SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Paracetamol Sandoz 1000 mg, tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1000 mg paracetamol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White, biconvex, oval shaped tablets debossed with a functional score line on one side and PC on the other side, with 21.0 ± 0.5 mm of length and 8.5±0.5 mm of width. 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.

[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).

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 3 tablets (3000 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).

[Nationally completed name] is not recommended for children below 15 years old. Other formulations containing paracetamol are available for those children.

Special population

Renal impairment
In case of renal insufficiency reduce the dose, depending on the degree of glomerular filtration according to the following table:

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

Due to the dose, this medicine is not indicated for this group of patients.

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

Other
The daily dose should not exceed 60 mg paracetamol/kg body weight/day (up to 2 g of paracetamol/day) and the minimum interval between doses should be 8 hours 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.

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.

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The tablet can be divided into equal doses.

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

Frequent use is discouraged.

Paracetamol should be administered with caution, avoiding prolonged treatments in patients with anaemia, heart or lung conditions or with severe renal and hepatic dysfunction (in the latter case, occasional use is acceptable, but prolonged administration of high doses may increase the risk of occurrence of adverse effects).

The use of paracetamol in patients who habitually consume alcohol (3 or more alcoholic beverages - beer, wine, liquor, etc.- a day) can cause liver damage.
In chronic alcoholics, no more than 2 g/day of paracetamol should be administered over several doses.

Caution is advised in asthmatic patients sensitive to acetylsalicylic acid, because bronchospastic reactions with paracetamol (cross-reaction) have been described in these patients, although they have only manifested in a minority of such patients, it can cause severe reactions in some cases, especially when administered in high doses.

Self-medication with paracetamol should be limited when taking anticonvulsants because concomitant use of both potentiates potentiates hepatotoxicity and decrease the bioavailability of paracetamol, especially in treatments with high doses of paracetamol.

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

The toxic symptoms associated with paracetamol can be produced either by the intake of a single overdose or by several doses with excessive doses of paracetamol.

Caution is advised if paracetamol is administered to patients with:

- moderate to severe renal impairment
- mild to severe 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.

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).

Prolonged use may be harmful, except under medical supervision. 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. 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.

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. Caution should be observed in case of simultaneous intake with enzyme inducers (see section 4.9).

Potentially more relevant interactions include (see section 4.4 and 4.9):
· Ethyl alcohol: chronic or excessive intake potentiates the hepatotoxicity of paracetamol, by possible induction of hepatic production of hepatotoxic products derived from paracetamol.
· Oral anticoagulants (acenocoumarol, warfarin): possible potentiation of the anticoagulant effect, by inhibition of the hepatic synthesis of coagulation factors. However, given the apparently low clinical relevance of this interaction in most patients, the analgesic therapeutic alternative with salicylates is

considered when there is therapy with anticoagulants. However, the dose and duration of treatment should be as low as possible, with periodic MONITORING of the INR.
· Anticonvulsants (phenytoin, phenobarbital, methylphenobarbital, primidone): decreased bioavailability of paracetamol
· 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).
Loop diuretics: The effects of diuretics may be reduced, as paracetamol may decrease renal excretion of prostaglandins and plasma renin activity.
· Isoniazid: decrease in the clearance of paracetamol, with possible potentiation of its action and / or toxicity, by inhibition of its hepatic metabolism.
· Lamotrigine: decrease in the bioavailability of lamotrigine, with possible reduction of its effect, by possible induction of its hepatic metabolism. Lamotrigine efficacy may be decreased.
· Metoclopramide and domperidone: increase the absorption of paracetamol in the small intestine, due to the effect of these drugs on gastric emptying.
· 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.
· Salicylamide can extend the half-life of paracetamol.
· 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.

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)

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.

Interference with analytical tests
Paracetamol can alter the values of the analytical determinations of uric acid and glucose.

4.6 Fertility, pregnancy and lactation

Pregnancy
A large amount of data in pregnant women indicate the absence of fetal/neonatal toxicity or congenital malformations. Epidemiological studies on the neurological development of children exposed to paracetamol in utero show inconclusive results. If clinically necessary, paracetamol may be used during pregnancy, but the minimum effective dose should be used for the shortest possible time and as often as possible.

Breast-feeding

Small amounts of paracetamol have been measured in breast milk several hours after administration of paracetamol to the mother. There have been no reports of adverse effects in breast-fed children. Paracetamol can be used in lactating women if the recommended dose is not exceeded.

Fertility
Chronic toxicity studies in animals show that high doses of paracetamol cause testicular atrophy and inhibition of spermatogenesis. The importance of this fact for use in humans is unknown.

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

a) Safety profile report

The adverse reactions that have been most reported during the period of use of paracetamol are: hepatotoxicity, renal toxicity, alterations in blood formula, hypoglycemia and allergic dermatitis.

b) Tabulated list of adverse reactions

Frequency	**Organ/System**	**Adverse reaction**
Rare (≥1/10 000<1/1 000)	Vascular disorders	Hypotension
	Hepatobiliary disorders	Increased levels of liver transaminases
	General disorders and alterations at the site of administration	Discomfort
Very rare (<1/10 000)	Disorders of the blood and lymphatic system	Thrombocytopenia, agranulocytosis, leukopenia, neutropenia, hemolytic anemia.
	Disorders of metabolism and nutrition	Hypoglycemia
	Hepatobiliary disorders	Hepatotoxicity (jaundice)
	Kidney and urinary disorders	Sterile pyuria (cloudy urine), adverse renal effects (see section 4.4. Special warnings and precautions for use)
	General disorders and alterations at the site of administration	Hypersensitivity reactions ranging from a simple rash or hives to anaphylactic shock.

	Skin and subcutaneous tissue disorders	Serious skin reactions have been reported.
Not known (cannot be estimated from the available data)	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.

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.
Overdose symptoms include dizziness, vomiting, loss of appetite, jaundice, abdominal pain, and kidney and 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). If an overdose has been ingested, the patient should be treated quickly in a medical center even if there are no significant symptoms or signs since, although these can cause death, they often do not manifest themselves immediately after ingestion, but from the third day. Death from liver necrosis may occur. Acute renal failure may also occur.
Paracetamol overdose is evaluated in four phases, which begin at the time of ingestion of the overdose:
• PHASE I (12-24 hours): nausea, vomiting, diaphoresis and anorexia;
• PHASE II (24-48 hours): clinical improvement; AST, ALT, bilirubin and prothrombin levels begin to rise
• PHASE III (72-96 hours): peak hepatotoxicity; values of 20,000 may appear for AST
• PHASE IV (7-8 days): recovery
Hepatotoxicity may occur. The minimum toxic dose is 6 g in adults and more than 100 mg/kg body weight in children. Doses above 20-25 g are potentially fatal. Symptoms of hepatotoxicity include nausea, vomiting, anorexia, malaise, diaphoresis, abdominal pain, and diarrhea. Hepatotoxicity does not manifest itself until after 48-72 hours after ingestion. If the ingested dose was greater than 150 mg/kg or the amount ingested cannot be determined, a sample of serum paracetamol must be obtained within 4 hours of ingestion. In the event that hepatotoxicity occurs, perform a liver function study and repeat the study at 24-hour intervals. Liver failure can trigger encephalopathy, coma, and death.
Plasma levels of paracetamol greater than 300 µg/ml, found within 4 hours of ingestion, have been associated with liver damage in 90% of patients. This begins to occur when plasma levels of paracetamol at 4 hours are greater than 120 µg/ml or greater than 30 µg/ml at 12 hours of ingestion.

Chronic ingestion of doses greater than 4 g/day may result in transient hepatotoxicity. The kidneys may suffer from tubular necrosis, and the myocardium may be injured.
Treatment: in all cases, aspiration and gastric lavage will be carried out, preferably within 4 hours of ingestion.
There is a specific antidote for the toxicity produced by paracetamol: N-acetylcysteine that can be administered intravenously or orally.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Paracetamol is an analgesic that also possesses antipyretic properties. The exact mechanism of action of paracetamol is unknown, although it is known that it acts at the level of the Central Nervous System and, to a lesser extent, blocking the generation of the painful impulse at the peripheral level. Paracetamol is thought to increase the pain threshold by inhibiting the synthesis of prostaglandins, by blocking cyclooxygenases in the Central Nervous System (specifically COX-3). However, paracetamol does not significantly inhibit cyclooxygenases in peripheral tissues. Paracetamol stimulates the activity of descending serotonergic pathways that block the transmission of nociceptive signals to the spinal cord from peripheral tissues. In this sense, some experimental data indicate that the administration of antagonists of different subtypes of serotonergic receptors administered intraspinally are able to nullify the antinociceptive effect of paracetamol.
The antithermal action is related to the inhibition of the synthesis of PGE1 in the hypothalamus, the physiological coordinating organ of the thermoregulation process.

5.2 Pharmacokinetic properties

Orally the bioavailability of paracetamol is 75-85%. It is widely and rapidly absorbed, the maximum plasma concentrations are reached depending on the pharmaceutical form with a time of 0.5 to 2 hours. The degree of plasma protein binding is 10%. The time that elapses to achieve the maximum effect is 1 to 3 hours, and the duration of action is 3 to 4 hours. The metabolism of paracetamol undergoes a hepatic first-pass effect, following a linear kinetics. However, this linearity disappears when doses greater than 2 g are administered. Paracetamol is metabolized mainly in the liver (90-95%), being eliminated mainly in urine as a conjugate with glucuronic acid, and to a lesser extent with sulfuric acid and cysteine; less than 5% is excreted unchanged. The elimination half-life is 1.5-3 hours (increases in case of overdose and in patients with hepatic impairment, the elderly and children). High doses can saturate the usual mechanisms of hepatic metabolization, which causes alternative metabolic pathways to be used that give rise to hepatotoxic and possibly nephrotoxic metabolites, due to glutathione depletion.

<u>Pathophysiological variations</u>

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 patients: the conjugation capacity is not modified. An increase in the elimination half-life of paracetamol has been observed.

5.3 Preclinical safety data

Paracetamol, at therapeutic doses, has no toxic effects and only at very high doses causes hepatic centrolobular necrosis in animals and man. Also at very high dose levels, paracetamol causes methemoglobinemia and oxidative hemolysis in dogs and cats and very rarely in humans. They have been observed in chronic, subchronic and acute toxicity studies, carried out with rats and mice, gastrointestinal lesions, changes in blood count, liver degeneration and renal parenchyma, including necrosis. On the one hand, the causes of these changes have been attributed to the mechanism of action and on the other hand, to the metabolism of paracetamol. It has also been seen in humans that metabolites appear to produce toxic effects and corresponding organ changes. In addition, very rare cases of chronic reversible aggressive hepatitis during prolonged use (e.g. 1 year) have been described with therapeutic doses. In the case of subtoxic doses, signs of intoxication may appear within 3 weeks of treatment. Therefore, paracetamol should not be taken for long periods of time and not at high doses.
Further research showed no evidence of a genotoxic risk of paracetamol relevant to therapeutic doses, i.e. at non-toxic doses.
Long-term studies in rats and mice produced no evidence of tumors with non-hepatotoxic doses of paracetamol.
There are no conventional studies using the currently accepted standards for the assessment of reproductive and developmental toxicity.

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, 20 (10x2), 30 (10x3), 50 (10x5), 100 (10x10) 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.
Hospitaaldreef 29
1315 RC Almere
Nederland

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

RVG 128940

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

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