Composition:

Each film coated tablet contains:

Active substance: Ketorolac tromethamine 10.00 mg.

Auxiliary substances: Microcrystallic cellulose 150.50mg, Maize starch (dry) 56.00mg, Magnesium stearate 1.00mg, Silicon colloidal dioxide 2.00mg.

Coating composition: Universal coating* 8.00mg.

*- composition of universal coating: Hypromellose, Titanium Dioxide, Polyethylene Glycol, Talc.

Description: Almost white, round, biconvex film coated tablets.

Pharmacotherapeutic group: Non steroidal anti-inflammatory drug (NSAID).

Pharmacodynamics

Ketorolac includes expressed analgetic effect, possesses also anti-inflammatory and moderate antipyretic effect.

Mechanism of effect is related to nonselective inhibition of activity of enzyme of cyclooxygenase 1 and 2, principally in peripheral tissues, as a result there appears biosynthesis of prostaglandins – modulators of pain sensitivity, thermoregulation and inflammation. Ketorolac represents itself a racemic mixture of [-]S and [+]R of enantiomers, in this regard anesthesia effect had caused [-]S form.

Preparation does not have effect on opioid receptors, does not oppress breathing, does not cause drug dependency, does not possess sedative and anaxiolytic effect.

Put together analgesic effect with morphine, it significantly exceeds to other NSAIDs.
After taking orally at the beginning of anesthesia effect it is marked accordingly, after 1 hour, the maximum effect is achieved in 2-3 hours.

**Pharmacokinetics**

When administered Ketorolac, it is well absorbed in the gastrointestinal tract – maximum concentration (Cmax) in blood plasma (0.7-1.1 µg / ml) is achieved in 40 minutes after taking 10 mg of dose on an empty stomach. A fat rich – diet reduces the maximum concentration of drug in blood and prevents its movement for 1 hour.

99 % medicine is related to the blood plasm proteins and an amount of free substance increases in blood with hypoalbuminemia.

Bioavailability 80 – 100%. Achievement period of equilibrium concentration (Css) is 24 hours at oral administration, when it is prescribed 4 times in a day (above subtherapeutic) and it is 10 mg – 0.39 – 0.79 µg / ml after an oral intake.

The divided volume is 0.15 – 0.33 l / kg. The divided volume of the medicine can be increased 2 twice in the patients with kidney failure, and its divided volume R-enantiomer – on 20 %.

It penetrates in breast milk: intake of 10 mg of ketorolac Cmax in milk by mother is achieved in 2 hours after the first dose and keeps 7.3 mg/ml, in 2 hours after intake of the second dose of ketorolac (using the medicine 4 times in a day) is 7.9 ng / ml.

More than 50 % administered dose is metabolized in the liver with the formation of pharmacologically inactive metabolites. Glucuronides are the principal metabolites, which are excreted by kidneys and r-hydroxyketrolac. There is excreted on 91 % by kidneys, 6 % - through intestine.

A period of halfexcretion (T \( \frac{1}{2} \)) with normal functions of kidneys in patients keeps in average 5.3 hours. T \( \frac{1}{2} \) increases in elderly patients and shortens in the young. The function of liver does not bring effect on T \( \frac{1}{2} \). It keeps 10.3 – 10.8 hours, with more sever kidney insufficiency – more than 13.6 hours in the patients with disorder of kidneys function at the
concentration of creatinine in the plasma of 19-50 mg/l (168-442 mkmole/l) T½.

It is not excreted by hemodialysis.

Indications

Pain syndrome of average and severe intensity of various origin: trauma, toothache, pain in the postpartum and postoperative period, oncological diseases, myalgia, arthralgia, neuralgia, radiculitis, sprains, strains, rheumatic diseases. Prescribed for symptomatic therapy, reducing pain and inflammation at the time of use, it does not affect on the progress of the diseases.

Contraindications

The increased sensitivity towards ketorolac or other non-steroidal anti-inflammatory drugs, “aspirin”asthma, bronchospasm, angioedema, hypovolemia (regardless of its reasons), dihydration.

Erosive-ulcerous affected of gastrointestinal tract at the acute stage, peptuic ulcer, hypocoagulation (including hymophilia).

Hepatic and/or kidney failure (creatinine plasms above 50 mg/l).

Hemorrhagic stroke (approved or suspicious), hemorrhagic diathesis, simultaneous intake with other NSAID, high risk of development or recurrence of hemorrhage (including after operations), disorder of bleeding.

Pregnancy, childbirth and period of lactation.

Child age up to 16 years (not established efficiency and safety).

Medicine is not taken for anesthesia before and during surgery because of high risk of bleeding, and also for the treatment of chronic pains.

Caution

Bronchial asthma, availability of factore increasing gastro-intestinal toxicity: alcoholism and tobacco smoking; cholecystitis, post-operation
period, chronic cardiac failure, inflammatory syndrome, arterial hypertension; disorder of kidney’s function, (creatinine of plasma below 50 mg/l); cholestasis, active hepatitis, sepsis; systemic lupus red, simultaneous intake with other non steroidal anti-inflammatory drugs, coronary heart disease, cerebrovascular disease, dislipidemia / hyperlipidemia, diabetes, peripheral artery diseases, chronic renal insufficiency (creatanine clearance is 30-60 ml/min), ulcerative defects of gastro-intestinal tract in history, the availability of infection H.pylori, long term use of non-steroidal anti-inflammatory drugs, severe somatic diseases, simultaneous intake of oral glucocorticosteroids (including citalopram, fluoksetin, paroksetine, sertraline), old age (above 65 years), pregnancy.

**Specific instructions**

Before using drug it is necessary to clarify the question of previous allergy to the drug or NSAID. The first dose regimen is given under the supervision of a physician because of the risk of development of allergic reactions.

Hypovolaemia increases the risk of development of nephrotoxic adverse reactions.

If necessary it may be prescribed in combination with narcotic analgesics.

Not recommended to administer as DRUGS for premedication, in support of anesthesia.

In combination with other NSAID there may be observed prevention of liquid, decompensation of cardiac activity, increase of AD. The effect of aggregation of blood platelet is prevented after 24 – 48 hours. Not to be used simultaneously with paracetamol more than 5 days.

Prescribe patients with clotting disorder only under constant control of blood platelet, especially it is important for the post operated patients, requiring careful control of hemostasis.
The risk of development of drug complications grows with the lengthening of treatment (in the patients with chronic pains) and increase of oral dose of the drug more than 40 mg/daily.

There are prescribed antacids DRUGS, mysoprostol, omeprazol for lowering the risk of NSAID development – gastropathy.

During treatment period it is necessary to follow precaution when driving vehicles and other hazardous works activity potentially, requiring high concentration and quickness of psychomotor reactions.

For lowering the risk of development of nondesirable phenomena from the GIT side it should be used the lowest effective dose of the lowest possible short-term course.

**Dosage**

Ketorolac is taken once inside or repeatedly depending upon the severity of pain.

The recommended dose is 20 mg to the patients from 16 years to 64, having body weight, exceeding 50 kg, at the first time, then 10 mg 4 times in a day, but not more than 40 mg / daily.

There is recommended dose of 10 mg at the first time and then 10 mg 4 times in a day to the adult patients, having body weight less than 50 kg or with kidney failure.

Maximum daily dose is 40 mg.

During intake the course of medicine should not be increased more than 5 days.

**Side effects**

Frequently – more than 3 %, not frequently – 1 – 3 %, rarely – less than 1 %.

*Digestive system:* frequently (especially in adult patients, older than 65 years, having erosive-ulcerous affectated of gastrointestinal tract) –
gastralgia, diarrhoea; less frequently - stomatitis, flatulence, constipation, vomiting, feeling of repletion; rarely – nausea, erosive-ulcerous affectd of gastrointestinal tract (including with perforation and / or bleeding – abdominal pain, spasm or burning senstation in the epigastric refion, melena, vomiting the type of “Coffee ground”, nausea, heartburn and others.), cholestatic jaundice, hepatitis, hepatomegaly, acute pancreatitis.

**Urine system:** rarely – acute kidney failure, pain in back with or without hematuria and / or azotemia, hemolytic uremic syndrome (hemolytic anemia, kidney failure, thrombocytopenia, purpura), frequently urination, increase or decrease of urine in volume, nephritis, edema of renal original.

**Organ feelings:** rarely: hearing loss, tinnitus, (including blurring of vision).

**Breathing syste:** rarely: bronchospasm or dysponia, rhinitis, larygenal edema (breathlessness, difficulty in breathing).

**CNS:** frequently – headache, dizziness, sleeplessness, rarely – aseptic meningitis (fever, sever headache, spasm, stiffness in the muscles of neck and/or back), heperactivity (mood of changes, anxiety), hallucination, depression, psychosis.

**Cardiac-vascular syste:** less frequently – increase of AD, rarely – pulmonary edema, swoon.

**Organs hematopoiesis:** rarely – anemia, eosinophilia, leucopenia.

**Haemostasis system:** rarely – bleeding from postoperative wound, nasal bleeding, rectal bleeding.

**Skin integuments:** less frequently – skin rash (including makulo popular rash), purpura, rarely - expholiative dermitet (fever with or without chills, redness, tightening or exfoliation of skin, swelling and/or sore tonsils), urticaria, Stevens-Johnson syndrome, lyell syndrome.

**Local reactions:** less frequently – burning or pain in local application.
**Allergic reactions:** rarely – hypersusceptibility or anaphylactoid reactions (the change of face colour skin, skin rash, urticaria, skin itching, tachypnea or dyspenia, eyelid edema, periorbital edema, breathlessness, trouble in breathing, severity in the breast cell, wheezing).

**Others:** frequently – edemas (faces, shins, ankles, fingers, steps, increasing body weight); less frequently – increased sweating, rarely – tongue edema, fever.

**Overdosage**

**Symptoms:** stomach pain, nausea, vomiting, erosive-ulcerous affected of GIT, disorder of kidney’s function, metabolic acidosis.

**Treatment:** conducting symptomatic therapy (maintain vital body functions). Dialysis – ineffective.

**Drug Interactions**

Simultaneous administration of ketorolac with acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs, calcium drugs, glucocorticosterioidal, ethanol, corticotropine may bring to the formation of gastrointestinal tract ulcers and development of gastro-intestinal bleedings.

Combined administration with paracetamol increases nephrotoxicity, with methotrexate – hepato – and nephrotoxicity. Combined administration of ketorolac and methotrexate are possible only during use of the low doses of the latter (to control methotrexate concentration in the blood plasma).

Probenitsid reduces plasma clearance and the divided volume of ketorolac, increases its concentration in the blood plasm and increases period of its semiejection.

On the background of ketorolac administration there may be lowering of methotrexate clearance and lithium and strengthening toxicity of these substances.
Simultaneous administration increases the risk of the origin of bleeding with indirect anticoagulants, heparin, thrombolytic, antiagreganty, cefoperazone, cefotetan and pentoxyfylline.

It reduces effect of hypotensive and diuretic medicines (prostaglandins synthesis is reduced in the kidneys).

In combination with opioid analgesics dose of the latter can be significantly reduced.

Antacids do not bring effect on the completeness of drug absorption.

There is increased hypoglycaemic effect of insuline and oral hypoglycaemic agents (required the recalculation of dose).

Combined administration with sodium valproate cases aggregation disorder of blood platelet. It increases concentration of verapamil and nifedipine in the blood plasm.

During administration with other nephrotoxicin drugs (including with gold drugs) there is increased the risk of development of nephrotoxicity. Drugs, blocking tubular secretion, reduce ketorolac clearance, and increase its concentration in the blood plasm.

**Packaging**

Blister pack of 10 tablets

**Storage conditions:**

Store in a dry place, protected from light, at a temperature not more than 25º C.

Keep in an inaccessible place for children.

**Shelf-life:**

3 years.

Do not use after expiry date indicated on the pack.
Disclaimer
(Packaging, Storage condition and Shelf life of a product is country specific, it may vary from country to country)