

APPROVED
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VARIATIONS APPLIED
By the Order of the Ministry of
Health of Ukraine
04.10.2017 No. 1214

PACKAGE LEAFLET
for medical use of a medicinal product

PARACETAMOL-DARNITSA

Qualitative and quantitative composition:

active substance: paracetamol;

1 tablet contains paracetamol 500 mg;

excipients: pregelatinized starch, povidone, microcrystalline cellulose, croscarmellose sodium, calcium stearate.

Pharmaceutical form. Tablets.

Basic physical and chemical properties: tablets white or almost white, flat cylindrical, with beveled and dashed. A grayish tint is allowed.

Pharmacotherapeutic group.

Analgesic and Antipyretic. ATC code N02B E01.

Pharmacological properties.

Pharmacodynamics properties.

Non-narcotic analgesic. Nonselective inhibits COX, affecting the centers of pain and thermoregulation. In inflamed tissues, cellular peroxidases neutralize the effect of paracetamol on COX, which explains the slight anti-inflammatory effect. There is no effect on the synthesis of prostaglandins in peripheral tissues, which causes the absence of paracetamol negative effect on water-salt metabolism (sodium and water retention) and the mucous membrane of the gastrointestinal tract. The possibility of methemoglobin and sulfhemoglobin formation is unlikely.

Pharmacokinetics properties.

Absorption is high, almost 100 %. In the systemic circulation, 15 % of the medicinal product, that absorbed, binds to plasma proteins. The time to reach the maximum blood concentration (T_{Cmax}) is 20–30 minutes. The therapeutically effective concentration of paracetamol in blood plasma is achieved when it is administered at a dose of 10–15 mg/kg. It penetrates the blood-brain barrier and into breast milk. The amount of the medicinal product in breast milk is less than 1 % of the dose of paracetamol taken by a nursing mother. Metabolized in the liver: 80 % enter into a conjugation reaction with glucuronic acid and sulfates to form inactive metabolites. Seventeen percent (17 %) of the medicinal product undergoes hydroxylation to form active metabolites that conjugated to glutathione to form inactive metabolites. With a lack of glutathione, these metabolites can block the enzyme systems of hepatocytes and cause their necrosis. The half-life

($T_{1/2}$) of paracetamol is 2–3 hours. In elderly patients, the clearance of the medicinal product decreases and increases $T_{1/2}$. Excreted by the kidneys – 3 % unchanged.

Clinical particulars.

Therapeutic indications.

Headache, including migraine and tension headache, toothache, back pain, rheumatic pain, muscle pain, recurrent pain in women, mild arthritis pain; relief of fever symptoms and pain from colds and flu.

Contraindications.

Hypersensitivity to the components of the medicinal product, severe liver and/or renal dysfunction, congenital hyperbilirubinemia, glucose-6-phosphate dehydrogenase deficiency, alcoholism, blood diseases, Gilbert's syndrome, severe anemia, leukopenia.

Interaction with other medicinal products and other forms of interaction.

The absorption rate of paracetamol may increase with the use of *metoclopramide* and *domperidone* and decrease with the use of *cholestyramine*.

The anticoagulant effect of *warfarin* and other *coumarins* with an increased risk of bleeding can be enhanced by concomitant long-term use of paracetamol. Periodic intake has no significant effect.

Barbiturates reduce the antipyretic effect of paracetamol.

Anticonvulsants (including *phenytoin*, *barbiturates*, *carbamazepine*), which stimulate the activity of liver microsomal enzymes, may increase the toxic effects of paracetamol on the liver due to increase in the degree of conversion of the medicinal product to hepatotoxic metabolites. Concomitant use of paracetamol with hepatotoxic medicinal product increases the toxic effects of medicinal products on the liver. Concomitant use of large doses of paracetamol with *isoniazid* increases the risk of developing hepatotoxic syndrome.

Paracetamol reduces the effectiveness of *diuretics*.

Do not use concomitantly with *alcohol*.

Special warnings and precautions for use.

In case of liver or renal diseases, consult a doctor before using the medicinal product. Before using the medicinal product, it is necessary to consult a doctor if the patient is using warfarin or similar drugs that have an anticoagulant effect.

It should be borne in mind that patients with alcoholic non-cirrhotic liver damage, the risk of hepatotoxic action of paracetamol increases.

The medicinal product may affect the results of laboratory tests on the content of glucose and uric acid in the blood.

Patients with severe infections, such as sepsis, that are accompanied by a decrease in glutathione levels while taking paracetamol, have an increased risk of metabolic acidosis. Symptoms of metabolic acidosis are deep, rapid or difficult breathing, nausea, vomiting, loss of appetite. If these symptoms occur, you should immediately consult a doctor.

Do not exceed these doses.

Do not take the medicinal product with other medicines containing paracetamol.

Patients should consult with doctor if they experience mild arthritis pain and need to take analgesics daily.

If symptoms persist, you should immediately consult a doctor. If the headache becomes persistent, you should contact a doctor.

Fertility, pregnancy and lactation.

Prescription of the medicinal product during these periods is possible only when the expected benefit to the mother outweighs the potential risk to the fetus or child.

Paracetamol passes into breast milk, but in clinically insignificant amounts. Available published data do not contain contraindications to breastfeeding.

Effects on ability to drive and use machines.

Not applicable.

Posology and method of administration.

The medicinal product is intended for oral administration.

Adults and children over 12 years old: 1–2 tablets 4 times a day if necessary. Do not take more than 8 tablets (4 000 mg) during 24 hours.

Children (6–12 years old): ½–1 tablet 3–4 times a day if necessary.

A single dose of paracetamol is 10–15 mg/kg body weight; the maximum daily dose is 60 mg/kg body weight. Do not take more than 4 doses during 24 hours.

The maximum period of use for children without consulting a doctor is 3 days.

The interval between receptions makes not less than 4 hours.

Do not exceed these doses.

Do not take with other medicines containing paracetamol.

Children.

Do not use in children under the age of 6 years.

Overdose.

Liver damage is possible in adults taking 10 g or more of paracetamol and in children taking more than 150 mg/kg body weight. In patients with risk factors (long-term use of carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St. John's wort or other drugs that induce liver enzymes; alcohol abuse; glutathione system deficiency, for example: indigestion, cystic fibrosis, HIV, starvation, cachexia) taking 5 g or more of paracetamol may cause liver damage.

Symptoms of overdose in the first 24 hours: pallor, nausea, vomiting, loss of appetite and abdominal pain. Liver damage can occur 12–48 hours after overdose. Disorders of glucose metabolism and metabolic acidosis may occur. In severe poisoning, liver failure can progress to encephalopathy, hemorrhage, hypoglycemia, coma, and be fatal. Acute renal failure with acute tubular necrosis may be manifested by severe lumbar pain, hematuria, proteinuria and develop even in the absence of severe liver damage. Cardiac arrhythmia and pancreatitis have also been reported.

With long-term use of the medicinal product in large doses on the part of the hematopoietic organs, aplastic anemia, pancytopenia, agranulocytosis, neutropenia, leukopenia, and thrombocytopenia may develop. When taking large doses from the central nervous system, dizziness, psychomotor agitation and disorientation are possible; from the urinary system – nephrotoxicity (renal colic, interstitial nephritis, capillary necrosis).

Treatment: in case of overdose emergency medical care is required. The patient should be taken to a hospital immediately, even if there are no early symptoms of overdose. Symptoms may be limited to nausea and vomiting, or may not reflect the severity of the overdose or the risk of organ damage. Treatment with activated charcoal should be considered if an excessive dose of paracetamol was taken within 1 hour. Plasma paracetamol concentrations should be measured 4 hours or later after ingestion (earlier concentrations are not significant). Treatment with N-acetylcysteine can be applied within 24 hours after taking paracetamol, but the maximum protective effect is obtained when it is used within 8 hours after taking it. The effectiveness of the antidote decreases sharply after this time. If necessary, the patient should be injected intravenously with N-acetylcysteine according to the current recommendations. In the absence of vomiting, oral methionine can be used orally as a suitable alternative in remote areas outside the hospital.

Undesirable effects.

In case of undesirable effects, you must stop using the medicinal product and immediately consult a doctor.

The development of such undesirable effects is possible:

immune system disorders: anaphylaxis, hypersensitivity reactions, including pruritus, rash on the skin and mucous membranes (usually generalized rash, erythematous rash, urticaria), angioneurotic edema, exudative erythema multiforme (including Stevens-Johnson syndrome) toxic epidermal necrolysis (Lyell's syndrome);

digestive system: nausea, epigastric pain;

endocrine disorders: hypoglycemia, up to hypoglycemic coma;

blood and lymphatic system disorders: thrombocytopenia, agranulocytosis, anemia, sulfhemoglobinemia and methemoglobinemia (cyanosis, shortness of breath, heart pain), hemolytic anemia, bruising or bleeding;

respiratory disorders: bronchospasm in patients' sensitive to acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs;

hepatobiliary disorders: liver dysfunction, increased activity of liver enzymes, usually without the development of jaundice.

Shelf life. 4 years.

Special precautions for storage.

Store in the original package at temperature not above 25 °C.

Keep out of the reach of children.

Nature and contents of container.

10 tablets in a blister; 1 blister in a pack; 10 tablets in blister in a pack.

Category of release.

Non-prescription medicine.

Manufacturer.

PrJSC "Pharmaceutical firm "Darnitsa".

The manufacturer's location and address of the place of business.

13, Boryspilska Street, Kyiv, 02093, Ukraine.

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