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INSTRUCTION
for medical use

DICLOSAFE®

Composition:
active substance: diclofenac;
1 suppository contains 50 mg of diclofenac sodium;
excipients: hard fat.

Pharmaceutical form. Suppositories.
Basic physical and chemical properties: White to light yellow colour torpedo shaped suppositories.

Pharmacotherapeutic group. Nonsteroidal anti-inflammatory and antirheumatic drugs.
Code ATC M01A B05.

Pharmacological properties.
Pharmacodynamics.
Diclofenac sodium is a non-steroidal anti-inflammatory agent that has a pronounced analgesic and anti-inflammatory effect. It is an inhibitor of prostaglandin-synthetase (cyclooxygenase).
Pharmacokinetics.
Absorption.
Absorption is rapid but slower than when using enteric-coated tablets.
After administration of suppositories of diclofenac sodium in a dose of 50 mg, the maximum plasma concentration (C_{max}) is achieved approximately in an hour, but the maximum concentration per unit of dosage is about $^2/_3$ of the concentration achieved after the use of intestinal-coated tablets (1.95 ± 0.8 μg/ml (1.9 μg/ml = 5, 9 μmol/L)).
Bioavailability.
As with oral formulations, the area under the pharmacokinetic concentration-time curve (AUC) is approximately half that obtained with the parenteral dose. After multiple use of the drug its pharmacokinetics does not change. The accumulation of the drug is not observed in case of keeping the recommended dosage.
Distribution.
The binding of diclofenac to serum proteins is 99.7%, mainly with albumin – 99.4%.

Diclofenac penetrates into synovial fluid, where its C_{max} is achieved 2–4 hours later than in plasma. The apparent half-life of synovial fluid is 3–6 hours. 2 hours after reaching C_{max} in blood plasma, the concentration of diclofenac in the synovial fluid remains higher than in the blood plasma; this phenomenon is observed for 12 hours.
Diclofenac was detected in a low concentration (100 ng/ml) in breast milk in one patient. The expected amount of the drug that penetrates into the infant's body with breast milk that is equivalent to a dose of 0.03 mg/kg/day.
Metabolism.
Diclofenac is metabolised partly by glucuronization of the unmodified molecule, but mainly through one-off and repeated hydroxylation and methoxylation, which results in the formation of several phenolic metabolites, most of which forms conjugates with glucuronic acid. Two of these phenolic metabolites are biologically active, but much less than diclofenac.
Elimination.
The total systemic clearance of diclofenac from blood plasma is 263 ± 56 ml/min (average + CI). The terminal half-life in blood plasma is 1–2 hours. The half-life in plasma of blood of four metabolites, including two pharmacologically active ones, is also short and it is 1–3 hours. About 60% of the administered dose is excreted in the urine as a glucuronide conjugate of the intact molecule and in the form of metabolites, most of which are also converted to glucuronide conjugates. Less than 1% of diclofenac is excreted unchanged. The remainder of the administered dose of the drug is excreted in the form of metabolites with feces.
Pharmacokinetics in some populations.
Elderly patients.
The effect of age on the absorption, metabolism, and elimination of the drug was not observed except that fact that in five elderly patients, a 15-minute intravenous infusion resulted in a higher concentration of 50% of the drug in plasma than it was expected in young healthy volunteers.
Patients with impaired renal function.
In patients with impaired renal function, who received therapeutic doses of the drug, accumulation of the unchanged active substance can not be expected, given the kinetics of the drug after a single use. In patients with creatinine clearance less than 10 ml/min, the calculated equilibrium concentrations of hydroxylated metabolites in blood plasma were approximately 4 times higher than in healthy volunteers. However, eventually all metabolites were excreted with bile.
Patients with impaired liver function.
In patients with chronic hepatitis or compensated cirrhosis of the liver, the pharmacokinetics, metabolism of diclofenac is similar in patients without liver disease.

Clinical characteristics.
Indication.
- Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, including spondylarthritis.
- Pain syndromes in spine.
- Rheumatic diseases of extra-articular soft tissues.
- Post-traumatic and post-operative pain syndromes, accompanied by inflammation and edema, in particular after dental and orthopedic surgery.
- Gynecological diseases accompanied by pain syndrome and inflammation, such as primary dysmenorrhea and adnexitis.
- Migraine attacks.
- Acute gout attacks.
- As an adjunct to severe inflammatory diseases of the ENT organs accompanied by painful sensations, for example, with pharyngotonchitis, otitis.

In accordance with the general therapeutic principles, the underlying disease should be treated with basic therapy. Fever itself is not an indication for the use of the drug.

Contraindication.

- Hypersensitivity to the active substance or to any drug excipient.
- Bleeding or perforation of the gastrointestinal tract in the medical history, associated with previous treatment with non-steroidal anti-inflammatory drugs (NSAIDs).
- Active form of peptic ulcer/bleeding or recurrent stomach ulcer/bleeding in history (two or more episodes of an established ulcer or bleeding).
- The III trimester of pregnancy.
- Inflammatory bowel disease (for example, Crohn's disease or ulcerative colitis).
- Hepatic failure.
- Renal failure (glomerular filtration rate (GFR) <15 ml/min/1.73 m^2).
- Congestive heart failure (NYXA II-IV).
- Ischemic heart disease in patients with angina pectoris, myocardial infarction.
- Treatment of perioperative pain in coronary artery bypass grafting (or using cardiac pump).
- Cerebrovascular diseases in patients who have had a stroke or have episodes of transient ischemic attacks.
- Diseases of the peripheral arteries.
- Proctitis.
- Sodium diclofenac, like other NSAIDs, is contraindicated in patients who have asthma attacks, urticaria, angioneurotic edema, acute rhinitis or nasal polyps in response to acetylsalicylic acid or other NSAIDs.

Interaction with other drugs and other types of interactions.

The mentioned below interactions include those that have been observed in the use of diclofenac in the form of enteric tablets and/or other dosage forms.

Lithium. In combination with diclofenac, it can increase lithium plasma concentrations. Monitoring of serum lithium levels is recommended.

Digoxin. In combination with diclofenac, it may increase digoxin concentrations in plasma. Monitoring of serum levels of digoxin is recommended.

Diuretic and antihypertensive drugs. As with other NSAIDs, the concomitant use of diclofenac with diuretics and antihypertensive agents (e.g. β-blockers, angiotensin-converting enzyme inhibitors (ACEs)) may decrease their antihypertising effect by inhibiting the synthesis of vasodilating prostaglandins. Therefore, such a combination should be used with caution, and patients, especially the elderly aged, should be closely monitored for blood pressure. Patients should receive adequate hydration, monitoring of renal function after initiation of concomitant therapy and on a regular basis after it is recommended, especially with regard to diuretics and ACE inhibitors, due to increased risk of nephrotoxicity.

Drugs known to cause hyperkalemia.

Concomitant treatment with potassium-sparing diuretics, cyclosporine, tacrolimus or trimethoprim may be associated with an increase in serum potassium levels, therefore patients should be monitored more frequently.

Anticoagulants and antiplatelet drugs. Concomitant use may increase the risk of bleeding, so it is advisable to take precautionary measures. Although clinical studies do not indicate the effect of diclofenac on the activity of anticoagulants, there are separate data about the increased risk of bleeding in patients taking diclofenac and anticoagulants at the same time. Therefore, in order to be sure that anticoagulant dosage changes are not required, careful monitoring of such patients is

recommended. Like other non-steroidal anti-inflammatory drugs, diclofenac in high doses may temporarily suppress platelet aggregation.

Other NSAIDs, including selective cyclooxygenase-2 inhibitors and corticosteroids.

Concomitant use of diclofenac and other NSAIDs or corticosteroids may increase the risk of gastrointestinal bleeding or ulceration. Concomitant use of two or more NSAIDs should be avoided.

Selective serotonin reuptake inhibitors (SSRI). Concomitant use of NSAIDs and SSRIs may increase the risk of gastrointestinal bleeding.

Antidiabetic drugs. Clinical studies have shown that diclofenac can be used concomitantly with oral antidiabetics and does not alter their therapeutic effect. However, there are some reports of development in such cases of hypoglycemia and hyperglycemia, which led to the need to change the dose of antidiabetic agents when using diclofenac. Therefore, it is recommended to monitor blood glucose levels during combined therapy.

There are also separate reports of metabolic acidosis at concomitant use with diclofenac, especially in patients with already existing renal dysfunction.

Methotrexate. Diclofenac may suppress the clearance of methotrexate in the renal tubule, which leads to increasing methotrexate levels. Caution should be exercised when administering NSAIDs, including diclofenac, less than 24 hours prior to the use of methotrexate, since in such cases the concentration of methotrexate in the blood may increase and its toxic effect may be increased. Significant cases of serious toxicity were reported when the interval between taking methotrexate and NSAIDs, including diclofenac, was within 24 hours. This interaction is mediated by accumulation of methotrexate as a result of renal excretion in the use of NSAIDs.

Cyclosporine. The effect of diclofenac, like of other NSAIDs, on the synthesis of prostaglandins in kidneys may increase the nephrotoxicity of cyclosporine; in this respect, diclofenac should be used at lower doses than in patients who do not take cyclosporine.

Tacrolimus. When using NSAIDs with tacrolimus, there might be increased risk of nephrotoxicity, which may be mediated through renal antiprostaglandine effects of NSAIDs and calcineurin inhibitors. Therefore, diclofenac should be used in such patients at lower doses than in patients not receiving tacrolimus.

Antibacterial quinolones. There are separate data on the development of seizures in patients who concomitantly take derivatives of quinolone and NSAIDs. This can occur in patients with epilepsy and history of seizures, and without it. Therefore, caution should be exercised when taking the decision about the use of quinolone in patients already taking NSAIDs.

Phenytoin. In case of concomitant use of phenytoin and diclofenac it is recommended to monitor the concentration of phenytoin in blood plasma due to the expected increase in the influence of phenytoin.

Colestipol and cholestyramine. These drugs can delay or reduce the absorption of diclofenac. Therefore, it is recommended that diclofenac should be prescribed at least 1 hour before or 4–6 hours after the use of colestipol/cholestyramine.

Cardiac glycosides. Concomitant use of cardiac glycosides and NSAIDs in patients may increase heart failure, reduce glomerular filtration rates and increase cardiac glycosides in plasma.

Mifepristone. NSAIDs should not be used within 8–12 days after the use of mifepristone, since NSAIDs can reduce the effect of mifepristone.

CYP2C9 inhibitors. Caution is advised when diclofenac is prescribed concomitantly with CYP2C9 inhibitors (for example, voriconazole), which may cause the significant increases in peak plasma concentrations and diclofenac exposure.

CYP2C9 inducers. Caution should be exercised when diclofenac is prescribed concomitantly with CYP2C9 inducers (e.g., rifampicin). This can lead to a significant increase in plasma concentrations and exposure to diclofenac.

Special precautions.

General.

Gastrointestinal ulcers, bleeding, or perforation can occur at any time during the use of NSAIDs, regardless of whether they are COX-2-selective, even in the absence of warning symptoms or a history of predisposition. To minimize undesirable effects, a minimum effective dose should be used within the shortest possible time.

Placebo-controlled studies have indicated an increased risk of thrombotic cardiovascular and cerebrovascular complications with the use of certain selective COX-2 inhibitors. It still remains unknown whether this risk directly correlates with COX-1/COX-2 selectivity of individual NSAIDs.

Avoid concomitant use of Diclosafe® with systemic NSAIDs, such as selective cyclooxygenase-2 inhibitors, due to the lack of any evidence of synergistic effects and the potential for additive side effects.

Since there are no comparative data from clinical studies on long-term treatment using the maximum dose of diclofenac, the possibility of such an increase in risk cannot be excluded. Until such data are available, careful benefit-risk assessment should be performed before using diclofenac in patients with clinically proven coronary heart disease, cerebrovascular disease, peripheral arterial occlusive disease, or significant risk factors (eg, hypertension, hyperlipidemia, diabetes, smoking). Because of this risk, the lowest effective dose should be used for the shortest period of time.

Caution should be exercised in patients over 65 years of age. In particular, it is recommended to use the lowest effective dose to weakened, elderly or low-body patients.

In rare cases, as with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, may even occur, even without prior exposure to diclofenac. Due to its pharmacodynamic properties, the drug Diclosafe®, like other NSAIDs, can mask the signs and symptoms of infection. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can cause myocardial infarction. Symptoms of such reactions may include chest pain associated with an allergic reaction to diclofenac.

The effect on the digestive tract.

In the use of all NSAIDs, including diclofenac, some cases of gastrointestinal bleeding were reported (cases of blood vomiting, melena), ulceration or perforation that could be lethal and occur at any time during the treatment, with or without a warning symptoms, or previous history of serious events from the gastrointestinal tract. These phenomena usually have more serious consequences for the elderly. If in patients taking diclofenac sodium, there are events of gastrointestinal bleeding or ulceration, the use of the drug should be discontinued.

As with other NSAIDs, including diclofenac, for patients with symptoms indicative of gastrointestinal tract impairment, medical supervision and special care are obligatory. The risk of bleeding, ulceration, or perforation in gastrointestinal tract increases with an increase in the dose of NSAIDs, including diclofenac, and in patients with a history of ulcer, especially with bleeding or perforation complications, and in elderly patients.

Older patients have an increased incidence of adverse reactions to NSAIDs, especially in relation to gastrointestinal bleeding and perforation, which can be fatal.

To reduce the risk of such a toxic effect on gastrointestinal tract, treatment should be initiated and maintained at the lowest effective dose.

For such patients, as well as those requiring concomitant use of drugs containing low doses of acetylsalicylic acid (ASA/aspirin or other medicinal products that are likely to increase the risk of undesirable effects on gastrointestinal tract), the use of combination therapy with the use of protective agents (such as proton pump inhibitors or misoprostol). Patients with a history of gastrointestinal toxicity, especially elderly patients, should inform of any unusual abdominal symptoms (especially bleeding in gastrointestinal tract). Cautions are also needed in patients

taking concomitant medications that can increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants (e.g. warfarin), antithrombotic agents (such as acetylsalicylic acid), or selective serotonin reuptake inhibitors.
NSAIDs, including diclofenac, may be associated with an increased risk of gastrointestinal anastomotic failure. Careful medical monitoring and caution are recommended when using Diclosafe® after surgery on the gastrointestinal tract.
The effect on the liver.
Careful medical supervision is required if the drug Diclosafe® is prescribed to patients with hepatic impairment, as their condition may deteriorate.
As with other NSAIDs, including diclofenac, the level of one or more liver enzymes may increase. This occurred very frequently in clinical trials with diclofenac (approximately 15% of patients), but was very rarely accompanied by clinical symptoms. Most of these cases are associated with increased threshold values. Moderate elevations (≥ 3 to < 8 times the upper limit of normal) were common (2.5% of cases), while the frequency of significant elevations (≥ 8 times the upper limit of normal) remained at approximately 1%. In the above-mentioned clinical studies, in 0.5% of patients, an increase in the levels of liver enzymes was accompanied by clinically pronounced liver damage. After discontinuing the use of diclofenac, the levels of liver enzymes returned to baseline values.
During long-term treatment with diclofenac, as a precautionary measure, regular liver function monitoring should be appointed. If liver damage persists or worsens and if clinical signs or symptoms may be associated with progressive liver disease, or if other manifestations (e.g., eosinophilia, rash) are observed, the use of Diclosafe® should be discontinued.
In addition to elevations in liver enzymes, there have been isolated reports of severe hepatic reactions, including jaundice and fulminant hepatitis, liver necrosis and hepatic failure, which have been fatal in some cases.
The course of diseases, such as hepatitis, can take place without prodromal phenomena. Cautions are required if the drug Diclosafe® is used in patients with hepatic porphyry due to the probability of provoking a porphyria attack.
The effect on the kidneys.
Because of the importance of prostaglandins in maintaining renal blood flow, long-term treatment with large doses of NSAIDs, including diclofenac, often (1–10%) leads to edema and hypertension.
Since fluid retention and edema have been reported in the treatment of NSAIDs, including diclofenac, special attention should be paid to patients with impaired cardiac or renal function, history of arterial hypertension, elderly patients, patients receiving concomitant therapy with diuretics, or drugs that significantly effect the renal function, and also to patients with a significant reduction in extracellular fluid volume for any reason, for example before or after a serious surgical intervention. In such cases, monitoring of renal function is recommended as a precautionary measure. Termination of therapy usually leads to a reversion to the condition that preceded the treatment.
The effect on the skin.
Due to the use of NSAIDs, including diclofenac sodium, severe skin reactions (some of them lethal) were reported very rarely, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis. In patients, the highest risk of developing these reactions is observed at the beginning of the course of therapy: the occurrence of the reaction is noted in most cases during the first month of treatment. The use of Diclosafe® should be discontinued at the first occurrence of skin rashes, mucosal lesions or any other signs of high sensitivity.
As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, may occur in individual cases, even without prior exposure to diclofenac.
Systemic lupus erythematosus and mixed connective tissue diseases.

Patients with systemic lupus erythematosus and mixed connective tissue diseases may have an increased risk of aseptic meningitis.

Cardiovascular and cerebrovascular effects.

In patients with established cardiovascular disease (eg, heart failure, established coronary heart disease, peripheral artery disease) or uncontrolled hypertension, the use of diclofenac is generally not recommended.

Appointing diclofenac to patients with significant risk factors for cardiovascular events (such as hypertension, hyperlipidemia, diabetes mellitus, smoking) can only be done after careful clinical evaluation and only in doses up to 100 mg per day, if the duration of therapy is more than 4 weeks.

Since cardiovascular risks of diclofenac may increase with increasing the dosage and duration of treatment, it should be used as soon as possible and at the lowest effective dose. The patient needs to be periodically reviewed for diclofenac use to relieve symptoms and respond to therapy.

For patients with a medical history of arterial hypertension and/or congestive heart failure of mild to moderate severity appropriate monitoring and advice should be provided as the cases of fluid retention and oedema have been reported during the use of NSAIDs, including diclofenac.

Clinical and epidemiological data suggest that the use of diclofenac, especially in high doses (150 mg/day) and in long-term treatment, may be associated with a slight increase in the risk of developing arterial thrombotic events (e.g., myocardial infarction or stroke).

It is necessary to periodically assess the patient's need for symptom relief and response to therapy, especially if the duration of therapy is more than 4 weeks.

Patients should be informed of the need to monitor for symptoms of serious arterial thromboembolic events (eg, chest pain, shortness of breath, weakness, slurred speech), which may occur without warning. In the event of such a phenomenon, patients should immediately consult a doctor.

The effect on hematological parameters.

With long-term use of diclofenac, as with other NSAIDs, monitoring of all blood parameters is recommended.

Diclofenac can reverse the platelet aggregation. It should be carefully observed in patients with hemostatic disorders, hemorrhagic diathesis or hematologic disorders.

Bronchial asthma in the past medical history.

In patients with bronchial asthma, seasonal allergic rhinitis, nasal congestion (i.e., nasal polyps), chronic obstructive pulmonary disease or chronic respiratory infections (especially those associated with allergies similar to rhinitis symptoms), reactions to NSAIDs are more likely to occur such as exacerbation of bronchial asthma (so-called analgesic intolerance/analgesic asthma), Quincke’s edema or urticaria. In this regard, special precautions are recommended for such patients (readiness to provide emergency care). This also applies to patients with allergic reactions to other substances such as rash, itching or urticaria.

As with other drugs that suppress the activity of prostaglandin synthetase, diclofenac and other NSAIDs can provoke bronchospasm development when used in patients with bronchial asthma or in patients with bronchial asthma in the past medical history.

Use during pregnancy or breastfeeding.

Pregnancy.

In the absence of absolute necessity, diclofenac should not be used in the first or second trimester of pregnancy. In the first and second trimesters of pregnancy, diclofenac sodium can be prescribed only if the expected benefit to the mother exceeds the potential risk for the fetus and only in the minimum effective dose, the duration of treatment should be as short as possible. The risk of impaired renal function in the fetus with subsequent oligohydramnios was observed with the use of NSAIDs (including diclofenac) from the 20th week of pregnancy.

As with other NSAIDs, the drug is contraindicated in the third trimester of pregnancy (possible inhibition of the contractile capacity of the uterus and premature closure of the arterial duct in the fetus). Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or the development of the embryo/fetus. Data from epidemiological studies indicate an increased risk of developing heart failure and gastroschisis after the use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk of cardiovascular disease has been increased from less than 1% to about 1.5%. It is possible that the risk increases with the dose and duration of treatment. It has been shown that administration of an inhibitor of prostaglandin synthesis in animals leads to increasing in pre- and post-implantation loss and embryonal/fetal mortality.
In addition, in animals taking prostaglandin synthesis inhibitor during the period of organogenesis, an increased incidence of various developmental disorders, including from cardiovascular system, was reported. If sodium diclofenac is used by a woman who wants to get pregnant, or in the first trimester of pregnancy, the dose of the drug should be as low as possible and the duration of treatment should be as short as possible.
During the third trimester of pregnancy, following the use of all inhibitors of prostaglandin synthesis, the following effects may occur:

- cardio-pulmonary toxicity (with premature closure of arterial duct and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligohydramnios.

Mother and new-born, as well as at the end of pregnancy:

- possible prolongation of bleeding time, anti-aggregate effect, which can be observed even at very low doses;
- inhibition of uterine contractions, which leads to delay or prolongation of labor.

Consequently, diclofenac sodium is contraindicated in the third trimester of pregnancy.
Breast-feeding.
Like other NSAIDs, diclofenac in small amounts penetrates into breast milk. In this regard, diclofenac suppositories should not be used in women during breastfeeding to avoid undesirable effects on the infant. If the treatment is vitally necessary, the child should be transferred to artificial feeding.
Fertility.
Like other NSAIDs, diclofenac can adversely effect the female fertility, so it is not recommended to prescribe a drug to women who are planning a pregnancy. Women who have problems with conception or undergo infertility studies should consider the expediency of diclofenac sodium discontinuation.
Based on the data of research in animals, it is impossible to exclude a violation of the reproductive function in males. The significance of these data for humans is unclear.

Effects on ability to drive and use machines.
Patients who have visual impairment, dizziness, vertigo, drowsiness, central nervous system disorders, lethargy or increased fatigue during diclofenac sodium therapy should not drive or operate complex mechanisms.

Administration and dosage.
Adverse effects can be minimized by using the lowest effective dose for the shortest period of time necessary to control symptoms.
Do not take internally, only for rectal administration. Suppositories should be inserted into the intestinum rectum as deeply as possible, preferably after cleansing the intestine. Suppositories should not be divided into parts, because such a change in the method of administration of the drug may lead to a disturbance in the distribution of the active substance.

The initial dose is usually 100–150 mg/day. For indolent symptoms, as well as for long-term therapy, a dose of 75*–100 mg/day is sufficient.
Divide the daily dose into 2–3 doses. To avoid night pain or morning stiffness before using the drug during the day, prescribe diclofenac in the form of rectal suppositories before going to bed (the daily dose of the drug should not exceed 150 mg).
In the primary dysmenorrhea, the daily dose should be selected individually, usually it is 50–150 mg/day. The initial dose can be 50–100 mg/day, but if it is necessary, it can be increased during several menstrual cycles up to a maximum of 150 mg/day.
The use of the drug should begin after the onset of the first pain symptoms and continue for several days, depending on the dynamics of regression of the symptoms.
To treat migraine attacks, the course should be started with a dose of 100* mg with the manifestation of the first signs of an attack. If necessary, the following suppositories (100 mg diclofenac) can be used on the same day. If necessary, the treatment can be continued in the following days (the daily dose of the drug should not exceed 150 mg, the dose should be divided into 2–3 applications).
*Apply in appropriate dosage.
In the treatment of juvenile rheumatoid arthritis, the daily dose can be up to 3 mg/kg, which is the maximum daily dose and should not exceed 150 mg per day. Suppositories of 50 mg can be prescribed to children over 14 years of age.
Elderly patients.
Although in elderly group of patients, the pharmacokinetics of diclofenac does not deteriorate to any clinically significant extent, non-steroidal anti-inflammatory drugs should be used with special caution by such patients, as they usually tend to be more prone to development of adverse reactions. In particular, weakened elderly patients or patients with low body mass index are advised to use the lowest effective doses; patients should also be examined for gastrointestinal bleeding in the treatment of NSAIDs.
Renal impairment.
Diclofenac is contraindicated in patients with renal failure (GFR <15 ml/min/1.73 m^2 (see section “Contraindications”).
Specific studies involving patients with impaired renal function have not been conducted, so recommendations for dose adjustments cannot be made. Diclofenac should be used with caution in patients with mild to moderate renal impairment (see section “Special precautions.”).
Liver impairment.
The use of diclofenac is contraindicated in patients with liver failure (see section “Contraindications”).
Specific studies involving patients with impaired liver function have not been conducted, so recommendations for dose adjustments cannot be made. Diclofenac should be used with caution in patients with mild and moderate liver impairment (see section “Special precautions.”).

Children.
Diclosafe®, 50 mg suppositories, should not be used by children under the age of 14 due to the high content of the active substance in it. The drug can be used by children over 14 years old.

Overdose
Symptoms.
There is no typical clinical picture characteristic of overdose of diclofenac. Overdose may cause symptoms such as headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, diarrhoea, dizziness, disorientation, agitation, coma, drowsiness, buzzing in ears or seizures. Acute renal failure and liver damage are possible in case of severe intoxication.
Treatment.

If necessary, symptomatic treatment is carried out. Supportive measures and symptomatic treatment are prescribed for complications such as arterial hypotension, renal failure, seizures, disorders of the gastrointestinal tract, and respiratory depression.
Specific measures such as forced diuresis, dialysis, or hemoperfusion are unlikely to be effective in eliminating NSAIDs, including diclofenac, due to extensive protein binding and extensive metabolism.
The use of activated carbon should be considered within one hour after application of a potentially toxic amount of the preparation. In addition, for adult patients, gastric lavage should be considered within 1 hour after the application of a potentially toxic amount of the drug. In case of frequent or prolonged seizures, intravenous diazepam should be administered. Taking into account the clinical condition of the patient, other measures may be indicated.

Adverse reactions.
The category of frequency of adverse reactions is defined as follows: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10000); frequency unknown (cannot be estimated from available data).
Blood and lymphatic system disorders: very rare – thrombocytopenia, leukopenia, anemia (hemolytic anemia, aplastic anemia), agranulocytosis.
Immune system disorders: rare – hypersensitivity, anaphylactic and anaphylactoid reactions (including arterial hypotension and shock); very rare – angioneurotic edema (including facial oedema).
Mental disorders: very rare – disorientation, depression, insomnia, irritability, nightmares, psychotic disorders.
Nervous system disorders: common – headache, dizziness; rare – somnolence, increased fatigability; very rare – paresthesia, memory impairment, seizures, anxiety, tremor, aseptic meningitis, taste disturbances, stroke; frequency unknown – confusion, hallucinations, sensory impairment, general malaise.
Eye disorders: very rare – visual disturbances, blurred vision, diplopia; frequency unknown – optic neuritis.
Ear and labyrinth disorders: common – vertigo; very rare – ear buzzing, hearing impairment.
Cardiac disorders: common – arterial hypertension; uncommon* – heart palpitations, chest pain, heart failure, myocardial infarction, arterial hypotension; very rare – vasculitis; frequency unknown – Kounis syndrome.
Respiratory system, chest and mediastinum disorders: rare – asthma (including shortness of breath); very rare – pneumonitis.
Gastrointestinal tract disorders: common – nausea, vomiting, diarrhoea, dyspepsia, epigastric pain, abdominal pain, flatulence, anorexia, decrease in appetite; rare – gastritis, gastrointestinal bleeding, hematemesis, melena, hemorrhagic diarrhoea, ulcers of stomach and intestines, accompanied or not accompanied by bleeding, gastrointestinal stenosis or perforation (sometimes lethal, especially in elderly patients), that may result in peritonitis, proctitis; very rare – colitis (including hemorrhagic colitis, ischemic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, impairment of the esophagus function, diaphragmatic intestinal stenosis, pancreatitis, exacerbation of hemorrhoids.
Hepatobiliary system disorders: common – increased transaminases; rare – hepatitis, jaundice, liver disorders; very rare – fulminant hepatitis, liver necrosis, hepatic failure.
Skin and subcutaneous tissue disorders: common – rash; very– urticaria; very rare – rashes, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic epidermal necrolysis), exfoliative dermatitis, hair loss, photosensitivity reaction, purpura, including allergic, Schönlein-Henoch purpura, pruritus.

Kidneys and urinary system: common – common– fluid retention, swelling; very rare –acute renal impairment (acute renal failure), hematuria, proteinuria, tubulointerstitial nephritis, nephrotic syndrome, papillary necrosis of kidneys.
General disorders and disorders at the place of administration: common – irritation at the place of administration; rare – edema.
Reproductive system and mammary glands: very rare – impotence.
*Indicators of frequency are based on data of long-term use at a high dose (150 mg/day).
Clinical data and epidemiological data suggest an increased risk of thrombotic complications (e.g., myocardial infarction or stroke) associated with the use of diclofenac, particularly at high therapeutic doses (150 mg daily) and long-term use.
Visual disorders.
Visual disorders such as visual impairment, visual deterioration and diplopia are effects of NSAIDs class and are generally reversible after discontinuation of the drug. The most probable mechanism of visual impairment is inhibition of the synthesis of prostaglandins and other related compounds, which violating the regulation of retinal blood flow, result in the development of visual disorders. If these symptoms occur during the treatment with diclofenac, an ophthalmic study should be conducted to exclude other possible causes.
Reporting of suspected adverse reactions.
Post-marketing reporting of adverse reactions is important. This makes it possible to monitor the benefit/risk ratio when using this medicinal product. Medical and pharmaceutical workers, as well as patients or their legal representatives should be notified of all cases of suspected adverse reactions and lack of efficacy of the medicinal product through the Automated Pharmacovigilance Information System at the link: https://aisf.dec.gov.ua/.

Shelf life.
3 years.

Storage conditions.
Store at the temperature below 25 °C in original package.
Keep it out of reach of children.

Package.
5 suppositories in a strip. 2 strips in a carton package.

Condition of supply.
By prescription.

Manufacturer.
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