Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol 500 mg tablets

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 to off-white oblong biconvex tablets, breakline with 5 on one side of the line and 00 on the other side of the line on one side of the tablet and breakline on the other side.
Dimensions: approx. 7.2 mm x 16.3 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.

Paracetamol is indicated in adults, adolescents and children from 22 kg (aged 6 years and older).

4.2 Posology and method of administration

The lowest effective dose should generally be used for the shortest possible duration.

Dose depends on age and body weight, generally 10 to 15 mg/kg body weight as a single dose, up to a recommended maximum of 60 mg/kg body weight as the total daily dose (not exceeding 4000 mg). See the table below for weight intervals and dosage examples.

In each case, the dosing interval depends on the symptoms and maximum total daily dose. It should be no less than 4 hours.

If pain persist beyond 5 days and fever persist beyond 3 days, get worse or other symptoms appear then a doctor should be consulted.
The patient's caregiver should be advised to contact a physician if high fever, signs of infection, or symptoms persist after more than 2 days of treatment in children under 12 years of age.

Dosage

Dosage is in accordance with the information in the following table:

Body weight (age)	**Single dose paracetamol**	**Number of tablets at a time**	**Max. daily dose (24 h) Paracetamol**
22 kg- 30 kg (children 6 – 9 years approximately)	250 mg	1/2 of 500 mg	1,000 - 1,500 mg (Maximum 3 tablets)
31 kg - 40 kg (children 10 - 12 years approximately)	500 mg	1	1,500 - 2,000 mg (Maximum 4 tablets)
41 kg – 55 kg (children 13 – 15 years approximately	500 mg	1 **or** 1 and ½	2,000 - 3,000 mg (Maximum 6 tablets)

>55 kg (adults and adolescents from 15 years of age and over)	500 mg	1or 2	4,000mg (Maximum 8 tablets)

The lower frequency of administration is intended for children in the lower limit of the relevant weight and/or age category. This medicinal product is not intended for use in children below 22 kg body weight (under 6 years of age) due to inadequacy of dose/unfeasibility of appropriately dosing these patients. For children under the age of 6 years, more suitable formulations are available.

Patients/users/children between 6 and 9 years of age (between 22 and 30 kg): the maximum single dose per intake is half a tablet (250 mg paracetamol).

Special populations:

Elderly patients
Dose adjustment is not required in the elderly. However, it should be taken into account that renal and/or hepatic insufficiency is more common in the elderly (see section 4.4).

Renal impairment
In patients with renal impairment and except medical advice, the minimum interval between each administration should be modified and the maximum daily dose should be reduced according to the following schedule:

Creatinine clearance	**Administration interval**	**Maximum daily dose (24 h) of paracetamol** *(number of tablets)*
cl 10-50 mL/min	500 mg every 6 hours	2000 mg *(4 tablets)*
cl <10 mL/min	500 mg every 8 hours	1500 mg *(3 tablets)*

Hepatic impairment
Paracetamol should be used with caution in the presence of hepatic insufficiency or Gilbert's syndrome. The dose should be reduced or the dosing interval prolonged.
A daily dose of 2000 mg should not be exceeded, for adults, without medical advice.

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

- adults and adolescents weighing less than 50 kg
- dehydration
- chronic malnutrition
- chronic alcohol consumption may lower the paracetamol toxicity threshold. In these patients, the length of time between two doses should be a minimum of 8 hours.

Method of administration
For oral use. The tablet should be swallowed with a glass of water.

4.3 Contraindications

Hypersensitivity to paracetamol or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

In order to avoid the risk of overdose, it should be ensured that co-administered medications do not contain paracetamol.

In the following cases, paracetamol should be used with particular caution, i.e. by increasing the dosing interval or reducing the dose (see section 4.2) and under medical surveillance:

- Hepatocellular insufficiency (Child-Pugh < 9)
- Chronic alcohol abuse
- Renal insufficiency (creatinine clearance < 10 ml/min)
- Gilbert's syndrome (Meulengracht's disease)
- Have a severe infection as this may increase the risk of metabolic acidosis. Signs of metabolic acidosis include:
- deep, rapid, difficult breathing
- feeling sick (nausea), being sick (vomiting)
- loss of appetite

- Acute hepatitis
- Concomitant treatment with medicinal products affecting hepatic functions
- Glucose-6-phosphate dehydrogenase deficiency
- Glutathione deficiency
- Haemolytic anaemia
- Dehydration
- Chronic malnutrition
- Elderly.

Additional precautions (see section 4.2)
Prolonged or frequent use is discouraged. Patients should be advised not to take other paracetamol containing products concurrently. Taking multiple daily doses in one administration can severely damage the liver; in such cases unconsciousness does not occur. However, in the event of overdosage, medical assistance should be sought immediately, even if the patient feels well, because of the risk of irreversible liver damage (see section 4.9). Prolonged use except under medical supervision may be harmful. In children and adolescents treated with 60 mg/kg daily of paracetamol, the combination with another antipyretic is not justified except in the case of ineffectiveness.

It is recommended to monitor asthmatic patients sensitive to acetylsalicylic acid, as mild bronchospastic reactions have been reported when paracetamol is administered (cross-reaction). Although such reactions only occurred in a minority of these patients, severe reactions can occur in some cases, especially when high doses of paracetamol are administered.

Alcohol should not be used during the treatment with paracetamol.

The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease. Caution should be exercised in cases of chronic alcoholism. In patients with alcohol abuse the dose has to be reduced (see section 4.2). The daily dose should not exceed 2 grams in such case.

Patients with impaired nutritional state caused by alcohol abuse, anorexia or wrong nutrition are advised against prolonged use and maximum doses because of risk of toxic liver reactions.

In the event of high fever, signs of secondary infection or if symptoms persist beyond three days, the doctor must be consulted.

Without the advice of a physician or dentist, medicinal products containing paracetamol should generally be used for only five days for pain and three days for fever and not at high doses.

With prolonged, high-dose, incorrect use of analgesics, headaches may occur which must not be treated with increased doses of the medicinal product.

In general, habitual intake of analgesics, particularly in combination with several analgesic substances, can lead to permanent renal damage with the risk of renal failure (analgesic nephropathy).

Headaches, as well as fatigue, muscle pain, nervousness and autonomic symptoms, may occur upon abrupt discontinuation following prolonged, high-dose, incorrect use of analgesics. The withdrawal symptoms resolve within a few days. Until this time, further intake of analgesics must be avoided and not re-started without medical advice.

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 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.

Effects on laboratory test results
Intake of paracetamol can affect uric acid tests using phosphotungstic acid and blood sugar tests using glucose oxidase-peroxidase.

4.5 Interaction with other medicinal products and other forms of interaction

- Intake of **probenecid** inhibits the binding of paracetamol to glucuronic acid, thereby leading to a reduction in paracetamol clearance by a factor of approximately 2. With concomitant intake of probenecid, the paracetamol dose should be reduced.
- Particular caution should be exercised with concomitant intake of **medications that lead to enzyme induction**, as well as with **potentially hepatotoxic substances** (see section 4.9). The metabolism of paracetamol is increased in patients taking enzyme-inducing medicinal products e.g. phenytoine, carbamazepine, phenobarbital, primidone and rifampicine. Isolated reports describe unexpected hepatotoxicity in patients taking enzyme-inducing medicinal products,
- With concomitant use of paracetamol and **AZT (zidovudine)**, susceptibility to the development of neutropenia and hepatotoxicity is increased. Chronic / multiple dose paracetamol use in patients on zidovudine therapy should be avoided administered only on medical advice. However, if chronic paracetamol and zidovudine are required, white blood count and liver function tests should be monitored particularly in malnourished patients.
- With concomitant intake of **agents that slow gastric emptying**, the absorption and onset of action of paracetamol may be delayed.
- Concomitant intake of **agents that accelerate gastric emptying**, e.g. metoclopramide and domperidone, speeds up the absorption and onset of action of paracetamol.
- **Cholestyramine** reduces the absorption of paracetamol. When concomitant use of paracetamol and cholestyramine is necessary, paracetamol should be taken at least 1 hour before or 4 hours after cholestyramine administration.

- 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).

- **Vitamin K antagonists**: enhancement of the effect of vitamin K antagonists can occur, especially with regular intake of high doses of paracetamol. In this case, a regular check of the International Normalized Ratio (INR) is recommended. The anticoagulant effect of **warfarin and other coumarins** may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

- **Lamotrigine**: paracetamol may decrease the bioavailability of lamotrigine, with possible reduction of its effects, due to possible induction of its metabolism in the liver.

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.

Breastfeeding
Paracetamol is excreted in breast milk, but not in a clinically significant amount in recommended doses. Available published data do not contraindicate breastfeeding.

Fertility
There are no adequate clinical data available on male or female fertility.

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

Adverse 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 database	Adverse reactions and frequency
Blood and lymphatic system disorders	*Very rare*: thrombocytopaenia, leukopenia, pancytopenia, neutropenia, haemolytic anaemia, agranulocytosis *Not known:* anaemia
Immune System disorders	*Very rare*: anaphylaxis (requiring discontinuation of treatment), cutaneous hypersensitivity reactions, including, among others, skin rashes
Metabolism and nutrition disorders	*Not known:* High anion gap metabolic acidosis*
Respiratory, thoracic and mediastinal disorders	*Very rare*: bronchospasm in patients sensitive to aspirin and other NSAIDs
Hepatobiliary disorders	*Very rare*: hepatotoxicity *Rare:* elevation of liver transaminases, hepatic dysfunction, hepatic failure, hepatic necrosis, jaundice *Not known:* hepatitis
Skin and subcutaneous tissue disorders	*Rare:* pruritus, rashes, sweating, angioedema, urticaria *Very rare:* cases of serious skin reactions have been reported (drug-induced Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalised exanthematous pustulosis (AGEP)) *Not known:* exanthema
Nervous system disorders	*Rare:* headache
Gastrointestinal disturbances	*Rare:* abdominal pain, diarrhea, nausea, vomiting and constipation
Kidney and urinary disorders	*Very rare:* sterile pyuria (cloudy urine) *Not known:* nephropathies (interstitial nephritis, tubular necrosis) following prolonged use of high doses
General disorders	*Rare:* dizziness, malaise
Injury, poisoning and complications	*Rare:* overdose and intoxication

*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 HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Paracetamol overdose may cause liver failure which can lead to liver transplant or death.

There is a risk of poisoning with paracetamol particularly in elderly subjects, young children, patients with liver disease, cases of chronic alcoholism and in patients with chronic malnutrition, in patients that use enzyme inducing substances and adults weighing under 50 kg. Overdosing may be fatal in these cases.

Symptoms

Symptoms generally appear within the first 24 hours and may comprise: nausea, vomiting, anorexia, pallor, and abdominal pain, or patients may be asymptomatic.

Overdose of paracetamol in a single administration in adults or in children can cause liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may cause coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin time that may appear 12 to 48 hours after administration. Liver damage is likely in adults who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue.

Some patients may be at increased risk of liver damage from paracetamol toxicity.

Acute renal failure with acute tubular necrosis may also develop.

Cardiac arrhythmias pancreatitis have also been reported.

Risk Factors include: If the patient:

- is on long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
- regularly consumes ethanol in excess of recommended amounts
- is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia

The above mentioned risk factors may lower the threshold for hepatotoxicity.

Management

Emergency Procedure:
Immediate treatment is essential in management of paracetamol overdose. Patients should be transferred to hospital urgently for immediate medical attention.

Administration of activated charcoal should be considered if >150mg/kg paracetamol has been taken within 1 hour.
Plasma paracetamol concentration should be measured at 4 hours or later after ingestion in the case of single acute overdose. Blood sampling should be used to determine the initial paracetamol plasma concentration.

Treatment with N-acetylcysteine, should be administered as soon as possible in accordance with National treatment guidelines.

Symptomatic treatment should be implemented.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other analgesics and antipyretics; Anilides. ATC code: N02BE01.

Paracetamol has analgesic and antipyretic actions. The analgesic and antipyretic mechanism of action of paracetamol has not been clearly elucidated. A central and peripheral action is probable. Marked inhibition of cerebral prostaglandin synthesis has been demonstrated, whereas peripheral prostaglandin synthesis is only weakly inhibited. Furthermore, paracetamol inhibits the effect of endogenous pyrogens on the hypothalamic temperatures regulation.

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 condition formulation and nutritional status (paracetamol can be taken independently of food become). The average bioavailability after oral administration is approximately 80% due to the first liver passage, regardless 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. Into the concentration saliva and breast milk is related to the concentration in plasma.

Biotransformation
Metabolism is almost the only pathway by which paracetamol is excreted. Paracetamol is conjugated with glucuronic acid in the liver in adults by uridine 5'-diphospho-glucuronosyltransferase (ULT) 1A1 (approx. 60%), sulphate (approx. 35%) by sulfotransferase (SULT) 1A1 and cysteine by N-acetylcysteine transferase (NAT) (approx. 3%). A small proportion (~5%) of paracetamol is converted in the body using cytochrome P450 (CYP) 2E1 and 2D6 into a highly reactive metabolite (N-acetyl-p-benzoquinonimine) 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 dose taken is excreted via the kidneys within 24 hours, mainly in the form of glucuronide (60-80%) and the sulphate conjugate (20-30%), and approximately 5% unchanged. The elimination half-life ranges from 1 to 4 hours with an average of 2.3 hours healthy volunteers. The total body clearance is 5 ml/min/kg body weight. The renal clearance of paracetamol is approximately 10 ml/min.

Special populations

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

Hepatic insufficiency
No changes in kinetics were found in patient suffering from liver disease, except in patients suffering from severe liver disease. With impaired liver function decreases total body clearance suggesting that the metabolic clearance is almost equal to the total body clearance. For patients with inadequate 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, 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 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

Extensive studies revealed no evidence of a relevant genotoxic risk for paracetamol within the therapeutic, i.e. nontoxic, dose range.

Long-term studies on rats and mice do not indicate any relevant tumorigenic effects at non-hepatotoxic doses of paracetamol.

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
Povidone K30
Stearic acid

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

PVC/aluminium non-perforated blister packs containing 10, 16, 20, 30, 50, 100 tablets.
PVC/aluminium perforated unit-dose blister packs containing 10x1, 16x1, 20x1, 30x1, 50x1, 100x1 tablets.

HDPE bottles with polypropylene child-resistant closure or continuous thread caps containing 100, 120, 300, 400, 1000 tablets per bottle.

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

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA1986/130/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th August 2026

10 DATE OF REVISION OF THE TEXT