

PACKAGE LEAFLET
for medical use of a medicinal product

CITRAMON EXTRA

Qualitative and quantitative composition:

active substances: paracetamol, caffeine;

1 tablet contains: 500 mg of paracetamol; 50 mg of caffeine;

excipients: cellulose microcrystalline, methylcellulose, croscarmellose sodium, povidone, calcium stearate.

Pharmaceutical form. Tablets.

Basic physical and chemical properties: white or off-white, round-shaped with flat surface, bevel-edged tablets with scored line.

Pharmacotherapeutic group. Analgesics and antipyretics. Paracetamol, combinations without psycholeptics. ATC Code N02B E51.

Pharmacological properties.

Pharmacodynamic properties.

Fixed combination.

Paracetamol has analgesic, antipyretic and mild anti-inflammatory effects, which are associated with its impact on the thermoregulatory center in the hypothalamus, and a less pronounced ability to inhibit production of prostaglandins in tissues.

Caffeine increases the spinal reflex excitability, stimulates the respiratory and hemodynamic centers, dilates blood vessels of the skeletal muscles, brain, heart, kidneys, reduces platelet aggregation; reduces somnolence, fatigue, increases mental and physical performance. In this combination, low-dose caffeine has virtually no stimulating effect on the central nervous system, however helps to improve the tone of blood vessels in the brain and speed up the blood flow.

Pharmacokinetic properties.

Paracetamol and caffeine are rapidly absorbed from the gastrointestinal tract and distributed throughout most body tissues. Plasma protein binding of paracetamol is minor at usual therapeutic concentrations.

Paracetamol and caffeine are metabolized mainly in the liver and excreted via urine as by-products. The mean plasma half-life after oral administration is about 2.3 hours for paracetamol and about 4.9 hours for caffeine.

Clinical particulars.

Therapeutic indications.

The drug has moderate analgesic and antipyretic effects. Therapeutic indications are headache, including migraine, toothache, neuralgia, rheumatic pain, period pain in women; to relieve symptoms of cold and flu, and sore throat.

Contraindications.

Known hypersensitivity to paracetamol, caffeine or any other ingredient; severe hepatic and/or renal impairment; congenital hyperbilirubinemia; glucose-6-phosphate dehydrogenase deficiency; alcoholism; blood disorders, severe anemia, leukopenia; states of overexcitement, sleep disturbances, epilepsy; pronounced increase in blood pressure, organic cardiovascular diseases, including severe atherosclerosis, severe arterial hypertension; decompensated heart failure, acute myocardial infarction, paroxysmal tachycardia, hyperthyroidism, acute pancreatitis, Gilbert's syndrome, severe diabetes mellitus, glaucoma; age above 60 years.

Do not combine with monoamine oxidase (MAO) inhibitors and during 2 weeks after discontinuation of MAO inhibitors.

The drug is contraindicated in patients on tricyclic antidepressants or β -blockers.

Interaction with other medicinal products and other forms of interaction.

Paracetamol

Concomitant use of paracetamol with *hepatotoxic drugs* enhances the liver toxicity.

Barbiturates, rifampicin, salicylamide, antiepileptic drugs, carbamazepine, phenytoin, ethanol, phenylbutazone, tricyclic antidepressants and other microsomal oxidation stimulants all increase the production of hydroxylated active metabolites that affect liver function leading to potential severe intoxication with insignificant drug overdose.

Barbiturates reduce the antipyretic effect of paracetamol.

Paracetamol may reduce the bioavailability of *lamotrigine* by reducing its effect due to possible induction of its liver metabolism.

Co-administration of paracetamol and *zidovudine* increases the risk of neutropenia.

Microsomal oxidation inhibitors (cimetidine) reduce the risk of hepatotoxic effects of Citramon Extra.

Concomitant use of high-dose paracetamol with *isoniazid* increases the risk of hepatotoxic syndrome.

Metoclopramide and domperidone increase the absorption of paracetamol.

Ethanol: concomitant use of paracetamol and ethanol increases the risk of hepatotoxic effects and acute pancreatitis.

Do not use simultaneously with *alcohol*.

Prolonged co-administration with *acetylsalicylic acid* or other *nonsteroidal anti-inflammatory drugs* may lead to kidney damage.

Coumarin derivatives (warfarin): prolonged use of paracetamol increases the risk of bleeding. Single dose administration has no major effects.

Cholestyramine reduces the absorption of paracetamol.

There is 5-fold increase of excretion time of *chloramphenicol* due to paracetamol.

Probenecid affects the plasma concentration of paracetamol and its excretion.

Paracetamol reduces the efficacy of *diuretics*.

Caffeine

Concomitant use of caffeine with *MAO inhibitors* can cause a dangerous increasing of blood pressure.

Caffeine increases the effect (improves bioavailability) of *antipyretic analgesics*, enhances the effects of *xanthine derivatives, α - and β -adrenomimetics, and psychostimulants*.

Cimetidine, hormonal contraceptives, and isoniazid increase the effects of caffeine.

Caffeine reduces the effect of *opioid analgesics, anxiolytics, hypnotics and sedatives*, is an antagonist of *anesthetics and other drugs that depress the central nervous system*, and is a competitive antagonist of *adenosine and adenosine triphosphate (ATP)*.

Co-administration of caffeine with *thyrotropic agents* increases the thyroid effect.

Caffeine decreases the concentration of *lithium* in the blood.

Caffeine accelerates the absorption of *ergotamine*.

Special warnings and precautions for use.

The doctor should be consulted regarding the possibility of treatment in patients with renal and hepatic impairment.

It should be noted that patients with liver disease are at increased risk of hepatotoxic effects of paracetamol.

Alcohol should not be consumed during therapy. At doses higher than 6–8 g per day, paracetamol may be toxic to the liver, although adverse hepatic effects may occur at much lower doses in the case of alcohol use, administration of inducers of liver enzymes or other substances that have hepatotoxic effects; and these effects are greater in patients with non-cirrhotic alcoholic liver disease. Prolonged alcohol consumption significantly increases the risk of hepatotoxic effects of paracetamol. In patients with hepatic impairment and patients taking high-dose paracetamol for a long time, it is recommended to perform liver function tests regularly.

If the patient is taking warfarin or similar drugs that have an anticoagulant effect, the doctor should be consulted prior to treatment. Restrictions on the drug use in such patients are primarily defined by the content of paracetamol.

When co-treated with oral anticoagulants and high-dose paracetamol, prothrombin time should be monitored.

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

Cases of hepatic impairment/liver failure have been reported in patients with low glutathione levels, such as severe exhaustion, anorexia, low body mass index, chronic alcoholism or sepsis. Patients with low glutathione levels, who receive paracetamol, are at increased risk of metabolic acidosis. Symptoms of metabolic acidosis are deep, rapid or difficult breathing, nausea, vomiting, loss of appetite. If such symptoms occur, medical advice should be sought.

Consumption of excessive amounts of caffeinated beverages (e.g., coffee, tea, and some other beverages) is not recommended during treatment with the medicinal product. This can result in sleep disturbances, tremor, chest discomfort due to palpitations, feeling of tension and irritability.

The indicated doses of the drug should not be exceeded.

This medicinal product should not be combined with other agents containing paracetamol.

If symptoms persist, medical advice should be sought.

If headache persists, medical advice should be sought.

Keep the medicine out of sight and reach of children.

Fertility, pregnancy and lactation.

The drug is not recommended during pregnancy, since it increases the risk of caffeine-induced miscarriage.

When taken at the recommended doses, paracetamol and caffeine are excreted into breast milk at clinically insignificant amounts. The medicinal product should not be used during breast-feeding. Caffeine in breast milk may have a stimulating effect on infants during breast-feeding but no significant toxicity has been observed.

Effects on ability to drive and use machines.

The drug has no significant effect.

Posology and method of administration.

The drug is intended for oral use.

Adults and children older 12 years: 1–2 tablets 4 times daily. The dosing interval is at least 4 hours. Do not take more than 8 tablets (4,000 mg paracetamol/400 mg caffeine) within 24 hours. The recommended dose should not be exceeded.

Do not take with other paracetamol-containing medicines.

The duration of treatment is determined by the doctor.

Children.

The drug is not recommended for use in children under 12 years of age.

Overdose.

Liver damage is possible in adults who have taken ≥ 10 g of paracetamol or in children who have taken more than 150 mg/kg on body weight.

Overdose with paracetamol can cause liver failure, which may require a liver transplantation or be fatal.

In patients with risk factors (prolonged treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St. John's wort or other liver enzyme-inducing medicinal products; regular consumption of excessive amounts of ethanol; glutathione cachexia (digestive disorders, mucoviscidosis, HIV infection, starvation, cachexia), intake of ≥ 5 g of paracetamol may cause liver damage.

Symptoms of overdose within the first 24 hours: pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent within 12 to 48 hours after the overdose and reach maximum in 4 to 6 days. Glucose metabolism impairment and metabolic acidosis may occur. In severe poisoning, liver failure can progress to encephalopathy, hemorrhages, hypoglycemia, coma, and lead to fatal outcome. Acute renal failure with acute tubular necrosis can manifest as severe low back pain, hematuria, proteinuria and may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

With the long-term use of the medicinal product in high doses, hematopoietic disorders such as aplastic anemia, pancytopenia, agranulocytosis, neutropenia, leukopenia, and thrombocytopenia may develop. High-dose therapy is associated with CNS disorders such as dizziness, psychomotor agitation and disorientation as well as with urinary tract disorders such as nephrotoxicity (renal colic, interstitial nephritis, capillary necrosis).

Acute medical management is required in the event of an overdose. The patient should be taken to a hospital immediately, even if there are no early symptoms of an overdose. Symptoms may be limited to nausea and vomiting or may not reflect the severity of an overdose or the risk of organ damage. If an overdose is confirmed or only suspected, the patient should be taken to the nearest medical facility where he or she shall receive emergency medical care and qualified treatment. Due to delayed liver damage, that should be done even if there are no early signs of an overdose.

The use of activated charcoal should be considered if an excessive dose of paracetamol has been taken within the last 1 hour. Plasma paracetamol concentration should be measured in 4 hours or later after dosing (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be initiated within the first 24 hours after paracetamol intake; however, the maximum protective effect is achieved within 8 hours after the intake. The efficacy of the antidote declines drastically after this time passes. If required, the patient should be given intravenous N-acetylcysteine in line with the recommended dosage. If there is no vomiting, oral methionine may be a suitable option for remote areas, outside the hospital.

Caffeine overdose may cause epigastric pain, vomiting, diuresis, tachypnea, extrasystoles, tachycardia or cardiac arrhythmia, effects on central nervous system (dizziness, insomnia, nervous excitement, irritability, affective state, anxiety, tremor, convulsions). Clinically significant symptoms of caffeine overdose are also associated with paracetamol-induced liver damage that which may occur with the intake of such amount of drug that causes an overdose with caffeine. There is no specific antidote, however, supportive measures such as the use of β -adrenoceptor antagonists may alleviate cardiotoxic effect. Recommended management includes gastric lavage, oxygen therapy, and diazepam in case of convulsions. Symptomatic therapy.

Undesirable effects.

The listed side effects have been obtained during post-marketing reports. Since these reactions have been reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency but they are likely to be very rare ($< 1/10,000$).

Respiratory, thoracic and mediastinal disorders: rhinitis, nasal congestion, bronchospasm in patients who are sensitive to acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs.

Gastrointestinal disorders: nausea, vomiting, heartburn, epigastric pain, mild laxative effect.

Hepatobiliary disorders: elevated activity of liver enzymes, usually without the development of jaundice, hepatotoxic effects, liver impairment, liver failure, hepatonecrosis (dose-dependent effect), jaundice.

Renal and urinary disorders: nephrotoxicity (incl. interstitial nephritis, papillary necrosis), and aseptic pyuria.

Endocrine disorders: hypoglycemia leading even to hypoglycemic coma.

Nervous system disorders: headache, nervousness, dizziness.

Psychiatric disorders: insomnia, restlessness, anxiety, and irritability.

Cardiovascular disorders: tachycardia, arrhythmia, hypertension, palpitations, edema.

Blood and lymphatic system disorders: thrombocytopenia, leukopenia, neutropenia, agranulocytosis, pancytopenia, anemia, aplastic anemia, sulfhemoglobinemia and methemoglobinemia (cyanosis, dyspnea, and heartache), hemolytic anemia, bruising or bleeding.

Immune system disorders: hypersensitivity reactions, including skin and mucosal rashes (usually generalized rash, erythematous rash), Stevens-Johnson syndrome, angioedema, anaphylaxis, anaphylactic shock, exudative erythema multiforme, toxic epidermal necrolysis (Lyell's syndrome), acute generalized exanthematous pustulosis.

Skin and subcutaneous tissue disorders: itching, rashes, hyperhidrosis, purpura, urticaria.

Concomitant use of the drug in the recommended doses with caffeine-containing products may enhance the side effects caused by caffeine such as dizziness, nervousness, insomnia, restlessness, anxiety, irritability, headache, gastrointestinal disorders, and palpitations.

Reporting of suspected side effects.

Reporting suspected side effects after authorization of the medicinal product is an important procedure. It allows continuing monitoring of the benefit-risk balance for the medicinal product. Healthcare professionals are asked to report any suspected side effect via the national reporting system.

Shelf life. 3 years.

Special precautions for storage.

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

Keep out of reach of children.

Nature and contents of container.

10 tablets in a blister; 1 blister in a carton box.

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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