DICLOFENAC

Rx DIFLOSID 25mg/mL

Solution for Injection (I.M. / I.V.)

NON-OPIOID ANALGESIC

FORMULATION:
Each 3 mL ampoule contains:
Diclofenac (as Sodium)..... 75 mg

PRODUCT DESCRIPTION:
Clear colorless solution free from particles. Diclofenac is a nonsteroidal anti-inflammatory drug taken or applied to reduce inflammation and as an analgesic reducing pain in certain conditions.

INDICATIONS:
For Intramuscular Use:
For acute forms of pain, including renal colic, exacerbations of osteo- and rheumatoid arthritis, acute back pain, acute gout, acute trauma and fractures, and post-operative pain.
For Intravenous Infusion Use:
For treatment or prevention of post-operative pain in the hospital setting.

DOSAGE AND ADMINISTRATION:
75 mg/3 mL daily, injected deep intramuscularly (in the gluteal region). In severe cases, 2 injections separated by an interval of 30 minutes, if necessary can be given per day. Maximum dosage of Diclofenac (as Sodium) is 150 mg and should not be given for more than 2 days or may also be given as a continuous or intermittent infusion in glucose 5% or sodium chloride 0.9% or as prescribed by the physician.

CONTRAINDICATIONS:
- Hypersensitivity to the active substance, sodium metabisulphite or any of the excipients;
- Active, gastric or intestinal ulcer, bleeding or perforation;
- History of gastrointestinal bleeding or perforation, relating to previous NSAID (Non-steroidal Anti-inflammatory Drug) therapy;
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding);
- Last trimester of pregnancy;
- Severe hepatic, renal or cardiac failure;
- Like other NSAIDs, Diclofenac is also contraindicated in patients in whom attacks of asthma, angioedema, urticaria or acute rhinitis are precipitated by ibuprofen, acetylsalicylic acid or other NSAID;
- Established Congestive Heart Failure (NYHA II-IV), Ischemic Heart Disease, Peripheral Arterial Disease and/or Cerebrovascular Disease.

Specifically for IV Use:
- Concomitant NSAID or anticoagulant use (including low dose heparin);
- History of haemorrhagic diathesis, a history of confirmed or suspected cerebrovascular bleeding;
- Operations associated with a high risk of haemorrhage;
- History of asthma;
- Moderate or severe renal impairment (serum creatinine > 160 µmol/L);
- Hypovolemia or dehydration from any cause.

PHARMACOKINETIC:
Absorption: After administration of 75mg diclofenac by intramuscular injection, absorption sets in immediately, and mean peak plasma concentrations of about 2.558 ± 0.968µg/ml (2.5µg/mL = 8µmol/L) are reached after about 20 minutes. The amount absorbed is in linear proportion to the size of the dose.
Intravenous infusion: When 75mg diclofenac is administered as an intravenous infusion over 2 hours, mean peak plasma concentrations are about 1.875 ± 0.436µg/ml (1.9µg/mL = 5.9µmol/L). Shorter infusions result in higher peak plasma concentrations.

PHARMACOTHERAPEUTIC:
Nonsteroidal anti-inflammatory drugs (NSAIDs).
Mechanism of action
diclofenac is a nonsteroidal agent with marked analgesic/anti- inflammatory properties. It is an inhibitor of prostaglandin synthetase, (cyclo-oxygenase). Diclofenac sodiumEin vitroEdoes not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in human beings. When used concomitantly with opioids for the managemeht of post-operative pain, Voltarol often reduces the need for opioids.

PREGNANCY AND LACTATION:
Pregnancy: Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal 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%.
The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has shown to result in increased pre-and post-implantation loss and embryo-foetal lethality.
The mother and the neonate, at the end of the pregnancy, possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses inhibition of uterine contractions resulting in delayed or prolonged labour Consequently, Voltarol is contra-indicated during the third trimester of pregnancy.
Lactation: Like other NSAIDs, diclofenac passes into breast milk in small amounts. Therefore, diclofenac should not be administered during breast feeding in order to avoid undesirable effects in the infant (see section 5.2 Pharmacokinetic properties).
Female 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. See also section 4.4 Special warnings and precautions for use, regarding female fertility.

OVERDOSE & TREATMENT:
There is no typical clinical picture resulting from diclofenac over dosage. Over dosage can cause symptoms such as headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, diarrhoea, dizziness, disorientation, excitation, coma, drowsiness, tinnitus, fainting or convulsions. In the case of significant poisoning acute renal failure and liver damage are possible. In case of overdosage/aggravated symptoms, appropriate monitoring and management should be implemented.

WARNINGS & PRECAUTIONS:
Diclofenac (as sodium) should not be given to patients with peptic ulceration and should be used with caution in patients with a history of such disorders. To reduce the risk of gastro-intestinal effects, the drug may be taken with or after food or milk. Antacids, histamine, H_2– receptors antagonists, Omeprazole, sucralfate, or misoprostol may be used for a similar purpose. However, food, milk and such measures may reduce the rate and extent of drug absorption. Diclofenac (as sodium) should be used with caution in patients with infection, since symptoms such as fever and inflammation may be masked, and also used with caution in patients with asthma or allergic disorders. Other general precautions to be observed include administration to patients with hemorrhagic disorders, hypertension, and impaired renal, hepatic or cardiac function. Regular use of Diclofenac Sodium in the third
trimester of pregnancy may result in pressures of fetal ductus arteriosus in the uterus, and possibly in persistent pulmonary.

ADVERSE EFFECTS:
General and administration site effects: Fluid Retention & Edema have been observed in some patients taking Diclofenac. Therefore as with other NSAIDs, Diclofenac should be used with caution in patients with history of cardiac de-compensation, hypertension, or other conditions predisposing to fluid retention. There may be pain, and occasionally tissue damage at the site of injection when given intramuscularly.
Hematologic: Anemia is sometimes seen in patients receiving Diclofenac or other NSAIDs. This may be due to fluid retention, gastrointestinal blood loss, or an incompletely described effect upon erythropoiesis. Others adverse effects include thrombocytopenia, leucopenia, hemolytic anemia, aplastic anemia and agranulocytosis.
Immune System: Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock), angioneurotic edema (including face edema).
Psychiatric effects: disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.
Nervous System: Headache, dizziness; Somnolence, tiredness; Paresthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident; Confusion, hallucinations, disturbances of sensation, malaise.
Eye disorders: Visual disturbances, blurred vision, diplopia; Optic neuritis.
Ear and Labyrinth disorders: Vertigo; Tinnitus and impaired hearing.
Cardiovascular Effects: Palpitations, chest pain, cardiac failure, myocardial infarction.
Vascular Effects: Hypertension, hypotension, vasculitis.
Respiratory, Thoracic and Mediastinal Effects: Asthma (including dyspnea); Pneumonitis.

Gastorintestinal Effects: Nausea, vomiting, diarrhea, abdominal pain, flatulence, anorexia; Gastritis, gastrointestinal ulcer with or without bleeding or perforation (sometimes fatal particularly in the elderly); Colitis (including hemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, esophageal disorder, diaphragm-like intestinal strictures, pancreatitis.
Hepatobiliary Effects: Transaminases increased; Hepatitis, jaundice, liver disorder; Fulminant hepatitits, hepatic necrosis, hepatic failure.
Skin and subcutaneous tissue Effects: Rash; Urticaria; Bullous eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura, allergic purpura, pruritus.
Renal Effects: As class, NSAIDs have been associated with renal papillary necrosis and other abnormal renal pathology long-term administration to animals. In patients treated with Diclofenac, rare cases of interstitial nephritis have been reported. A second form of renal toxicity, generally associated with NSAIDs, is seen in patients with conditions leading to a reduction in renal blood flow or blood volume, where renal prostaglandins have a supported role in the maintenance of renal perfusion. In these patients, administration of NSAIDs results in a dose-dependent decrease in prostaglandin synthesis and, secondarily, in a reduction of renal blood flow, which may precipitate over acute renal failure. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Other adverse effects include hematuria and proteinuria.*Porphyria:* The use of Diclofenac in patients with hepatic Porphyria should be avoided.
Aseptic Meningitis: As with other NSAIDs, aseptic meningitis with fever and coma has been observed on rare occasional patients on Diclofenac therapy. Although it is probably more likely to occur in patients with systemic lupus erythematous and related connective tissue diseases, it has been reported in patients who do not have underlying chronic diseases. If signs or symptoms of meningitis develop in a patient on Diclofenac, the possibility of it being related to Diclofenac therapy should be considered.

REPORTING OF SUSPECTED ADVERSE REACTIONS:
To allow continued monitoring of the benefit/risk balance of the medicinal product, reporting of suspected adverse reaction is necessary. Healthcare professionals are encouraged to report any suspected adverse reaction directly to the importer/distributor and/or to FDA: www.fda.gov.ph. Patients are advised to seek immediate medical attention at the first sign/s of adverse reactions.

DRUG INTERACTIONS:
The following interactions include those observed with diclofenac gastro-resistant 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.
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 Voltarol has an influence on the effect of anticoagulants, there are isolated reports of an increased risk of haemorrhage 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 nonsteroidal anti-inflammatory agents, 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 SSRI's 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 hypoglycaemic and hyperglycaemic 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.
Methotrexate: Diclofenac can inhibit the tubular renal clearance of methotrexate hereby increasing methotrexate levels. Caution isrecommended when NSAIDs, including diclofenac, are 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 antiprostagladin effects of both NSAID and calcineurin inhibitor.
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 glomerular filtration rate.
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.
Potent cytochrome P2C9 inhibitors: Caution is recommended when coprescribing
diclofenac with potent cytochrome P2C9 inhibitors (such as voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism.

CAUTION:
Foods, Drugs, Devices & Cosmetics Act prohibits dispensing without prescription.

STORAGE CONDITION:
Store at temperatures not exceeding 30°C.

AVAILABILITY:
USP Type I Amber Glass Ampoule x 3 mL In 2 Plastic Trays x 5's (Box of 10's)

FDA REGISTRATION No.:DRP-6689
RENEWAL OF AUTHORIZATION: 04 July 2019
REVISION OF PACKAGE INSERT: 09 November 2021

Manufactured by:
GEOFMAN PHARMACEUTICALS
GEOFMAN 20/23, Korangi Industrial Area, Karachi, Pakistan.

Imported & Distributed by:
SAHAR INTERNATIONAL TRADING INC.
SAHAR 354 Aguirre Ave., Phase-III, BF Homes, Parañaque City.