg, tablets>
Mild to moderate pain associated with osteoarthritis of the hip and knee.

[Nationally completed name] is indicated for adults and adolescents aged 15 years and older.

4.2 Posology and method of administration

Posology
The lowest effective dose should be used.
Do not exceed the recommended dose because of the risk of serious liver damage (see sections 4.4 and 4.9)

<[Nationally completed name] 500 mg, tablets:>
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 to 6 tablets per 24 hours.

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

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

Depending on recurring symptoms, repeat administration is allowed. The minimum dose interval should be 4 hours. Thus, when symptoms of pain or fever recur, administration cannot be repeated before 4 hours.

<[Nationally completed name] 1000 mg, tablets:>
Adults and adolescents aged 15 years and older (above 55 kg body weight)
Start with half a tablet (500 mg of paracetamol), and if needed 1 tablet (1000 mg); the maximum daily dose is 4 tablets (4000 mg of paracetamol).

Depending on recurring symptoms, repeat administration is allowed. When using half tablets, the dose interval should be at least 4 hours. When using the whole tablets, the dose interval should be at least 6 hours.
Thus, when symptoms of pain recur, administration cannot be repeated before 4 hours (half tablet) or 6 hours (whole tablet).

Paediatric population
[Nationally completed name] is not recommended for children and adolescents below 15 years.

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.

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 moderate hepatic impairment
- Gilbert's syndrome (familial non-haemolytic jaundice)
- chronic alcoholism
- dehydration
- chronic malnutrition

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.

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

Prolonged or frequent use is discouraged.

Prolonged use may be harmful, except under medical supervision. For adolescents treated with a paracetamol dose of 60 mg/kg body weight/day, the concomitant use of another antipyretic is not allowed, except where there is a lack of efficacy.

In case of high fever, symptoms of secondary infection or if symptoms persist, a physician should be consulted.

Caution is advised if paracetamol is administered to patients with:
- moderate to severe renal impairment
- hepatic impairment (including Gilbert's syndrome)
- acute hepatitis
- glucose-6-phosphate dehydrogenase deficiency
- hemolytic anemia
- alcohol abuse
- chronic malnutrition
- dehydration
- concomitant administration of medicinal products which affect liver function (see section 4.5)

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 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.

Single administration of several times the maximum daily dose may severely damage the liver. In such cases, unconsciousness does not occur. However, immediate medical assistance should be sought in

the event of overdose, even if the patient feels well, because of the risk of serious, delayed and irreversible liver damage (see section 4.9).

Underlying liver diseases increase the risk of paracetamol-related liver damage. Patients who have experienced impaired liver or kidney function should seek medical advice before using this medicinal product.

This medicinal product contains paracetamol. Patients should be advised not to take other paracetamol-containing medicinal products concurrently, including combination products, due to the risk of severe liver damage in case of overdose (see section 4.9).

The risk of overdose is increased in patients with non-cirrhotic alcoholic liver disease. In case of chronic alcoholism, caution is advised. In these cases, the daily dose of paracetamol should not exceed 2 grams. During treatment with paracetamol, alcohol should not be used.

Cases of hepatic impairment or hepatic failure have been reported in patients with glutathione depletion, such as in patients with:
- severe malnutrition
- anorexia
- low body mass index
- chronic alcoholism
- sepsis

In patients with glutathione depletion, the use of paracetamol may increase the risk of metabolic acidosis (see section 4.9).

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

After prolonged use (> 3 months) of any type of analgesic with intake every other day or more frequently, headache can develop or become worse. Headache which is caused by excessive use of analgesics (medication overuse headache) must not be treated by increasing the dose of the analgesic. If this situation is experienced or suspected, the use of analgesics should be discontinued and medical advice should be sought.

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, and 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 barbiturates and tricyclic antidepressants, may cause an increase in severity of paracetamol overdose due to the increased and accelerated formation of toxic metabolites. Caution should be observed in case of simultaneous intake with enzyme inducers (see section 4.9).

Salicylamide can extend the half-life of paracetamol.

Isoniazid can inhibit the metabolism of paracetamol, which may potentiate liver toxicity of paracetamol.

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)

The half-life of chloramphenicol may be significantly increased by paracetamol.

Simultaneous, chronic use of paracetamol and zidovudine will increase the frequency of neutropenia, probably due to a decreased metabolism of zidovudine and due to competitive prevention of conjugation. Therefore, paracetamol and zidovudine should only be administered concomitantly on medical advice.

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.

The rate of absorption of paracetamol may be increased by metoclopramide or domperidone and reduced by cholestyramine.

Probenecid inhibits the conjugation of paracetamol with glucuronic acid and thus leads to a reduction in paracetamol clearance by approximately 50%. In patients concurrently taking probenecid, the paracetamol dose should be reduced.

Concomitant intake of paracetamol and lamotrigine may decrease the bioavailability of lamotrigine, possibly by induction of metabolism in the liver. Lamotrigine efficacy may be decreased.

Interference with laboratory tests
The use of paracetamol may affect the determination of uric acid using phosphotungstic acid and the determination of blood glucose using 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.

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	High anion gap metabolic acidosis
Psychiatric disorders	Depression, confusion, hallucinations		
Nervous system disorders	Tremor, headache		
Eye disorders	Visual disorders		
Cardiac disorders	Oedema		
Respiratory, thoracic and mediastinal disorders		Bronchospasm*	
Gastrointestinal disorders	Bleeding, abdominal pain, diarrhoea, nausea, vomiting		
Hepatobiliary disorders	Abnormal liver function/ hepatic enzyme increased, hepatic failure, hepatic necrosis, jaundice		Hepatotoxicity

System Organ Class	Rare	Very rare	Frequency not known
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)

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

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).

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 prothrombin, 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.

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.
- 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 10 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 impairment
In case of severe renal impairment (creatinine clearance less than 10 ml/min), the elimination of paracetamol and its metabolites is delayed.

Elderly
The conjugation capacity is not changed in the elderly.

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

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

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

500 mg tablets

10, 12, 16, 20, 24, 30, 50, 120 or 240 tablets in PVC/aluminium blister packs or 100 tablets in a HDPE bottle with a PP child resistant closure.

1000 mg tablets
8, 10, 16, 20, 30, 40, 60, 90 or 120 tablets in PVC/aluminium blister packs or 100 tablets in a HDPE bottle with a PP child resistant closure.

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.
Hospitaaldreef 29
1315 RC Almere
Nederland

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

RVG 111619

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

Datum van eerste verlening van de vergunning: 17 april 2012
Datum van laatste verlenging: 12 april 2017

10. DATUM VAN HERZIENING VAN DE TEKST

Laatste gedeeltelijke wijziging betreft de rubrieken 4.4, 4.5 en 4.8: 23 januari 2025