

PACKAGE LEAFLET
for medical use of a medicinal product

IBUPROFEN-DARNITSA

Qualitative and quantitative composition:

active substance: ibuprofen;

1 tablet contains ibuprofen 200 mg;

list of excipients: cellulose microcrystalline, sodium croscarmellose, silica colloidal anhydrous, maize starch, magnesium stearate.

Pharmaceutical form. Tablets.

Main physical and chemical properties: tablets white or almost white, round, with a biconvex surface.

Pharmacotherapeutic group.

Anti-inflammatory and anti-rheumatic products, non-steroids. Propionic acid derivatives.

ATC code M01A E01.

Pharmacological properties.

Pharmacodynamic properties.

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID), a derivative of propionic acid, which has been shown to be effective in inhibiting the synthesis of prostaglandins, mediators of pain and inflammation. Ibuprofen has analgesic, antipyretic and anti-inflammatory effects. In addition, ibuprofen reversibly inhibits platelet aggregation.

Experimental evidence suggests that ibuprofen can competitively suppress the effect of low-dose aspirin (acetylsalicylic acid) on platelet aggregation when these medicinal products are used concomitantly. Some pharmacodynamic studies indicate that single doses of ibuprofen 400 mg within 8 hours before or within 30 minutes of aspirin (acetylsalicylic acid) immediate release (81 mg) reduced the effect of aspirin (acetylsalicylic acid) on thromboxane formation or platelet aggregation. Although there is uncertainty regarding the extrapolation of these data to the clinical situation, it cannot be ruled out that regular long-term use of ibuprofen may reduce the cardioprotective effect of low doses of acetylsalicylic acid. With the systematic use of ibuprofen, such a clinically significant effect is unlikely.

Ibuprofen relieves pain, reduces inflammation and lowers fever.

Pharmacokinetic properties.

Ibuprofen is rapidly absorbed in the gastrointestinal tract and binds to blood plasma proteins.

The maximum blood plasma concentration is determined 45 minutes after administration on an empty stomach. If this medicine is used with food, peak levels are observed 1-2 hours after use. Ibuprofen is metabolized in the liver, excreted by the kidneys unchanged or in the form of metabolites. The half-life is –almost 2 hours. There are no significant differences in the pharmacokinetic profile in elderly patients.

Clinical particulars.

Therapeutic indications.

Symptomatic treatment of headache, toothache, dysmenorrhea, neuralgia, back pain, joint pain, muscle pain, rheumatic pain, and treatment of cold and flu symptoms.

Contraindications.

- Hypersensitivity to ibuprofen or to any other component of the medicinal product.
- A history of hypersensitivity reactions (such as asthma, rhinitis, angioneurotic edema, or urticaria) after administration of ibuprofen, acetylsalicylic acid (aspirin), or other NSAIDs.
- Gastric and duodenal ulcer/bleeding in active form or history of relapses (two or more severe episodes of confirmed peptic ulcer disease or bleeding).
- History of gastrointestinal bleeding or perforation of the gastrointestinal wall associated with NSAID use.
- Severe heart failure (NYHA class IV), severe renal failure or severe hepatic failure.
- Active inflammatory bowel disease.
- Hemorrhagic diathesis or other coagulation disorders.
- The last trimester of pregnancy.

Interaction with other medicinal products and other forms of interaction

In general, caution should be exercised when using NSAIDs in combination with other medicinal products that may increase the risk of gastrointestinal ulcers, gastrointestinal bleeding, or impaired renal function.

Ibuprofen, like other NSAIDs, should not be used in combination with:

- *acetylsalicylic acid (aspirin)*, as this can increase the risk of undesirable effects, except when aspirin (dose not exceeding 75 mg per day) is prescribed by a doctor. Experimental data indicate that with the simultaneous use of ibuprofen can suppress the antiplatelet effect of low doses of aspirin. However, the limited data and the uncertainty regarding the extrapolation of *ex vivo* data to the clinical picture do not lead to clear conclusions about the systematic use of ibuprofen. Therefore, in the case of unsystematic use of ibuprofen, such clinically significant effects are considered unlikely;
- *other NSAIDs*, including selective cyclooxygenase-2 inhibitors. Concomitant use of two or more NSAIDs should be avoided as this may increase the risk of undesirable effects.

Ibuprofen should be used with caution in combination with the following medicinal products:

anticoagulants: NSAIDs can increase the effect of anticoagulants such as warfarin;

antihypertensive medicinal products (ACE inhibitors and angiotensin II antagonists) and diuretics: NSAIDs can reduce the effect of these medicinal products. In some patients with impaired renal function (patients with dehydration or in elderly patients with impaired renal function), concomitant use of ACE inhibitors or angiotensin II antagonists and agents that inhibit cyclooxygenase can lead to further deterioration of kidney function, including possible acute renal failure that is usually reversible. These interactions should be considered in patients receiving coxib concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, such combination should be used with caution, especially in the elderly patients. If treatment is necessary, ensure that the patient is sufficiently hydrated and take into account the need to monitor renal function at the beginning of combination therapy, as well as with a certain frequency thereafter. Diuretics may increase the risk of nephrotoxic effects of NSAIDs;

corticosteroids: increased risk of ulcers and bleeding in the gastrointestinal tract;

antiplatelet agents and selective serotonin reuptake inhibitors: increased risk of gastrointestinal bleeding;

cardiac glycosides: NSAIDs can increase cardiac dysfunction, decrease renal glomerular filtration and increase plasma glycoside levels;

lithium: there is evidence of a potential increase in plasma lithium levels;

methotrexate: there is a possibility of an increase in the level of methotrexate in the blood plasma;

ciclosporin: increased risk of nephrotoxicity;

mifepristone: NSAIDs should not be used earlier than 8-12 days after mifepristone administration, as they may reduce its effectiveness;

tacrolimus: the risk of nephrotoxicity may increase with the simultaneous use of NSAIDs with tacrolimus;

zidovudine: increased risk of hematologic toxicity with the combined use of zidovudine and NSAIDs. There is evidence of an increased risk of hemarthrosis and hematoma in HIV-infected patients with hemophilia in the case of concomitant treatment with zidovudine and ibuprofen;

quinolone antibiotics: Patients who use ibuprofen and quinolone antibiotics at the same time may have an increased risk of seizures.

Special warnings and precautions for use.

The undesirable effects associated with ibuprofen can be minimized by using the lowest effective dose needed to treat the symptoms for the shortest period of time.

In elderly patients, there is an increased incidence of undesirable effects to NSAIDs, especially gastrointestinal bleeding and perforation, which can be fatal.

Effects on the respiratory system.

In patients who suffer from bronchial asthma or allergic diseases or have these diseases in history, bronchospasm may occur.

Other NSAIDs.

Avoid the simultaneous use of ibuprofen with other NSAIDs, including selective inhibitors of cyclooxygenase-2, as this increases the risk of adverse reactions.

Systemic lupus erythematosus and mixed connective tissue diseases.

Ibuprofen should be used with caution in systemic lupus erythematosus and mixed connective tissue disease due to the increased risk of aseptic meningitis. Cases of aseptic meningitis have been reported with ibuprofen. Although this effect is more likely in patients with systemic lupus erythematosus and other connective tissue diseases, such cases have also been reported in some patients without chronic diseases, therefore, this should be taken into account when using this medicinal product.

Effects on the cardiovascular and cerebrovascular systems.

Patients with a history of hypertension and/or heart failure should start treatment with caution (consultation with a doctor is required), since cases of fluid retention, hypertension and edema have been reported with ibuprofen therapy, like other NSAIDs.

Clinical study data and epidemiological data indicate that the use of ibuprofen, especially in high doses (2400 mg per day), as well as long-term use, can lead to a slight increase in the risk of arterial thrombotic complications (for example, myocardial infarction or stroke). In general, epidemiological data do not suggest that a low dose of ibuprofen (e.g. ≤ 1200 mg per day) may increase the risk of myocardial infarction.

Patients with uncontrolled hypertension, congestive heart failure (NYHA class II – III) diagnosed with coronary artery disease, peripheral arterial disease and / or cerebrovascular disease should be treated with ibuprofen only after careful clinical evaluation. High doses (2400 mg per day) should be avoided.

The clinical picture should also be carefully assessed before initiating long-term treatment of patients with risk factors for cardiovascular complications (such as hypertension, hyperlipidemia, diabetes, smoking), especially if high doses of ibuprofen (2400 mg per day) are required.

Hepatic/Renal effects.

Caution should be exercised in patients with renal insufficiency due to the possibility of impaired renal function. Ibuprofen should be used with caution in patients with kidney or liver disease, especially during concomitant diuretic therapy, as inhibition of prostaglandins can lead to fluid retention and further deterioration of renal function. These patients should receive the lowest dose of ibuprofen and regularly monitor renal function. In case of dehydration, ensure adequate fluid intake. There is a risk of kidney failure in children (ages 6 and up) and dehydrated adolescents.

In general, the systematic use of analgesics, especially combinations of different pain relievers, can lead to long-term kidney damage with the risk of renal failure (analgesic nephropathy). The highest risk of this reaction exists in elderly patients, patients with renal failure, heart failure, and hepatic failure, as well as in those receiving diuretic or ACE inhibitor therapy. After discontinuation of NSAID therapy, the condition observed before treatment usually returns.

Like other NSAIDs, ibuprofen can cause small, temporary increases in certain liver function tests, as well as significant increases in AST and ALT levels. In case of a significant increase in these indicators, treatment should be discontinued.

With long-term use of ibuprofen, it is necessary to regularly check the indicators of liver function, renal function, as well as hematological function / blood picture.

Effects on fertility in women.

There is limited evidence that drugs that inhibit cyclooxygenase / prostaglandin synthesis can interfere with ovulation. This effect is reversible upon discontinuation of treatment.

Effects on the gastrointestinal tract.

NSAIDs should be used with caution in patients with a history of gastrointestinal diseases (ulcerative colitis, Crohn's disease), since their condition may worsen.

There are reports of cases of gastrointestinal bleeding, perforation, ulcers, which can be fatal, occurring at any stage of treatment with NSAIDs, regardless of the presence of warning symptoms or the presence of severe disorders of the gastrointestinal tract in the history.

The risk of gastrointestinal bleeding, perforation or ulceration increases with increasing doses of NSAIDs in patients with a history of peptic ulcer disease, especially complicated by bleeding or perforation, and in the elderly. These patients should start treatment with the lowest dose.

Combination therapy with protective medicinal products (such as misoprostol or proton pump inhibitors) is recommended for these patients, as well as for patients who require the concomitant use of low doses of acetylsalicylic acid or other medicinal products that may increase the risk from the gastrointestinal tract.

Patients with a history of gastrointestinal toxicity, especially elderly patients, should be informed of any unusual gastrointestinal symptoms (especially gastrointestinal bleeding), in particular at the beginning of treatment.

Long-term use of any pain relievers to treat headaches can worsen the condition. In such cases, you should consult a doctor and stop treatment. The consideration should be given to the possibility of headache due to medicinal product abuse in patients with frequent or daily headache despite (or due to) regular use of headache medications.

Caution should be exercised when treating patients concomitantly using medicinal products that may increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants (e.g. warfarin), selective serotonin reuptake inhibitors, or antiplatelet agents (e.g. aspirin).

In case of gastrointestinal bleeding or ulceration in patients receiving ibuprofen, treatment should be stopped immediately.

Skin and subcutaneous tissue disorders.

Very rarely, against the background of the use of NSAIDs, severe forms of skin reactions can occur, which can be fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis. The risk of such reactions is highest at the beginning of therapy, in most cases such reactions began within the first month of treatment. At the first sign of a skin rash, pathological changes in the mucous membranes or any other signs of hypersensitivity, ibuprofen should be discontinued.

In exceptional cases, chickenpox can cause severe infectious complications from the skin and soft tissues. Currently, the influence of NSAIDs on the worsening of these infections cannot be ruled out, therefore it is recommended to avoid the use of the medicinal product in case of chickenpox.

Important information about excipients.

This medicine contains 6.8 mg of sodium, i.e. it is practically free of sodium.

Fertility, pregnancy and lactation

During the first and second trimesters of pregnancy, the use of the medicinal product should be avoided. The medicinal product is contraindicated in the third trimester of pregnancy.

Suppression of prostaglandin synthesis can adversely affect pregnancy and / or embryo / fetal development. Epidemiological data indicate an increased risk of miscarriage, congenital heart defects and gastroschisis after the use of prostaglandin synthesis inhibitors in early pregnancy. The risk is thought to increase with dose and duration of therapy.

NSAIDs should not be used in the I and II trimester of pregnancy only if the potential benefit to the patient does not outweigh the potential risk to the fetus. If ibuprofen is used by a woman trying to become pregnant or during the first and second trimesters of pregnancy, the lowest possible dose should be used for the shortest period of time.

During the third trimester of pregnancy, all inhibitors of prostaglandin synthesis may pose the following risks:

- to the fetus: cardiopulmonary toxicity (characterized by premature closure of the ductus arteriosus and pulmonary hypertension); impaired renal function, which can progress to renal failure, which is accompanied by oligohydramnios;
- for the mother and the newborn at the end of pregnancy: an increase in bleeding time is possible, an antiplatelet effect, which can develop even at very low doses; suppression of uterine contractions, which leads to a delay or an increase in the duration of labor.

In limited studies, ibuprofen has been found in breast milk at a very low concentration, so it is unlikely to adversely affect a breastfed infant.

Effects on ability to drive and use machines

Provided that it is used in accordance with the recommended doses and duration of treatment, the medicinal product does not affect the reaction rate when driving or operating other mechanisms.

Posology and method of administration.

For short-term oral use only. The tablets should be swallowed with water and not chewed.

The lowest effective dose required to treat symptoms should be used for the shortest period of time. If symptoms persist for more than 5 days after starting treatment or if they worsen, consult a doctor.

The medicinal product is prescribed to adults and children weighing more than 20 kg (approximately 6 years). The recommended daily dose of the medicinal product is 20-30 mg/kg body weight. Do not exceed a dose of 30 mg/kg body weight per day.

Children weighing 20 to 30 kg (aged 6 to 11 years): 200 mg (1 tablet) per dose. A repeat dose as needed after 6 hours. Do not exceed a dose of 600 mg (3 tablets) per day.

Adults and children weighing more than 30 kg: 200–400 mg (1–2 tablet) per dose. A repeat dose as needed after 4 -6 hours. Do not exceed a dose of 1200 mg (6 tablets) per day.

Elderly people do not need special dosage.

Children.

Do not use in children weighing less than 20 kg and under 6 years of age.

Overdose.

Symptoms of overdose occur within 4 hours after application.

The use of the medicinal product in children at a dose of more than 400 mg/kg may cause symptoms of intoxication. In adults, the effect of the dose is less pronounced. The half-life in overdose is 1.5-3 hours.

Symptoms. In most patients, the use of a clinically significant amount of NSAIDs caused nausea, vomiting, epigastric pain, or, less commonly, diarrhea. Tinnitus, headache, and gastrointestinal bleeding may also occur. In severe poisoning, toxic damage to the central nervous system is observed, which is manifested by drowsiness, vertigo, dizziness, lethargy, sometimes - agitated state, ataxia, disorientation or coma. Sometimes patients develop seizures. In more severe poisoning, hyperkalemia, metabolic acidosis, and increased prothrombin time / INR (probably through interactions with circulating blood clotting factors) may occur. Acute renal failure and liver damage, hypotension, hypothermia, cyanosis, dyspnea / acute respiratory distress syndrome and short-term episodes of apnea (in children after using large amounts of the drug) may occur. In patients with bronchial asthma, an exacerbation of asthma may occur. Possible nystagmus, blurred vision and loss of consciousness.

Treatment. There is no specific antidote. Treatment should be symptomatic and supportive, and include airway management and monitoring of cardiac function and vital signs until the patient is normalized. When using small amounts of the medicinal product (less than 50 mg / kg ibuprofen), it is recommended to drink water to minimize disturbances from the gastrointestinal cycle. Oral administration of activated charcoal or gastric lavage is recommended within 1 hour after the application of a potentially toxic dose of the medicinal product. The benefits of measures such as forced diuresis, hemodialysis and hemoperfusion have not been proven, since ibuprofen has a high degree of binding to plasma proteins.

For frequent or prolonged muscle spasms, treatment should be given by intravenous diazepam or lorazepam. In the case of bronchial asthma, bronchodilators should be used. Seek medical attention.

Undesirable effects.

Adverse events have been ranked under headings of frequency using the following convention: very common ($>1/10$); common ($>1/100$, $<1/10$); uncommon ($>1/1000$, $<1/100$); rare ($>1/10000$, $<1/1000$); very rare ($<1/10000$); unknown (cannot be calculated according to available data). Within each frequency group, undesirable effects are listed in descending order of severity.

The following adverse reactions refer to those that have been observed with short-term use of ibuprofen in non-prescription doses. When treating chronic conditions, additional undesirable effects may occur with long-term treatment.

The most common adverse reactions were from the gastrointestinal tract. In general, adverse reactions are dose-dependent, including the risk of gastrointestinal bleeding depending on the dose and duration of treatment.

Respiratory, thoracic and mediastinal disorders: unknown: airway reactivity, including asthma, bronchospasm or shortness of breath.

Gastrointestinal disorders: uncommon: abdominal pain, nausea, dyspepsia; rare: diarrhea, flatulence, constipation and vomiting; very rare: gastric and duodenal ulcers, perforations or gastrointestinal bleeding, melena, bloody vomiting, sometimes fatal (especially in elderly patients), ulcerative stomatitis, gastritis; unknown: exacerbation of colitis and Crohn's disease.

Hepatobiliary disorders: very rare: liver-function abnormalities.

Renal and urinary disorders: very rare: acute renal impairment, papillonecrosis, especially with prolonged use, associated with an increase in the level of urea in the blood serum, and edema; unknown: renal failure.

Nervous system disorders: uncommon: headache, aseptic meningitis. The pathogenic mechanism of drug-induced aseptic meningitis is not clear. The available data on aseptic meningitis associated with NSAIDs indicate a hypersensitivity reaction (due to the time relationship with the medicinal product and the disappearance of symptoms after medicinal product withdrawal). In patients with autoimmune diseases (systemic lupus erythematosus and mixed connective tissue disease), isolated cases of symptoms of aseptic meningitis (stiff neck, headache, nausea, vomiting, fever, or disorientation) were observed.

Cardiac disorders: unknown: hypertension, heart failure, edema.

Clinical studies and epidemiological data indicate that the use of ibuprofen (especially in high doses of 2400 mg per day) and with long-term treatment may be associated with a slightly increased risk of arterial thrombotic complications (for example, myocardial infarction or stroke).

Blood and lymphatic system disorders: very rare: hematopoietic disorders (including anemia, leukopenia, thrombocytopenia, pancytopenia and agranulocytosis). The first signs of such disorders are fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe wasting, bleeding, and hematomas of unknown etiology.

Immune system disorders: uncommon: hypersensitivity reactions accompanied by urticaria and pruritus; very rare: severe hypersensitivity reactions, symptoms of which may include edema of the face, tongue and larynx, shortness of breath, tachycardia, arterial hypotension (anaphylaxis, angioedema, or severe shock). Hypersensitivity reactions may include: nonspecific allergic reactions and anaphylaxis, airway reactivity, including bronchial asthma, exacerbation of asthma, bronchospasm and shortness of breath, or various forms of skin reactions, including pruritus, urticaria, purpura, angioedema, less often exfoliative dermatosis and bulatosis, including toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme.

Skin and subcutaneous tissue disorders: uncommon: various skin rashes; very rare: severe skin reactions such as bullous reactions, including Stevens-Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis, may occur.

Investigations: very rare: decrease in hemoglobin.

Reporting of suspected adverse reactions.

Reporting suspected adverse reactions after registration of the medicinal product is an important procedure. This allows for continued monitoring of the benefit/risk ratio for the respective medicinal product. Healthcare providers should be informed of any suspected adverse reactions through the national alert system.

Shelf life. 3 years.

Special precautions for storage.

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

Keep out of the reach of children.

Nature and contents of container.

10 tablets in a blister; 1 or 2 or 5 blisters in a pack.

Category of release.

Non-prescription medicine.

Manufacturer. PrJSC “Pharmaceutical Firm “Darnitsa”.

Address of the manufacturer.

13, Boryspilska Street, Kyiv, 02093, Ukraine.

Date of the last revision.

14.11.2019