

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol 500 mg Capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 500 mg paracetamol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard (Capsules).

White to off-white crystalline powder filled in size '0' capsules with ivory colour body and ivory colour cap, having a nominal lock length of 21.4 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For use in the short-term management of mild pain and fever and for symptoms of common colds and flu in adults, the elderly and children aged over 10 years. Paracetamol may also be used in the symptomatic relief of mild to moderate pain associated with osteoarthritis in adults and the elderly, as diagnosed by a doctor.

4.2 Posology and method of administration

Adults (including the elderly) and children aged 16 years and over:

One or two capsules up to four times daily as required.

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).

Hepatic impairment

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

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).

In all patients over 16 years of age, the maximum daily dose of paracetamol should not exceed 60 mg/kg/day (up to a maximum of 2 g per day) in the following situations, unless directed by a physician: (see section 4.4)

- Weight less than 50kg
- Dehydration
- Malnutrition
- Chronic alcoholism.

Children aged 10-15 years:

One capsule up to four times daily as required.

Children should not be given Paracetamol 500 mg Capsules for more than 3 days without consulting a doctor.

Not recommended for children under 10 years of age.

These doses should not be repeated more frequently than every 4 hours and not more than 4 doses should be given in any 24 hour period.

The lowest dose necessary to achieve efficacy should be used. The maximum daily dose must not be exceeded.

Method of administration

Paracetamol Capsules is for oral administration

4.3 Contraindications

Hypersensitivity to paracetamol or any of the other constituents.

4.4 Special warnings and precautions for use

Contains paracetamol. Do not use with any other paracetamol-containing products. The concomitant use with other products containing paracetamol may lead to an overdose. Paracetamol overdose may cause liver failure which can lead to liver transplant or death.

Paracetamol should be administered with caution under the following circumstances (see section 4.2 where relevant):

- Glucose-6-phosphate dehydrogenase deficiency
- Haemolytic anaemia
- Glutathione deficiency
- Dehydration
- Elderly

Hepatotoxicity at therapeutic dose of paracetamol

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.

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.

Caution in patients with glutathione depleted states such as sepsis; the use of paracetamol may increase the risk of metabolic acidosis.

In general, medicinal products containing paracetamol should be taken for only a few days without the advice of a physician or dentist and not at high doses.

Do not exceed the stated dose.

If symptoms persist, consult your doctor. Prolonged use except under medical supervision may be harmful.

This product should only be used when clearly necessary.

Keep out of the sight and reach of children.

4.5 Interaction with other medicinal products and other forms of interaction

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine. The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily 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 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 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.

Lactation

Paracetamol is excreted in breast milk. However, the level of paracetamol present is not considered to be harmful. Available published data do not contraindicate breastfeeding.

4.7 Effects on ability to drive and use machines

No significant effect.

4.8 Undesirable effects

Events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by System Organ Class and frequency.

Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1,000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1000$), very rare ($< 1/10,000$), not known (cannot be estimated from available data).

Adverse event frequencies have been estimated from spontaneous reports received through post marketing data.

Body System	Undesirable Effect	Frequency
Blood and lymphatic system disorders	Thrombocytopenia	Very rare
Immune System disorders	Anaphylaxis, Cutaneous hypersensitivity reactions, including, among others, skin rashes, angioedema, Stevens Johnson syndrome and Toxic Epidermal Necrolysis. Very rare cases of serious skin reactions	Very rare
Respiratory, thoracic and mediastinal disorders	Bronchospasm in patients sensitive to aspirin and other NSAIDs	Very rare
Hepatobiliary disorders	Hepatic dysfunction	Very rare
Metabolism and nutrition disorders	High anion gap metabolic acidosis	Not known

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 HPRC Pharmacovigilance, website: www.hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

4.9 Overdose

Paracetamol overdose may cause liver failure which can lead to liver transplant or death. Acute pancreatitis has been observed, usually with hepatic dysfunction and liver toxicity.

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. Overdosing may be fatal in these cases.

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 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. 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.

Acute renal failure with acute tubular necrosis may also develop.

Cardiac arrhythmia has also been reported.

Emergency Procedure:
Immediate transfer to hospital.

Blood sampling to determine initial paracetamol plasma concentration. In the case of a single acute overdose, paracetamol plasma concentration should be measured 4 hours post ingestion.

Administration of activated charcoal should be considered if >150mg/kg paracetamol has been taken within 1 hour.

The antidote 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: Anilides. ATC Code: N02B E01.

Paracetamol has analgesic and antipyretic actions.

5.2 Pharmacokinetic properties

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

Concentration in plasma reaches a peak in 30 - 60 minutes. Plasma protein binding is variable. Plasma half-life is 1 - 4 hours.

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

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

Mannitol, glycerol distearate, magnesium stearate.

Composition of hard gelatin capsule shell - iron oxide yellow (E172), FD &C red 3 (E127), titanium dioxide (E171), sodium lauryl sulphate, polyethylene glycol, gelatin.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Do not store above 30°C

Store in the original package to protect from moisture.

6.5 Nature and contents of container

PVC-Aluminium thermoformed blisters packs, containing 6, 12, 24, 48, 96 or 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Azure Pharmaceuticals Ltd.

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8 MARKETING AUTHORISATION NUMBER

PA22871/016/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

March 2025