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INSTRUCTION
for medical use

FANIGAN®

Composition:
active substances: paracetamol, diclofenac sodium;
1 tablet contains paracetamol 500 mg, diclofenac sodium 50 mg;
excipients: corn starch, povidone K-30, croscarmellose sodium, microcrystalline cellulose, magnesium stearate, Sunset Yellow FCF (E 110).

Pharmaceutical form. Tablets.
General physical and chemical properties: orange capsule-shaped tablets with white speckles.

Pharmacotherapeutic group. Non-steroidal anti-inflammatory and antirheumatic drugs. ATC code M01A B55.

Pharmacokinetic properties.
Pharmacodynamics.
Fanigan is a combined drug with a pronounced anti-inflammatory, analgesic, and antipyretic effect. Pharmacological activity of the drug is due to the properties of diclofenac and paracetamol, which are the components of the drug.
Diclofenac sodium has a pronounced anti-inflammatory and analgesic, and a moderate antipyretic effect. It is an inhibitor of prostaglandin synthetase (cyclooxygenase).
Diclofenac sodium *in vitro* does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in patients. Paracetamol has a pronounced analgesic, slight antipyretic, and anti-inflammatory effect. The mechanism of action is associated with inhibition of prostaglandin synthesis in CNS.
Pharmacokinetics.
Diclofenac.
Diclofenac sodium is rapidly absorbed in blood; the maximum plasma concentration is achieved after 1–2 hours. Binding with the plasma proteins is over 99%. It easily penetrates into the tissues and synovial liquid, where its concentration grows slowly, after 4 hours it reaches higher levels than in the blood plasma. Food may slow down the absorption rate, without any effect on completeness of absorption. Bioavailability is about 5%.
The half-life in plasma is 1–2 hours; in synovial fluid it is 3–6 hours. About 35% are excreted in the form of metabolites with the feces; about 65% are metabolized in the liver and excreted by the kidneys in the form of inactive derivatives, about 1% in the unchanged form.
Paracetamol.

Paracetamol is rapidly and almost completely absorbed in the gastrointestinal tract. Its maximum plasma concentration is achieved after 30–60 minutes. The half-life is 1–4 hours. It is well distributed in all the body fluids. Binding with the blood proteins is variable. Paracetamol is metabolized in the liver and excreted mainly by the kidneys in the form of conjugated metabolites. After a repeated dose of the drug, pharmacokinetic parameters of the active substances remain unchanged. On condition of compliance with the recommended intervals between taking the tablets, cumulation of the drug is not detected.

Clinical characteristics.

Indications.

– Acute pain (muscular, headache, toothache localized in the spine), non-articular rheumatism, rheumatoid arthritis, ankylosing spondylitis, osteoarthrosis, spondylarthritis, acute gout attacks, primary dysmenorrhea, adnexitis, pharyngotonsillitis, otitis.
– Post-traumatic and post-operative pain syndrome.

Contraindications.

Hypersensitivity to diclofenac, paracetamol or to any other component of the drug.
Acute gastric or intestinal ulcer; gastrointestinal bleeding or perforation.
Bleeding or perforation of the gastrointestinal tract in anamnesis related to previous treatment with non-steroidal anti-inflammatory drugs (NSAIDs).
Active form of peptic ulcer/bleeding or recurrent peptic ulcer/bleeding in anamnesis (two or more separate episodes of diagnosed ulcer or bleeding).
High risk of development of post-operative bleeding, blood incoagulability, hemostasis disorders, hematopoietic disorders, or cerebrovascular bleeding.
Hepatic failure.
Renal failure (glomerular filtration rate <15 mL/min/1.73 m^2).
Congestive heart failure (NYHA functional class II–IV).
Ischemic heart disease in patients with angina, or who have had myocardial infarction.
Contraindicated in patients having asthma attacks (“aspirin asthma”), angioedema, urticaria or acute rhinitis, nasal polyps, and other allergic symptoms in response to the use of ibuprofen, diclofenac, paracetamol, acetylsalicylic acid, or other NSAIDs.
Diseases of the blood, hemodyscrasia of unknown genesis, leukopenia, pronounced anemia.
Congenital hyperbilirubinemia, Gilbert’s syndrome.
Glucose-6-phosphate dehydrogenase deficiency.
Inflammatory bowel disease (Crohn’s disease or ulcerative colitis).
Alcoholism.
Do not use for treatment of postoperative pain during coronary artery bypass grafting (or during use of an artificial circulation device).
Diseases of peripheral arteries.
Cerebrovascular disease in patients who have suffered a stroke or have episodes of transient ischemic attacks.

Interaction with other medicinal products and other forms of interaction.

Diclofenac.

Lithium. If used simultaneously, diclofenac may increase the plasma concentration of lithium. It is recommended to monitor serum levels of lithium.
Digoxin. If used simultaneously, diclofenac may increase the plasma concentration of digoxin. It is recommended to monitor serum levels of digoxin.
Diuretics and antihypertensive agents. As well as other NSAIDs, concomitant use of diclofenac with diuretics and antihypertensive agents (such as β-blockers, angiotensin-converting enzyme (ACE) inhibitors) may reduce their antihypertensive effect by inhibition of synthesis of vasodilatory prostaglandins. Thus, such a combination is used with caution, and patients,

especially the elderly, should be under close supervision regarding their blood pressure level. Patients should receive adequate hydration, it is also recommended to monitor the renal function after initiation of concomitant therapy and at regular intervals thereafter, especially for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity.

Drugs that are known to cause hyperkalemia. Concomitant treatment with potassium-sparing diuretics, cyclosporine, tacrolimus, or trimethoprim may be associated with increased levels of potassium in the blood serum, so monitoring of the patient should be performed more frequently.

Anticoagulants and antithrombotic agents. Concomitant use can increase the risk of bleeding, so it is recommended to take precautions. Although there are no conclusive data on the effect of diclofenac on the activity of anticoagulants, there is some evidence of increased bleeding risk in patients who used both diclofenac and anticoagulants. Therefore, to assure that no change in anticoagulant dosage is not required, careful monitoring of these patients is recommended. Like other non-steroidal anti-inflammatory drugs, diclofenac at high doses may temporarily inhibit platelet aggregation.

Other NSAIDs, including selective cyclooxygenase-2 inhibitors and corticosteroids. Concomitant administration of diclofenac and other NSAIDs or corticosteroids may increase the risk of gastrointestinal bleeding or ulcers. Avoid simultaneous use of two or more NSAIDs.

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

Antidiabetic drugs. It has been proved that diclofenac may be used with oral antidiabetics without changing their therapeutic effect. However, there are some reports about the development of both hypoglycemia and hyperglycemia in these cases, which required antidiabetic agents' dosage adjustment during the use of diclofenac. For this reason, it is recommended to control blood glucose level during the combined therapy as a precautionary measure.

There have also been isolated reports of metabolic acidosis when diclofenac was co-administered with metformin, especially in patients with pre-existing renal impairment.

Methotrexate. Diclofenac may inhibit clearance of methotrexate in the renal tubules, leading to the increased levels of methotrexate. Caution should be exercised when using NSAIDs, including diclofenac, less than 24 hours before or after the use of methotrexate, since in such cases the blood concentration of methotrexate may increase, and its toxic effect may intensify. There is evidence of serious cases of toxicity when the interval between the use of methotrexate and NSAIDs, including diclofenac, was within 24 hours. This interaction is mediated through accumulation of methotrexate resulting in violation of renal excretion in the presence of NSAIDs.

Cyclosporine. The effect of diclofenac, as well as other NSAIDs, on prostaglandin synthesis in the kidneys may increase cyclosporine nephrotoxicity; in this regard, diclofenac should be used in lower doses than in patients who do not use cyclosporine.

Tacrolimus. When using NSAIDs with tacrolimus, the risk of nephrotoxicity may increase, which may be mediated through renal antiprostaglandin effects of NSAIDs and calcineurin inhibitors.

Antibacterial quinolones. The development of seizures in patients who used both NSAIDs and quinolone derivatives is possible. This may be observed in patients both with and without epilepsy and seizures in the anamnesis. Therefore, caution should be exercised when deciding on the use of quinolone in patients who are already receiving NSAIDs.

Phenytoin. When using phenytoin concomitantly with diclofenac, it is recommended to monitor plasma phenytoin concentrations due to the expected increase in exposure of phenytoin.

Colestipol and cholestyramine. These agents can induce a delay or decrease in absorption of diclofenac. Therefore, it is recommended to administer diclofenac at least one hour before or 4 to 6 hours after administration of colestipol/cholestyramine.

Cardiac glycosides. Concomitant use of cardiac glycosides and NSAIDs may enhance heart failure, reduce GFR and increase the level of glycosides in blood plasma.

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

Inhibitors of CYP2C9. Caution is required when co-prescribing diclofenac with potent CYP2C9 inhibitors (e.g., voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac.
CYP2C9 inducers. Caution is required when co-prescribing diclofenac with CYP2C9 inducers (e.g., rifampicin), which could result in a significant decrease in plasma concentration and exposure to diclofenac.
Paracetamol.
Absorption rate of paracetamol may increase when using metoclopramide and domperidone, and may decrease when using cholestyramine. Anticoagulant effect of warfarin and other coumarins may increase in concomitant regular daily use of paracetamol, with an increased risk of bleeding. When administered periodically, it has no significant effect.
Barbiturates reduce the antipyretic effect of paracetamol.
Caution should be exercised in the simultaneous use of paracetamol with flucloxacillin, since simultaneous use is associated with metabolic acidosis with a high anion deficit, especially in patients with risk factors (see the section "Special warnings and precautions for use").
Anticonvulsants (including phenytoin, barbiturates, carbamazepine) which stimulate the activity of microsomal liver enzymes may increase the toxic effects of paracetamol on the liver due to increased metabolism of the drug into hepatotoxic metabolites. In concomitant use of paracetamol with hepatotoxic agents, their toxic effect on the liver increases.
Concomitant use of high doses of paracetamol and isoniazid, rifampicin increases the risk of hepatotoxic syndrome. Paracetamol reduces the efficacy of diuretics.
Do not use with alcohol.

Special warnings and precautions for use.
General
To minimize the adverse effects, the treatment should be started with the lowest effective dose for the shortest period of time necessary to control the symptoms.
For diclofenac.
The concomitant use of diclofenac with systemic NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects.
There is an increased risk of thrombotic cardiovascular and cerebrovascular complications with the use of certain selective COX-2 inhibitors. A direct correlation of this risk with the selectivity of individual NSAIDs to COX-1/COX-2 has not yet been established. Due to the lack of comparable data from clinical trials on long-term treatment with maximum doses of diclofenac, the possibility of such an increased risk cannot be ruled out. Therefore, a thorough risk-benefit assessment should be performed before prescribing diclofenac to patients with clinically proven coronary heart disease, cerebrovascular disorders, peripheral arterial occlusion, or significant risk factors (such as hypertension, hyperlipidemia, diabetes, smoking). The lowest effective dose should be administered for the shortest possible duration of treatment.
The effects of NSAIDs on the kidneys include fluid retention with edema and/or hypertension. Therefore, diclofenac should be used with caution in patients with impaired cardiac function and other conditions that contribute to fluid retention. Caution should also be exercised in patients taking concomitant diuretics or ACE inhibitors or at increased risk of hypovolemia.
The consequences are usually more serious in elderly patients. Caution should be exercised when prescribing the drug to the elderly. Caution is required when used in patients over 65 years of age. In particular, it is recommended to use the lowest effective dose of debilitated elderly patients or patients with low body weight.
In case of gastrointestinal bleeding or ulceration in patients treated with diclofenac, the drug should be discontinued.
As with other NSAIDs, allergic reactions may be observed, including anaphylactic/anaphylactoid reactions, even without prior effect of diclofenac.

Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to diclofenac.
Due to its pharmacodynamic properties, diclofenac, like other NSAIDs, may mask the signs and symptoms of infection.
Effect on the gastrointestinal tract.
When using all NSAIDs, whether COX-2 selective or not, including diclofenac, there have been registered the cases of gastrointestinal bleedings (cases of hematemesis, melena), ulcer formation or perforation, which may be lethal and occur at any time during treatment with or without the warning symptoms or previous anamnesis of serious gastrointestinal events. These events usually have more serious consequences in the elderly patients. If the events of gastrointestinal bleeding or ulcer formation are observed in patients receiving diclofenac, the drug should be discontinued.
As with other NSAIDs, including diclofenac, for patients with symptoms that indicate digestive tract (DT) disorders, medical supervision and special caution are mandatory. The risk of bleeding, ulceration or perforation in DT increases with increasing doses of NSAIDs, including diclofenac. Elderly patients have an increased frequency of adverse reactions to the use of NSAIDs, especially regarding the gastrointestinal bleeding and perforation which may be lethal.
To reduce the risk of toxic effects on DT, the treatment is started and continued with the lowest effective doses. For such patients, as well as those requiring concomitant use of medicinal products containing low doses of acetylsalicylic acid (ASA/aspirin or other medicinal agents that may increase the risk of the adverse effect on DT), the use of combined therapy with protective agents (e.g., proton pump inhibitors or misoprostol) should be considered. Patients with gastrointestinal toxicity in the anamnesis, especially the elderly, should report any unusual abdominal symptoms (especially DT bleedings). Caution is also required for patients concomitantly receiving the drugs that may increase the risk of ulcer or bleeding, such as systemic corticosteroids, anticoagulants (e.g., warfarin), antithrombotic agents (e.g., ASA) or selective serotonin reuptake inhibitors.
NSAIDs, including diclofenac, may be associated with increased risk of gastrointestinal anastomotic leak. Close medical surveillance and caution are recommended when using diclofenac after gastrointestinal surgery.
Effect on the liver.
Thorough medical supervision is required when prescribing diclofenac in patients with impaired hepatic function, as their condition may worsen.
With NSAIDs, including diclofenac, the level of one or several liver enzymes may increase. Elevated enzyme levels were generally reversible after discontinuation of the drug. This has been observed very frequently with diclofenac in clinical studies (in approximately 15% of patients) but is very rarely accompanied by clinical symptoms. Most of these cases involve borderline increases. Frequently (in 2.5% of cases) the increases observed were moderate (≥3 to <8 times the upper limit of normal), while the incidence of marked increases (≥8 times the upper limit of normal) remained around 1%. Elevated liver enzyme levels were accompanied by clinically manifest liver damage in 0.5% of cases in the previously mentioned clinical studies.
With long-term treatment with the drug regular monitoring of liver function and liver enzyme levels is recommended. If liver function abnormalities persist or worsen and if clinical signs or symptoms suggestive of liver disease develop, or if other manifestations occur (e.g., eosinophilia, rash), the use of Fanigan should be discontinued.
In addition to elevated liver enzymes, there have been rare reports of severe hepatic reactions, including jaundice and fulminant hepatitis, hepatic necrosis and hepatic failure which, in isolated cases, had a fatal outcome.
The course of diseases such as hepatitis can occur without prodromal symptoms. Caution is required if Fanigan is used in patients with hepatic porphyria, since it may trigger an attack.
Effect on the kidneys.
NSAIDs, including diclofenac, reduce prostaglandin levels, which are important for maintaining renal blood flow.

As frequent cases (1–10%) of fluid retention, edema, and hypertension have been reported in association with NSAID therapy, including diclofenac, particular caution is called for in patients with impaired cardiac or renal function, with a history of hypertension, in elderly, in patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and in those patients with substantial extracellular volume depletion from any cause, e.g., before or after major surgery. Monitoring of renal function is recommended as a precautionary measure when using diclofenac in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

Effect on the skin.

Serious skin reactions (some of them fatal, including exfoliative dermatitis, Steven-Johnson syndrome, and toxic epidermal necrolysis) have been reported very rarely in association with the use of NSAIDs. Patients appear to be at highest risk for 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. Treatment with Fanigan should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

SLE and mixed connective tissue disease.

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue diseases, the risk of developing aseptic meningitis increases when treated with diclofenac.

Cardiovascular and cerebrovascular effects.

Treatment with diclofenac is generally not recommended in patients with established cardiovascular disease (congestive heart failure, ischemic heart disease, peripheral arterial disease) or uncontrolled hypertension.

Patients with significant risk factors for cardiovascular disease (e.g., hypertension, hyperlipidemia, diabetes mellitus, and smoking) should be treated with diclofenac only after careful consideration and only at doses not more than 100 mg daily for a course of treatment of more than 4 weeks. As the cardiovascular risks with diclofenac use increase with dose and duration of exposure, the lowest effective daily dose should be used for the shortest duration possible. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.

For patients with a history of arterial hypertension and/or congestive heart failure of mild or moderate severity, appropriate monitoring and recommendations are necessary, as cases of fluid retention and edema have been reported during the use of NSAIDs, including diclofenac.

Diclofenac should be used with caution in patients who take concomitant diuretics or ACE inhibitors, or who are at increased risk of hypovolemia.

Clinical trial and epidemiological data suggest that the use of diclofenac, particularly at high dose (150 mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

It is not recommended to administer diclofenac in patients with uncontrolled hypertension, congestive heart failure, stable coronary heart disease and/or cerebrovascular disease; if necessary, the use is possible only after a careful risk-benefit assessment only at the dosage of not more than 100 mg per day. Such assessment should be carried out before starting the long-term treatment in patients with risk factors of cardiovascular events (e.g., patients with arterial hypertension, hyperlipidemia, diabetes mellitus, and smoking).

Patients should be informed about the possibility of serious thromboembolic events (e.g., chest pain, shortness of breath, weakness, slurring of speech), which may occur at any time. In this case, it is necessary to immediately consult a physician.

Effect on hematological parameters.

During prolonged use of this drug, as well as other NSAIDs, it is recommended to monitor the complete blood count.

Diclofenac may temporarily inhibit platelet aggregation. Patients with impaired hemostasis, hemorrhagic diathesis or hematological disorders should be under careful observation.

Asthma in the anamnesis.

In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions on NSAIDs like asthma exacerbations (so-called intolerance to analgesics / analgesics-asthma), Quincke's oedema or urticaria are more frequent. Therefore, special precaution is recommended in such patients (readiness for emergency). This is applicable as well for patients who are allergic to other substances, e.g., with rash, pruritus, or urticaria.
Like other drugs that inhibit prostaglandin synthetase activity, diclofenac sodium and other NSAIDs can precipitate bronchospasm if administered to patients suffering from, or with a previous history of bronchial asthma.
Fertility.
The use of diclofenac sodium, as well as other NSAIDs, may impair female fertility and therefore is not recommended in women attempting to conceive. If a woman has difficulties conceiving or is undergoing investigation of infertility, withdrawal of Fanigan should be considered.
Based on animal studies, reproductive dysfunction in males cannot be ruled out. The relevance of this finding for humans is unclear.
Effect on pregnancy and/or embryo/foetus development
Inhibition of prostaglandin synthesis by diclofenac may adversely affect pregnancy and/or embryo/foetus development. Data from epidemiological studies indicate an increased risk of miscarriage and/or the risk of developing heart defects and gastroschisis after using a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk of cardiovascular disease was increased from less than 1% to approximately 1.5%. It has been shown that in animals, administration of an inhibitor of prostaglandin synthesis leads to an increase in pre- and post-implantation loss and mortality of the embryo/foetus. In addition, in animals treated with prostaglandin synthesis inhibitor during the period of organogenesis, an increased frequency of various malformations, including those of the cardiovascular system, was registered.
Starting from the 20th week of pregnancy, the use of diclofenac can cause oligohydramnios due to foetal kidney dysfunction. This may occur soon after starting treatment and is usually reversible after stopping treatment.
During the third trimester of pregnancy, all inhibitors of prostaglandin synthesis can lead to the development in the foetus of:
- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- impaired kidney function (see above).
In the mother and newborn at the end of pregnancy of:
- possible prolongation of bleeding time, anti-aggregation effect, which can occur even at very low doses;
- suppression of uterine contractions, which leads to delay or prolongation of childbirth.

<u>For paracetamol.</u>
The drug contains paracetamol, therefore it should not be used with any other paracetamol-containing medicines, for example, to reduce fever, treat pain, flu and colds symptoms, or insomnia. The concomitant use with other products containing paracetamol may lead to an overdose. Paracetamol overdose may cause liver failure, which can lead to liver transplant or death. Patients who have been diagnosed with liver or kidney impairment must seek medical advice before taking this medication.
It should be borne in mind that patients with liver disease have an increased risk of hepatotoxic effects of paracetamol.
Cases of hepatic dysfunction/failure have been reported in patients with depleted glutathione levels, such as those who are severely malnourished, anorexic, have a low body mass index or are chronic heavy users of alcohol, or have sepsis.

Caution is recommended when paracetamol is used concurrently with flucloxacillin due to an increased risk of metabolic acidosis with high anion deficit, especially in patients with severe renal failure, sepsis, malnutrition and other sources of glutathione deficiency (eg, chronic alcoholism), as well as those taking maximum daily doses of paracetamol. Careful monitoring, including measurement of urinary 5-oxoproline, is recommended.
In patients with glutathione depleted states the use of paracetamol may increase the risk of metabolic acidosis. Signs of metabolic acidosis include deep, rapid, difficult breathing, nausea, vomiting, loss of appetite. Contact a doctor immediately if you get these symptoms. Do not take more than the recommended dose. Prolonged use except under medical supervision may be harmful.
This product should be used only when clearly necessary.
If symptoms persist consult your doctor.
Keep out of the reach and sight of children.
Contains coloring agent sunset yellow FCF (E 110), which may cause allergic reactions.

Pregnancy and breastfeeding.
The drug Fanigan is contraindicated during pregnancy or breastfeeding.

Effects on ability to drive and use machines.
Patients who experience visual disturbances, dizziness (vertigo), somnolence, drowsiness, fatigue, or other central nervous system disturbance while taking diclofenac should refrain from driving or operating machinery.

Administration and dosage.
Do not take more than the recommended dose. The lowest effective dose should be used, during the shortest time needed to achieve the therapeutic goal.
The dose is determined by the doctor for each patient individually, depending on the age of the patient, the nature and course of the disease, individual tolerance, and therapeutic efficacy of the drug.
Adults and children aged over 14 – 1 tablet 2–3 times per day after meal.
The interval between the doses is not less than 4 hours.
The duration of treatment is not more than 5–7 days and depends on the course of the disease.
The maximum daily dose of the drug for adults and children aged over 14 is not more than 3 tablets.
The maximum period of use without consulting a doctor is 3 days.
Do not use with any other paracetamol-containing products.
Elderly patients (over 65 years of age).
Although the pharmacokinetics of diclofenac are not impaired to any clinically relevant extent in elderly patients, nonsteroidal anti-inflammatory drugs should be used with particular caution in such patients who generally are more prone to adverse reactions. In particular it is recommended that the lowest effective dosage be used in frail elderly patients or those with a low body weight and the patient should be monitored for GI bleeding during NSAID therapy.
Present cardiovascular disease or significant risk factors.
Patients with significant risk factors for cardiovascular events (e.g., hypertension, hyperlipidemia, diabetes mellitus, smoking) should only be treated with the drug after careful clinical evaluation. As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.
Patients with renal impairment.
The drug is contraindicated in patients with renal failure (glomerular filtration rate <15 mL/min/1.73 m^2, see "Contraindications" section).

No specific studies have been carried out in patients with renal impairment, therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering diclofenac to patients with mild to moderate renal impairment (see "Special warnings and precautions for use" section).
Patients with hepatic impairment.
The drug is contraindicated in patients with hepatic failure (see "Contraindications" section).
No specific studies have been carried out in patients with hepatic impairment, therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering diclofenac to patients with mild to moderate hepatic impairment (see "Special warnings and precautions for use" section).

Pediatric population.
The drug is contraindicated in children under 14 years.

Overdose.
Diclofenac.
Symptoms.
There is no typical clinical picture resulting from diclofenac overdosage. Overdosage can cause symptoms such as headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, diarrhea, dizziness, disorientation, excitation, coma, drowsiness, tinnitus, or convulsions. In the case of significant poisoning acute renal failure and liver damage are possible.
Treatment.
Management of acute poisoning with NSAIDs, including diclofenac, essentially consists of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression. Special measures such as forced diuresis, dialysis or hemoperfusion are probably of no help in eliminating NSAIDs, including diclofenac, as the active ingredients of the drug are largely bound to plasma proteins and subjected to intensive metabolism. Activated charcoal is recommended after ingestion of a potentially toxic overdose, and gastric decontamination (e.g., vomiting, gastric lavage) after ingestion of a potentially life-threatening overdose.
Paracetamol.
Paracetamol overdose may cause liver failure which may require liver transplant or lead to death. Clinical signs of liver injury occur usually 24 to 48 hours after overdose and peak after 4 to 6 days. There is a risk of poisoning, particularly in elderly subjects, in young adolescents, in patients with liver disease, in cases of chronic alcoholism, in patients with chronic malnutrition.
Symptoms of overdose generally appear within the first 24 hours: pallor, nausea, vomiting, anorexia and abdominal pain. Asymptomatic overdose is also possible. Overdose of paracetamol in a single administration in adults or in children can cause liver cell necrosis likely to induce complete and irreversible necrosis, resulting in impaired glucose metabolism, metabolic acidosis, hepatocellular insufficiency, encephalopathy, hemorrhage, hypoglycemia, coma, and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 48 hours after administration. Liver damage is likely in adults who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of paracetamol metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested) become irreversibly bound to liver tissue. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, hematuria, and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and acute pancreatitis have also been observed, usually with hepatic dysfunction and liver toxicity.
In case of prolonged use of large doses, hematopoietic system disorders may occur: aplastic anemia, pancytopenia, agranulocytosis, neutropenia, leukopenia, thrombocytopenia. Large doses

may bring on nervous system disorders, such as dizziness, psychomotor agitation, and disorientation, urinary system disorders: nephrotoxicity (renal colic, interstitial nephritis, papillary necrosis), digestive system disorders: hepatonecrosis.
Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage.
Risk factors for paracetamol overdose include:

- long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes;
- regular abuse of alcohol;
- decrease in the level of glutathione, e.g., with eating disorders, starvation, cachexia, cystic fibrosis, HIV infection.

Treatment: urgent measures of supportive and symptomatic therapy.
In case of overdose, emergency medical assistance is necessary. Treatment of overdose or even suspected overdose should be started immediately, the patient should be taken to hospital, even despite of lack of significant early overdose symptoms, as liver damage may not develop immediately. Plasma concentration of paracetamol should be measured 4 hours after the intake or later (earlier concentrations are unreliable).
If the excessive dose of paracetamol (over 150 mg/kg) has been taken within 1 hour, advisability of use of the activated carbon should be considered. Treatment with N-acetylcysteine or methionine may be of benefit. Symptomatic treatment is also required.

Adverse reactions.
Blood and lymphatic disorders: thrombocytopenia, leukopenia, agranulocytosis, anemia, including aplastic and hemolytic anemia (especially for patients with glucose-6-phosphate dehydrogenase deficiency).
Immune system disorders: hypersensitivity reactions, anaphylactic and anaphylactoid reactions (including hypotension and shock), angioedema (including face edema).
Skin and subcutaneous tissue disorders: rash; urticaria; erythema, bullous reactions, eczema, erythema, exudative erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), exfoliative dermatitis, alopecia, photosensitivity, purpura (including allergic purpura), pruritus.
Psychiatric disorders: disorientation, depression, insomnia, nightmare, irritability, psychotic disorder, hallucinations.
Nervous system disorders: headache, dizziness; drowsiness, fatigue; paresthesia, memory impairment, convulsion, tremor, aseptic meningitis, taste disturbances, cerebrovascular disorders, stroke; confusion, impaired sensitivity, general malaise.
Eye disorders: visual impairment, vision blurred, diplopia; optic neuritis.
Ear and labyrinth disorders: vertigo; tinnitus, hearing impaired.
Cardiac disorders: palpitations, chest pain, heart failure, myocardial infarction, hypertension, hypotension, vasculitis; Kounis syndrome.
Respiratory, thoracic and mediastinal disorders: asthma (including dyspnea); bronchospasm (especially in patients sensitive to acetylsalicylic acid and other NSAIDs), pneumonitis.
Gastrointestinal disorders: nausea, vomiting, diarrhea, dyspepsia, abdominal pain, flatulence, anorexia; gastritis, gastrointestinal hemorrhage (hematemesis, melena, diarrhea hemorrhagic), gastrointestinal ulcer, with or without bleeding, gastrointestinal stenosis, or perforation (sometimes fatal, especially in elderly patients), which can lead to peritonitis; colitis (including hemorrhagic colitis, ischemic colitis and exacerbation of ulcerative colitis Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, esophageal dysfunction, diaphragm-like intestinal stenosis, pancreatitis.
Hepatobiliary disorders: transaminases increased; hepatitis, jaundice, liver disorder; fulminant hepatitis, hepatic necrosis, hepatic dysfunction, hepatic failure.

Renal and urinary disorders: fluid retention, edema; acute kidney damage (acute renal failure), hematuria, proteinuria, interstitial nephritis, nephrotic syndrome, renal papillary necrosis.
Reproductive system and breast disorders: impotence.
General disorders and administration site conditions: edema.
Clinical trials and epidemiological data suggest that there is a slightly increased risk of thrombotic complications (e.g., myocardial infarction and stroke) with the use of diclofenac, particularly with the use of high therapeutic doses (150 mg per day) and during long-term treatment.
Visual disturbances. Visual disturbances such as visual impairment, blurred vision or diplopia appear to be NSAID class effects and are usually reversible on discontinuation. A likely mechanism for the visual disturbances is the inhibition of prostaglandin synthesis and other related compounds that alter the regulation of retinal blood flow resulting in potential visual impairments. If such symptoms occur during diclofenac treatment, an ophthalmological examination may be considered to exclude other causes.
Also, after taking paracetamol, the following side effects are possible: epigastric pain, hypoglycemia, up to hypoglycemic coma, sulfhemoglobinemia and methemoglobinemia (cyanosis, shortness of breath, heart pain), hemolytic anemia, bruising or bleeding, increased activity of liver enzymes, usually without the development of jaundice.

Reporting of suspected adverse reactions.
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Medical and pharmaceutical workers, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of effectiveness of the medicinal product through the Pharmacovigilance Automated Information System at: https://aisf.dec.gov.ua.

Shelf life. 3 years.

Storage conditions.
Store in original package at a temperature below 25ºC.
Keep out of reach of children.

Package.
4 tablets in a blister; 25 blisters in a carton package.
10 tablets in a blister; 10 blisters in a carton package.

Conditions of supply. By prescription.

Manufacturer.
Kusum Healthcare Pvt Ltd.

Location of manufacturer and its address of its business activity.
SP-289 (A), RIICO Industrial area, Chopanki, Bhiwadi, Dist. Alwar (Rajasthan), India

Date of last revision.