APPROVED
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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 torpedo shaped suppositories.

Pharmacotherapeutic group. Anti-inflammatory and antirheumatic products, non-steroids.
Code ATC M01A B05.

Pharmacological properties.
Pharmacodynamics.
Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAID) that has a pronounced analgesic and anti-inflammatory effect. It is an inhibitor of prostaglandin-synthetase (cyclooxygenase).
Pharmacokinetics.
Absorption
Absorption is rapid; although the rate of absorption is slower than from enteric-coated tablets.
After the administration of 50 mg suppositories, peak plasma concentrations (C_{max}) are attained on average within 1 hour, but maximum concentrations per dose unit are about two thirds of those reached after administration of enteric-coated tablets (1.95 ± 0.8 μg/ml (1.9 μg/ml ≡ 5.9 μmol/l)).
Bioavailability
As with oral preparations the area under the pharmacokinetic concentration-time curve (AUC) is approximately a half of the value obtained from a parenteral dose. Pharmacokinetic behavior does not change on repeated administration. Accumulation does not occur, provided the recommended dosage intervals are observed.
Distribution
The active substance is 99.7% protein bound, mainly to albumin (99.4%).
Diclofenac enters the synovial fluid, where its C_{max} are measured 2–4 hours after the peak plasma values have been attained. The apparent half-life for elimination from the synovial fluid is 3–6 hours. Two hours after reaching the C_{max}, concentrations of the active substance are already higher in the synovial fluid than they are in the plasma and remain higher for up to 12 hours.
Diclofenac was detected in a low concentration (100 ng/mL) in breast milk in one nursing mother. The estimated amount ingested by an infant consuming breast milk is equivalent to a 0.03 mg/kg/day dose.

Metabolism
Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites, most of which are converted to glucuronide conjugates. Two phenolic metabolites are biologically active, but to a much lesser extent than diclofenac.
Elimination
The total systemic clearance of diclofenac in plasma is 263 ± 56 mL/min (mean value ± SD). The terminal half-life in plasma is 1–2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1–3 hours. About 60% of the administered dose is excreted in the urine in the form of the glucuronide conjugate of the intact molecule and as metabolites, most of which are also converted to glucuronide conjugates. Less than 1% of diclofenac is excreted as unchanged substance. The rest of the dose is eliminated as metabolites in the faeces.
Pharmacokinetics in special populations
Elderly patients
No relevant age-dependent differences in the drug's absorption, metabolism, or excretion have been observed, other than the finding that in five elderly patients, a 15-minute IV infusion resulted in 50% higher plasma concentrations than expected with young healthy subjects.
Patients with renal impairment
In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule. At a creatinine clearance of less than 10 mL/min, the calculated steady-state plasma levels of the hydroxy metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile.
Patients with hepatic disease
In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

Clinical characteristics.
Indications.
- Inflammatory and degenerative forms of rheumatism such as rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis including spondylarthritis;
- painful syndromes of the vertebral column;
- rheumatism of extra-articular soft tissues;
- post-traumatic and post-operative pain, accompanied by inflammation and swelling, e.g., following dental or orthopedic surgery;
- painful and/or inflammatory conditions in gynecology, e.g., primary dysmenorrhea or adnexitis;
- migraine attacks;
- acute attacks of gout;
- as an adjuvant in severe painful inflammatory infections of the ear, nose or throat, e.g., pharyngotonsillitis, otitis.

In keeping with general therapeutic principles, the underlying disease should be treated with basic therapy, as appropriate. Fever alone is not an indication.

Contraindications.
- Hypersensitivity to the active substance or any of the excipients;
- history of gastrointestinal bleeding or perforation, relating to previous NSAID therapy;
- active gastric or duodenal peptic ulcer/hemorrhage or history of recurrent peptic ulcer/hemorrhage (two or more distinct episodes of proven ulceration or bleeding);
- III trimester of pregnancy;
- inflammatory bowel diseases (e.g., Crohn's disease or ulcerative colitis);

- hepatic failure;
- renal failure (glomerular filtration rate (GFR) <15 mL/min/1.73 m^2);
- established congestive heart failure (NYHA 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 suffered a stroke or have episodes of transient ischemic attacks;
- peripheral arterial disease;
- proctitis;
- like other NSAIDs, diclofenac is also contraindicated in patients in whom attacks of asthma, urticaria, angioedema, acute rhinitis, or nasal polyps are precipitated by acetylsalicylic acid or other NSAIDs.

Interaction with other medicinal products and other forms of interaction.
The following interactions include those observed with diclofenac enteric tablets and/or other pharmaceutical forms of diclofenac.
Lithium. If used concomitantly, diclofenac may increase plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.
Digoxin. If used concomitantly, diclofenac may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.
Diuretics and antihypertensive agents. Like other NSAIDs, concomitant use of diclofenac with diuretics and antihypertensive agents (e.g., beta-blockers, angiotensin converting enzyme (ACE) inhibitors may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis. Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity.
Drugs known to cause hyperkalemia. Concomitant treatment with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored frequently.
Anticoagulants and anti-platelet agents. Caution is recommended since concomitant administration could increase the risk of bleeding. Although clinical investigations do not appear to indicate that diclofenac has an influence on the effect of anticoagulants, there are reports of an increased risk of hemorrhage in patients receiving diclofenac and anticoagulant concomitantly. Therefore, to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is required. As with other NSAIDs, diclofenac in a high dose can reversibly inhibit platelet aggregation.
Other NSAIDs including cyclooxygenase-2 selective inhibitors and corticosteroids. Co-administration of diclofenac with other systemic NSAIDs or corticosteroids may increase the risk of gastrointestinal bleeding or ulceration. Avoid concomitant use of two or more NSAIDs.
Selective serotonin reuptake inhibitors (SSRIs). Concomitant administration of NSAIDs and SSRIs may increase the risk of gastrointestinal bleeding.
Antidiabetics. Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However there have been isolated reports of hypoglycemic and hyperglycemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.
There have also been isolated reports of metabolic acidosis when diclofenac was co-administered with antidiabetic agents, especially in patients with pre-existing renal impairment.

Methotrexate. Diclofenac can inhibit the tubular renal clearance of methotrexate hereby increasing methotrexate levels. Caution is recommended when diclofenac is administered less than 24 hours before treatment with methotrexate, since blood concentrations of methotrexate may rise, and the toxicity of this substance be increase. Cases of serious toxicity have been reported when methotrexate and NSAIDs including diclofenac are given within 24 hours of each other. This interaction is mediated through accumulation of methotrexate resulting from impairment of renal excretion in the presence of the NSAID.
Ciclosporin. Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin due to the effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin.
Tacrolimus. Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus. This might be mediated through renal antiprostaglandin effects of both NSAID and calcineurin inhibitor. Therefore, diclofenac should be given at doses lower than those that would be used in patients not receiving tacrolimus.
Quinolone antibacterials. Convulsions may occur due to an interaction between quinolones and NSAIDs. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving an NSAID.
Phenytoin. When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to 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 in patients may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.
Mifepristone. NSAIDs should not be used for 8–12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.
CYP2C9 inhibitors. Caution is recommended when co-prescribing diclofenac with CYP2C9 inhibitors (such as voriconazole), which could result in a significant increase in plasma C_{max} and exposure to diclofenac.
CYP2C9 inducers. Caution is recommended when co-prescribing diclofenac with CYP2C9 inducers (such as rifampicin), which could result in a significant reduction in peak plasma concentrations and exposure to diclofenac.

Special warnings and precautions for use.
General
Gastrointestinal ulceration, bleeding or perforation may occur at any time during treatment with diclofenac, whether COX-2 selective or not, even in the absence of warning symptoms or a predisposing history. Undesirable effects may be minimized by using the lowest effective dose of Diclosafe® for the shortest duration necessary.
An increased risk of thrombotic cardiovascular and cerebrovascular complications with certain COX-2 selective inhibitors have been seen in placebo-controlled trials. It is not yet known whether this risk correlates directly with the COX-1/COX-2 selectivity of individual NSAIDs.
The concomitant use of Diclosafe® with systemic NSAIDs including COX-2 selective inhibitors should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects.
As no comparable clinical study data are available at present for long-term treatment with the maximum dosage of diclofenac, the possibility of a similarly elevated risk cannot be ruled out. Until such data becomes available, a careful risk-benefit assessment must be carried out prior to using diclofenac in patients with clinically confirmed coronary heart disease, cerebrovascular

disorders, peripheral arterial occlusive disease or considerable risk factors (e.g., hypertension, hyperlipidemia, diabetes mellitus, smoking). Due to this risk, the lowest effective dose should be given for the shortest possible duration of treatment.
Caution is indicated when using the drug in patients over 65 years of age. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight.
As with other NSAIDs including diclofenac, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug. Like other NSAIDs, Diclosafe® may mask signs and symptoms of infection due to its pharmacodynamic properties.
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.
Gastrointestinal effects
Gastrointestinal bleeding (hematemesis, melaena), ulceration or perforation which can be fatal has been reported with all NSAIDs including diclofenac and may occur at any time during treatment, with or without warning symptoms or a previous history of serious GI events. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving diclofenac, the drug should be withdrawn.
As with all NSAIDs, close medical surveillance is imperative and particular caution should be exercised when prescribing diclofenac in patients with symptoms indicative of gastrointestinal disorders. The risk of GI bleeding, ulceration or perforation is higher with increasing diclofenac doses, and in patients with a history of ulcer, particularly if complicated with hemorrhage or perforation, and in the elderly.
The elderly have increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.
To reduce the risk of GI toxicity, the treatment should be initiated and maintained at the lowest effective dose.
Combination therapy with protective agents (e.g., proton pump inhibitors or misoprostol) should be considered for these patients, and also for patients requiring concomitant use of medicinal products containing low dose acetylsalicylic acid (ASA/aspirin or medicinal products likely to increase gastrointestinal risk. Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding). Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants such as warfarin, anti-platelet agents such as acetylsalicylic acid or SSRIs.
NSAIDs, including diclofenac, may be associated with increased risk of gastrointestinal anastomotic leak. Close medical surveillance and caution are recommended when using Diclosafe® after gastrointestinal surgery.
Hepatic effects
Close medical surveillance is required when prescribing Diclosafe® to patients with impairment of hepatic function as their condition may be exacerbated.
As with other NSAIDs, including diclofenac, values of one or more liver enzymes may increase.
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. Elevated enzyme levels were generally reversible after discontinuation of the drug.

During prolonged treatment with diclofenac, regular monitoring of hepatic function is indicated as a precautionary measure. If abnormal liver function tests persist or worsen, if clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (e.g., eosinophilia, rash), Diclosafe® 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, is possible without prodromal symptoms. Caution is required when using Diclosafe® in patients with hepatic porphyria, since it may trigger an attack.

Renal effects

Owing to the importance of prostaglandins in maintaining renal blood flow, prolonged treatment with high doses of NSAIDs, including diclofenac, frequently (1–10%) results in oedema and hypertension.

As fluid retention and oedema have been reported in association with NSAID therapy, including diclofenac, particular caution is required in patients with impaired cardiac or renal function, in patients with a history of hypertension, in elderly patients, in patients receiving concomitant treatment with diuretics or medicinal products that may significantly impact renal function, and in 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 in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

Skin effects

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-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. Diclosafe® should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases with diclofenac without earlier exposure to the drug.

Systemic lupus erythematosus and mixed connective tissue disease

In patients with systemic lupus erythematosus and mixed connective tissue disorders there may be an increased risk of aseptic meningitis.

Cardiovascular and cerebrovascular effects

Treatment with diclofenac is generally not recommended in patients with established cardiovascular disease (e.g., heart failure, established 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 of up to 100 mg daily if treated for more than 4 weeks. As the cardiovascular risks of diclofenac may 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.

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with diclofenac therapy.

Clinical trial and epidemiological data suggest that use of diclofenac (particularly at high doses, 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).

The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially when treatment continues for more than 4 weeks.

Patients should remain alert for the signs and symptoms of serious arterial thromboembolic events (e.g., chest pain, shortness of breath, weakness, slurring of speech), which can occur without warning. Patients should be instructed to see a physician immediately in case of such an event.

Hematological effects

During prolonged treatment with diclofenac, as with other NSAIDs, monitoring of the blood count is recommended.

Diclofenac may reversibly inhibit platelet aggregation. Patients with defects of hemostasis, bleeding diathesis or hematological abnormalities should be carefully monitored.

Pre-existing asthma

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 than in other patients. 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 skin reactions, 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.

Use during pregnancy or breastfeeding.

Pregnancy.

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and or cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1% up to approximately 1.5%.

In animals, administration of a prostaglandin synthesis inhibitor has shown to result in increased pre-and post-implantation loss and embryo-fetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during organogenetic period.

First/second trimester of pregnancy

During the first and second trimester of pregnancy, diclofenac can be prescribed only when the expected benefit to the woman exceeds the potential risk to the fetus. If diclofenac is used by a woman attempting to conceive, or during the first or second trimester of pregnancy, the dose of Diclosafe® should be kept as low and duration of treatment as short as possible.

Oligohydramnios / fetal renal impairment

From the 20th week of pregnancy onward, diclofenac use may cause oligohydramnios resulting from fetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation.

Antenatal monitoring for oligohydramnios should be considered after exposure to diclofenac for several days from gestational week 20 onward. Diclofenac should be discontinued if oligohydramnios is found.

Third trimester of pregnancy

Diclofenac is contraindicated during the third trimester of pregnancy.

All prostaglandin synthetase inhibitors may:

- expose the fetus to the following risks: cardiopulmonary toxicity (with premature closure of the ductus arteriosus, and pulmonary hypertension, renal dysfunction (see above);

- expose the mother and child to the following risks: possible prolongation of bleeding time, an effect of inhibition of platelet aggregation even at very low doses; inhibition of uterine contractions, resulting in delayed or prolonged labor.

Breastfeeding

As with other NSAIDs, small amounts of diclofenac pass into the breast milk. As a precaution, diclofenac suppositories should therefore not be used by women who are breastfeeding in order to avoid undesirable effects in the infant. If treatment is essential, the infant should be switched to bottle feeding.

Fertility

As with other NSAIDs, the use of diclofenac may impair female fertility and is not recommended in women attempting to conceive. In women who may have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of diclofenac should be considered.

In animals, based on relevant data, impairment of male fertility cannot be ruled out. The relevance of this finding for humans is unclear.

Effects on the ability to drive and use machines.

Patients who experience visual disturbances, dizziness, vertigo, somnolence, central nervous system disturbances, drowsiness or fatigue while taking diclofenac should refrain from driving or operating machinery.

Administration and dosage.

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms.

Not to be taken by mouth, as per rectal administration only. The suppositories should be inserted well into the rectum. It is recommended to insert the suppositories after passing stools. The suppositories should not be cut apart, as such a change in the method of administration may lead to uneven distribution of the active substance.

The recommended initial daily dose is 100–150 mg. In milder cases, as well as for long-term therapy, 75*–100 mg daily is usually sufficient.

The total daily dosage should be divided into 2–3 doses. To suppress nocturnal pain and morning stiffness, treatment during the day can be supplemented by the administration of a suppository at bedtime (up to a maximum daily dose of 150 mg).

In primary dysmenorrhea, the daily dosage should be individually adjusted and is generally 50–150 mg. Initially, a dose of 50–100 mg should be given and, if necessary, raised in the course of several menstrual cycles up to a maximum of 150 mg/day.

Treatment should be started upon appearance of the first pain symptoms and continued for a few days, depending on the dynamics of symptoms regression.

Treatment of migraine attacks should be started with a dose of 100 mg at the first signs of an impending attack. Additional suppositories up to 100 mg diclofenac may be taken on the same day if required. Should the patient require further therapy on the following days, the maximum daily dosage should be limited to 150 mg in 2–3 divided doses.

* Use in the appropriate dosage.

For treatment of juvenile rheumatoid arthritis, the daily dosage can be raised up to a maximum of 3 mg/kg body weight, which is the maximum daily dose and should not exceed 150 mg per day. 50 mg suppositories are recommended for use in children over 14 years of age.

Elderly

Although the pharmacokinetics of diclofenac are not impaired to any clinically relevant extent in elderly patients, diclofenac 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 diclofenac therapy.
Renal impairment
Diclofenac is contraindicated in patients with renal failure (GFR <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 renal dysfunction (see "Special warnings and precautions for use" section).
Hepatic impairment
Diclofenac 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).

Children.
Diclosafe®, 50 mg suppositories are not recommended for use in children and adolescents below 14 years of age because of their dosage strength. The drug can be used by children over 14 years old.

Overdose.
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, fainting or convulsions. In the case of significant poisoning acute renal failure and liver damage are possible.
Treatment
Patients should be treated symptomatically as required. 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, due to the high protein binding and extensive metabolism.
Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of potentially toxic amounts. Frequent or prolonged convulsions should be treated with intravenous diazepam. Other measures may be indicated by the patient's clinical condition.

Adverse reactions.
Adverse reactions are ranked using the following convention: very common (>1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1000); very rare (<1/10,000); not known: cannot be estimated from available data.
Blood and lymphatic system disorders: very rare – thrombocytopenia, leukopenia, anemia (including hemolytic and aplastic anemia), agranulocytosis.
Immune system disorders: rare – hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock); very rare – angioedema (including facial oedema).
Psychiatric disorders: very rare – disorientation, depression, insomnia, irritability, nightmares, psychotic disorder.
Nervous system disorders: common – headache, dizziness; rare – somnolence, tiredness; very rare – paresthesia, memory impairment, convulsions, anxiety, tremor, aseptic meningitis, dysgeusia,

cerebrovascular accident; not known – confusion, hallucinations, disturbances of sensation, malaise.
Eye disorders: very rare – visual disturbances, vision blurred, diplopia; not known – optic neuritis.
Ear and labyrinth disorders: common – vertigo; very rare – tinnitus, impaired hearing.
Cardiac disorders: common – hypertension; uncommon* – palpitations, chest pain, heart failure, myocardial infarction, hypotension; very rarely – vasculitis; not known – Kounis syndrome.
vascular disorders: very rare: hypertension, vasculitis.
Respiratory, thoracic and mediastinal disorders: rare – asthma (including dyspnea); very rare – pneumonitis.
Gastrointestinal disorders: common – nausea, vomiting, diarrhea, dyspepsia, epigastric pain, abdominal pain, flatulence, anorexia, decreased appetite; rare – gastritis, gastrointestinal bleeding, hematemesis, melena, hemorrhagic diarrhea, gastrointestinal ulcer with or without bleeding, gastrointestinal stenosis or perforation (sometimes fatal particularly in the elderly), which can lead to 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, esophageal dysfunction, diaphragm-like intestinal strictures, pancreatitis, exacerbation of hemorrhoids.
Hepatobiliary disorders: common – increased transaminases; rare – hepatitis, jaundice, hepatic dysfunction; very rare – fulminant hepatitis, hepatic necrosis, hepatic failure.
Skin and subcutaneous tissue disorders: common – rash; rare – urticaria; very rare – bullous dermatitis, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic epidermal necrolysis), exfoliative dermatitis, alopecia, photosensitivity reaction, purpura, including allergic purpura, Henoch-Schoenlein purpura, pruritus.
Renal and urinary tract disorders: common – fluid retention, oedema; very rare – acute kidney injury (acute renal failure), hematuria, proteinuria, tubulointerstitial nephritis, nephrotic syndrome, renal papillary necrosis.
General disorders and administration site conditions: rare – application site irritation; rare – oedema.
Reproductive system and breast disorders: very rare – impotence.
* The frequency reflects data from long-term treatment with a high dose (150 mg/day).
Clinical trial and epidemiological data consistently point towards an increased risk of arterial thrombotic events (e.g., myocardial infarction or stroke) associated with the use of diclofenac, particularly at high doses (150 mg daily) and in long term treatment.
Visual effects.
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 changes in vision. If such symptoms occur during diclofenac treatment, an ophthalmological examination may be considered to exclude other causes.
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 temperature below 25°C.
Keep out of reach of children.

Package.
5 suppositories in a strip; 2 strips in a carton pack.

Conditions of supply.
By prescription.

Manufacturer.
KUSUM HEALTHCARE PVT LTD.

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

Date of last revision.