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.
Excipient(s) with known effect: each tablet contains 30 mg wheat starch.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Round, flat tablets, with a facet and a score line on the one side, with a 13 mm diameter and 4 mm thickness. Colour – white to almost white.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Paracetamol is recommended for the short-term treatment of the mild to moderate pain such as headache, toothache, musculoskeletal disorders and menstrual pain and for fever associated with cold and flu.

Paracetamol is indicated in adults and adolescents aged 12 or older.

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 (3000 mg).

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.

For dosing according to the body weight and age see the table.

Age	Body weight	Single dose	Maximum daily dose	Dosing interval
12 – 15 years	40-55 kg	500 mg	2-3 g (maximum of 4-6 tablets per 24 hours)	at least 4 – 6 hours
> 15 years	40-55 kg	500 mg	2-3 g (maximum of 4-6 tablets per 24 hours)	at least 4 – 6 hours
	> 55 kg	500 – 1,000 mg	3 g (maximum of 6 tablets per 24 hours)	

Paracetamol is not recommended for children under 12 years of age. Other formulations containing paracetamol are available. The paediatric dosage shall be based on the body weight with a maximum daily dose of 60 mg/kg body weight, not exceeding 3000 mg for total daily dose.

If the pain persists for more than 5 days or the fever lasts for more than 3 days, or gets worse or other symptoms appear, a doctor should be consulted.
The 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).

Renal impairment

Paracetamol should be used with caution in patients with renal impairment as a reduced dose and/or prolonged dosing interval may be necessary (see section 4.4).

In patients with renal insufficiency, the dose should be reduced:

Glomerular filtration rate	Dose
10–50 ml/min	500 mg every 6 hours
< 10 ml/min	500 mg every 8 hours

Hepatic impairment
Paracetamol should be used with caution in patients with hepatic impairment (including Gilbert's syndrome) as a reduced dose or prolonged dosing interval may be necessary (see section 4.4).

Method of administration: swallow the tablet with water and, if necessary, the tablet can be divided into halves.

4.3 Contraindications

Paracetamol should not be taken in case of:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients should be advised to consult their doctor when the pain lasts for more than 5 days or the temperature remains high for more than 3 days or if these symptoms are accompanied by cough, headache, rash, nausea and vomiting.

The paracetamol content in other concomitantly taken combined medicinal products should be checked in order to avoid the risk of inadvertent overdosing.
Paracetamol should be administered with caution under the following circumstances (see section 4.2):

- glucose-6-phosphate dehydrogenase deficiency
- haemolytic anaemia
- glutathione deficiency
- dehydration
- elderly
- Gilbert's syndrome

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 section 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.

Clinical signs of liver damage generally only start after a few days and climax after 4-6 days as a rule. An antidote should be administered as soon as possible. See also section 4.9.

Caution should be exercised in patients with asthma who are sensitive to acetylsalicylic acid, as mild reactions of bronchospasm have been reported with paracetamol (cross-reaction).

The risks of overdose are greater in those with non-cirrhotic alcoholic liver disease due to alcohol intake. Caution should be exercised in patients with chronic alcoholism. In such cases, the dose should not exceed 2 g daily. Alcohol should not be used during treatment with paracetamol.

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 or 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.

Patients with impaired kidney function (with levels of the creatinine clearance below 10 ml/min) are advised to take paracetamol in intervals of no less than 8 hours between two doses.

This medicine contains less than 1 mmol sodium (23 mg) per tablet that is to say essentially 'sodium free'.

This medicine contains only very low levels of gluten (from wheat starch) and is very unlikely to cause problems if you have coeliac disease.
One tablet contains no more than 3 micrograms of gluten. If the patient has wheat allergy (different form coeliac disease) he/she should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant use of paracetamol might potentiate the effect of coumarin anticoagulants.

Cholestyramine reduces the absorption of paracetamol. Metoclopramide and domperidone may increase the rate of absorption of paracetamol. However, concurrent use does not need to be avoided.

The concomitant use of paracetamol with phenothiazines may lead to hypothermia.

Enzyme inducers, such as phenytoin, carbamazepine, phenobarbital, isoniazid, St John's wort may increase the risk of hepatotoxicity.

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

Paracetamol may affect the plasma concentrations of chloramphenicol. Monitoring of chloramphenicol plasma levels is recommended if combining paracetamol with chloramphenicol injection treatment.

Oral contraceptives and Rifampicin reduce the effects of paracetamol.

Paracetamol should not be taken together with alcohol because induction of the microsomal ethanol-oxidising system (MEOS) may result in an increase of its hepatotoxicity. Patients consuming more than 50 ml hard alcohol per day should consult a doctor before taking 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).

4.6 Fertility, pregnancy and lactation

Pregnancy:
A large amount of data on pregnant women indicates neither malformities, 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 very low concentrations in the mother's milk and is not known to cause adverse effects to breast-fed children.

4.7 Effects on ability to drive and use machines

There are no data for adverse influence on the active attention, coordination of movements and reflexes when paracetamol is taken.

4.8 Undesirable effects

The adverse drug reactions are categorized by systems and organs with the following frequency by using the following convention: 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), with unknown frequency (cannot be estimated from the available data).

In therapeutic doses, the adverse drug reactions are a low number and rare.
In rare cases haemolytic anaemia, neutropenia, leukopenia and very rarely – pancytopenia and thrombocytopenia with haemorrhagic diathesis are observed. Paracetamol may cause allergic reactions – itching and rash, and more rarely – difficulty in breathing, constriction in the throat, swelling of the lips, tongue, face.

System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Rare	Platelet disorders, stem cell disorders, agranulocytosis, thrombocytopenia, neutropenia, leukopenia, haemolytic anaemia, pancytopenia
Immune system disorders	Rare	Allergies (excluding angioedema)
	Very rare	Anaphylactic shock, hypersensitivity reaction (requiring discontinuation of treatment)
Metabolism and nutrition disorders	Very rare	Hypoglycaemia
	Not known	High anion gap metabolic acidosis*
Psychiatric disorders	Rare	Depression, confusion, hallucination
Nervous system disorders	Rare	Tremor, headache
Eye disorders	Rare	Abnormal vision
Respiratory, thoracic and mediastinal disorders	Very rare	Bronchospasm
Gastrointestinal disorders	Rare	Haemorrhage, abdominal pain, diarrhoea, nausea, vomiting
Hepatobiliary disorders	Rare	Elevated liver transaminase, abnormal hepatic function, hepatic failure, hepatic necrosis, jaundice
	Very rare	liver damage
Skin and subcutaneous tissue disorders	Rare	Rash, urticaria, angioedema, Allergic dermatitis
	Very rare	Serious skin reactions have been reported
	Not known	Stevens-Johnson syndrome, toxic epidermal necrolysis
Renal and urinary system	Very rare	Sterile pyuria (cloudy urine), renal side effects

*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.

Liver damage with paracetamol has occurred in conjunction with alcohol abuse. The risk of kidney damage cannot be entirely ruled out with long-term use.

Interstitial nephritis has been reported incidentally after prolonged use of high doses. Some cases of erythema multiforme, oedema of the larynx, anaemia, liver alteration and hepatitis, renal alteration (severe renal impairment, haematuria, anuresis) and vertigo have been reported.

Very rare cases of serious skin reactions have been reported.

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

Acute overdosing of paracetamol may result in dosage-dependent hepatotoxicity and acute renal impairment. In addition, taking paracetamol for a long time, as well as the concomitant use with enzyme inductors, such as anticonvulsants and isoniazid, also poses risk of hepatotoxicity or chronic nephropathy.

In undernourished patients and in vegetarians, the glutathione levels are decreased and this increase of risk of hepatotoxicity.

In clinical terms, paracetamol-induced hepatotoxicity is expressed in: cyanosis, anaemia, vomiting, fever, rash, methemoglobinemia and stimulation of the central nervous system progressing to delirium, convulsions, coma, vascular collapse and death.

Chronic nephropathy is characterised by interstitial nephrites and papillary necrosis.
Chronic alcoholics (who consume more than 100 ml hard alcohol every day) are exposed to much higher risk of stomach bleeding and pancreatitis.

Paracetamol-induced hepato- and nephrotoxicity are attributable to the formation of oxidative metabolite, N-acetyl-para-benzoquinone imine (NAPQI), in the liver and to a lower extent – in the kidneys. NAPQI connects through a covalent bond to the sulfhydryl groups of the tissue macromolecules, which results in cellular necrosis. The taking of N-acetylcysteine or methionine up to 10-12 hours after acute overdosing may decrease the hepatotoxicity by connection to NAPQI. But these agents do not prevent renal toxicity. The maximum daily dose of paracetamol is 4 g.

Long-term administration of high doses of paracetamol(2-3 times maximum daily dose) may result in impairment of the liver functions (the skin and the eyes become yellow, nausea, stomach pain or discomfort, easily getting tired).

Treatment in case of overdose: Immediate transfer to hospital. Blood sampling to determine initial paracetamol plasma concentration. The stomach must be emptied by causing emesis or active carbon Gastric lavage
The antidote N-acetylcysteine, should be administered as soon as possible in accordance with National treatment guidelines. The cardiac function and the serum electrolytes should be monitored and corrected if need arises. In case of appearance of convulsions or central nervous system agitation, should be administered diazepam.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other analgesics and antipyretics, ATC code: N02BE01
Paracetamol is an analgesic that acts peripherally, probably blocking the generation of impulses in bradykinin-sensitive chemoreceptors that cause the pain. Although it is a prostaglandin synthase inhibitor, the synthase of the CNS appears to be more sensitive to this than the peripheral one. This may explain why the paracetamol does not have an anti-inflammatory activity.
The analgesic effect starts within 30 minutes, with maximum effect within 1 to 2 hours and lasts up to 4 to 5 hours. The antipyretic effect starts within 30 to 60 minutes. The maximum antipyretic effect is between 2 to 3 hours and the effect lasts up to 8 hours.

5.2 Pharmacokinetic properties

Absorption
After oral use, paracetamol is rapidly and almost completely absorbed by the gastrointestinal tract.
Paracetamol plasma peak concentration is reached in 30 to 60 minutes

Distribution
Paracetamol is rapidly distributed throughout most body fluids, presenting a minimum binding to plasma proteins at therapeutic concentrations.

Metabolism
Hepatic Metabolism: Paracetamol is metabolized in the liver and excreted in the urine mainly as glucuronide and sulfate conjugates; less than 5% is excreted as unchanged form.
A small fraction (less than 4 %) is transformed through cytochrome P450 into a metabolite that is conjugated with glutathione. In massive intoxications, the amount of this metabolite is high.
The conjugation capacity is not modified in the elderly.

Elimination
The plasma elimination half-life is approximately 2 hours.

5.3 Preclinical safety data

Extensive studies revealed no evidence of a relevant genotoxic risk for paracetamol within the therapeutic, i.e. non-toxic, 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.

Besides that, there is no pre-clinical data of relevance to the prescriber which is additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Wheat starch
Cellulose, microcrystalline (PH 101)
Sodium starch glycolate (type A)
Povidone (K25)
Magnesium stearate (Vegetable grade)
Talc
Silica, colloidal anhydrous (Aerosil 200/Hydrophilic Pyrogenic Silica)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC/aluminium blisters, 12, 20 and 24 tablets

Not all packs sizes may be marketed.

6.6 Special precautions for disposal

Waste material should be disposed of safely. Patients/carers should be encouraged to return any unused product to the Pharmacy, where it should be disposed of following national and local requirements.

7 MARKETING AUTHORISATION HOLDER

Bluefish Pharmaceuticals AB
P.O. Box 49013
100 28 Stockholm
Sweden

8 MARKETING AUTHORISATION NUMBER

PA1436/040/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd September 2022

10 DATE OF REVISION OF THE TEXT

April 2025