

PACKAGE LEAFLET
for medicinal use of medicinal product

DICLOFENAC-DARNITSA

Qualitative and quantitative composition:

active substance: diclofenac;

1 ml of solution contains diclofenac sodium 25 mg;

excipients: mannitol (E 421), sodium metabisulphite (E 223), benzyl alcohol, propylene glycol, sodium hydroxide, water for injections.

Pharmaceutical form. Solution for injection.

Basic physicochemical properties: clear colourless or slightly yellowish liquid with a slight specific odour.

Pharmacotherapeutic group

Nonsteroidal anti-inflammatory preparations. Derivatives of acetic acid and related compounds.
Code ATC M01A B05.

Pharmacological properties

Pharmacodynamic properties.

Diclofenac-Darnitsa contains diclofenac sodium, a non-steroidal compound with pronounced antirheumatic, anti-inflammatory, analgesic and antipyretic properties. Suppression of biosynthesis of prostaglandins, which play an important role in the occurrence of inflammation, pain and fever, is considered the main mechanism of the preparation action. In rheumatic diseases, the anti-inflammatory and analgesic properties of the preparation cause a clinical response characterized by the disappearance of signs and symptoms: rest and movement pains, morning stiffness and joints edema, and a marked improvement in the movement function.

Diclofenac has a pronounced analgesic effect on moderate and severe pains of non-rheumatic origin for 15-30 minutes. Diclofenac has also demonstrated a significant effect on migraine attacks.

In posttraumatic and postoperative conditions with inflammation, diclofenac quickly relieves spontaneous pains and pains during movements and reduces edema caused by inflammation and wounds.

When applying the preparation simultaneously with opioid analgesics for the removal of postoperative pain, diclofenac significantly reduces the need for them.

Diclofenac sodium, in vitro in concentrations equivalent to those that have been achieved in a human being, does not inhibit the synthesis of proteoglycans in the cartilaginous tissue. Diclofenac-Darnitsa, a solution for injections in ampoules, is especially necessary for the beginning of treatment of inflammatory and degenerative rheumatic diseases and pain syndrome due to inflammation of non-rheumatic origin.

Pharmacokinetic properties.

Absorption. When 75 mg of diclofenac is injected, the absorption begins immediately, and the mean maximum plasma concentrations, which are approximately 2.5 µg/ml (8 µmol/l), are achieved after 20 minutes. The volume of absorption can be linearly dependent on the dose value.

If 75 mg of diclofenac is to be introduced by infusion for 2 hours, the mean maximum plasma concentrations are about 1.9 µg/ml (5.9 µmol/l). A shorter infusion time leads to higher maximum plasma concentrations, while longer infusions result in concentrations that are proportional to the infusion rate after 3-4 hours. After an intramuscular injection or taking

gastro-resistant tablets or the use of suppositories, blood plasma concentrations decrease rapidly after reaching peak levels.

Bioavailability. The area under the concentration curve (AUC) after any intramuscular or intravenous introduction is approximately twice as large as after oral or rectal introduction, since approximately half of the active substance is metabolized during the first passage through the liver ("first pass" effect) in the case when the preparation is introduced orally or rectally.

Pharmacokinetic properties do not change after repeated introduction. When the recommended dosage intervals are met, accumulation of the preparation does not take place.

Distribution. 99.7 % of diclofenac binds to blood plasma proteins, mainly albumin (99.4 %). The estimated volume of distribution is 0.12 - 0.17 l/kg.

Diclofenac enters the synovial fluid, where maximum concentrations are established 2-4 hours after reaching a peak in the blood plasma. The estimated half-life of the synovial fluid is from 3 to 6 hours. Two hours after reaching the peak level in the blood plasma, diclofenac concentrations in the synovial fluid exceed this level in the blood plasma and remain high for 12 hours.

Diclofenac has been detected in a low concentration (100 ng/ml) in the breast milk of a woman who breastfed. The estimated amount of the preparation that enters the body of an infant with the breast milk is equivalent to 0.03 mg/kg per 24 hours.

Biotransformation. The metabolism of diclofenac takes place partly by glucuronization of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, which leads to the formation of several phenolic metabolites (3'-hydroxy-, 4'-hydroxy-, 5-hydroxy-, 4',5-dihydroxy-, and 3'-hydroxy-4'-methoxy-diclofenac), most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active, but their effect is much less than that of diclofenac.

Excretion. The total systemic clearance of diclofenac in the blood plasma is 263 ± 56 ml/min (mean value \pm SD). The terminal plasma half-life is 1-2 hours. Four metabolites, including two active metabolites, also have a short half-life from the plasma that is 1-3 hours. One metabolite, 3'-hydroxy-4'-methoxy-diclofenac, has a much longer half-life from the blood plasma. However, this metabolite is actually inactive.

Approximately 60 % of the introduced dose is excreted with the urine in the form of a glucuronide conjugate of an intact molecule and in the form of metabolites, most of which are also converted into glucuronide conjugates. Less than 1 % is excreted as an unchanged substance. Remains of the dose are eliminated in the form of metabolites through the bile and feces.

Special groups of patients

Elderly patients. There was no difference in age dependence in absorption, metabolism, or excretion of the preparation. However, in some elderly patients, a 15-minute intravenous infusion has resulted in the plasma concentration of 50 % higher than that observed in young healthy individuals.

Patients with impaired kidney function. In patients with impaired kidney function, if the usual dosage regimen is observed, one cannot wait for the accumulation of the active substance. In conditions of creatinine clearance less than 10 ml/min, the levels of hydroxy-metabolites in the blood plasma when reaching a steady state are approximately 4 times higher than in patients with normal kidney function.

Thus, the metabolites are finally excreted by the bile.

Patients with liver diseases. In patients with chronic hepatitis or compensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in healthy volunteers.

Clinical particulars.

Therapeutic indications.

The medicine for intramuscular introduction is intended for treatment of:

- inflammatory and degenerative forms of rheumatism, rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, spondyloarthritis, vertebral pain syndrome, non-rheumatic rheumatism;
- acute attacks of gout;
- kidney and biliary colic;
- pain and swelling after injuries and surgeries;
- severe migraine attacks.

The medicine for intravenous introduction is intended to treat or prevent a postoperative pain.

Contraindications

- Known hypersensitivity to the active ingredient, metabisulfite or any other components of the preparation.
- Like other non-steroidal anti-inflammatory preparations (NSAIDs), diclofenac is also contraindicated for patients, for whom the use of ibuprofen, acetylsalicylic acid or other non-steroidal anti-inflammatory preparations provokes an attack of bronchial asthma, angioedema, hives, or acute rhinitis, nasal polyps or allergy-like symptoms.
- Bleeding or perforation of the gastrointestinal tract in an anamnesis associated with previous treatment with NSAIDs.
- Active form of peptic ulcer/bleeding or recurrent peptic ulcer/bleeding history (two or more separate episodes of an established ulcer or bleeding).
- Inflammatory bowel disease (for example, Crohn's disease or ulcerative colitis).
- Liver failure.
- Kidney failure.
- Congestive heart failure (NYHA II-IV).
- Coronary heart disease in patients (stenocardia, a previous myocardial infarction).
- Cerebrovascular diseases in patients, who have had a stroke or who have episodes of transient ischemic attacks.
- Diseases of peripheral arteries.
- Treatment of perioperative pain in coronary artery bypass grafting (or use of an artificial circulation device).
- High risk of postoperative bleeding, blood coagulation, hemostasis disorders, hematopoietic disorders or cerebrovascular bleeding.
- III trimester of pregnancy.

In this dosage form, the preparation is contraindicated in children.

Intravenous infusions are contraindicated in:

- simultaneous use of NSAIDs or anticoagulant (including low doses of heparin);
- hemorrhagic diathesis in history or confirmed/suspected cerebrovascular hemorrhage;
- surgical interventions with a high risk of bleeding;
- bronchospasm and history of bronchial asthma;
- moderate or severe kidney failure (blood serum creatinine level > 160 mmol/l);
- hypovolemia or dehydration of various genesis.

Interaction with other medicinal products and other forms of interaction

The interactions observed with the use of diclofenac preparations in the form of an injection solution and/or other dosage forms are given below.

Lithium. With the simultaneous use of diclofenac, it may increase the concentration of lithium in the blood plasma. It is recommended to monitor the level of lithium in the blood serum.

Digoxin. With the simultaneous use of diclofenac, it may increase the concentration of digoxin in the blood plasma. It is recommended to monitor levels of digoxin in the blood serum.

Diuretics and antihypertensive agents. Like other NSAIDs, the concomitant use of diclofenac with diuretics or antihypertensive agents (for example, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors) can lead to a decrease in their antihypertensive effect through inhibition of the synthesis of vasodilating prostaglandins. Thus, such a combination should be

used with caution, and patients, especially the elderly, should be carefully monitored for blood pressure. Patients should receive proper hydration, monitoring of kidney function is recommended after the initiation of concomitant therapy and regularly thereafter, especially with regard to diuretics and ACE inhibitors because of the increased risk of nephrotoxicity.

Preparations that cause hyperkalemia. Concomitant treatment with potassium-sparing diuretics, cyclosporine, tacrolimus or trimethoprim may be associated with an increase in potassium levels in the blood serum, so patient monitoring should be performed more often.

Other NSAIDs and corticosteroids. Simultaneous administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the incidence of adverse reactions from the gastrointestinal tract. It should avoid the simultaneous use of two or more NSAIDs.

Anticoagulants and antithrombotic agents. It is recommended to take measures, as concomitant administration may increase the risk of bleeding. Although clinical studies do not indicate the effect of diclofenac on the activity of anticoagulants, there are separate data on the increased risk of bleeding in patients, who receive diclofenac and anticoagulants simultaneously. Therefore, careful monitoring of such patients is recommended. Like other NSAIDs, diclofenac in high doses can temporarily suppress platelet aggregation.

Selective serotonin reuptake inhibitors (SSRIs). Simultaneous administration of systemic NSAIDs and SSRIs may increase the risk of bleeding in the digestive tract.

Antidiabetic preparations. Clinical studies have shown that diclofenac can be used together with oral hypoglycemic agents without affecting their clinical effect. However, isolated cases of both hypoglycemic and hyperglycemic effects are known, requiring changes in the dosage of antidiabetic preparations in the treatment of diclofenac. Such conditions require monitoring of blood glucose levels, which is a precautionary measure with concomitant therapy.

Probenecid. Medicines containing probenecid may delay the excretion of diclofenac.

Cholestipol and cholestyramine. Simultaneous use of diclofenac and cholestipol or colestyramine reduces the absorption of diclofenac by approximately 30 % and 60 %, respectively.

Therefore, it is recommended that diclofenac be administered at least 1 hour before or 4-6 hours after colestipol/cholestyramine administration.

Preparations stimulating enzymes that metabolize medical products. Preparations stimulating enzymes, such as rifampicin, carbamazepine, phenytoin, Hypericum perforatum, are theoretically able to reduce diclofenac concentrations in the blood plasma.

Methotrexate. With the introduction of NSAIDs less than 24 hours before or after treatment with methotrexate, it is recommended to be careful, as the concentrations of methotrexate in the blood can be increased and the toxicity of this substance may be increased. Diclofenac can inhibit the clearance of methotrexate in the kidney tubules, which leads to an increase in the level of methotrexate. This interaction is mediated through the accumulation of methotrexate as a result of impaired kidney excretion in the presence of NSAIDs.

Cyclosporine and tacrolimus. Diclofenac, like other NSAIDs, can increase the nephrotoxicity of cyclosporine through an effect on kidney prostaglandins. This risk arises in the treatment of tacrolimus. In this regard, it should be used in lower doses.

Antibacterial quinolones.

Convulsions may occur in patients who have co-administered quinoline and NSAIDs, regardless of the presence or absence of epilepsy or a history of seizures. Therefore, caution should be exercised when considering the use of quinoline in patients already receiving NSAIDs.

Phenytoin. When using phenytoin simultaneously with diclofenac, it is recommended to monitor the concentration of phenytoin in the blood plasma in connection with the expected increase in phenytoin exposure.

Cardiac glycosides. Simultaneous use of cardiac glycosides and NSAIDs can increase heart failure, reduce the rate of glomerular filtration and increase the level of glycosides in the blood plasma.

Mifepristone. NSAIDs should not be used within 8-12 days after the administration of mifepristone, since NSAIDs may reduce its effect.

Inducers CYP2C9. Caution should be exercised when co-administering diclofenac with CYP2C9 inducers (eg rifampicin). This may lead to a significant decrease in plasma concentrations and exposure to diclofenac.

Special warnings and precautions for use

Side effects can be minimized by applying the minimum effective dose for the shortest possible period necessary to control the symptoms.

The use of the preparation with systemic NSAIDs, including selective cyclooxygenase-2 inhibitors, should be avoided, due to the lack of any synergistic benefits for additional side effects.

It is necessary to be cautious when prescribing the medication to elderly patients. In particular, the lowest effective doses are recommended for elderly patients with poor health and for patients with low body weight.

As with other NSAIDs, allergic reactions, including anaphylactic / anaphylactoid reactions, may also occur with diclofenac. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can cause a myocardial infarction. A symptom of this reaction may be chest pain, which occurs in combination with an allergic reaction to diclofenac.

Like other NSAIDs, diclofenac, due to its pharmacodynamic properties, can mask the signs and symptoms of infection.

Sodium metabisulfite in solution for injection can lead to separate severe hypersensitivity reactions and to bronchospasm.

Effect on the digestive system

With the use of all NSAIDs, including diclofenac, cases of gastrointestinal bleeding (vomiting with blood, melena), the formation of ulcers or perforations, which can be lethal and observed at any time during treatment with both preventive symptoms and without them, have been reported. These phenomena usually have more serious consequences in elderly patients. If patients taking diclofenac are experiencing gastrointestinal bleeding or ulceration, the preparation use should be discontinued.

With the use of all NSAIDs, including diclofenac, careful medical supervision is necessary; the particular caution should be exercised in appointing diclofenac to patients with symptoms indicative of gastrointestinal disturbances, or having a stomach or bowel ulcer, bleeding, and a history of perforation. The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing doses of NSAIDs, including diclofenac, as well as in patients with a history of ulcers, especially with complications such as bleeding or perforation.

Elderly patients have an increased incidence of adverse reactions with NSAIDs, especially such as gastrointestinal bleeding and perforation, which can be fatal.

To reduce the risk of toxic effects on the digestive system in patients with a history of ulcer, especially with complications of bleeding or perforation, and in elderly patients, treatment should be initiated and maintained at the lowest effective doses.

For such patients, as well as patients requiring the concomitant use of preparations containing low doses of acetylsalicylic acid (ASA) or other preparations that are likely to increase the risk of undesirable effects on the digestive system, combination therapy with protective medicinal products (for example, proton pump inhibitors or misoprostol) shall be taken.

Patients with a history of gastrointestinal toxicity, especially the elderly, should report any unusual abdominal symptoms (especially bleeding in the digestive tract). Cautions are also needed for patients receiving concomitant medications that may increase the risk of ulcers or bleeding, such as systemic corticosteroids, anticoagulants (for example, warfarin), antithrombotic agents (for example, acetylsalicylic acid) or selective serotonin reuptake inhibitors.

NSAIDs, including diclofenac, may be associated with an increased risk of anastomotic failure. Careful supervision of patients and caution when using after surgery on the organs of the gastrointestinal tract is recommended.

Effect on the liver

The careful medical supervision is necessary if diclofenac is prescribed to patients with affected liver function, as their condition may worsen.

As with other NSAIDs, the level of one or more liver enzymes may increase. During prolonged treatment with the preparation as a precautionary measure, regular supervision of liver functions should be prescribed.

If liver function disorders persist or worsen, if clinical signs or symptoms can be associated with progressive liver disease or if other manifestations (for example, eosinophilia, rash) are observed, the preparation use should be discontinued.

The course of diseases, such as hepatitis, can occur without prodromal symptoms.

Precautions are necessary if the preparation is used in patients with hepatic porphyria, because of the likelihood of provocation of an attack.

Effect on the kidneys

Since NSAIDs, including diclofenac, have been reported for fluid retention and edema, special attention should be paid to patients with cardiac or kidney dysfunction, history of arterial hypertension, elderly patients, patients receiving diuretic therapy or preparations that significantly affect kidney function, and patients with a significant reduction in the extracellular volume of the fluid for any reason, for example before or after a serious surgical procedure. In such cases, monitoring of kidney function is recommended as a precautionary measure. Discontinuation of therapy usually leads to a return to the condition that preceded the treatment.

Effect on the skin

In connection with the use of NSAIDs, including diclofenac, serious skin reactions (some of them can be lethal) were very rare, including exfoliative dermatitis, Stevens-Johnson's syndrome and toxic epidermal necrolysis. Obviously, a high risk of these reactions is observed at the beginning of the course of therapy, in most cases - during the first month of treatment. The use of diclofenac should be discontinued at the first appearance of skin rashes, lesions of the mucous membrane or any other signs of hypersensitivity.

Systemic lupus erythematosus (SLE) and mixed connective tissue diseases

Patients with SLE and mixed connective tissue diseases may have an increased risk of developing aseptic meningitis.

Cardiovascular and cerebrovascular effects

Prescribing diclofenac to patients with significant risk factors for cardiovascular events (for example, hypertension, hyperlipidemia, diabetes, smoking) can only be done after a thorough clinical evaluation. As the cardiovascular risks of diclofenac can grow with increasing dose and duration of treatment, it should be used as short period as possible and at the most effective dose. The patient's needs for diclofenac should be periodically reviewed to alleviate symptoms and respond to therapy. It should be used with caution in patients aged 65 years or over. For patients with a history of hypertension and/or congestive heart failure of mild or moderate severity, appropriate monitoring and counselling are necessary, since cases of fluid retention and edema have been reported in connection with NSAID administration, including diclofenac.

Clinical studies and epidemiological data suggest that diclofenac, especially in high doses (150 mg per 24 hours) for a long time, may be associated with a slight increase in the risk of developing arterial thrombotic events (for example, myocardial infarction or stroke). Patients with uncontrolled arterial hypertension, congestive heart failure, persistent coronary heart disease, peripheral arterial disease and/or cerebrovascular disease should not be prescribed diclofenac; if necessary, use is only possible after a thorough risk-benefit assessment in only a dosage not exceeding 100 mg per 24 hours. Such an assessment should be made before beginning long-term treatment of patients with risk factors for cardiovascular events (for example, hypertension, hyperlipidemia, diabetes and smoking).

Patients should be informed of the possibility of serious cases (chest pain, shortness of breath, weakness, speech impairment) that can happen at any time. In this case, you should immediately consult a doctor.

Effect on hematologic indices

With prolonged use of the preparation, as well as other NSAIDs, monitoring of the blood test is recommended.

Like other NSAIDs, diclofenac can temporarily suppress platelet aggregation. It should be carefully monitored for patients with hemostasis disorders, hemorrhagic diathesis or hematologic disorders.

Asthma in anamnesis

In patients with bronchial asthma, seasonal allergic rhinitis, patients with edema of the nasal mucosa (nasal polyps), chronic obstructive pulmonary diseases or chronic respiratory infections (especially those associated with allergic rhinitis-like symptoms), reactions to NSAIDs occur more often than others, that are similar to exacerbation of asthma (so-called analgesic intolerance/analgesic asthma), Quincke's edema or urticaria. In connection with this, such patients are recommended special measures (readiness for emergency care). This also applies to patients with allergies to other substances, which is manifested by skin reactions, itching or hives.

Like other preparations that inhibit prostaglandin synthetase activity, diclofenac sodium and other NSAIDs can provoke the development of bronchospasm in patients suffering from bronchial asthma, or in patients with a history of bronchial asthma.

Important information on excipients.

This medicine contains sodium metabisulphite (E 223), which may rarely cause hypersensitivity reactions or bronchospasm.

Fertility, pregnancy and lactation.

Pregnancy

In the first and second trimesters of pregnancy, the preparation Diclofenac-Darnitsa can be prescribed only if the expected benefit to the mother exceeds the potential risk to the fetus, only in the minimum effective dose. The duration of treatment should be as short as possible. Like other NSAIDs, the preparation is contraindicated in the last trimester of pregnancy (it is possible to observe some reducing the contractility of the uterus and premature closure of the arterial duct in the fetus).

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryo/fetus development. Data from epidemiological studies indicate an increased risk of miscarriages and/or a risk of developing heart defects and gastroschisis after using an inhibitor of prostaglandin synthesis in early pregnancy. The absolute risk of cardiovascular malformations has increased from less than 1% to approximately 1.5 %.

It is possible that the risk increases with increasing dose and duration of treatment. It has been shown that for animals the administration of a prostaglandin synthesis inhibitor leads to an increase in pre- and postimplantation losses and embryo/fetus mortality.

In addition, for animals that received a prostaglandin synthesis inhibitor in the period of organogenesis, an increased incidence of various developmental anomalies, including those from the cardiovascular system, was recorded. If Diclofenac-Darnitsa should be used by women who seek to become pregnant, or in the first trimester of pregnancy, the dose should be as low as possible, and the duration of treatment - as short as possible.

During the third trimester of pregnancy, all inhibitors of prostaglandin synthesis can affect the fetus in the following way:

- Cardiopulmonary toxicity (with premature closure of the arterial duct and pulmonary hypertension);
- Impaired kidney function, which can progress to kidney failure with oligohydroamnion.

Effect on the mother and new-born, and also at the end of pregnancy:

- Lengthening of bleeding time, antiplatelet effect, this can be observed even at very low doses;
- Inhibition of contractions of the uterus, which leads to a delay or lengthening of labor.

So, Diclofenac-Darnitsa is contraindicated in the third trimester of pregnancy.

The period of lactation. Like other non-steroidal anti-inflammatory preparations, diclofenac penetrates into breast milk in small amounts. Thus, to avoid undesirable effects on the baby, Diclofenac-Darnitsa should not be used during breast-feeding.

Fertility. Like other NSAIDs, Diclofenac-Darnitsa can affect the fertility of women. The preparation should not be used by women planning a pregnancy. Women, who have difficulty with fertilization or who have any undergone examination due to infertility, should stop using Diclofenac-Darnitsa.

Effects on ability to drive and use machines

Patients, who have visual impairment, dizziness, drowsiness, or other disturbances from the central nervous system during treatment with Diclofenac-Darnitsa, should refrain from driving motor vehicles and working with other mechanisms.

Posology and method of administration

The medicine should be used at the lowest recommended doses for the shortest period of time, considering the treatment objectives for each patient separately.

Do not use for more than 2 days. If necessary, the treatment can continue with Diclofenac-Darnitsa tablets.

Intramuscular injections

In order to prevent any damage to nerve or other tissues at the injection site, the following rules must be observed.

The dose is usually 75 mg (1 ampoule) per 24 hours, which should be injected by a deep injection into the upper outer sector of the gluteus maximus. In severe cases, the daily dose can be increased to 2 injections of 75 mg, between which an interval of several hours (1 injection per each buttock) should be maintained. As an alternative, 75 mg can be combined with other dosage forms of Diclofenac-Darnitsa (for example, tablets) to a total maximum daily dose of 150 mg.

In a migraine attack, clinical experience is limited to cases with the initial application of 1 ampoule of 75 mg, the dose should be administered immediately after application of diclofenac suppositories of 100 mg on the same day (if necessary). The total daily dose should not exceed 175 mg on the first day.

There is no available data on the use of the preparation for the treatment of migraine attacks for more than 1 day.

Intravenous infusions

Diclofenac-Darnitsa, a solution for injections, should not be administered as a bolus injection.

Immediately before the infusion of Diclofenac-Darnitsa, depending on the required duration, 1 ampoule of the preparation should be diluted in 100-500 ml of 0.9 % sodium chloride solution or 5 % glucose solution buffered with sodium bicarbonate solution for injection (0.5 ml of 8,4 % solution or 1 ml of 4.2% solution, or a corresponding volume of another concentration), which was taken from a freshly opened container. Only clear solutions should be used. If the solution has crystals or sediment, it cannot be used for infusions.

Two alternative dosage regimens of Diclofenac-Darnitsa, a solution for injections, are recommended.

- For treatment of a moderate and severe postoperative pain, 75 mg should be administered continuously from 30 minutes to 2 hours. If necessary, the treatment can be repeated after 4-6 hours, but the dose should not exceed 150 mg per 24 hours.
- For prophylaxis of a postoperative pain after 15 minutes - 1 hour after surgery, a loading dose of 25-50 mg should be introduced, after which a continuous infusion of approximately 5 mg/hour to a maximum daily dose of 150 mg should be applied.

Patients of advanced age

Although in elderly patients the pharmacokinetics of the preparation does not deteriorate to any clinically significant degree, NSAIDs should be used with caution in patients, who are generally more prone to developing unwanted reactions. In particular, attenuated elderly patients or patients with a low body mass index are recommended to use the lowest effective doses (see also the "Special warnings and precautions for use" section); also patients should be examined for gastrointestinal bleeding in the treatment of NSAIDs. The recommended maximum daily dose of Diclofenac-Darnitsa is 150 mg.

Each ampoule is for single use only. The solution should be used immediately after opening the ampoule. Any unused amount must be disposed of.

Children.

Diclofenac-Darnitsa in the given dosage form that is a solution for injections is contraindicated for children.

Overdose.

Symptoms. A typical clinical picture of diclofenac overdose effects is absent. The overdose can cause symptoms such as headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, diarrhea, dizziness, disorientation, agitation, coma, drowsiness, ringing in the ears, loss of consciousness or convulsions. In case of severe poisoning, acute kidney failure and liver damage are possible.

Treatment. Within 1 hour after applying a potentially toxic amount of the preparation inside, the possibility of using activated carbon should be considered. In addition, adults should consider the possibility of gastric lavage within 1 hour after using a potentially toxic amount of the preparation. With frequent or prolonged cramps, intravenous diazepam should be administered. Taking into account the clinical condition of the patient, other measures can be shown. Treatment is symptomatic.

Undesirable effects

Clinical studies and epidemiological data indicate an increased risk of thrombotic complications (for example, myocardial infarction or stroke) associated with diclofenac, in particular in high therapeutic doses (150 mg per 24 hours) and with prolonged use.

The following side effects include those ones associated with Diclofenac-Darnica injections and/or other dosage forms of diclofenac in short-term and long-term use.

Adverse reactions are listed by system organ class: very common ($\geq 1/10$), common ($\geq 1/100$, $<1/10$), uncommon ($\geq 1/1000$, $\leq 1/100$), rare ($\geq 1/10000$), $\leq 1/1000$), very rare ($\leq 1/10000$), frequency unknown (cannot be estimated from the available data).

Eye disorders: very rare: visual disturbances (blurred vision and diplopia); frequency unknown: optic neuritis. Such visual disturbances are effects of the NSAID class and, as a rule, they are reversible after drug withdrawal. The most likely mechanism of visual impairment is inhibition of the synthesis of prostaglandins and other related compounds, which, by disrupting the regulation of retinal blood flow, contribute to the development of visual disturbances. If such symptoms occur during treatment with diclofenac, an ophthalmologic examination should be performed to rule out other possible causes.

Ear and labyrinth disorders: common: vertigo;
very rare: ringing in the ears, hearing impairment.

Respiratory, thoracic and mediastinal disorders:
rare: asthma (including dyspnea), bronchospasm;
very rare: pneumonitis.

Gastrointestinal disorders:

common: nausea, vomiting, diarrhea, dyspepsia, abdominal pain, flatulence, loss of appetite, anorexia;

rare: gastritis, gastrointestinal bleeding, vomiting with blood impurities, hemorrhagic diarrhea, melena, gastric or intestinal ulcer with or without bleeding, gastrointestinal stenosis with perforation (sometimes fatal, especially in elderly patients), which can lead to peritonitis;

very rare: colitis (including hemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, including ulcerative stomatitis, glossitis, swallowing disorder, membrane strictures of the small intestine, pancreatitis.

Hepatobiliary disorders:

common: increased levels of transaminases; uncommon: liver dysfunction, especially with long-term therapy, hepatitis with or without jaundice (in rare cases, instant hepatitis is possible, even without previous symptoms);

very rare: instant hepatitis, hepatonecrosis, liver failure.

Renal and urinary disorders:

common: edema, especially in patients with hypertension or renal failure;

very rare: acute renal failure, hematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis.

Nervous system disorders:

common: headache, dizziness, drowsiness;

rare: fatigue; very rare: paresthesia, taste disturbance, memory impairment, convulsions, anxiety, tremor, aseptic meningitis *, stroke;

frequency unknown: sensitivity disorder, sensory disturbance.

Psychiatric disorders:

very rare: disorientation, depression, insomnia, night terrors, irritability, mental disorders, confusion, hallucinations.

Cardiac disorders:

very rare: palpitations, chest pain, heart failure, myocardial infarction, hypertension, hypotension, vasculitis;

frequency unknown: Kounis syndrome.

Blood and lymphatic system disorders:

very rare: thrombocytopenia, leukopenia, anemia (including hemolytic and aplastic anemia), agranulocytosis.

Immune system disorders:

common: hypersensitivity reactions such as skin rash and itching;

uncommon: urticaria;

rare: anaphylactic and pseudoanaphylactic reactions (including hypotension and shock)

very rare: angioneurotic edema (including facial edema), allergic vasculitis;

Skin and subcutaneous tissue disorders:

common: rash;

uncommon: hair loss;

rare: urticaria;

very rare: exanthema, eczema, erythema, erythema multiforme, photosensitivity reactions, purpura (including Shenlein-Genoch allergic purpura), bullous rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis (exorbital dermatitis, Laelli syndrome).

Reproductive system disorders:

very rare: impotence.

General disorders and administration site conditions:

common: injection site reactions, pain and / or hardening at the injection site, general malaise;

rare: swelling, necrosis at the injection site;

very rare: abscess at the injection site.

* Cases of exacerbation of inflammatory processes of infectious origin (eg, development of necrotic fasciitis) associated with systemic NSAIDs have been reported very rarely. This may be due to the mechanism of action of NSAIDs. Symptoms of aseptic meningitis, such as neck stiffness, headache, nausea, vomiting, fever, or dizziness, have been reported very rarely with diclofenac. Patients with autoimmune diseases (systemic lupus erythematosus, mixed connective tissue disease) are prone to such conditions.

Reported suspected adverse reactions.

Reporting suspected adverse reactions after registration of a medicinal product is an important procedure. This allows for continued monitoring of the benefit/risk ratio for the respective drug. Healthcare providers should be informed of any suspected adverse reactions through the national alert system.

Shelf life. 3 years.

Special precautions for storage.

Store in the original package at temperature not above 25°C. Do not freeze.

Keep out of reach of children.

Incompatibilities

Diclofenac-Darnitsa, solution for injections, cannot be mixed with other solutions for injections in the same tank.

Solutions for injections of sodium chloride 0.9 % or glucose 5 % without sodium bicarbonate as an additive have a risk of oversaturation, which can lead to the formation of crystals or sediment.

Other solutions for injections should not be used.

Nature and contents of container.

3 ml in an ampoule; 10 ampoules in a box; 5 ampoules in a blister, 1 or 2 blisters in a pack.

Category of release.

Prescription only medicine.

Manufacturer.

PrJSC "Pharmaceutical firm "Darnitsa"

The manufacturer's location and address of the place of business.

13, Boryspilska Street, Kyiv, 02093, Ukraine.

Date of the last revision.

17.08.2020