INSTRUCTION
for medical use of medicinal product
LEKTALGIN®

Composition:
active ingredient: ketorolac tromethamine;
1 mL of solution contains 30 mg ketorolac tromethamine in recalculation on 100% dry substance;
excipients: sodium chloride, propylene glycol, disodium edetate, chlorobutanol hemihydrate, tromethamine, water for injection.

Pharmaceutical form. Solution for injections.
Basic physical and chemical properties: clear yellowish liquid.

Pharmacotherapeutic group. Anti-inflammatory and anti-rheumatic products, non-steroids. Acetic acid derivatives and related substances. ATC Code M01A B15.

Pharmacological properties.
Pharmacodynamics.
Ketorolac is a non-steroidal anti-inflammatory drug (NSAID), cyclooxygenase (COX) inhibitor, pyrrolizine carboxylic acid derivative that exhibits a pronounced analgesic action. Due to the properties of this dosage form its analgesic effect last for 10-12 hours. It can relieve or reduce mild and moderate pain.
This drug, like other NSAIDs, has antipyretic and anti-inflammatory effect. It can inhibit platelet aggregation.
Pharmacokinetics.
After intramuscular administration ketorolac gradually enters the systemic circulation from its depot at the injection site.
A peak plasma concentration (C_{max} = 3 mg/L) is reached within 40-50 min (T_{max}). Plasma protein binding is more than 99%. Up to 10% of the administered dose is metabolized in the liver, and the remainder via kidneys. The drug is predominantly excreted in the urine (up to 90%) with 60% of the administered dose as unchanged. Up to 10% of a given dose is excreted in the faeces. Half-life ($T_{1/2}$) is between 4 and 6 hours. In renally impaired patients and in elderly there is a reduction in clearance and an increase in the terminal half-life of ketorolac tromethamine. Ketorolac crosses the placenta and is excreted in human milk.

Clinical particulars.
Indications.
Short-term management of moderate to severe acute post-operative pain.
Contraindications.
Hypersensitivity to ketorolac or any of the inactive ingredients or other NSAIDs.
Active peptic ulcer, any recent history of gastrointestinal bleeding, ulceration or perforation or history of gastrointestinal bleeding.
Active or a history of gastrointestinal bleeding or cerebrovascular bleeding. High haemorrhagic risk or incomplete haemostasis, bleeding diathesis.
Severe renal impairment (serum creatinine >160 μmol/L).
The risk of renal failure due to dehydration.
Coagulation disorders.
Patients on antiplatelet drugs (acetylsalicylic acid), anti-coagulants including warfarin and low dose heparin (2500-5000 units twelve hourly).
Severe heart failure, hepatic failure.
Patients with allergic reactions such as asthma, rhinitis, angioedema or urticaria to other prostaglandin synthesis inhibitors.
History of bronchial asthma, bronchospasm, nasal polyps, angioedema.
The drug is contraindicated in labour.

Concurrent treatment with other NSAIDs including selective cyclooxygenase inhibitors, acetylsalicylic acid, warfarin, pentoxifylline, probenecid or lithium salts.
Hypersensitivity to acetylsalicylic acid or other prostaglandin synthesis inhibitors (severe anaphylactic-like reactions have been observed in such patients).
Ketorolac is contraindicated as analgesia before surgery and intra-operatively.
Ketorolac is contraindicated for epidural or intrathecal administration.

Interactions with other medicinal products and other forms of interaction
Ketorolac is highly bound (mean 99.2%) to plasma proteins. Ketorolac tromethamine does not alter the pharmacokinetics of other drugs due to enzyme induction or inhibition mechanisms.
Warfarin, digoxin, salicylates and heparin. In vitro binding of warfarin to plasma proteins is significantly reduced by Ketorolac tromethamine. Ketorolac does not alter *in vitro* digoxin protein binding. *In vitro* studies indicate that, at therapeutic concentrations of salicylates (300 µg/mL), the binding of Ketorolac was reduced from approximately 99.2% to 97.5%, representing a potential twofold increase in unbound Ketorolac plasma levels. Therapeutic concentrations of *digoxin, warfarin, ibuprofen, naproxen, piroxicam, acetaminophen, phenytoin and tolbutamide* did not alter Ketorolac tromethamine protein binding.
Acetylsalicylic acid. When Ketorolac tromethamine is administered with acetylsalicylic acid, its protein binding is reduced, although the clearance of free Ketorolac tromethamine is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of Ketorolac tromethamine and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects.
Probenecid. Concomitant administration of Ketorolac tromethamine tablets and probenecid is contraindicated.
Nondepolarizing muscle relaxants. The concurrent use of Ketorolac tromethamine with muscle relaxants has not been formally studied.
Zidovudine. Concomitant use of NSAIDs with zidovudine increase the risk of haematological toxicity. There is evidence of an increased risk of haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.
Concomitant use with *anticoagulants* may increase bleeding. Concomitant use with *anticoagulants* (warfarin) is contraindicated.
Additive adverse effects may develop in concomitant use with other NSAIDs.
Diuretics – Ketorolac tromethamine can reduce the diuretic effect resulting in increased nephrotoxicity of Ketorolac.
β-blockers, ACE inhibitors – antihypertensive action of β-blockers can be reduced by Ketorolac, resulting in possible development of renal impairment.
Ciclosporins – the increased risk of nephrotoxicity.
Corticosteroids – caution should be taken when co-administering with corticosteroids because of the increased risk of gastrointestinal bleeding.
Quinolones – increased risk of convulsions.
Mifepristone – Ketorolac should not be used for eight to twelve days after mifepristone administration as it can reduce the effects of mifepristone.
Oxpentifylline – When ketorolac is administered concurrently with oxpentifylline, there is an increased tendency to bleeding.
Lithium - inhibition of renal lithium clearance.
Opioid analgetics – Ketorolac increases the opiod analgesic effect reducing the dosage of concomitant opioid analgetics.
Cardiac glycosides – Concomitant use of cardiac glycosides and NSAIDs in patients may exacerbate cardiac failure, reduce glomerular filtration rate and increase plasma glycoside levels.
Methotrexate – Caution is advised when methotrexate is administered concurrently.
Antiepileptic drugs – Sporadic cases of seizures have been reported during concomitant use of Ketorolac tromethamine and antiepileptic drugs (phenytoin, carbamazepine).
Psychoactive drugs – Hallucinations have been reported when Ketorolac tromethamine was used in patients taking psychoactive drugs (fluoxetine, thiothixene, alprazolam).
Pentoxifylline – increased tendency to bleeding.
Drugs containing garlic, onion, ginkgo biloba may potentiate the effect of Ketorolac and

increase the risk of haemorrhagic complications.

Special warnings and precautions for use.
For hospital use.
Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms.
The combined duration of intramuscularly and orally dosed Ketorolac tromethamine in adults shall not exceed 5 days.
Physicians should be aware that in some patients pain relief might not occur until 30 minutes after IM administration.
Patients with heart failure, impaired renal or hepatic function, postoperative hypovolemia, those taking diuretics should be closely monitored for diuresis and renal function.
Fertility.
Ketorolac tromethamine should be withdrawn in women attempting to conceive and who are undergoing investigation for infertility.
Gastrointestinal effects.
Ketorolac tromethamine can cause severe gastrointestinal adverse reactions. These events can occur at any time during use and without warning symptoms. These adverse reactions can be fatal. The risk of clinically serious gastrointestinal bleeding is dose dependent. However, even short-term therapy is not without risk. In addition to past history of ulcer disease, other factors that increase the risk for adverse reactions include concomitant use of oral corticosteroids, or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population. If any effects are suspected, Ketorolac should be discontinued. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.
NSAIDs should be given with care to patients with a history of inflammatory bowel disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated.
Haematological effects.
Patients on anti-coagulation therapy may be at increased risk of bleeding if given ketorolac tromethamine concurrently. The concomitant use of ketorolac and prophylactic low-dose heparin (2500-5000 units twelve hourly) has not been studied extensively and may also be associated with an increased risk of bleeding. Patients already on anti-coagulants or who require low-dose heparin should not receive ketorolac tromethamine. Patients who are receiving other drug therapy that interferes with haemostasis should be carefully observed if ketorolac tromethamine is administered. Ketorolac inhibits platelet aggregation and prolongs bleeding time. Unlike the prolonged effects from acetylsalicylic acid, platelet function returns to normal within 24 to 48 hours after ketorolac is discontinued. Ketorolac tromethamine should not be used in patients who have had operations with a high risk of haemorrhage or incomplete haemostasis. Ketorolac tromethamine possesses no sedative or anxiolytic properties.
Renal impairment.
As with other NSAIDs, ketorolac should be used with caution in patients with impaired renal function or a history of kidney disease because it is an inhibitor of prostaglandin synthesis. Patients at greatest risk of this reaction are those with impaired renal function, hypovolaemia, heart failure, liver dysfunction, those taking diuretics and the elderly.
Patients with lesser renal impairment should receive a reduced dose of ketorolac (not exceeding 60 mg/day IM) and their renal status should be closely monitored. Patients should be well hydrated before treatment. In patients on renal dialysis, ketorolac clearance was reduced to approximately half the normal rate and terminal half-life increased approximately three-fold.
Cardiovascular and cerebral effects.
Appropriate monitoring is required for patients with a history of hypertension and/or mild to moderate congestive heart failure.
To minimize the potential risk for adverse cardiovascular events in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease should only be treated with Ketorolac tromethamine after

careful risk-benefit assessment. This assessment should be performed before long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).
Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for ketorolac.
Hepatic impairment.
Ketorolac tromethamine should be administered with caution to patients with liver dysfunction or a history of hepatic diseases. Meaningful elevations (greater than three times normal) of serum ALT and AST occurred in controlled clinical trials in less than 1% of patients.
In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations (e.g., eosinophilia, rash) occur, ketorolac should be discontinued.
Respiratory effects.
Patients should be monitored due to the high risk of bronchospasm.
In patients with systemic lupus erythematosus and mixed connective tissue disorders there may be an increased risk of aseptic meningitis.
Serious skin reactions including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported. Patients appear to be at the highest risk of these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. Ketorolac tromethamine should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

Use during pregnancy and in nursing women.
In view of the known effects of NSAIDs on the foetal cardiovascular system Ketorolac tromethamine is contraindicated during pregnancy, labour or delivery.
Ketorolac should not be used during lactation, because of its prostaglandin synthesis inhibiting effect.

Effects on ability to drive and use machines.
Patients may experience dizziness, drowsiness, visual disorder, headache, vertigo, insomnia or depression with the use of Ketorolac tromethamine. If patients experience these, or other similar undesirable effects, caution should be exercised in carrying out activities that require alertness.

Posology and method of administration.
For hospital use. The time to onset of analgesic effect following administration is approximately 30 minutes, maximum analgesia occurs within one to two hours. Analgesia normally lasts for eight to twelve hours. Dosage should be adjusted according to the severity of the pain and the patient response.
The administration of continuous multiple daily doses of ketorolac intramuscularly should not exceed two days because adverse events may increase with prolonged usage. There has been limited experience with dosing for longer periods since the vast majority of patients have transferred to oral medication or no longer require analgesic therapy after this time.
Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms. Ketorolac is contraindicated for epidural or intrathecal administration.
Adults.
The recommended initial dose of Ketorolac tromethamine solution for injections is 10 mg followed by 10 to 30 mg every four to six hours as required. In the initial post-operative period, Ketorolac tromethamine may be given as often as every two hours if needed. The lowest effective dose should be given. A total daily dose of 90 mg for non-elderly and 60 mg for the elderly, patients with renal impairment and patients less than 50 kg should not be exceeded. The maximum duration of treatment should not exceed two days. The dosage in patients under 50 kg should be reduced. Opioid analgesics (e.g. morphine, pethidine) may be used concomitantly.

Ketorolac does not interfere with opioid binding and does not exacerbate opioid-related respiratory depression or sedation. Patients receiving Lektalgin®, and who are converted to oral Lektalgin®, should receive a total combined daily dose not exceeding 90 mg (60 mg for the elderly, patients with renal impairment and patients less than 50 kg). The oral component should not exceed 40 mg on the day the change of formulation is made. Patients should be converted to oral treatment as soon as possible.
Elderly.
For patients over 65 years, the lower end of the dosage range is recommended and a total daily dose of 60 mg should not be exceeded.
Patients with renal impairment.
Ketorolac should not be used in moderate to severe renal impairment and a reduced dosage given in lesser impairment (not exceeding 60 mg/day IM).

Paediatric patients.
The product is contraindicated for children below 16 years.

Overdose.
Symptoms: lethargy, drowsiness, nausea, vomiting, and epigastric pain, gastrointestinal bleeding, hypertension, acute renal failure, respiratory depression and coma. Anaphylactoid reactions have been reported, and may occur following an overdose.
Treatment. Symptomatic and supportive care. There is no specific antidote. Emesis and/or activated charcoal (60 to 100 g in adults) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose (5 to 10 times the usual dose).
Forced diuresis, alkalization of urine, haemodialysis or haemoperfusion may not be useful due to high protein binding. Single overdoses of Ketorolac have been variously associated with abdominal pain, nausea, vomiting, hyperventilation, peptic ulcers and/or erosive gastritis and renal dysfunction which have resolved after discontinuation of dosing.

Undesirable effects.
Gastrointestinal disorders: anorexia, abdominal discomfort, fullness, nausea, dyspepsia, gastrointestinal pain, epigastric pain, diarrhoea, rarely – flatulence, eructation, vomiting, constipation, erosive and ulcerative changes, including gastrointestinal bleeding or perforation, sometimes lethal (especially in elderly), haematemesis, gastritis, peptic ulcer, pancreatitis, melena, rectal bleeding, ulcerative stomatitis, esophagitis, exacerbation of colitis and Crohn's disease.
Hepatobiliary disorders: very rare – liver disorder, hepatic failure, jaundice, hepatitis, hepatomegaly, transaminases increased.
Central and peripheral nervous system disorders: headache, dizziness, syncope, fatigue, weakness, irritability, dry mouth, thirst, hyperactivity (mood changes, restlessness), nervousness, confusion, paraesthesia, functional disorders, abnormal dreams, depression, drowsiness, sleep disturbances, insomnia, inability to concentrate, euphoria, hallucinations, agitation, hyperkinesia, convulsions, psychotic reactions, abnormal thinking, aseptic meningitis (with related symptoms), nuchal rigidity, anxiety, vertigo, disorientation, thought disorder.
Sensory organs: abnormal taste, blurred vision, optic neuritis, retrobulbar neuritis, tinnitus, hearing loss.
Musculoskeletal disorders: myalgia.
Urinary system disorders: severe referred renal pain, dysuria, increased urinary frequency, oliguria, hyponatremia, hyperkalaemia, haematuria, proteinuria, increased urea and serum creatinine, azotaemia, urinary retention, acute renal failure, renal failure, interstitial nephritis, papillary necrosis, nephrotic syndrome, haemolytic uremic syndrome, flank pain (with or without haematuria).
Cardiac and vascular disorders: pallor, flushing, chest pain, heartbeating, bradycardia, cardiac failure, hypertension, oedema, palpitations. Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or

stroke).
Blood and lymphatic system disorders: purpura, leukopenia, eosinophilia, thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia, haemolytic anaemia, resulting in possible ecchymosis, bruising, epistaxis, reduced blood clotting rates, prolonged bleeding time and increased postoperative bleeding wounds.
Respiratory disorders: shortness of breath, tachypnea or dyspnoea, chest tightness, wheezing, asthma, complications of asthma, pulmonary oedema.
Reproductive disorders: infertility.
Skin disorders: pruritus, urticaria, photosensitivity reactions, Lyell's syndrome, dermatitis bullous, dermatitis exfoliative, toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome, rash, including maculopapular and weeping, dyschroia.
Allergic reactions: anaphylaxis, anaphylactoid reactions, urticaria, respiratory reactivity, asthma, exacerbation of asthma, bronchospasm, laryngeal oedema, angioneurotic oedema, eyelid oedema, periorbital oedema, face swelling of face, legs, fingers, feet, tongue oedema, dyspnoea, hypotension, flushing, exfoliative dermatitis, bullous dermatosis. These may also occur in individuals with or without a history of hypersensitivity to ketorolac or other NSAIDs. These may also occur in individuals with a history of angioedema, bronchospastic reactivity. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome.
Body as a whole: asthenic syndrome, malaise, oedema, fever with or without chills, excessive sweating, increased body mass index; pain, swelling and hyperaemia at the injection site.

Shelf life. 2 years.

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

Incompatibilities.
Ketorolac injection should not be mixed in a small volume (e.g. in a syringe) with morphine sulfate, pethidine hydrochloride, promethazine hydrochloride or hydroxyzine hydrochloride, as precipitation of ketorolac will occur.

Nature and contents of container. 1 mL per ampoule; 10 or 100 ampoules in a carton, or 5 ampoules in a blister, 2 blisters in a carton.

Prescription status. By prescription.

Manufacturer. Joint Stock Company «Lekhim-Kharkiv».

Location of the manufacturer and address of carrying out its activities.
Ukraine, 61115, Kharkiv region, Kharkiv, Severyna Pototskoho street, building 36.

Date of the last revision.