(given i.m. or i.v.) should not be given for more than 2 days; if necessary, treatment can be continued with tablets or suppositories.
Combinations with other dosage forms of Diclofenac (tablets or suppositories) can be used up to the maximum daily dosage of 150mg.
Renal colic: One 75 mg ampoule intramuscularly. A further ampoule may be administered after 30 minutes if necessary. The recommended maximum daily dose of 150 mg in any combination of the three formulations of Diclofenac should not be exceeded.
"Diclofenac Injection can also be given by an intravenous infusion, never as a bolus."
Ampoules for intravenous use:
Prior to infusion it must be diluted with 100-500ml of either sodium chloride solution (0.9%) or glucose solution (5%). Both solutions should be buffered with sodium bicarbonate solution (0.5ml 8.4% or 1ml 4.2%).
For the treatment of moderate to severe post-operative pain, 75mg should be infused over a period of 30 minutes to 2 hours. This can be repeated after 4-6 hours, without exceeding 150mg within any 24-hour period.
For the prevention of post-operative pain, a loading dose of 25mg-50mg should be infused after surgery over 15 minutes to an hour, followed by a continuous infusion of around 5mg per hour up to a maximum of 150mg daily.
Elderly:
The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest dose should be used and the patient should be monitored for GI bleeding during NSAID therapy. To be taken preferably with or after food.
Children (aged 1 - 12 years):
Diclomax ampoules are not recommended for use in children
Not to be used in newly born or premature infants.
Advice:
For intramuscular injections, the following directions must be adhered to in order to prevent damage to a nerve or other tissue at the injection site:
The solution should be injected slowly and securely intramuscularly after a control aspiration. A depot into the vicinity of nerves should be avoided. If more severe pain or malaise occurs during the injection, the procedure should be discontinued.
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control the symptoms

OVERDOSE

a) Symptoms
Symptoms of overdose include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, fainting occasionally convulsions. In cases of significant poisoning acute renal failure and liver damage are possible.
b) Therapeutic measure
Patients should be treated symptomatically as required.
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 a potentially life-threatening overdose.
Good urine output should be ensured.
Renal and liver function should be closely monitored.
Patients should be observed for at least four hours after 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.
Supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, gastro-intestinal irritation, and respiratory depression; specific therapies such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism.

EXPIRY DATE

Do not use later than the date of expiry.

STORAGE

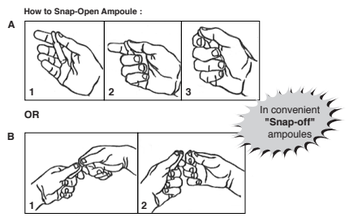
Store below 30^{0}C, protected from light.
Keep out of reach of children.

INSTRUCTIONS FOR USE/HANDLING

Diclomax solution for injection should not be mixed with other injection solutions.
Diclofenac ampoules can be given either intramuscularly by deep intragluteal injection into the upper outer quadrant, or intravenously by slow infusion after dilution as per following instructions.
Depending on the intended duration of infusion (Refer "Dosage and method of administration"), mix 100-500 ml of isotonic saline (sodium chloride 0.9 % solution) or glucose 5 % solution with sodium bicarbonate injectable solution (0.5 ml of 8.4 % or 1 ml of 4.2 % or 0.56 ml of 7.5 % or a corresponding volume of a different concentration) taken from a freshly opened container; add the contents of one Diclomax ampoule to this solution. Only clear solutions should be used. If crystals or precipitates are observed, the infusion solution should not be used.
Intravenous infusions should be initiated immediately after preparing the infusion. The infusion solutions should not be stored.
WARNING : " NOT FOR VETERINARY USE "

PRESENTATION

5 composite packs of 5 snap-off ampoules of 3 ml.



torrent

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.

at : Shantisthal, At & Post - Shirgaon, Tal - Palghar, Dist. Thane - 401 407.

8026322-805

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

DICLOMAX

(Diclofenac Sodium Injection I.P.)

COMPOSITION:

Each ml contains :
Diclofenac sodium I.P. 25 mg
Benzyl alcohol I.P. 4 % w/v
Water for injection I.P. q. s.

PHARMACOLOGICAL PROPERTIES

Mechanism of action

Diclomax contains diclofenac sodium, a non-steroidal compound with pronounced antirheumatic, anti-inflammatory, analgesic, and antipyretic properties. Inhibition of prostaglandin biosynthesis, which has been demonstrated in experiments, is considered to be fundamental to its mechanism of action. Prostaglandins play an important role in causing inflammation, pain and fever.
Diclofenac sodium *in vitro* does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in humans.

Pharmacodynamic effects

In rheumatic diseases, the anti-inflammatory and analgesic properties of Diclofenac elicit a clinical response characterised by marked relief from signs and symptoms such as pain at rest, pain on movement, morning stiffness, and swelling of the joints, as well as by an improvement in function.
Diclofenac has also been found to exert a pronounced analgesic effect in moderate and severe pain of non-rheumatic origin, an effect which sets in within 15-30 minutes. Diclofenac has also been shown to have a beneficial effect in migraine attacks.
In post-traumatic and postoperative inflammatory conditions, Diclofenac rapidly relieves both spontaneous pain and pain on movement and reduces inflammatory swelling and wound oedema. When used concomitantly with opioids for the management of post-operative pain, Diclofenac significantly reduces the need for opioids.
Diclofenac ampoules are particularly suitable for initial treatment of inflammatory and degenerative rheumatic diseases, and of painful conditions due to inflammation of non-rheumatic origin.

Pharmacokinetic Properties

Absorption

After administration of 75 mg Diclofenac by intramuscular injection, absorption sets in immediately, and mean peak plasma concentrations of about 2.5 mcg/mL (8 micromol/L) are reached after about 20 minutes. The amount absorbed is in linear proportion to the size of the dose.
When 75 mg Diclofenac is administered as an intravenous infusion over 2 hours, mean peak plasma concentrations are about 1.9 mcg/mL (5.9 micromol/L). Shorter infusions result in higher peak plasma concentrations, while longer infusions give plateau concentrations proportional to the infusion rate after 3 to 4 hours. In contrast, plasma concentrations decline rapidly once peak levels have been reached following intramuscular injection or administration of gastro-resistant tablets or suppositories.
The area under the concentration curve (AUC) after intramuscular or intravenous administration is about twice as large as it is following oral or rectal administration, because about half the active substance is metabolised during its first passage through the liver ("first pass" effect) when administered via the oral or rectal routes.
Pharmacokinetic behaviour does not change after repeated administration. No accumulation occurs provided the recommended dosage intervals are observed.

Distribution

99.7 % of Diclofenac binds to serum proteins, mainly to albumin (99.4%). The apparent volume of distribution calculated is 0.12-0.17 L/kg.
Diclofenac enters the synovial fluid, where maximum concentrations are measured 2-4 hours after peak plasma values have been reached. The apparent half-life for elimination from the synovial fluid is 3-6 hours. Two hours after reaching peak plasma levels, concentrations of the active substance are already higher in the synovial fluid than in the plasma, and they remain higher for up to 12 hours.

Biotransformation

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 (3'-hydroxy-, 4'-hydroxy-, 5-hydroxy-, 4',5-dihydroxy-, and 3'-hydroxy-4'-methoxy-diclofenac), most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active, but to a much lesser extent than Diclofenac

Elimination

Total systemic clearance of Diclofenac from 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. One metabolite, 3'-hydroxy-4'-methoxy-diclofenac, has a much longer plasma half-life. However, this metabolite is virtually inactive.
About 60% of the administered dose is excreted in the urine as the glucuronide conjugate of the intact molecule and as metabolites, most of which are also converted to glucuronide conjugates. Less than 1% is excreted as unchanged substance. The rest of the dose is eliminated as metabolites through the bile in the faeces.

Characteristics in patients

Few elderly patients a 15-minute intravenous infusion resulted in 50% higher plasma concentrations than expected from the data on young healthy subjects.
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.
In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of Diclofenac are the same as in patients without liver disease.

Preclinical Safety Data

Diclofenac did not influence fertility of the parent animals (rats) nor the pre-, peri-, and postnatal development of the offspring. No teratogenic effects were detected in mice, rats and rabbits. No mutagenic effects could be demonstrated in various *in vitro* and *in vivo* experiments, and no carcinogenic potential was detected in long-term studies in rats and mice.

THERAPEUTIC INDICATIONS

Intramuscular injection

Diclomax is used in the treatment of:

- Exacerbation of inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, ankylosing spondylitis and osteoarthritis
- Acute attacks of gout
- Renal colic
- Post-traumatic and postoperative pain, inflammation and swelling

- Pain following dental surgery
- Painful inflammatory conditions in gynaecology
- Acute back pain

Intravenous infusion

Treatment or prevention of postoperative pain in a hospital setting.

CONTRAINDICATIONS

Hypersensitivity to diclofenac or to any of the excipients. NSAIDs should not be administered to patients with active or a history of recurrent peptic ulcer/ haemorrhage (two or more distinct episodes of proven ulceration or bleeding). NSAIDs are contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin or other nonsteroidal anti-inflammatory drugs.
Specifically for intravenous 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 risk of haemorrhage.
A history of asthma.
Hypovolaemia or dehydration from any cause.
Severe heart failure, hepatic failure and renal failure.
During the last trimester of pregnancy.
History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

Warnings:
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.
Like other NSAIDs, Diclofenac may mask the signs and symptoms of infection due to its pharmacodynamic properties.
Concomitant use of NSAIDs with intravenous diclofenac is contraindicated
Cardiovascular, Renal and Hepatic impairment The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients.
Gastro-intestinal: Close medical surveillance is imperative in patients with symptoms indicative of gastrointestinal disorders, with a history suggestive of gastro-intestinal ulceration, with ulcerative colitis, Crohn's disease, or haematological abnormalities.
Gastrointestinal bleeding, ulceration and perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.
Gastro-intestinal bleeding or ulcerative/perforation, haematemesis and melaena have in general more serious consequences in the elderly. They can occur at any time during treatment with or without warning symptoms or a previous history. In the rare instances where gastro-intestinal bleeding or ulceration occurs in patients receiving Diclofenac injection, the drug should be withdrawn.
The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e g misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk.
Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.
Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, selective serotonin-reuptake inhibitors and anti-platelet agents. Concomitant use of anticoagulants with intravenous diclofenac is contraindicated.
When GI bleeding or ulceration occurs in patients receiving diclofenac, the treatment should be withdrawn. NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated.
Hepatic: Close medical surveillance is also imperative in patients suffering from severe impairment of hepatic function.
SLE and mixed connective tissue disease. In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis. Dermatological 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 high 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. Diclofenac injection should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.
Hypersensitivity reactions: As with other nonsteroidal anti-inflammatory drugs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug.
Precautions:
Cardiovascular and cerebrovascular effects:
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 NSAID therapy.
Clinical trial and epidemiological data suggest that use of diclofenac, particularly at high doses (150mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).
Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with diclofenac after careful consideration. Similar consideration should be made before initiating longer term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).
Renal: Patients with renal, cardiac or hepatic impairment and the elderly should be kept under surveillance, since the use of NSAIDs may result in deterioration of renal function. The lowest effective dose should be used and renal function monitored.
The importance of prostaglandins in maintaining renal blood flow should be taken into account in patients with impaired cardiac or renal function, those being treated with diuretics or recovering from major surgery. Effects on renal function are usually reversible on withdrawal of Diclofenac injection.
Respiratory disorders: Use of intravenous diclofenac is contraindicated in patients with a history of asthma.
Hepatic: If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), Diclofenac injection should be discontinued. Hepatitis may occur without prodromal symptoms. Use of Diclofenac injection in patients with hepatic porphyria may trigger an attack.
Haematological: Diclofenac injection may reversibly inhibit platelet aggregation. Patients with defects of haemostasis, bleeding diathesis or haematological abnormalities should be carefully monitored.
The elderly: The elderly are at increased risk of the consequences of adverse reactions.

Caution is required in patients with a history of heart failure or hypertension since oedema has been reported in association with NSAIDs. The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.
Long-term treatment: All patients who are receiving non-steroidal anti-inflammatory agents should be monitored as a precautionary measure e.g. renal function, hepatic function (elevation of liver enzymes may occur) and blood counts. This is particularly important in the elderly.

Impaired female fertility

The use of Diclofenac injection may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Diclofenac injection should be considered.

Pregnancy and Lactation

Because of insufficient data, administration of Diclofenac ampoules during pregnancy and lactation is not recommended.

Effects on Ability to Drive and Use Machines

Patients experiencing dizziness or other central nervous disturbances, including visual disturbances, should not drive or operate machinery.

UNDESIRABLE EFFECTS

The undesirable effects including with other dosage forms of Diclofenac either in short term or long term use the following frequency were used: frequent > 10 %, occasional > 1 - 10 %, rare > 0.001 - 1 %, isolated cases < 0.001 %.

Gastrointestinal tract

Occasional: epigastric pain; other gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal cramps, dyspepsia, flatulence, anorexia.
Rare: gastrointestinal bleeding, gastric or intestinal ulcer with or without bleeding or perforation.
Isolated cases: aphthous stomatitis, glossitis, oesophageal lesions, diaphragm-like intestinal strictures, lower gut disorders such as non-specific haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease, constipation, pancreatitis.

Central nervous system

Occasional: headache, dizziness, vertigo.
Rare: drowsiness.
Isolated cases: sensory disturbances, including paraesthesias, memory disturbances, disorientation, insomnia, irritability, convulsions, depression, anxiety, nightmares, tremor, psychotic reactions, aseptic meningitis.

Special senses

Isolated cases: blurred vision, diplopia, impaired hearing, tinnitus, taste disturbances.

Skin

Occasional: rashes or skin eruptions.
Rare: urticaria
Isolated cases: bullous eruptions, eczema, erythema multiforme, Stevens-Johnson syndrome, acute toxic epidermolysis, exfoliative dermatitis, loss of hair, photosensitivity reactions; purpura, including allergic purpura.

Kidney

Rare: oedema.
Isolated cases: acute renal failure, urinary abnormalities such as haematuria and proteinuria, interstitial nephritis, nephrotic syndrome, papillary necrosis.

Liver

Occasional: elevation of serum aminotransferase values.
Rare: hepatitis with or without jaundice.
Isolated cases: fulminant hepatitis.

Blood

Isolated cases: thrombocytopenia, leucopenia, haemolytic anaemia, aplastic anaemia, agranulocytosis.

Hypersensitivity

Rare: hypersensitivity reactions such as asthma, systemic anaphylactic/anaphylactoid reactions including hypotension.
Isolated cases: vasculitis, pneumonitis.

Cardiovascular system

Isolated cases: palpitation, chest pain, hypertension, congestive heart failure.

Other organ systems

Occasional: intramuscular injection site reactions such as local pain and induration.
Isolated cases: local abscesses and necrosis at the intramuscular injection site.

INTERACTIONS WITH OTHER DRUGS AND OTHER TYPES OF INTERACTIONS

(including interactions observed with other pharmaceutical forms of Diclofenac)
Lithium, digoxin: Diclofenac may raise plasma concentrations of lithium and digoxin.
Diuretics: Like other NSAIDs, Diclofenac may decrease the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels, which should therefore be monitored.
NSAIDs: Concomitant administration of systemic NSAIDs may increase the frequency of side effects.
Anticoagulants: Although clinical investigations do not appear to indicate that Diclofenac affects the action of anticoagulants, there are isolated reports of an increased risk of haemorrhage in patients receiving Diclofenac and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.
Antidiabetics: Clinical studies have shown that Diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, isolated cases have been reported of both hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of hypoglycaemic agents during treatment with Diclofenac.
Methotrexate: Caution is called for if NSAIDs are administered less than 24 hours before or after treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased.
Cyclosporin: The effects of NSAIDs on renal prostaglandins may increase the nephrotoxicity of cyclosporin.
Quinolone antibacterials: There have been isolated reports of convulsions, which may have been due to concomitant use of quinolones and NSAIDs.
Antihypertensives: reduced antihypertensive effect.
Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.
Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding.
Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding.
Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.
Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine.

DOSAGE AND DIRECTIONS FOR USE:

Ampoules for Intramuscular use: The following directions for intramuscular injection must be adhered to in order to avoid damage to a nerve or other tissue at the injection site.
Adults:
One ampoule once (or in severe cases twice) daily intramuscularly by deep intragluteal injection into the upper outer quadrant. If two injections daily are required it is advised that the alternate buttock be used for the second injection. Diclofenac injection 75 mg / 3 ml