INSTRUCTION
for medical use of the medicinal product
LEKFIN
IBUPROFEN

Composition:
active ingredient: ibuprofen;
1 tablet contains 400 mg of ibuprofen;
excipients: microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, colloidal silicon dioxide, sodium laurylsulfate, magnesium stearate, hypromellose, titanium dioxide (E 171), talc, macrogol 4000.
Dosage form. Coated tablets.
Main physical and chemical properties: film-coated tablets, elongated, white or almost white-colored, with convex upper and lower surfaces.
Pharmacotherapeutic group.
Musculo-skeletal system. Antiinflammatory and antirheumatic products. Antiinflammatory and antirheumatic products, non-steroids. Propionic acid derivatives. Ibuprofen. ATX code M01A E01.
Pharmacological properties.
Pharmacodynamic properties.
Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID), a propionic acid derivative that has a targeted effect against pain, fever and inflammation by inhibiting the synthesis of prostaglandins – the mediators of pain and inflammation. In addition, ibuprofen inversely inhibits platelet aggregation.
Experimental evidence suggests that ibuprofen can competitively suppress the effect of low-dose acetylsalicylic acid/aspirin on platelet aggregation when both these drugs are used concomitantly. Some pharmacodynamic studies show that when taking a single 400 mg dose of ibuprofen within 8 hours before or 30 minutes after taking acetylsalicylic acid/immediate release aspirin (81 mg), there is a decreased effect of acetylsalicylic acid/aspirin on thromboxane formation or platelet aggregation. Although there is uncertainty about the extrapolation of these data to clinical situations, it cannot be excluded that regular long-term use of ibuprofen may reduce the cardioprotective effect of low doses of acetylsalicylic acid. With occasional use of ibuprofen, such a clinically significant effect is considered unlikely (see section *Interaction with other medicinal products and other types of interactions*).
Pharmacokinetic properties.
Absorption. Ibuprofen is rapidly absorbed mainly in the small intestine and binds to blood plasma proteins. After oral administration of 200-600 mg of ibuprofen, the maximum plasma concentration of 15-55 μg/ml (C_{max}) is reached in an average of 1-2 hours (t_{max}).
If the drug is taken after a meal, the absorption of ibuprofen is much slower, and the maximum concentrations in blood plasma will be lower.
After oral administration of a single dose of 400 mg ibuprofen, the peak concentration of 8-13 μg/ml in blood plasma is reached after 6 hours.
Distribution. 99% of ibuprofen gets bound to plasma proteins. This binding is reversible.
Metabolism. More than 50-60% of an oral dose of ibuprofen is metabolized in the liver to two inactive metabolites. The metabolism of ibuprofen in children and adults is similar.
Excretion. The half-life in blood plasma is 1½-2 hours. The short half-life means that even after re-administration of ibuprofen no accumulation occurs. Ibuprofen and its metabolites get almost completely excreted by the kidneys 24 hours after taking the drug.
There are no significant differences in the pharmacokinetic profile of elderly patients.
Clinical characteristics.
Therapeutic indications.
Symptomatic treatment of mild and moderate pain of various origins (headache, toothache, painful menstruation), including colds and fevers.
Contraindications.
- Hypersensitivity to ibuprofen or to any of the components of the drug.
- Hypersensitivity reactions (such as bronchial asthma, rhinitis, angioneurotic edema, or urticaria)

that have been observed previously in a patient's medical history after taking ibuprofen, acetylsalicylic acid/aspirin, or other NSAIDs.

- Peptic ulcer or duodenal ulcer / active bleeding or a history of relapses (two or more severe episodes of confirmed peptic ulcer or bleeding in the past).
- Acute or previous inflammatory bowel disease (such as Crohn's disease, ulcerative colitis).
- A history of gastrointestinal bleeding or perforation associated with previous NSAID use.
- Increased tendency to bleeding.
- Severe renal failure (creatinine clearance < 30 ml/min).
- Severe hepatic failure (liver cirrhosis, ascites).
- Severe heart failure (class III-IV according to classification of the NYHA (New York Heart Association).
- Treatment of postoperative pain after coronary artery bypass grafting (or use of an artificial blood circulation device).
- Last trimester of pregnancy (see section *Use during pregnancy or breast-feeding*).

Interaction with other medicinal products and other types of interactions.

- *Other NSAIDs*, including selective cyclooxygenase-2 inhibitors: concomitant use of multiple NSAIDs may increase the risk of gastrointestinal ulcers and bleeding due to the synergistic effect. Therefore, concomitant use of ibuprofen with other NSAIDs should be avoided (see section *Special warnings and precautions for use*);
- *corticosteroids*: increase the risk of ulcers and bleeding in the gastrointestinal tract (see section *Special warnings and precautions for use*);
- *alcohol:* enhances gastrointestinal side effects, increases the risk of gastrointestinal bleeding;
- *antihypertensive drugs, β-blockers and diuretics*: NSAIDs may reduce the effect of diuretics and other antihypertensive drugs, such as ACE inhibitors, angiotensin antagonists and β-blockers. In some patients with impaired renal function (for example, dehydrated patients or elderly patients with impaired renal function), concomitant use of an ACE inhibitor or angiotensin II antagonist with the drugs that inhibit cyclooxygenase can lead to further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, such combinations should be prescribed with caution, especially to the elderly patients. If a long-term treatment is necessary, please ensure that the patient is sufficiently hydrated and take into account the need to monitor renal function at the beginning of combination therapy and thereafter. Diuretics increase the risk of nephrotoxic effects of NSAIDs;
- *probenecid and sulfinpyrazone*: may delay the excretion of ibuprofen, the uricosuric effect of probenecid and sulfinpyrazone gets weakened;
- *anticoagulants:* NSAIDs may increase the therapeutic effect of anticoagulants such as warfarin (see section *Special warnings and precautions for use*);
- *antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs)*: higher risk of gastrointestinal bleeding when taken with NSAIDs (see section *Special warnings and precautions for use*);
- *aminoglycosides*: NSAIDs may reduce the excretion of aminoglycosides;
- *acetylsalicylic acid/aspirin:* should not be used in combination with ibuprofen, as this increases the risk of adverse reactions. Experimental data suggest that concomitant use of ibuprofen may inhibit the effect of low doses of acetylsalicylic acid/aspirin on platelet aggregation. However, uncertainty about the possibility of extrapolating these data to clinical situations does not allow making definitive conclusions that regular long-term use of ibuprofen may reduce the cardioprotective effect of low doses of acetylsalicylic acid/aspirin. In case of unsystematic use of ibuprofen, such clinically significant effects are considered unlikely (see section *Special warnings and precautions for use*);
- *sulfonylurea drugs:* the effect of oral antidiabetic drugs (sulfonylureas) may be enhanced by the action of ibuprofen and other NSAIDs. Hypoglycaemia has been reported rarely in patients receiving ibuprofen while on sulphonylurea therapy. Blood glucose levels should be monitored regularly and the dose of antidiabetic drugs adjusted if necessary;
- *histamine H_2 antagonists:* no clinically significant interaction of ibuprofen with cimetidine or ranitidine has been reported;

- *digoxin:* NSAIDs may increase the concentration of digoxin in blood plasma;
- *phenytoin:* NSAIDs may increase the concentration of phenytoin in blood plasma;
- *lithium:* NSAIDs may reduce lithium excretion;
- *methotrexate:* NSAIDs may inhibit tubular secretion of methotrexate and reduce the clearance of methotrexate;
- *baclofen:* the use of NSAIDs increases the toxicity of baclofen;
- *cholestyramine:* concomitant administration with cholestyramine may decrease the absorption of ibuprofen in the gastrointestinal tract, but the clinical significance of this is unknown.
- *cyclosporine:* increased risk of nephrotoxicity;
- *tacrolimus:* increased risk of nephrotoxicity;
- *herbal extracts:* Ginkgo biloba may potentiate the risk of bleeding associated with NSAIDs;
- *mifepristone:* a decrease in the efficacy of the drug is theoretically possible given the antiprostaglandin properties of NSAIDs. Limited data suggest that concomitant use of NSAIDs on the day of prostaglandin administration does not alter the effect of mifepristone or prostaglandins on cervical maturation or uterine contractility and does not reduce the clinical efficacy of medical abortion;
- *quinolone antibiotics:* animal studies have shown that quinolone-related cramps may occur more frequently with NSAIDs. Concomitant use with ibuprofen increases the risk of cramps;
- *zidovudine:* an increased risk of hematologic toxicity with concomitant use of zidovudine and NSAIDs is known. There is evidence of an increased risk of hemarthrosis and hematoma in HIV-infected patients with hemophilia who received concomitant treatment with zidovudine and ibuprofen;
- *CYP2C9 inhibitors:* co-administration of ibuprofen with CYP2C9 inhibitors may increase ibuprofen exposure (CYP2C9 substrate). One study showed that voriconazole and fluconazole (CYP2C9 inhibitors) increased S(+)-ibuprofen exposure by approximately 80–100%. Reducing ibuprofen dosage should be considered when co-administered with CYP2C9 inhibitors, especially when administering high doses of ibuprofen to patients who take voriconazole or fluconazole;
- concomitant use of ibuprofen and potassium-sparing diuretics may lead to hyperkalemia (serum potassium testing is recommended);
- *cardiac glycosides:* NSAIDs may exacerbate cardiac dysfunction, decrease glomerular filtration rate of the kidneys and increase the level of glycosides in blood plasma.

Special warnings and precautions for use.

General precautions

Side effects of ibuprofen in general can be reduced by applying the minimum effective dose required to treat symptoms in the shortest period of time (see section *Method of administration and dosage* and gastrointestinal, cardiovascular risks below).

Prolonged use of any pain relievers for headaches can worsen this condition. If this situation is suspected or confirmed, consult a physician and discontinue treatment. Consideration should be given to the likelihood of headaches caused by abuse of the drug in patients with frequent or daily headaches despite (or due to) regular use of headache medications.

Some selective COX-2 inhibitors have shown to increase the risk of thrombotic cardiovascular and cerebrovascular complications in placebo-controlled studies. It is not yet known whether this risk is directly correlated with the selectivity of COX-1/COX-2 for particular NSAIDs. As there are currently no comparable clinical trial data for ibuprofen with maximum doses and long-term therapy, a similarly increased risk cannot be excluded. Until relevant data are available, ibuprofen should be used in patients with clinically proven coronary heart disease, cerebrovascular disease, peripheral artery disease, or significant risk factors (for example, high blood pressure, hyperlipidemia, diabetes mellitus, smoking) only after a thorough risk-benefit assessment. Also because of this risk, the lowest effective dose should be given during the shortest duration of therapy.

Renal effects of NSAIDs include fluid retention with edema and/or hypertension. Therefore, ibuprofen should be used with caution in patients with cardiac dysfunction and other conditions that are prone to fluid retention. Caution should also be exercised in patients who take concomitant diuretics or ACE inhibitors, as well as those at increased risk of hypovolemia.

Concomitant use of NSAIDs with alcohol may increase the side effects associated with the active substance, in particular from the gastrointestinal tract or central nervous system (CNS).
Masking the symptoms of underlying infections. Ibuprofen can mask the symptoms of an infectious disease, which can delay the initiation of appropriate treatment and thus complicate the course of the disease. This has been observed in bacterial community-acquired pneumonia and bacterial complications of chickenpox. When ibuprofen is used to subdue an increased body temperature or to relieve pain caused by infection, monitoring of the infectious disease is recommended. In an out-of-hospital setting, the patient should see a doctor if symptoms persist or worsen.
Respiratory disorders. Ibuprofen should be prescribed with caution to patients with asthma, chronic rhinitis, or a history of allergic disease, as ibuprofen has been reported to cause bronchospasm, urticaria or angioneurotic edema in such patients.
Impaired function of the heart, kidneys and liver. NSAIDs should be used with caution in patients with impaired renal, hepatic or cardiac function, as this may lead to impaired renal function.
The usual concomitant use of such pain killers further increases this risk.
Patients with impaired renal, hepatic or cardiac function should use the lowest effective dose for the shortest period of time, and also monitor renal function, especially in cases of long-term treatment (see section *Contraindications*).
Other NSAIDs. Concomitant use of ibuprofen with other NSAIDs, including selective cyclooxygenase-2 inhibitors, increases the risk of adverse reactions and should be avoided.
Elderly patients. Elderly patients have an increased incidence of NSAID adverse reactions, especially gastrointestinal bleeding and perforation, which can be fatal.
Gastrointestinal bleeding, ulcers, perforations. NSAIDs should be used with caution in patients with chronic inflammatory bowel disease (ulcerative colitis, Crohn's disease), as these conditions may be exacerbated (see *Contraindications*).
There are reports of cases of gastrointestinal bleeding, perforation, ulcers, including fatal, which occurred at any stage of NSAID treatment, regardless of the presence of warning symptoms or the presence of severe gastrointestinal disorders in the anamnesis.
The risk of gastrointestinal bleeding, perforation and ulceration increases with increasing doses of NSAIDs in patients with a history of ulcer, especially those complicated by bleeding or perforation, as well as in the elderly group. These patients should start treatment with minimal doses. Caution should be exercised when treating patients who receive concomitant medications that increase the risk of gastric toxicity or bleeding, such as oral corticosteroids, anticoagulants (for example, warfarin), SSRIs, or antiplatelet agents, such as acetylsalicylic acid/aspirin (see section *Interaction with other medicinal products and other types of interactions*). For long-term treatment, these patients, as well as patients requiring concomitant use of low doses of acetylsalicylic acid/aspirin or other drugs that increase the risk to the gastrointestinal tract, may require a combination therapy with misoprostol or proton pump inhibitors.
Patients with a history of gastrointestinal disorders, especially elderly patients, should report any unusual gastrointestinal symptoms (mainly bleeding), especially gastrointestinal bleeding at the beginning of treatment.
In case of gastrointestinal bleeding or ulceration in patients receiving ibuprofen, treatment should be stopped immediately.
Ibuprofen should be prescribed only under strict indications and under medical supervision for gastrointestinal complaints and liver dysfunction, as their condition may worsen (see *Adverse reactions*).
Cardiovascular and cerebrovascular effects. Patients with a history of uncontrolled hypertension, congestive heart failure (NYHA class II) should be careful when starting ibuprofen treatment (consultation with a doctor is required), since cases of fluid retention, arterial hypertension and edema associated with ibuprofen therapy, as well as other NSAIDs, have been reported.
Clinical studies suggest that the use of ibuprofen, especially in high doses (2400 mg per day), may be associated with a slightly increased risk of arterial thrombotic complications (for example, myocardial infarction or stroke). In general, epidemiological data do not suggest that low doses of ibuprofen (for example, ≤ 1200 mg daily) may lead to an increased risk of arterial thrombotic complications.

Patients with uncontrolled arterial hypertension, congestive heart failure (NYHA class II-III), with diagnosed coronary artery disease, peripheral arterial disease and/or cerebrovascular disease should be treated with ibuprofen only after a thorough assessment of the clinical picture. High doses of the drug (2400 mg per day) should be avoided. Clinical picture should also be carefully evaluated before starting a long-term treatment of patients with risk factors for cardiovascular complications (for example, arterial hypertension, hyperlipidemia, diabetes mellitus, smoking), especially if high doses of ibuprofen (2400 mg per day) are required.

Skin reactions. Very rarely, severe skin reactions that can be fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, may occur with NSAIDs (see *Adverse reactions*). The highest risk of such reactions is observed in the early stages of therapy; in most cases, the onset of such reactions occurs within the first month of treatment. A case of acute generalized exanthematous pustulosis has also been reported following the use of ibuprofen-containing medicines.

Ibuprofen should be discontinued at the first signs and symptoms of skin lesions, such as skin rashes, mucosal lesions, or any other signs of hypersensitivity.

In exceptional cases, chickenpox can cause severe infectious complications on the skin and soft tissues. At present, the effect of NSAIDs on the worsening of these infections cannot be excluded, so it is recommended to avoid the use of ibuprofen in the case of chickenpox.

Effects on the kidneys. Ibuprofen should be used with caution in patients with significant dehydration. There is a risk of renal impairment, especially in children, adolescents and elderly patients with dehydration. As with other NSAIDs, long-term use of ibuprofen can lead to papillary necrosis of the kidneys and other pathological changes in the kidneys. Renal toxicity was also observed in patients in whom renal prostaglandins played a compensatory role in maintaining renal perfusion. NSAIDs in such patients may cause a dose-dependent decrease in prostaglandin production and, secondarily, a decrease in renal blood flow, which may lead to renal failure.

Patients with renal impairment, heart failure, liver dysfunction, taking diuretics and angiotensin-converting enzyme (ACE) inhibitors, as well as elderly patients are at high risk of developing such a reaction. After discontinuation of NSAID therapy, a return to the pre-treatment condition is usually achieved.

The systematic use of analgesics, especially a combination of several painkillers, can lead to persistent renal dysfunction with a risk of renal failure (analgesic nephropathy). This risk may be increased due to salt loss and dehydration.

Hematological effects. Ibuprofen may temporarily inhibit platelet function (affect platelet aggregation) and increase bleeding time. Therefore, it is recommended to closely monitor the condition of patients with blood clotting disorders.

Aseptic meningitis, systemic lupus erythematosus and mixed connective tissue diseases. Ibuprofen should be used with caution in case of manifestations of systemic lupus erythematosus and mixed connective tissue diseases due to the increased risk of aseptic meningitis. However, ibuprofen also showed symptoms of aseptic meningitis in patients who did not have any of these chronic conditions.

Effects on fertility in women. According to limited evidence, drugs that inhibit cyclooxygenase/prostaglandin synthesis may affect the ovulation process. This effect is reversible after cessation of treatment. Long-term use (applies to a dose of 2400 mg per day, and treatment duration of more than 10 days) of ibuprofen may impair female fertility and is not recommended for women trying to get pregnant. This medicine should not be used by women who have difficulty conceiving or are being tested for infertility.

Porphyrin metabolism. Caution should be exercised in patients with congenital disorders of porphyrin metabolism (for example, acute intermittent porphyria).

Surgical interventions. Caution should be exercised immediately after extensive surgery.

Other effects. Severe acute hypersensitivity reactions (such as anaphylactic shock) are very rare. At the first signs of a hypersensitivity reaction after drug administration it is necessary to stop therapy. In such cases it is necessary to carry out both symptomatic, and specialized treatment.

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

This medicine contains 26.67 mg of lactose monohydrate. Patients with rare congenital problems of fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase deficiency should not take this medicine.

Fertility, pregnancy and lactation.

Fertility.

Ibuprofen may impair female fertility and is not recommended for use to women planning a pregnancy. Women who have problems with their ability to conceive or are being tested for infertility should consider stopping ibuprofen.

Pregnancy

Suppression of prostaglandin synthesis may adversely affect pregnancy and/or embryo/fetal development. Epidemiological data indicate an increased risk of miscarriage, congenital heart defects and gastroschisis after using prostaglandin synthesis inhibitors at an early stage of pregnancy. The absolute risk of cardiovascular malformations increased from less than 1% to 1.5%. The risk is thought to increase with dose and duration of therapy. In animals, the use of inhibitors of prostaglandin synthesis led to an increase in the incidence of pre- and post-implantation miscarriages and mortality of embryos/fetuses. In addition, an increased frequency of various malformations, including malformations of the cardiovascular system, has been reported in animals treated with prostaglandin synthesis inhibitors during a period of organogenesis.

Ibuprofen should not be taken in the first two trimesters of pregnancy unless it is absolutely necessary. Women who are trying to conceive, as well as during the first and second trimesters of pregnancy, should use the lowest possible dose for the shortest period of time.

Ibuprofen is contraindicated in the third trimester of pregnancy. During the third trimester of pregnancy, all inhibitors of prostaglandin synthesis can affect the fetus, causing the following risks:

- cardiopulmonary toxicity (characterized by premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure, accompanied by oligohydramnios.

At the end of pregnancy, inhibitors of prostaglandin synthesis in the mother and newborn can cause:

- possible prolongation of bleeding time, antiplatelet effect, which can develop even at very low doses;
- suppression of uterine contractions, which leads to a delay or increase in the duration of labor.

Childbirth.

It is not recommended to take ibuprofen during childbirth. The onset of labor may be delayed and its duration may increase with increasing tendency to bleed in both mother and baby.

Breast-feeding.

In limited studies, ibuprofen has been found in very low concentrations in breast milk, so it is unlikely that it could adversely affect a breastfed infant. As a precautionary measure, ibuprofen is not recommended for use to women during breastfeeding.

Effects on ability to drive and use machines.

No relevant studies were performed. Taking ibuprofen can affect the speed of response of patients, which should be kept in mind when engaging in activities that require increased concentration, such as driving or operating other machinery. The effect on the speed of response is greatly enhanced in combination with alcohol.

After taking NSAIDs, side effects such as dizziness, drowsiness, fatigue and visual disturbances are possible. If such events occur during the use of NSAIDs, patients should not drive or operate other machines.

Posology and method of administration.

For internal use by adults and children over 12 years of age with a body weight > 40 kg. For short-term use only. Side effects can be minimized by applying the lowest effective dose for the shortest period of time required to control symptoms.

The tablets should be taken preferably during or after a meal; please do not chew; swallow with water.

A single dose for children over 12 years of age weighing > 40 kg and adults is 1 tablet (400 mg ibuprofen). If necessary, you can use 1 tablet every 6 hours. The maximum daily dose is 1200 mg (3 tablets per day). Apply the minimum effective dose required to treat symptoms for the shortest period of time.

If in adolescents the symptoms worsen or persist for more than 3 days, it is necessary to consult a doctor to clarify the diagnosis and adjust the treatment regimen.
If in adults the fever persists for more than 3 days or the pain does not disappear within 4 days, or the symptoms worsen, it is necessary to consult a doctor to clarify the diagnosis and adjust the treatment regimen.
The duration of treatment should be determined by a doctor individually, depending on the course of disease and the patient's condition.
Elderly patients do not require special dose adjustment, except in cases of severe renal or hepatic insufficiency. Due to the possibility of side effects, elderly patients require careful supervision.
Patients with mild to moderate renal impairment do not require dose reduction (for patients with severe renal impairment, see section *Contraindications*).
Patients with mild to moderate hepatic impairment do not require dose reduction (for patients with severe hepatic impairment, see section *Contraindications*).

Children.

Do not use in children under 12 years of age and weighing < 40 kg.

Overdose.

Symptoms of toxicity were not usually observed at doses below 100 mg/kg in children and adults. However, in some cases, supportive measures may be required. The use of the drug in children at a dose of 400 mg/kg may lead to symptoms of intoxication. In adults, the dose response is less prominent. The half-life for overdose is 1.5-3 hours.
Symptoms. In most patients, symptoms of overdose develop within 4-6 hours after taking significant amounts of ibuprofen.
The most common symptoms of overdose include nausea, vomiting, abdominal pain, torpidity and drowsiness. Manifestations in the central nervous system (CNS) include: headache, ringing in the ears, dizziness, cramps and loss of consciousness. Rarely, nystagmus, metabolic acidosis, hypothermia, renal symptoms, gastrointestinal bleeding, coma, apnea, and CNS and respiratory depression have been reported. Cardiovascular toxicity, including the development of arterial hypotension, bradycardia and tachycardia, has also been reported.
In case of significant overdose, the development of renal failure and liver damage is possible. Significant overdose is usually well tolerated if you do not take other drugs. In case of severe poisoning, metabolic acidosis may occur.
Treatment. There is no specific antidote for ibuprofen overdose. If the amount taken exceeds 400 mg/kg, it is recommended to perform gastric lavage/emptying followed by symptomatic treatment within 1 hour after taking it. Activated charcoal should be administered within 1 hour after taking a potentially toxic amount and the patient should be observed for at least four hours.
Treatment should include ensuring airway patency and monitoring the cardiac function and vital signs until the patient's condition returns to normal. Adequate diuresis must be provided.
Frequent or prolonged cramps should be treated with intravenous diazepam. Other measures may be indicated according to the patient's clinical condition.

Undesirable effects.

The following adverse reactions were observed during short-term use of ibuprofen at doses not exceeding 1200 mg per day. Additional side effects may occur during the long-term treatment of chronic diseases.
Adverse reactions that have occurred with the use of ibuprofen are listed below by organ systems and the frequency of their manifestation.
The frequency of adverse reactions is defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and Not known (cannot be estimated from the available data).
The most common adverse reactions are those to NSAIDs that affect the gastrointestinal tract by their nature. In general, adverse reactions are dose dependent, including the risk of gastrointestinal bleeding which depends on the dose and duration of treatment.
Peptic ulcers, perforations or bleeding, sometimes fatal, especially in elderly patients (see section *Special warnings and precautions for use*), nausea, vomiting, diarrhea, flatulence, constipation, indigestion (dyspepsia), abdominal pain, melena, hematemesis may occur.

Ulcerative stomatitis, exacerbation of colitis and Crohn's disease have been reported after use (see section *Special warnings and precautions for use*). Gastritis is less common. Perforation of the gastrointestinal tract has been reported rarely with ibuprofen.
Exacerbation of skin infections caused by infection (for example, development of necrotizing fasciitis) has been described with concomitant use of NSAIDs. In exceptional cases, varicella infection can lead to severe skin infections and soft tissue complications. If there are any signs of infection or it gets worse while using ibuprofen, the patient should see a doctor immediately.
Clinical studies suggest that the use of ibuprofen, especially at high doses (2400 mg per day), may be associated with a slightly increased risk of arterial thrombotic complications (such as myocardial infarction or stroke) (see section *Special warnings and precautions for use*).
Infections and infestations: uncommon – rhinitis; rare – aseptic meningitis (especially in patients with pre-existing autoimmune disorders such as systemic lupus erythematosus and mixed connective tissue disease) with symptoms of occipital muscle tightness, headache, nausea, vomiting, fever or disorientation (see section *Special warnings and precautions for use*).
Cases of exacerbation of skin inflammation caused by infection (for example, development of necrotic fasciitis) during NSAID use have been described. If signs of infection occur or worsen during the use of ibuprofen, the patient should consult a doctor immediately.
Blood and lymphatic system disorders: rare – aplastic anemia, leukopenia, thrombocytopenia, neutropenia, agranulocytosis, hemolytic anemia, which may occur with long-term treatment, the first signs of which are fever, sore throat, surface sores in oral cavity, flu-like symptoms, severe exhaustion, unexplained bleeding and hematomas of unknown etiology.
Immune system disorders: uncommon – hypersensitivity. *Hypersensitivity reactions* have been reported after treatment with ibuprofen. Such reactions include non-specific allergic reactions and anaphylaxis, respiratory reactions including bronchial asthma, exacerbation of asthma, bronchospasm or shortness of breath, various skin disorders including rashes of various types, pruritus, urticaria, purpura, angioneurotic edema; very rare – exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).
Rare – anaphylactic reaction, lupus erythematosus syndrome, autoimmune hemolytic anemia.
Psychiatric disorders: uncommon – insomnia, anxiety disorders; rare – depression, confusion, agitation, hallucinations; very rare – mental disorders.
Nervous system disorders: common – headache, dizziness, decreased sensitivity (especially in combination with alcohol); uncommon – paresthesia, drowsiness.
Eye disorders: uncommon – deterioration of vision, usually reversible, if treatment is stopped; rare– toxic amblyopia, toxic optic neuropathy, optic neuritis.
Ear and labyrinth disorders: uncommon – hearing loss, vertigo, long-term treatment may cause ringing in the ears and dizziness.
Cardiac disorders: very rare – heart failure, edema, heart attack.
Vascular disorders: very rare – hypertension.
Clinical study data indicate that the use of ibuprofen, especially in high doses (2400 mg per day), may slightly increase the risk of arterial thrombotic complications (for example, myocardial infarction or stroke (see section *Special warnings and precautions for use*).
Respiratory, thoracic and mediastinal disorders: uncommon – bronchial asthma, bronchospasm, dyspnea, the risk of acute pulmonary edema in patients with heart failure.
Gastrointestinal disorders: common – abdominal pain, dyspepsia, diarrhea, vomiting, nausea, flatulence, constipation, melena, hematemesis, perforation or gastrointestinal bleeding; uncommon – gastritis, duodenal ulcer, gastric ulcer, ulcerative stomatitis, gastrointestinal bleeding, which can in some cases be fatal, especially in the elderly group of patients; very rare – pancreatitis; frequency not known – pyrosis, ulceration of the oral cavity, esophagitis, development of intestinal strictures, exacerbation of ulcerative colitis and Crohn's disease (see section *Contraindications*).
Hepatobiliary disorders: uncommon – hepatitis, jaundice, impaired liver function; very rare – liver failure.
Skin and subcutaneous tissues disorders: common – rash; rare – urticaria, pruritus, purpura, angioneurotic edema, photosensitivity reactions; very rare – severe skin reactions (for example, erythema multiforme, bullous reactions, including Stevens-Johnson syndrome and toxic epidermal

necrolysis); frequency unknown – drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), acute generalized exanthematous pustulosis.
In exceptional cases, chickenpox can cause severe skin infections and soft tissue complications (see also *Infections and infestations*).
Renal and urinary disorders: rare – toxic nephropathy in various forms, including tubulointerstitial nephritis, nephrotic syndrome and renal failure; very rare – acute renal failure, papillary necrosis, especially in cases of long-term use, both of which are associated with increased urea levels in blood plasma; edema, hypernatremia (sodium retention), decreased urination.
General disorders and administration site conditions: common – malaise/fatigue, irritability; rare – edema.
Laboratory research: very rare – decrease in hemoglobin levels.
Shelf life. 3 years.
Storage.
Store in original packaging below 30 ºC.
Keep out of the reach of children.
Packaging.
10 tablets in a blister; 1, 2 or 5 blisters in a cardboard box.
Prescription status.
OTC
Manufacturer / applicant.
Group of Pharmaceutical Companies "Lekhim"
Private Joint Stock Company "Technolog"
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