Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol Teva 500 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg paracetamol.

Excipients with known effect:
Each film-coated tablet contains 12 µg of glucose and sorbitol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White to off-white, oval shaped biconvex tablet, breakline on one side of the tablet and plain on the other. The tablet is approximately 7.9 x 17.1 mm in size with a height of approximately 5.0-6.5 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 Teva is indicated in adults, adolescents and children aged 6 years and over.

4.2 Posology and method of administration

Posology
Dosage is in accordance with the information in the following table.
Dose depends on age and body weight, generally 10 to 15 mg/kg body weight as a single dose, up to a maximum of 60 mg/kg body weight as the total daily dose.

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

For children under the age of 6 years, more suitable formulations are available.

If symptoms persist beyond 3 days, a doctor should be consulted.

Body weight (age)	**Single dose (equivalent paracetamol dose) (number of tablets)**	**Max. daily dose (24 h) (equivalent paracetamol dose) (number of tablets/doses**	**Minimum interval between doses**
22 kg - 30 kg (children 6 – 9 years approximately)	250 mg (1 half tablet)	1,000 – 1,500 mg (maximum of 2-3 tablets/4-6 doses)	4 - 6 hours
30 kg- 40 kg (children 9 – 12 years approximately)	500 mg (1 tablet)	1,500 – 2,000 mg (maximum of 3-4 tablets/ doses)	4 -6 hours

40 kg - 55 kg (children 12 - 15 years approximately)	500 mg (1 tablet)	2,000 – 3,000 mg (maximum of 4-6 tablets/ doses)	4 - 6 hours
>55 kg (adults and adolescents aged 15 years and over)	500 – 1,000 mg (1-2 tablets)	3,000 mg (maximum of 6 tablets/ 3-6 doses)	4 - 6 hours

The maximum daily dose (24 hours) stated in the table must not be exceeded under any circumstances.

The lowest dose necessary to achieve efficacy should be used.
Maximum duration of continued use without medical advice: 3 days.

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
Paracetamol should be used with caution in the presence of renal insufficiency and increased interval between doses is recommended in cases of severe renal insufficiency. Where creatinine clearance is between 10-50 ml/min, the minimum interval between administrations should be 6 hours. When creatinine clearance is lower than 10 ml/min, the minimum interval between two administrations should be 8 hours.

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 2,000 mg should not be exceeded, for adults, without medical advice.

Without medical advice, a maximum daily dose of 60 mg/kg body weight (till a maximum of 2,000 mg/day) should not be exceeded in the case of:

- Body weight below 50 kg
- Liver impairment
- Gilbert's syndrome (familial non-haemolytic jaundice)
- Chronic alcohol abuse
- 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 the active substance 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. with increase of the dosing interval or at a reduced 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.

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.

Cases of paracetamol induced hepatotoxicity, including fatal cases, have been reported in patients taking paracetamol at doses within the therapeutic range.
These cases were reported in patients with one or more risk factors for hepatotoxicity including low body weight (<50 kg), renal and hepatic impairment, chronic alcoholism, concomitant intake of hepatotoxic drugs, and in acute and chronic malnutrition (low reserves of hepatic glutathione). Paracetamol should be administered with caution to patients with these risk factors. Caution is also advised in patients on concomitant treatment with drugs that induce hepatic enzymes and in conditions which may predispose to glutathione deficiency (see sections 4.2 and 4.9). Doses of paracetamol should be reviewed at clinically appropriate intervals and patients should be monitored for emergence of new risk factors for hepatotoxicity which may warrant dosage adjustment.

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 a few days 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.

Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

Paracetamol Teva contains glucose:
Patients with rare glucose-galactose malabsorption should not take this medicinal product.

Paracetamol Teva contains sorbitol:
The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol on medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

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 and 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.
- 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.
- Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic 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.
- Lamotrigine: paracetamol may decrease the bioavailability of lamotrigine, with possible reduction of its effects, due to possible induction of its metabolism in the liver.

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

4.6 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 lowers 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 Teva 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* (³1/10); *Common* (³1/100 to <1/10); *Uncommon* (³1/1,000 to <1/100); *Rare* (³1/10,000 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 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))
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 *Not known:* exanthema
Nervous system disorders	*Rare:* headache
Gastrointestinal disturbances	*Rare:* abdominal pain, diarrhoea, 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

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 generally appear within the first 24 hours and may consist of: 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 levels 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.

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: Analgesics; Other Analgesics and Antipyretics; Anilides.
ATC code: N02B E01

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

Paracetamol is rapidly and almost completely absorbed from the gastro-intestinal tract.

Human pharmacokinetic data demonstrate that early absorption of paracetamol (fraction of dose over the first 60 minutes) is 32% greater from Paracetamol Teva compared to standard paracetamol tablet ($p<0.0001$) and less between-subject and less within-subject variability ($p<0.0001$) in early absorption of paracetamol from Paracetamol Teva compared to standard paracetamol tablets.

Human pharmacokinetic data demonstrate that maximum plasma concentration of paracetamol is reached at least 25% faster for Paracetamol Teva compared to standard paracetamol tablets in fasted and fed states ($p <0.01$). Concentration in plasma reaches a peak in 25 minutes.

Total extent of absorption of paracetamol from Paracetamol Teva is equivalent to that from standard paracetamol tablets.

In a BV study, the following results were obtained compared to the reference product Panadol Film-coated tablets *Study number: BE-1967-19):

	Reference Product (R)			**Test Product (T)**		
Pharmacokinetic Parameter(s)	**Arithmetic mean**	**Standard deviation**	**CV (%)**	**Arithmetic mean**	**Standard deviation**	**CV (%)**
*T_{max} (^{h})	0.68	0.25-2.25		0.42	0.22-1.33	

*median & range reported

Human scintigraphy data demonstrate that Paracetamol Teva generally start to disintegrate by 5 minutes post dose. Human pharmacokinetic data demonstrate that paracetamol can generally be detected in plasma by 10 minutes.

Plasma protein binding is variable. Plasma half-life is 1 – 4 hours. Maximum plasma concentration of paracetamol is reached faster for Paracetamol Teva compared to standard paracetamol tablet in fasted and fed states ($p < 0.01$).

Paracetamol is relatively uniformly distributed throughout most body fluids.

Excretion is almost exclusively renal, in the form of conjugated metabolites.

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

Tablet core:
Starch, pregelatinized (maize)
Calcium carbonate
Povidone (K-25)
Crospovidone (type B)
Alginic acid
Silica, colloidal anhydrous
Magnesium stearate

Film coating:
Hypromellose

Polydextrose (contains sorbitol and glucose)
Triglycerides, medium chain
Macrogol 3350
Calcium carbonate
Deoiled sunflower lecithin (E322)
Macrogol 400

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

PVC/PVdC-Aluminium blisters and OPA/Alu/PVC-Aluminium blisters.
Pack sizes: 10, 20, 30, 50 and 100 film-coated 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

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA1986/101/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st April 2022

10 DATE OF REVISION OF THE TEXT

September 2022