INSTRUCTION
for medical use of medicinal product
LEKFENAC®

Composition:
active ingredient: diclofenac;
1 suppository contains 100 mg of diclofenac sodium (0.1 g);
excipient: hard fat.

Pharmaceutical form. Rectal suppositories.

Pharmacotherapeutic group. Non-steroidal anti-inflammatory and antirheumatic drugs.
ATC code M01A B05.

Clinical particulars.
Indications.
– Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondyloarthritis, osteoarthritis, including spondyloarthritis;
– spinal pain syndromes;
– rheumatic diseases of extraarticular soft tissues;
– acute gout attack;
– post-traumatic and postoperative pain syndromes associated with inflammation and edema, in particular, after dental and orthopedic surgeries;
– migraine attacks;
– gynecological diseases associated with pain syndrome and inflammation, e.g. primary dysmenorrhea and adnexitis;
– as an adjunctive agent in severe inflammatory diseases of ENT organs associated with pain sensations, e.g. in pharyngitis, tonsillitis, otitis.
In accordance with general therapeutic principles, the underlying disease should be treated with basic therapy agents. Fever itself is not an indication for use of this product.

Contraindications.
– Hypersensitivity to the active ingredient or any of the excipients;
– a history of gastrointestinal hemorrhage or perforation associated with prior therapy using NSAIDs;
– the active form of peptic ulcer / bleeding or recurrent peptic ulcer / bleeding history (two or more distinct episodes of established ulceration or bleeding);
– inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis);
– last 3 months of pregnancy;
– proctitis;
– proounced liver, kidney or heart failure;
– congestive heart failure (NYHA II-IV);
– coronary heart disease in patients with angina pectoris, a history of myocardial infarction;
– cerebrovascular diseases in patients who have had a stroke or have episodes of transient ischemic attacks;
– peripheral arterial diseases;
– treatment of perioperative pain in coronary artery bypass surgery (or the use of cardiopulmonary bypass);
The drug product is contraindicated in patients who have a response to acetylsalicylic acid or other NSAIDs in the form of attacks of asthma, urticaria, angioedema, or acute rhinitis.

Posology and method of administration.

The drug product should be used in the lowest effective doses within the shortest time period with consideration of treatment task in each individual patient.
To assure delivery of a dose different from 100 mg, diclofenac suppositories of the relevant strength should be used.
No for oral intake; for rectal administration only.
The suppositories should be administered into the rectum as deep as possible, preferably after purgation.
The initial dose usually comprises 100-150 mg daily. In case of non-pronounced symptoms or long-term therapy, the dose 75-100 mg/daily is sufficient.
The daily dose is split into 2-3 intakes. In order to avoid nocturnal pain or morning stiffness before the drug product administration in the afternoon, Lekfenac® as rectal suppositories is prescribed before sleep (the product daily dose may not exceed 150 mg).
In primary dysmenorrhea, the daily dose is selected on a case-by-case basis; it usually comprises 50-150 mg/day. The initial dose may be 50-100 mg/day, but it can be increased as needed to the maximum one, comprising 200 mg/day, within several menstrual cycles. Use of the drug product should be started after onset of the first pain symptoms and continued for several days depending on the symptoms regression dynamics.
For treatment of migraine attacks, the course is started from the dose 100 mg at onset of the first signs of attack initiation. As needed, the second suppository (100 mg of diclofenac) may be used on the same day. Therapy can be continued as needed on the following days (the daily product dose may not exceed 150 mg, split into 2-3 intakes).
Elderly patients. Although the pharmacokinetics of Lekfenac® is not impaired to any clinically relevant extent in elderly patients, non-steroidal anti-inflammatory drugs should be used with particular caution in such patients who, generally, are more prone to adverse reactions. In particular, it is recommended that the lowest effective dosage be used in frail, elderly patients or those with a low body weight; besides, the patients should be monitored for gastrointestinal bleeding during NSAID therapy.
Adverse events.
Blood and lymphatic system disorders: thrombocytopenia, leukopenia, anemia (hemolytic anemia, aplastic anemia), agranulocytosis.
Immune system disorders: hypersensitivity, anaphylactic and anaphylactoid reactions (including arterial hypotension and shock); angioedema (including face edema).
Psychiatric disorders: disorientation, depression, insomnia, irritability, nightmares, psychotic disorders.
Nervous system disorders: headache, dizziness; somnolence, tiredness; paresthesias, memory impairment, convulsions, anxiety, tremor, aseptic meningitis, taste disturbances, stroke; confusion, hallucinations, disturbances of sensation, malaise.
Eye disorders: visual disturbances, blurred vision, diplopia; optic neuritis.
Ear and labyrinth disorders: vertigo, tinnitus, hearing disorders.
Cardiovascular system disorders: palpitations, chest pain, cardiac failure, myocardial infarction, arterial hypertension, arterial hypotension, vasculitis.
Respiratory, thoracic and mediastinal disorders: asthma (including dyspnea); pneumonitis.
Gastrointestinal disorders: nausea, vomiting, diarrhea, dyspepsia, abdominal pain, flatulence, anorexia; gastritis, gastrointestinal hemorrhage, hematemesis, melaena, haemorrhagic diarrhea, gastric and intestinal ulcers with or without bleeding or perforation (sometimes fatal, particularly in elderly patients); colitis (including hemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, esophageal disorder, diaphragm-like intestinal strictures, pancreatitis.
Hepatobiliary disorders: elevated transaminases; hepatitis, jaundice, liver disorders; fulminant hepatitis, hepatic necrosis, hepatic failure.
Skin and subcutaneous tissue disorders: rash; urticaria; bullous eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic epidermal necrolysis), exfoliative dermatitis, loss of hair, photosensitivity reaction, purpura, allergic purpura, pruritus.

Renal and urinary disorders: acute renal failure, hematuria, proteinuria, interstitial nephritis, nephrotic syndrome, renal papillary necrosis.
General disorders and administration site conditions: application site irritation, edema, injection site abscess.
Reproductive system and breast disorders: impotence.
Clinical trial and epidemiological data are indicative of increased risk of arterial thrombotic events (such as myocardial infarction or stroke) associated with the use of diclofenac, particularly at high therapeutic doses (150 mg daily) and in long term treatment.

Overdose.
There is no typical clinical picture resulting from diclofenac overdose. Overdose can cause vomiting, gastrointestinal bleeding, diarrhea, dizziness, tinnitus, and convulsions. Treatment of acute NSAID poisoning consists in maintenance and symptomatic therapy.
This regards treatment of such manifestations as arterial hypotension, renal failure, convulsions, and respiratory depression. Such specific therapeutic measures as forced dieresis, hemodialysis or hemoperfusion are unlikely to be effective for NSAID elimination, as the active substances of these drug products bind plasma proteins and undergo extensive metabolism to a large extent.

Pregnancy and lactation.
Pregnancy.
Lekfenac® may be prescribed during pregnancy trimesters I and II only provided the expected benefits for a pregnant woman outweigh the potential risk for the fetus, and only in the minimum effective dose; treatment duration should be as short as possible. As well as other NSAIDs, this drug product is contraindicated during the last trimester of pregnancy (inhibition of uterine contractile ability and preliminary closure of fetal ductus arteriosis is possible). Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and or cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1% up to approximately 1.5%.
The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has shown to result in increased pre-and post-implantation loss and embryo-fetal lethality.
In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during organogenetic period. If Lekfenac® is used by a woman attempting to conceive, or during the 1st trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.
During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the fetus to:
– cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
– renal dysfunction, which may progress to renal failure with oligo-hydroamniosis.
Effects on the mother and the neonate, at the end of the pregnancy, are as follows:
– possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
– inhibition of uterine contractions resulting in delayed or prolonged labor.
Consequently, Lekfenac® is contraindicated during the third trimester of pregnancy.
Lactation.
Like other NSAIDs, diclofenac passes into breast milk in small amounts. Therefore, Lekfenac® suppositories should not be administered during breast feeding in order to avoid undesirable effects in the infant.
Female fertility.

As with other NSAIDs, diclofenac may impair female fertility, therefore, it is not recommended in women attempting to conceive. In women who may have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Lekfenac® should be considered.

Children.
The drug product is not used in children.

Administration details.
General.
Undesirable effects may be minimized by using the lowest effective dose for the shortest possible duration.
The concomitant use of Lekfenac® with systemic NSAIDs such as cyclooxygenase-2 selective inhibitors should be avoided due to the absence of any evidence demonstrating synergistic effect and the potential for additive undesirable effects.
Caution is necessary in elderly patients. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with low body weight.
In rare cases, as well as with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can occur even without earlier exposure to diclofenac. Like other NSAIDs, Lekfenac® may mask the signs and symptoms of infection due to its pharmacodynamic properties.
Gastrointestinal effects.
Events of gastrointestinal bleeding (haematemesis, melaena) ulceration or perforation which can be fatal have been reported with all NSAIDs including diclofenac; these may occur at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events. They generally have more serious consequences in elderly patients. If gastrointestinal bleeding or ulceration occurs in patients receiving diclofenac, the drug product should be withdrawn.
As with the use of other NSAIDs, medical surveillance and particular caution are mandatory in patients with symptoms indicative of gastrointestinal (GI) disorders. The risk of GI bleeding, ulceration or perforation is higher with increasing doses of NSAIDs including diclofenac, and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in elderly patients.
Elderly patients have increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation, which may be fatal.
To reduce the risk of GI toxic effects, the treatment should be initiated and maintained at the lowest effective doses.
Combination therapy with protective agents (e.g. proton pump inhibitors or misoprostol) should be considered for these patients, and also for those requiring concomitant use of medicinal products containing low dose acetylsalicylic acid (ASA/aspirin or medicinal products likely to increase the risk of GI adverse events). Patients with a history of gastrointestinal toxicity, particularly elderly ones, should report any unusual abdominal symptoms (especially GI bleeding). Caution is also needed in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants (e.g. warfarin), antithrombotic agents (e.g. acetylsalicylic acid) or selective serotonin-reuptake inhibitors.
Hepatic effects.
Close medical surveillance is required when prescribing Lekfenac® to patients with impairment of hepatic function as their condition may worsen.
As with other NSAIDs, including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with Lekfenac®, regular monitoring of hepatic function is indicated as a precautionary measure. If liver dysfunction persists or worsens, if clinical signs or symptoms are associated with progressive liver disease, or if other manifestations occur (e.g. eosinophilia, rash), Lekfenac® should be discontinued. Course of certain diseases such as hepatites may occur without prodromal symptoms. Caution is necessary when Lekfenac® is used in patients with hepatic porphyria, since it may trigger an attack.

Renal effects.
As fluid retention and edema events have been reported in association with NSAIDs therapy, including diclofenac, particular caution is called for in patients with impaired cardiac or renal function, history of arterial hypertension, elderly patients, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery. Monitoring of renal function is recommended as a precautionary measure in such cases. Therapy discontinuation is usually followed by recovery to the pre-treatment state.
Skin effects.
Serious skin reactions (some of them fatal), including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs, including Lekfenac®. The highest risk of these reactions is observed early in the course of therapy: the onset of the reaction occurs in the majority of cases within the first month of treatment. Lekfenac® should be discontinued at the first appearance of skin rash, mucosal lesions or any other signs of hypersensitivity.
Systemic lupus erythematosus and mixed connective tissue diseases.
Patients with systemic lupus erythematosus and mixed connective tissue diseases may be at increased risk of aseptic meningitis.
Cardiovascular and cerebrovascular effects.
Appropriate monitoring and advice are required for patients with a history of arterial hypertension and/or mild to moderate congestive heart failure as fluid retention and edema have been reported in association with NSAID therapy, including diclofenac.
Clinical trial and epidemiological data are indicative that the use of diclofenac, particularly at high doses (150 mg daily) and in long term treatment can be associated with slightly increased risk of arterial thrombotic events (for example myocardial infarction or stroke).
Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidemia, diabetes mellitus, smoking) can be prescribed with diclofenac after careful clinical consideration.
As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need in the use of diclofenac for symptomatic relief and response to therapy should be re-evaluated periodically. The drug product should be used with caution in patients above 65 years old.
Patients should be informed about the possibility of serious antithrombotic events (chest pain, edema, weakness, speech disorders), which could happen any time. In this case, the doctor should be contacted immediately.
Hematological effects.
During prolonged treatment with diclofenac, as with other NSAIDs, monitoring of all blood parameters is recommended.
Diclofenac may reversibly inhibit platelet aggregation. Patients with defects of hemostasis, bleeding diathesis or hematological abnormalities should be carefully monitored.
A history of asthma.
In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially linked to allergic rhinitis-like symptoms), reactions on NSAIDs like asthma exacerbations (so-called intolerance to analgesics/analgesic asthma), Quincke's edema or urticaria are more frequent than in other patients. Therefore, special precautions are recommended in such patients (readiness for emergency). This is applicable as well for patients with allergic reactions such as skin rash, pruritus or urticaria, to other substances.
Like other drugs that inhibit prostaglandin synthetase activity, diclofenac sodium and other NSAIDs can invoke bronchospasm if administered to patients suffering from bronchial asthma, or with a history of bronchial asthma.
Female fertility.
The use of Lekfenac® may impair female fertility and is not recommended in women attempting to conceive. As regards women who may have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Lekfenac® should be considered.

Effects on ability to drive and use machines.
Patients who experience visual disturbances, dizziness, somnolence, central nervous system disturbances, drowsiness or fatigue during therapy with Lekfenac®, should abstain from driving or operating machinery.

Interaction with other medicinal products and other forms of interaction.
Lithium. If used concomitantly, diclofenac may increase lithium plasma concentrations. Monitoring of the serum lithium level is recommended.
Digoxin. If used concomitantly, diclofenac may increase digoxin plasma concentrations. Monitoring of the serum digoxin level is recommended.
Diuretics and antihypertensive agents. Like other NSAIDs, concomitant use of diclofenac with diuretics and antihypertensive agents (e.g. β-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis. Therefore, such combination should be used with caution, and patients, especially elderly ones, should be under close medical monitoring of blood pressure. Patients should be adequately hydrated, and monitoring of renal function is recommended as well after initiation of concomitant therapy periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity.
Drugs causing hyperkalemia. Concomitant treatment with potassium-sparing diuretics, cyclosporine, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which is why more frequent monitoring of the patients' condition is required.
Anticoagulants and antithrombotic agents. Concomitant administration could increase the risk of bleeding, which is why precautions are recommended. Although clinical investigations do not indicate that diclofenac has an influence on the effect of anticoagulants, there are reports of an increased risk of hemorrhage in patients receiving diclofenac and anticoagulants concomitantly. Therefore, to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is required. As with other nonsteroidal anti-inflammatory agents, diclofenac in high doses can reversibly inhibit platelet aggregation.
Other NSAIDs including cyclooxygenase-2 selective inhibitors and corticosteroids. Co-administration of diclofenac with other NSAIDs or corticosteroids may increase the risk of gastrointestinal bleeding or ulceration. Avoid concomitant use of two or more NSAIDs.
Selective serotonin reuptake inhibitors (SSRIs). Concomitant administration of NSAIDs and SSRIs may increase the risk of gastrointestinal bleeding.
Antidiabetics. Clinical studies have shown that diclofenac can be used together with oral antidiabetic agents without modifying their therapeutic effect. However there have been isolated reports of hypoglycemic and hyperglycemic effects in such cases, necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of blood glucose level is recommended during concomitant therapy.
Methotrexate. Diclofenac can inhibit the tubular renal clearance of methotrexate hereby increasing methotrexate levels. Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before treatment with methotrexate, since blood concentrations of methotrexate may rise and its toxicity may increase. Cases of serious toxicity have been reported when methotrexate and NSAIDs including diclofenac were given within the interval of 24 hours. This interaction is mediated through accumulation of methotrexate resulting from impairment of renal excretion in the presence of NSAID.
Cyclosporine. The effect of diclofenac, like other NSAIDs, on renal prostaglandin synthesis may increase the nephrotoxicity of cyclosporine; therefore, diclofenac should be given at lower doses than those intended for patients not receiving cyclosporine.
Tacrolimus. Increased risk of nephrotoxicity is possible when NSAIDs are given with tacrolimus. This might be mediated through renal antiprostagladin effects of NSAIDs and calcineurin inhibitors.
Antibacterial quinolones: There are individual data evidencing development of convulsions in patients taking quinolone derivatves and NSAIDs concomitantly. This may be observed in patients

with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of quinolones in patients who are already receiving an NSAID.
Phenytoin. When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.
Colestipol and cholestyramine. These agents can induce a delay or decrease in absorption of diclofenac. Therefore, it is recommended to administer diclofenac at least one hour before or 4 to 6 hours after administration of colestipol/cholestyramine.
Cardiac glycosides. Concomitant use of cardiac glycosides and NSAIDs in patients may exacerbate cardiac failure, reduce glomerular filtration rate (GFR) and increase plasma glycoside levels.
Mifepristone. NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.
Potent CYP2C9 inhibitors. Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism.

Pharmacological properties.
Pharmacodynamics.
Lekfenac® contains diclofenac sodium – a substance of nonsteroidal structure exerting pronounced analgesic and anti-inflammatory action. It is an inhibitor of prostaglandin synthetase (cyclooxygenase).
Pharmacokinetics.
Absorption. The drug product plasma concentration shows linear dependence on the dose value. Pharmacokinetic behavior does not change after repeated administration of the drug product. Accumulation does not occur.
Distribution. Diclofenac serum protein binding is 99.7%, mainly to albumin – 99.4%.
Diclofenac enters the synovial fluid, where its maximum concentrations are achieved 2-4 hours later than in blood plasma. The apparent half-life for elimination from the synovial fluid is 3-6 hours. Two hours after reaching the peak plasma values, concentrations of the active substance are already higher in the synovial fluid than they are in the plasma; this phenomenon is observed for 12 hours.
Metabolism. Diclofenac is metabolized partially via glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites, most of which form conjugates with glucuronic acid. Two of these phenolic metabolites are biologically active, but to a much lesser extent than diclofenac.
Elimination. The total systemic clearance of diclofenac in plasma is 263±56 ml/min. The terminal half-life in plasma is 1-2 hours. Plasma half-life of four metabolites, including the two pharmacologically active ones, is also quite short and comprises 1-3 hours. About 60% of the administered dose is excreted in urine in the form of the glucuronide conjugate of the intact molecule and as metabolites, most of which are also converted to glucuronide conjugates. Less than 1% of diclofenac is excreted in unaltered form. The rest of the dose is eliminated as metabolites in the feces.
Pharmacokinetics in individual patient groups. No effect of the patient age on absorption, metabolism, or excretion of the drug has been observed.
In patients suffering from renal impairment receiving therapeutic drug doses, no accumulation of the unchanged active substance can be expected based on the single-dose kinetics. In patients with creatinine clearance of less than 10 ml/min, the calculated steady-state plasma levels of the hydroxy metabolites were about 4 times higher than in healthy volunteers. However, all the metabolites were ultimately cleared through the bile.
Patients with hepatic disease. In patients with chronic hepatitis or compensated liver cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver diseases.

Pharmaceutical particulars.
Main physicochemical properties: white or white with yellowish or creamy tint, bullet-shaped suppositories. Presence of white deposit on suppository surface is permitted.

Shelf life. 2 years.

Storage. Store at temperature not exceeding 25 °C. Keep away from children.

Package. 5 suppositories in a blister; 2 blisters in a pack.

Prescription status. By prescription.

Manufacturer. Joint Stock Company «Lekhim-Kharkiv».

Manufacturer's location and place of business.
Ukraine, 61115, Kharkiv region, Kharkiv, Severyna Pototskoho street, building 36.

Date of last revision.