Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol Zentiva 500 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg of paracetamol.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White capsule shaped tablet with flat edges, dimensions approx. 17×7 mm, S score line 1 (S|1) on one side. The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Short-term symptomatic treatment of mild to moderate pain and/or fever.

Paracetamol Zentiva 500 mg tablets are intended for adults, adolescents and children with body weight above 21 kg (aged 6 years and over).

4.2 Posology and method of administration

Posology
The lowest effective dose should be used for the shortest time possible. The maximum daily dose must not be exceeded.
Paracetamol is dosed depending on body weight and age, usually 10 – 15 mg/kg body weight as a single dose, up to a maximum daily dose of 60 mg/kg body weight. For dosing according to the body weight and age see the tables.

Paracetamol Zentiva 500 mg tablets are not intended for children less than 6 years of age with body weight less than 21 kg.

Approximate age	Body weight	Single dose	Maximum daily dose
6 – 8 years	21 – 24 kg	250 mg (½ tablet)	1 g (2 tablets)
9 – 10 years	25 – 33 kg	250 mg (½ tablet)	1.5 g (3 tablets)
10 – 12 years	34 – 41 kg	500 mg (1 tablet)	2 g (4 tablets)
12 – 15 years	42 – 49 kg	500 mg (1 tablet)	2.5 g (5 tablets)
> 15 years	50 – 60 kg	500 mg (1 tablet)	3 g (6 tablets)
	> 60 kg	500 – 1000 mg (1 – 2 tablets)	3 g (6 tablets)*

* Only after medical consultation, the maximum daily dose in patients with body weight > 60 kg can be increased to 4 g of paracetamol.

Single dose may be repeated as needed, with an interval of at least 4 – 6 hours.

Renal impairment

Paracetamol should be used with caution in patients with renal impairment as a reduced dose and/or prolonged dosing interval is necessary (see section 4.4). The maximum single dose should not exceed 500 mg.

- Dosing interval of 6 hours is recommended at the glomerular filtration rate 50 – 10 mL/min.
- Dosing interval of 8 hours is recommended at the glomerular filtration rate less than 10 mL/min.

Hepatic impairment
Paracetamol should be used with caution in patients with mild to moderate hepatic impairment or Gilbert's syndrome as the dose should be reduced or the dosing interval extended (see section 4.4). In these patients, the daily dose should not exceed 60 mg/kg (maximum 2 g/day). The use of this medicinal product is contraindicated in patients with severe hepatic insufficiency (see section 4.3).

Elderly
Experience has indicated that normal adult dosage of paracetamol is usually appropriate. However, in frail, immobile elderly subjects or in elderly patients with renal or hepatic impairment, a reduction in the amount or frequency of dosing may be appropriate (see section 4.4).

Method of administration
Oral use.
Tablets should be swallowed with a sufficient amount of liquid.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Severe hepatic insufficiency.
- Acute hepatitis.

4.4 Special warnings and precautions for use

Patients should be warned not to simultaneously use other paracetamol-containing medicinal products.

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 used with caution in patients with glucose-6-phosphate dehydrogenase deficiency, in haemolytic anaemia, in case of glutathione deficiency, chronic malnutrition, chronic alcoholism, dehydration, in elderly and in patients with mild to moderate hepatic impairment and/or renal impairment (see section 4.2).

Regular monitoring of liver function tests is recommended in patients with impaired hepatic function and those receiving high doses of paracetamol over a long period. The risk of serious hepatotoxic effects increases significantly with increasing dose and duration of treatment. Underlying liver disease increases the risk or paracetamol related liver damage. The risk of overdose is higher in patients with non-cirrhotic liver damage caused by alcohol.

Intake of alcohol has to be avoided during the therapy. Long-term alcohol consumption significantly increases the risk of hepatotoxicity of paracetamol.

Measurement of prothrombin time is required in concomitant therapy with oral anticoagulants and long-term regular daily intake of paracetamol.

The possibility of kidney impairment cannot be ruled out in the long-term treatment.

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.

4.5 Interaction with other medicinal products and other forms of interaction

The absorption rate of paracetamol may be enhanced by metoclopramide or domperidone. However, concurrent use does not need to be avoided.

Cholestyramine reduces the absorption of paracetamol. Paracetamol should be administered at least 1 hour before or 4 – 6 hours after cholestyramine.

Long-term co-administration with acetylsalicylic acid or other NSAIDs may lead to renal damage.

The anticoagulant effect of warfarin or other coumarin products may be increased together with an increased risk of bleeding with long-term regular daily intake of paracetamol. Occasional use has no significant effect.

Hepatotoxic substances may elevate potential accumulation and overdose with paracetamol.
Paracetamol may affect the pharmacokinetics of chloramphenicol. Therefore, an analysis of chloramphenicol in plasma is recommended in the event of combination treatment with chloramphenicol for injection.

Probenecid reduces clearance of paracetamol by almost 50%. Thus, the paracetamol dose may be halved during concomitant treatment.

Inducers of microsomal enzymes (e.g. rifampicin, phenobarbital, phenytoin, carbamazepine, St. John's Wort) decrease the bioavailability of paracetamol through an increased glucuronidation, and the risk of hepatic toxicity is increased. Such combinations should be avoided.
Concomitant use of paracetamol and zidovudine may result in an increased risk of neutropenia.
Concomitant use of paracetamol and isoniazid may result in an increased risk of hepatotoxicity.
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).

4.6 Fertility, pregnancy and lactation

Pregnancy
A large amount of data on pregnant women indicate neither malformative, nor foeto/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 passes into breast milk but is unlikely to affect the child at therapeutic doses. It is not necessary to discontinue breast-feeding during short-term treatment with the recommended doses of this medicinal product.

Fertility
No clinical data are available.

4.7 Effects on ability to drive and use machines

Paracetamol Zentiva 500mg tablets have no influence on the ability to drive and use machines.

4.8 Undesirable effects

Administration of paracetamol may cause the following undesirable effects (classified into groups according to MedDRA terminology with indication of the frequency of incidence as follows: 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).

MedDRA system organ class	Frequency	Undesirable effect

Blood and lymphatic system disorders	Very rare	Thrombocytopenia
Immune system disorders	Rare	Skin hypersensitive reaction incl. rash and angioedema
	Very rare	Anaphylaxis
Respiratory, thoracic and mediastinal disorders	Very rare	Bronchospasm*
Hepatobiliary disorders	Very rare	Abnormal liver function
Skin and subcutaneous tissue disorders	Very rare	Cases of serious skin reactions such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis

* In patients sensitive to acetylsalicylic acid or other NSAIDs.

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

In case of an overdose of paracetamol, immediate medical attention is required, even if no symptoms of overdose are present.

Symptoms

Overdose with even relatively low paracetamol doses may result in a severe damage of the liver and, sometimes, acute renal tubular necrosis.

Nausea, vomiting, lethargy, anorexia, pallor and sweating may occur within 24 hours, or patients may be asymptomatic. Abdominal pain may be the first symptom of liver damage and occurs in 1 – 2 days. Overdose of paracetamol can cause liver cell necrosis likely to induce complete 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 are observed together with prolonged prothrombin time that may appear 12 to 48 hours after administration. Prolongation of the prothrombin time is one of indicators of an impaired liver function, and therefore its monitoring is recommended. Complications of liver failure include cerebral oedema, bleeding, hypoglycaemia, hypotension, infections and renal failure.

Liver damage is likely in patients who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of toxic metabolite become irreversibly bound to liver tissue. Some patients may be at increased risk of liver damage from paracetamol toxicity. Risk factors include:

- Patients with liver disease.
- Elderly patients.
- Young children.
- Patients receiving long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St. John's Wort or other drugs that induce liver enzymes.
- Patients who regularly consume alcohol in excess of recommended amounts.
- Patients with glutathione depletion e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Acute renal failure can occur without presence of severe hepatic impairment. Other manifestations of intoxication are myocardial damage, cardiac arrhythmias and pancreatitis.

Management

Hospitalization is required. Blood sampling should be done to determine initial paracetamol plasma concentration. In the case of a single acute overdose, paracetamol plasma concentration should be measured 4 hours post ingestion. Induction of vomiting, gastric lavage, especially if paracetamol has been ingested less than 4 hours before, then methionine (2.5 g orally) must be given, furthermore support measures are appropriate. Administration of activated charcoal to reduce gastrointestinal absorption is controversial. Specific antidote N-acetylcysteine should be given as soon as possible, within 8 – 15 hours after poisoning, but beneficial effects have been observed with acetylcysteine later administration too. Acetylcysteine should be administered in accordance with national treatment guidelines, it is usually administered to adults, adolescents and children IV in 5% glucose, the initial dose should be 150 mg/kg of body weight in the course of 15 minutes. Furthermore, 50 mg/kg in an infusion of 5% glucose for a period of 4 hours, and then 100 mg/kg until the 16th resp. 20th hour from the start of therapy.

Acetylcysteine can also be administered orally within 10 hours of ingestion of a toxic dose of paracetamol at a dose of 70 – 140 mg/kg 3 times a day. Haemodialysis or haemoperfusion is in place in very severe intoxication. Symptomatic treatment should be implemented.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, anilides;
ATC code: N02BE01.

Paracetamol is an analgesic – antipyretic without anti-inflammatory effect. The mechanism of action is probably similar to the action of acetylsalicylic acid and is dependent on prostaglandin inhibition in the central nervous system.

The analgesic effect of paracetamol after a single dose of 0.5 – 1 g lasts 3 – 6 hours, antipyretic 3 – 4 hours.

5.2 Pharmacokinetic properties

Absorption
Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. Maximum plasma concentrations are reached within 30 – 60 minutes after oral administration.

Distribution
Paracetamol is relatively evenly distributed throughout the body fluid. Plasma protein binding varies; 20 – 30% can be bound in concentrations caught in acute intoxication. Paracetamol crosses the placental barrier and is excreted in breast milk.

Biotransformation and elimination
Excretion is practically exclusively renal in the form of conjugate metabolites. About 5% paracetamol is excreted unchanged. The elimination half-life is 1 – 4 hours after therapeutic doses. In severe hepatic insufficiency, it is prolonged for up to 5 hours. At renal insufficiency the half-life is not prolonged, but due to slowed renal excretion a paracetamol dose reduction is required.

5.3 Preclinical safety data

Conventional studies with paracetamol 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 maize starch
Maize starch
Talc (E 553)
Stearic acid (E 570)
Povidone (E 1201)

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/Alu blister.
Pack sizes: 10, 12, 16, 20, 24, 30, 50, 100, 120 or 300 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Zentiva k.s.
Dolni Mecholupy,
U Kabelovny 130
Prague
102 37
Czech Republic

8 MARKETING AUTHORISATION NUMBER

PA1701/007/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th February 2023

10 DATE OF REVISION OF THE TEXT

December 2023