INSTRUCTION
for medical use of the medicinal product
LEKFIN
IBUPROFEN

Composition:
active ingredient: ibuprofen;
1 coated tablet contains 200 mg of ibuprofen;
excipients: potato starch, hypromellose (hydroxypropyl methylcellulose), magnesium stearate, povidone, colloidal silicon dioxide, titanium dioxide (E 171), talc, polysorbate 80, polyethylene glycol 6000 (macrogol 6000), carmoisine (E 122).

Dosage form. Coated tablets.
Main physical and chemical properties: pink-colored, round, film-coated tablets with convex upper and lower surfaces. When broken and viewed under a magnifying glass, a tablet core surrounded by a solid continuous layer can be seen.

Pharmacotherapeutic group. Antiinflammatory and antirheumatic products, non-steroids. Propionic acid derivatives. Ibuprofen. ATC code M01A E01.

Pharmacological properties.
Pharmacodynamic properties.
Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID), propionic acid derivative that has proved to be effective by inhibiting prostaglandin synthesis. In humans, ibuprofen reduces pain associated with inflammation, edemas, and fever. In addition, ibuprofen inversely inhibits platelet aggregation. Experimental evidence suggests that ibuprofen can competitively suppress the effect of low-dose aspirin (acetylsalicylic acid) 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 81 mg of immediate release aspirin (acetylsalicylic acid), there is a decreased effect of aspirin (acetylsalicylic acid) 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.
Ibuprofen relieves pain, reduces inflammation and fever.
Pharmacokinetic properties.
Ibuprofen is rapidly absorbed after oral administration and is rapidly distributed throughout the body. Excretion is rapid and complete, it occurs via the kidneys.
Maximum plasma concentrations are reached 45 minutes after oral administration on an empty stomach. When taken with food, peak levels are observed after 1–2 hours. This timing may vary for different dosage forms.
The half-life is approximately 2 hours.
In limited studies, ibuprofen has been found in breast milk at very low concentrations.

Clinical characteristics.
Therapeutic indications.
Symptomatic treatment of headache and toothache, dysmenorrhea, neuralgia, back pain, joint pain, muscle pain, rheumatic pain, as well as cold and flu symptoms.

Contraindications.
• Hypersensitivity to ibuprofen or to any of the excipients of the drug.
• A history of hypersensitivity reactions (for example, asthma, rhinitis, angioedema, or urticaria) that have occurred after using 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).
• A history of gastrointestinal bleeding or perforation associated with NSAID use.
• Severe heart failure (NYHA class IV), severe renal failure, or severe liver failure.
• The last trimester of pregnancy.
• Active inflammatory bowel disease.
• Hemorrhagic diathesis or other blood clotting disorders.

Interaction with other medicinal products and other types of interactions.
Ibuprofen, like other NSAIDs, should not be used in combination with:
- *aspirin (acetylsalicylic acid)*: it is usually not recommended to use ibuprofen at the same time as acetylsalicylic acid because of the potential increase of adverse reactions, unless a physician has prescribed aspirin in a low dose (no more than 75 mg per day).
Experimental data indicate that ibuprofen can competitively suppress the effect of low-dose aspirin (acetylsalicylic acid) on platelet aggregation in case of their simultaneous use. 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;
- *other NSAIDs, including selective cyclooxygenase-2 inhibitors*: the simultaneous use of two or more NSAIDs should be avoided, as this may increase the risk of adverse reactions.
Ibuprofen should be used with caution when combined with the following drugs:
- *corticosteroids*: increased risk of ulcers or bleeding in the gastrointestinal tract;
- *antihypertensive drugs and diuretics*: NSAIDs can reduce the effect of these drugs. In some patients with impaired renal function (for example, in patients with dehydration or in elderly patients), the simultaneous use of an ACE inhibitor or an 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. The advisability of such combinations in patients using coxibs simultaneously with ACE inhibitors or angiotensin II antagonists should be considered. Therefore, such combinations 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;
- *anticoagulants:* NSAIDs can enhance the effect of anticoagulants such as warfarin;
- *antiplatelet agents and selective serotonin reuptake inhibitors:* increased risk of gastrointestinal bleeding;
- *cardiac glycosides:* NSAIDs can increase cardiac dysfunction, decrease renal glomerular filtration function and increase the level of glycosides in blood plasma;
- *lithium:* there is evidence of a potential increase in plasma lithium levels;
- *methotrexate:* there is evidence of a potential increase in plasma methotrexate levels;
- *cyclosporine:* increased risk of nephrotoxicity;
- *mifepristone:* NSAIDs should not be used earlier than 8-12 days after mifepristone, since NSAIDs can reduce the effectiveness of mifepristone;
- *tacrolimus:* the risk of nephrotoxicity may increase with the simultaneous use of NSAIDs and tacrolimus;
- *zidovudine:* an increased risk of hematological toxicity with the combined use of zidovudine and NSAIDs. An increase in the risk of hemarthrosis and hematoma has been recorded in HIV-infected patients with hemophilia who received concomitant treatment with zidovudine and ibuprofen;
- *quinolone antibiotics:* patients who simultaneously take NSAIDs and quinolone antibiotics may have an increased risk of cramps.

Special warnings and precautions for use.
Side effects can be minimized by using the lowest effective dose needed to relieve symptoms for a short period of time.

In the elderly users, there is an increased incidence of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation, which can be fatal.
Respiratory effects.
In patients who suffer from bronchial asthma or allergic diseases, or have a history of these diseases, bronchospasm may occur.
Other NSAIDs.
Avoid the simultaneous use of ibuprofen with other NSAIDs, including selective cyclooxygenase-2 inhibitors.
Systemic lupus erythematosus and mixed connective tissue disease.
Ibuprofen should be used with caution in case of manifestations of 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 drug.
Cardiovascular and cerebrovascular effects.
Patients with a history of hypertension and / or heart failure should be careful when starting ibuprofen treatment (consultation with a doctor is required), since cases of fluid retention, hypertension and edema associated with NSAID therapy 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.
Effects on the kidneys / liver.
Caution should be exercised in patients with renal insufficiency due to the possibility of impairment of renal function. Ibuprofen should be used with caution in patients with kidney or liver diseases, and especially during concomitant diuretic therapy, since inhibition of prostaglandins can lead to fluid retention and further impairment of renal function. These patients should receive the lowest possible dose of ibuprofen and their renal function should be monitored on a regular basis. In case of dehydration, adequate fluid intake must be ensured. There is a risk of kidney failure in children (over 6 years of age) and adolescents with dehydration.
In general, the systematic use of analgesics, especially combinations of various pain relievers, can lead to long-term renal damage with the risk of renal failure (analgesic nephropathy). The highest risk of this reaction exists in elderly patients, patients with renal insufficiency, heart failure and hepatic insufficiency, as well as in those receiving diuretic or ACE inhibitor therapy. After discontinuation of NSAID therapy, a return to the pre-treatment condition is usually achieved.
Like other NSAIDs, ibuprofen can cause slight temporary increases in certain indicators of liver function, as well as significant increases in AST and ALT levels. In case of a significant increase in these indicators, treatment should be discontinued.
With prolonged 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 inhibiting cyclooxygenase / prostaglandin synthesis can impair fertility in women by affecting ovulation. This process is reversible after discontinuing 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), as these conditions may worsen.

There are reports of cases of gastrointestinal bleeding, ulceration or perforation, which can be fatal, occurring at any stage of treatment with all NSAIDs, regardless of the presence of warning symptoms or disorders of the gastrointestinal tract in a patient's past medical history.
The risk of gastrointestinal bleeding, ulceration or perforation increases with increasing doses of NSAIDs in patients with a history of ulcers, especially those complicated by bleeding or perforation, as well as in the elderly group. Such patients should begin treatment with the lowest available dose. Combination therapy with protective drugs (for example, misoprostol or proton pump inhibitors) is recommended for these patients, as well as for patients who require the simultaneous use of low doses of acetylsalicylic acid or other drugs that can increase the risks for the gastrointestinal tract.
Patients with a history of gastrointestinal toxicity, especially the elderly patients, should report any unusual symptoms from the gastrointestinal tract (especially gastrointestinal bleeding), in particular, at the beginning of treatment.
Long-term use of any pain relievers for headaches can worsen your condition. In such cases, you should consult a doctor and stop treatment. Consideration should be given to the likelihood of headaches caused by abuse of the medicinal drug in patients with frequent or daily headaches despite (or due to) regular use of headache medications.
Caution should be exercised when treating patients who receive concomitant medications that may increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants (for example, warfarin), selective serotonin reuptake inhibitors, or antiplatelet agents (for example, aspirin).
In case of gastrointestinal bleeding or ulceration in patients who receive ibuprofen, treatment should be stopped immediately.
Effects on the skin and subcutaneous tissue.
Very rare serious skin reactions that can lead to death have been reported, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis that occur with NSAIDs (see Adverse Reactions).
A high 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, which arose after the use of drugs containing ibuprofen, was also reported.
Ibuprofen should be discontinued at the first signs and symptoms of skin lesions, such as skin rashes, mucosal lesions, or any other sign of hypersensitivity.
In exceptional cases, chickenpox can cause severe infectious complications on the skin and soft tissues. During a chickenpox period, the effect of NSAIDs on the worsening of these infections cannot be excluded. Therefore, it is recommended to avoid using ibuprofen in case of chickenpox.
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 infection is recommended. In an out-of-hospital setting, the patient should see a doctor if symptoms persist or worsen.

Fertility, pregnancy and lactation.
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 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. If ibuprofen is used by a woman who is trying to become pregnant or during the first and second trimesters of pregnancy, the lowest possible dose should be used for a short period of time.

During the third trimester of pregnancy, all inhibitors of prostaglandin synthesis may pose the following risks:
for the fetus: cardiopulmonary toxicity (characterized by premature closure of the ductus arteriosus and pulmonary hypertension); impaired renal function, which can progress to renal failure, accompanied by oligohydramnios;
for the mother at the end of pregnancy: an increase in the bleeding period is possible; antiplatelet effect, which can develop even at very low doses; inhibition of uterine contractions, which leads to a delay or an increase in the duration of labor.
So, ibuprofen is contraindicated during the third trimester of pregnancy.
In limited studies, ibuprofen has been found in breast milk at a very low concentration, so it is unlikely that it could adversely affect a breastfed infant.

Effects on ability to drive and use machines.
Provided that the drug is used in accordance with the recommended doses and duration of treatment, no effect on the ability to drive vehicles or operate other mechanisms is expected.

Posology and method of administration.
For oral administration. Side effects can be minimized by using the minimum effective dose for the shortest period of time necessary to control symptoms (see Special Warnings and Precautions for Use).
The minimum effective dose should be used for the short period necessary to relieve pain (no more than 5 days) or symptoms of fever (3 days). If you need to use the drug for more than 5 days (if symptoms persist), please consult a doctor.
The drug can be prescribed for adults and children weighing more than 20 kg (older than 6 years old).
Usual doses are at the rate of 20 to 30 mg/kg of body weight per day. Do not exceed the dose of 30 mg/kg of body weight per day.
Children weighing from 20 to 30 kg (from 6 to 11 years old) should take a dose of 200 mg (1 tablet); if necessary, the same dose can be repeated 6 hours later, but in any case, do not use more than 600 mg (3 tablets) per day.
Adults and children weighing more than 30 kg should take a dose of 200-400 mg (1-2 tablets) every 4-6 hours if necessary. The tablets must be taken with water. Do not use more than 1200 mg (6 tablets) in 24 hours.
Elderly patients do not require special dosages.
Patients with mild to moderate renal and hepatic impairment do not require any dose adjustment.

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

Overdose.
Most reported overdose cases are asymptomatic. The risk of symptoms occurs when the dose of ibuprofen is higher than 80-100 mg/kg. 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. Overdose symptoms occur within 4 hours after taking the drug. In most patients, the use of a clinically significant amount of NSAIDs caused mild overdose symptoms, including nausea, vomiting, epigastric pain, or, less commonly, diarrhea. Tinnitus, headache, and gastrointestinal bleeding may also occur. In case of more severe poisoning, toxic damage to the central nervous system is possible in the form of vertigo, dizziness, lethargy, drowsiness, and sometimes – an agitated state, ataxia, disorientation or coma. Sometimes patients develop cramps. In severe poisoning, hyperkalemia, metabolic acidosis and an increase in PT/INR may occur (probably due to interaction with blood clotting factors circulating in the bloodstream). In rare cases, moderate to severe symptoms such as acute renal failure, liver damage, hypotension, hypothermia, cyanosis, shortness of breath / acute respiratory distress syndrome and short-term episodes of apnea (in children after using large amounts of the drug) have been observed. Patients with bronchial asthma may experience an exacerbation of the disease. Nystagmus, blurred vision and loss of consciousness are also possible.

Treatment. There is no specific antidote. Treatment should be symptomatic and supportive, and include ensuring airway patency and monitoring heart and vital signs until the condition returns to normal. When using small amounts of the drug (less than ibuprofen 50 mg/kg), it is recommended to drink water in order to minimize disturbances from the gastrointestinal tract. When using large amounts, it is recommended to use activated charcoal orally or gastric lavage if no more than 1 hour has elapsed after the patient has used a potentially toxic dose of the drug and the patient has not used a life-threatening amount of the drug. If ibuprofen has already been absorbed, alkaline agents can be used to help eliminate acidic ibuprofen in the urine. The benefits of such measures 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 cramps, treatment should be given by intravenous diazepam or lorazepam. For the treatment of bronchial asthma bronchodilators should be used. Please, seek medical advice from your doctor.

Undesirable effects.

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). Within each group, the frequencies of adverse reactions are listed in decreasing order of severity.

The list of the following adverse reactions refers to those observed with the short-term use of ibuprofen in OTC doses. In cases of a long-term treatment of chronic conditions, additional side effects may occur.

The most common adverse reactions are 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.

Blood and lymphatic system disorders:

very rare: hematopoiesis disorder (anemia, leukopenia, thrombocytopenia, pancytopenia, agranulocytosis). The first signs are fever, sore throat, surface sores in oral cavity, flu-like symptoms, severe exhaustion, unexplained bleeding, and hematomas of unknown etiology.

Immune system disorders:

Hypersensitivity reactions[1]; uncommon: urticaria and itching; very rare: severe hypersensitivity reactions, the symptoms of which may include swelling of the face, tongue and larynx, shortness of breath, tachycardia, arterial hypotension (anaphylactic reactions, angioedema or severe shock); frequency unknown: airway reactivity, including bronchial asthma, exacerbation of asthma, bronchospasm or shortness of breath.

Nervous system disorders:

uncommon: headache; very rarely: aseptic meningitis[2]

Cardiac disorders:

Not known: heart failure, edema.

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

Vascular disorders:

Not known: arterial hypertension.

Digestive system:

uncommon: abdominal pain, nausea, dyspepsia; rarely: diarrhea, flatulence, constipation and vomiting; very rare: gastric ulcer and duodenal ulcer, perforation or gastrointestinal bleeding, melena, bloody vomiting, sometimes fatal (especially in elderly patients), ulcerative stomatitis, gastritis;

not known: exacerbation of colitis and Crohn's disease.

Hepatobiliary disorders:

very rare: impaired liver function.

Skin and subcutaneous tissues disorders:

uncommon: various skin rashes;

very rare: severe forms of skin reactions such as bullous reactions, including Stevens-Johnson syndrome, erythema multiforme and toxic epidermal necrolysis may occur;

not known: acute generalized exanthematous pustulosis.
Respiratory tract and mediastinal organs:
Not known: airway reactivity, including asthma, bronchospasm, or dyspnea.
Renal and urinary disorders:
very rare: acute renal dysfunction, papilonecrosis, especially when long-term use is associated with an increase in serum urea levels, and edema;
not known: renal failure.
Laboratory research:
very rare: decrease in hemoglobin levels.
Description of the adverse reactions with superscripts:
[1] There are reports of the occurrence of hypersensitivity reactions after treatment with ibuprofen. These reactions include (a) nonspecific allergic reactions and anaphylaxis, (b) reactions from the respiratory tract, including bronchial asthma, exacerbation of asthma, bronchospasm or shortness of breath, or (c) various skin disorders, including various types of rash, itching, urticaria, purpura, angioedema, and less often – exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).
[2] The mechanism of pathogenesis of drug-induced aseptic meningitis is fully understood. However, the available data on aseptic meningitis associated with taking NSAIDs indicate a hypersensitivity reaction (through the temporal relationship to taking the drug and the disappearance of symptoms after drug withdrawal). In particular, during the ibuprofen treatment in patients with existing autoimmune disorders (such as systemic lupus erythematosus, mixed connective tissue disease), isolated cases of symptoms of aseptic meningitis (such as stiff neck, headache, nausea, vomiting, fever, and disorientation) were observed.

Shelf life. 3 years.

Storage.
Store in original packaging below 25 ºC.
Keep out of the reach of children.

Package.
10 tablets in a blister;
10 tablets in a blister; 5 blisters in a cardboard box;
10 tablets in a blister; 90 blisters in a cardboard box.

Prescription status.
OTC

Manufacturer / applicant.
Group of Pharmaceutical Companies “Lekhim”
Private Joint Stock Company “Technolog”
Site address: Building 8, Stara Prorizna Street, Uman City
Cherkasy region, 20300, Ukraine

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