

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Paracetamol - Asteria, 500 mg, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of Paracetamol - Asteria contains 500 mg of paracetamol, as active substance

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL particulars

4.1 Therapeutic indications

Therapeutic indications:

For the short-term relief of pain and antipyretic including:

-Headache

-Musculoskeletal pain.

-Dysmenorrhoea

-Toothache.

-Cold and flu symptoms

It can also be used for symptomatic relief of pain from mild to moderate intensity in osteoarthritis diagnosed by a doctor.

4.2 Posology and method of administration

For oral administration only.

Adults (including the elderly) and children aged 16 years and over: 1-2 tablets up to 4 times daily as required.

Children 10 - 15 years: 1 tablet up to 4 times daily as required. Maximum duration of continued use without medical advice: 3 days.

Minimum dosing interval: 4 hours. No more than four doses in any 24 hour period.

Children: Not recommended for children under the age of 10 years. Patients with renal / hepatic impairment: Patients with severe hepatic or severe renal insufficiency are not recommended to use the drug. Patients who have been diagnosed with kidney/liver impairment must seek medical advice before taking this medication.

Do not exceed the stated dose.

The lowest dose necessary to achieve efficacy should be used.

4.3 Contraindications

- Hypersensitivity to the active substance (paracetamol) or to any of the excipients listed in section 6.1.
- Severe hepatic disease.

4.4 Special warnings and precautions for use

At therapeutic doses, paracetamol is relatively non-toxic. However, the appearance of allergic skin reactions, even anaphylactic situations, is possible.

There are described cases of liver necrosis in patients receiving high doses of paracetamol.

In the following situations the medicine should only be used with special care (i.e. with adjustment of the dose or dosing intervals) and under medical supervision:

- hepatic impairment (e.g. due to chronic alcohol abuse, hepatitis).
- renal impairment
- Gilbert's disease (also known as Meulengracht disease).

Caution is advised in the administration of paracetamol to patients with severe renal impairment with severe hepatic impairment or with severe haemolytic anaemia.

Paracetamol should be used with caution in case of dehydration or chronic malnutrition.

The maximum dose of 4 tablets per day in adults should not be exceeded, except for expressed medical indication. The prolonged use of this medicine can cause renal disorders.

The prolonged use of analgesics and the inappropriate use of high doses can cause headache, which should not be treated with increased doses of the medicine.

The medicine should not be used for more than 10 days in adults, except if prescribed by the doctor.

In high fever situations (over 39 °C), fever that lasts for more than 3 days or recurrent fever, paracetamol should not be used unless prescribed by the doctor, because these conditions may indicate a serious illness that requires medical assessment and treatment.

During the treatment with Paracetamol – Asteria, other paracetamol containing products should not be taken.

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

Simultaneous administration of paracetamol with other drugs that increase enzyme induction at a hepatic level, e.g. certain sedatives and anticonvulsants (including phenobarbital, phenytoin, carbamazepine) and rifampicin may cause or worsen liver damage.

The same applies to the administration of paracetamol in situations of chronic alcoholism.

Simultaneous administration of paracetamol and chloramphenicol can markedly delay the excretion of chloramphenicol, increasing its plasma concentrations and causing an increased risk of toxicity.

It is not possible to assess the clinical significance of interactions between paracetamol and coumarin derivatives. The long-term use of this medicine in patients who are receiving treatment with oral anticoagulants should only be done under medical supervision.

A potentiation of the warfarin effects with the continued intake of high doses of paracetamol was observed.

Concomitant use of paracetamol and AZT (zidovudine) may increase the incidence or the worsening of neutropenia. Paracetamol should only be taken simultaneously with AZT if it is recommended by the doctor.

When paracetamol is administered simultaneously with agents that cause delayed gastric emptying, e.g. cimetidine and propantheline, the absorption and onset of action of paracetamol may be delayed.

The concomitant intake of drugs that cause the acceleration of gastric emptying, e.g. metoclopramide and domperidone, increases the absorption and accelerate the onset of paracetamol action.

Cholestyramine reduces the absorption of paracetamol. Thus, to prevent this from occurring, paracetamol should be administered one hour before or 4 hours after the resin.

The combination of paracetamol and antiepileptic agents (including phenytoin, barbiturates, carbamazepine) that induce the hepatic enzymes can increase the hepatotoxicity induced by paracetamol due to the increased conversion of the drug to hepatotoxic metabolites. Generally the reduction of the doses in patients concomitantly receiving therapeutic doses of paracetamol and

antiepileptics is not necessary. However, patients should limit the self-medication with paracetamol when they are treated with antiepileptics.

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 fetoneonatal 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. However, as in case of taking any other drug, it is necessary to follow the doctor's instructions and take the medicine with caution during the first trimester. **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 influence on the ability to drive and use machines.

4.8 Undesirable effects

There have been rare reports of blood dyscrasias including thrombocytopenia and agranulocytosis but there were not necessarily casually related to paracetamol. The frequency of adverse events associated with paracetamol are tabulated below: Very rare (< 1/10,000):

Blood and lymphatic system disorders	Thrombocytopaenia
Immune System disorders	Anaphylaxis Cutaneous hypersensitivity reactions including skin rashes, Angiodema, Stevens Johnson syndrome and Toxic Epidermal Necrolysis.
Respiratory, thoracic and mediastinal disorders	Bronchospasm in patients sensitive to aspirin and other NSAIDs

Hepatobiliary disorders	Hepatic dysfunction
-------------------------	---------------------

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 online to the Center of Drug and Medical Technologies Expertise of MoH of RA via www.pharm.am or call the hotline numbers: (+374 10) 20-05-05, (+374 96) 22-05-05.

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. The risk of intoxication with paracetamol is higher in elderly people, small children, patients with liver diseases, chronic malnutrition, people with chronic alcoholism. In these cases overdose may be fatal. After a single use of high dose of paracetamol, complete and irreversible liver necrosis leading to hepatocellular insufficiency, metabolic acidosis, encephalopathy, coma, and death may be developed in adults and children. Liver damage is possible in adults who have taken 10 g or more of paracetamol. Ingestion of 5 g or more of paracetamol may lead to liver damage if the patient has risk factors, such as:

- ♣ the patient has long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes;
- ♣ patient regularly consumes ethanol in excess of recommended amount;
- ♣ patient with the risk of glutathione deplete (eating disorders, cystic fibrosis, HIV infection, starvation, cachexia). Symptoms of paracetamol overdosage in the first 24 hours are nausea, vomiting, anorexia, skin pallor, abdominal pain. In some cases there can be no symptoms. Within 12 to 48 hours after an overdose, elevated levels of hepatic transaminases (AST, ALT), lactate dehydrogenase, and bilirubin may occur. 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. Treatment: 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. Immediate medical management is required in the event of overdose, even if symptoms of overdose are not present.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: *Other analgesics and antipyretics, anilides, Paracetamols*
ATC code: *N02B E01*

5.1 Pharmacodynamic properties

Paracetamol is an analgesic and antipyretic. It's mechanism of action is believed to include inhibition of prostaglandin synthesis, primarily within the central nervous system.

5.2 Pharmacokinetic properties

Absorption

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. The maximum plasma concentration is reached within 30-60 minutes. The half-life ($t_{1/2}$) - 1-4 hours.

Distribution

Binding to the plasma proteins is minimal at therapeutic concentrations. Paracetamol is relatively evenly distributed in most body fluids. Plasma protein binding is low and may vary.

Metabolism

Paracetamol is metabolised in the liver and excreted in the urine mainly as glucuronide and sulphate conjugates.

Elimination

Less than 5% is excreted as unmodified paracetamol.

5.3 Preclinical safety data

In high concentrations, paracetamol is genotoxic, both *in vivo* and *in vitro*. The genotoxic activity of paracetamol depends on several mechanisms; however, non-toxic or therapeutic doses do not reach the required threshold for such mechanisms to be triggered.

There is evidence of the carcinogenic potential of paracetamol in mice and rats, at hepatotoxic doses (increased incidence of liver and bladder tumours). Long-term studies on food have shown that paracetamol is not carcinogenic in non-hepatotoxic doses, up to 300 mg/kg/day for rats and 1g/kg/day for mice. Given the current knowledge on hepatotoxicity, metabolism and threshold levels for the mechanisms associated with paracetamol genotoxicity, animal studies do not suggest the existence of a carcinogenic potential for paracetamol in humans, at non-hepatotoxic doses.

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

6. PHARMACEUTICAL INFORMATION

6.1. List of excipients

Pregelatinized starch, povidone and stearic acid.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4. Special precautions for storage

Do not store above 25°C.

6.5. Nature and content of container

Paracetamol-Asteria 500mg tablets, is available as white, round tablets, scored on one side.

Paracetamol –Asteria 500mg tablets is packed in PVC/Alu blisters.

The blisters are packed in the appropriate printed carton boxes, contains 20 tablets: 10 tablets per blister, 2 blisters per box.

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

ASTERIA LLC
72/3 Nairi Zaryan street
Yerevan 0051
Republic of Armenia

8. *MARKETING AUTHORISATION NUMBERS*

<to be completed by the country after registration>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF MARKETING AUTHORISATION

Date of first authorization: <to be completed by the country after registration>