31mm

31mm

XXXXXX

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

DICLORAN INJECTION

Diclofenac Sodium Injection

DOSAGE FORMS:
Parenteral, INJECTION

COMPOSITION
Each mL contains:
Diclofenac Sodium BP……25mg.
Benzyl Alcohol BP……..4% w/v
(As Preservative)

DESCRIPTION:
A clear, colourless to slightly yellow solution.

PHARMACODYNAMICS:
Pharmacodynamic properties
Mechanism of action (MOA)
Dicloran 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.

Pharmacodynamics (PD)
In rheumatic diseases, the anti-inflammatory and analgesic properties of diclofenac elicit a clinical response characterized 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.
In post-traumatic and post-operative inflammatory conditions, diclofenac rapidly relieves both spontaneous pain and pain on movement and reduces inflammatory swelling and wound edema.
Dicloran 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 to 30 minutes.
When used concomitantly with opioids for the management of post-operative pain, Dicloran significantly reduces the need for opioids.
Dicloran ampoules are particularly suitable for initial treatment of inflammatory and degenerative rheumatic diseases, and of painful conditions due to inflammation of non-rheumatic origin.

Pharmacokinetics:
Absorption
After administration of 75 mg diclofenac by intramuscular injection, absorption sets in immediately, and mean peak plasma concentrations of about 2.5 micrograms/mL (8 micromol/L) are reached after about 20 minutes.
When 75 mg diclofenac is administered as an intravenous infusion over 2 hours, mean peak plasma concentrations are about 1.9 micrograms/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 metabolized 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 to 0.17 L/kg.
Diclofenac enters the synovial fluid, where maximum concentrations are measured 2 to 4 hours after peak plasma values have been reached. The apparent half-life for elimination from the synovial fluid is 3 to 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/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 (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 to 2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1 to 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.
Linearity/non-linearity
The amount absorbed is in linear proportion to the size of the dose.
Special populations
Geriatric patients: No relevant age-dependent differences in the drug's absorption, metabolism, or excretion have been observed. However, in a few elderly patients a 15-minute intravenous infusion resulted in 50% higher plasma concentrations than expected from the data on young healthy subjects.
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.
Hepatic impairment: In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

INDICATIONS AND USAGE
Intramuscular injection
Treatment of:
• Exacerbations of inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, spondylarthritis, painful syndromes of the vertebral column, non-articular rheumatism.
• Acute attacks of gout.
• Renal colic and biliary colic.
• Post-traumatic and post-operative pain, inflammation and swelling.
Intravenous infusion
Treatment or prevention of post-operative pain in a hospital setting.

DOSAGE AND ADMINISTRATION
Dosage
As a general recommendation, the dose should be individually adjusted. Adverse effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms.
General target population:
Adults
Dicloran solution for injection should not be given for more than 2 days; if necessary, treatment can be continued with Dicloran tablets or suppositories.
Special populations
Renal impairment
Dicloran is contraindicated in patients with renal failure (GFR<15 mL/min/1.73m^2).
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 Dicloran to patients with renal impairment.
Hepatic impairment
Dicloran is contraindicated in patients with hepatic failure.
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 Dicloran to patients with mild to moderate hepatic impairment.

Pediatric patients (below 18 years of age)
Because of their dosage strength, the ampoules of Dicloran solution for injection are not suitable for children and adolescents.
Geriatric patients (aged 65 years or above)
No adjustment of the starting dose is generally required for elderly patients. However, caution is indicated on basic medical grounds, especially for frail elderly patients or those with a low body weight.
Established cardiovascular disease or significant cardiovascular risk factors
Treatment with Diclofenac is generally not recommended in patients with established cardiovascular disease (congestive heart failure, established ischemic heart disease, peripheral arterial disease) or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension, or significant risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking) should be treated with Dicloran only after careful consideration and only at doses ≤100 mg daily when initial treatment with Dicloran solution for injection continues with Dicloran tablets or suppositories for more than 4 weeks.
Method of administration
Intramuscular injection
The following directions for intramuscular injection must be followed in order to avoid damage to a nerve or other tissue at the injection site (which may result in muscle weakness, muscle paralysis, hypoesthesia and Embolia cutis medicamentosa (Nicolau syndrome)).
The dose is generally one 75 mg ampoule daily, given by deep intragluteal injection into the upper outer quadrant using aseptic technique. In severe cases (e.g. colic), the daily dose can exceptionally be increased to two injections of 75 mg, separated by an interval of a few hours (one into each buttock). Alternatively, one ampoule of 75 mg can be combined with other pharmaceutical forms of Dicloran (e.g. tablets, suppositories) up to a total maximum daily dose of 150 mg.
Intravenous infusion
Dicloran solution for injection must not be given as an intravenous bolus injection.
Immediately before starting an intravenous infusion, Dicloran solution for injection must be diluted with saline 0.9% or glucose 5% infusion solution buffered with sodium bicarbonate according to the instructions given in section INSTRUCTIONS FOR USE AND HANDLING.
Two alternative dosage regimens of Dicloran solution for injection are recommended.
For the *treatment* of moderate to severe post-operative pain, 75 mg should be infused continuously over a period of 30 minutes to 2 hours. If necessary, treatment may be repeated after a few hours, but the dose should not exceed 150 mg within any period of 24 hours.
For the *prevention* of post-operative pain, a loading dose of 25 mg to 50 mg should be infused after surgery over 15 minutes to 1 hour, followed by a continuous infusion of about 5 mg per hour up to a maximum daily dose of 150 mg.

WARNING AND PRECAUTIONS:
Gastrointestinal effects
Gastrointestinal bleeding ulceration or perforation, which can be fatal, have 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 gastrointestinal events. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving Dicloran, the treatment should be discontinued.
As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing Dicloran in patients with symptoms indicative of gastrointestinal (GI) disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation. The risk of GI bleeding is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with hemorrhage or perforation and in the elderly.
To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with hemorrhage or perforation, and in the elderly, 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 low-dose acetylsalicylic acid (ASA), or other drugs 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, anti-platelet agents or selective serotonin-reuptake inhibitors.
Close medical surveillance and caution should also be exercized in patients with ulcerative colitis or Crohn's disease, as their condition may be exacerbated.
NSAIDs, including diclofenac, may be associated with increased risk of gastro-intestinal anastomotic leak. Close medical surveillance and caution are recommended when using Dicloran after gastro-intestinal surgery.
Cardiovascular effects
Treatment with NSAIDs including diclofenac, particularly at high dose and in long term, may be associated with an increased risk of serious cardiovascular thrombotic events (including myocardial infarction and stroke).
Treatment with Dicloran is generally not recommended in patients with established cardiovascular disease (congestive heart failure, established ischemic heart disease, peripheral arterial disease) or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension, or significant risk factors for cardiovascular disease (e.g., hypertension, hyperlipidemia, diabetes mellitus and smoking) should be treated with Dicloran only after careful consideration and only at doses ≤100 mg daily when treatment continues 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, especially when treatment continues for more than 4 weeks.
Patients should remain alert for the signs and symptoms of serious arteriothrombotic events (e.g., chest pain, shortness of breath, weakness, slurring of speech), which can occur without warnings. Patients should be instructed to see a physician immediately in case of such an event.
Hematologic effects
During prolonged treatment with Dicloran, as with other NSAIDs, monitoring of the blood count is recommended. Like other NSAIDs, diclofenac may temporarily inhibit platelet aggregation. Patients with defects of hemostasis should be carefully monitored.
Respiratory effects (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 edema or urticaria are more frequent than in other patients. Therefore, special caution 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.
Special caution is recommended when Dicloran is used parenterally in patients with bronchial asthma because symptoms may be exacerbated.
Hepatobiliary effects
Close medical surveillance is required when prescribing Dicloran to patients with impaired hepatic function, as their condition may be exacerbated.
As with other NSAIDs, including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with Dicloran (e.g., in the form of tablets or suppositories), 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), Dicloran should be discontinued. Hepatitis may occur with use of diclofenac without prodromal symptoms.
Caution is called for when using Dicloran in patients with hepatic porphyria, since it may trigger an attack.
Skin reactions
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, including Dicloran. Patients appear to be at highest risk of 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. Dicloran 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.
Renal effects
As fluid retention and edema have been reported in association with NSAID therapy, including diclofenac, particular caution is called for in patients with impaired cardiac or renal function, history of hypertension, the elderly, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and in those patients with substantial extracellular volume depletion of any cause, e.g., before or after major surgery. Monitoring of renal function is recommended as a precautionary measure when using Dicloran in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.
Injection site reactions
Injection site reactions have been reported after the administration of Dicloran intramuscularly, including injection site necrosis and embolia cutis medicamentosa, also known as Nicolau Syndrome (particularly after inadvertent subcutaneous administration). Appropriate needle selection and injection technique should be followed during i.m. administration of Dicloran.
Geriatric patients
Caution is indicated in the elderly on basic medical grounds, especially in frail elderly patients or those with a low body weight.
Interactions with NSAIDs
The concomitant use of Dicloran with systemic NSAIDs including cyclooxygenase-2 selective inhibitors, should be avoided due to undesirable effects.
Special excipients
The sodium metabisulphite in the solution for injection can lead to isolated severe hypersensitivity reactions and bronchospasm.
Masking signs of infections
Like other NSAIDs, diclofenac may mask the signs and symptoms of infection due to its pharmacodynamic properties
The solution is to be inspected visually for particulate matter and discoloration prior to administration and should only be used if it is clear and free from particles.

INTERACTIONS
The following interactions include those observed with Dicloran solution for injection and/or other pharmaceutical forms of diclofenac.
Observed interactions to be considered
CYP2C9 inhibitors: Caution is recommended when co-prescribing diclofenac with CYP2C9 inhibitors (such as voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac.
Lithium: If used concomitantly, diclofenac may raise 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 or antihypertensive agents (e.g., beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect. 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 and periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity.
Ciclosporin and tacrolimus: Diclofenac, like other NSAIDs may increase the nephrotoxicity of ciclosporin and tacrolimus 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 or tacrolimus.
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.
Quinolone antibacterials: There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs.
Anticipated interactions to be considered
Other NSAIDS and corticosteroids: Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects.
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 affects the action of anticoagulants, there are reports of an increased risk of hemorrhage in patients receiving diclofenac and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.
Selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of systemic NSAIDs, including diclofenac, 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 both 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 metformin, especially in patients with pre-existing renal impairment.
Phenytoin: When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.
Methotrexate: Caution is recommended when NSAIDs, including diclofenac 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.
CYP2C9 inducers: Caution is recommended when co-prescribing diclofenac with CYP2C9 inducers (such as rifampicin), which could result in a significant decrease in plasma concentration and exposure to diclofenac.

SIDE EFFECTS
Tabulated summary of adverse drug reactions
Adverse drug reactions from clinical trials and/or spontaneous or literature cases (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).
The following undesirable effects include those reported with Dicloran solution for injection and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.
The following undesirable effects include those reported with Dicloran solution for injection and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.
Table 1 Adverse drug reactions

Infections and infestations	
Very rare:	Injection site abscess.
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 face edema).
Psychiatric disorders	
Very rare:	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.
Nervous system disorders	
Common:	Headache, dizziness.
Rare:	Somnolence.
Very rare:	Paresthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, dysgeusia, cerebrovascular accident.
Eye disorders	
Very rare:	Visual impairment, blurred vision, diplopia.
Ear and labyrinth disorders	
Common:	Vertigo.
Very rare:	Tinnitus, impaired hearing.
Cardiac disorders	
Uncommon*:	Myocardial infarction, cardiac failure, palpitations, chest pain
Frequency not known:	Kounis syndrome
Vascular disorders	
Very rare:	Hypertension, vasculitis.
Respiratory, thoracic and mediastinal disorders	
Rare:	Asthma (including dyspnoea).
Very rare:	Pneumonitis.
Gastrointestinal disorders	
Common:	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, decreased appetite.
Rare:	Gastritis, gastrointestinal hemorrhage, hematemesis, hemorrhagic diarrhoea, melena, gastrointestinal ulcer (with or without bleeding, gastrointestinal stenosis, or perforation, which may lead to peritonitis).
Very rare:	Colitis (including hemorrhagic, colitis, ischemic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, esophageal disorder, intestinal diaphragm disease, pancreatitis.
Hepatobiliary disorders	
Common:	Transaminases increased.
Rare:	Hepatitis, jaundice, liver disorder.
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, toxic epidermal necrolysis (Lyell's syndrome), exfoliative dermatitis, alopecia, photosensitivity reaction, purpura, Henoch-Schoenlein purpura, pruritus.
Renal and urinary disorders	
Very rare:	Acute kidney injury (acute renal failure), hematuria, proteinuria, nephrotic syndrome, tubulointerstitial nephritis, renal papillary necrosis.
General disorders and administration site conditions	
Common:	Injection site reaction, injection site pain, injection site induration.
Rare:	Edema, injection site necrosis

*The frequency reflects data from long-term treatment with a high dose (150 mg/day).
Adverse drug reactions from spontaneous reports and literature cases (frequency not known)
The following adverse drug reaction has been derived from post-marketing experience with Dicloran. Because this reaction was reported voluntarily from a population of uncertain size, it is not possible to reliably estimate its frequency which is therefore categorized as not known.
Table 2 Adverse drug reaction from spontaneous reports and literature cases (frequency not known)

Injection site reactions	
	Embolia cutis medicamentosa (Nicolau syndrome).

Description of selected adverse drug reactions
Arteriothrombotic events
Meta-analysis and pharmacoepidemiological data point towards an increased risk of arteriothrombotic events (for example myocardial infarction) associated with the use of diclofenac, particularly at a high dose (150 mg daily) and during 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.
CONTRAINDICATIONS
• Known hypersensitivity to the active substance, sodium metabisulphite or to any of the other excipients.
• Active gastric or intestinal ulcer, bleeding or perforation.
• Last trimester of pregnancy.
• Hepatic failure.
• Renal failure (GFR < 15 mL/min/1.73m^2).
• Severe cardiac failure.
• Like other non-steroidal anti-inflammatory drugs (NSAIDs), Dicloran is also contraindicated in patients in whom the use of acetylsalicylic acid or other NSAIDs can precipitate asthma, angioedema, urticaria, or acute rhinitis (i.e., NSAID-induced cross-reactivity reactions).

PREGNANCY & LACTATION
Pregnancy
Risk Summary
There are insufficient data on the use of diclofenac in pregnant women. Some epidemiological studies suggest an increased risk of miscarriage after use of a prostaglandin synthesis inhibitor (such as NSAIDs) in early pregnancy, however the overall data are inconclusive. Diclofenac has been shown to cross the placental barrier in humans. Use of NSAIDs, including diclofenac, can cause uterine inertia, premature closure of the fetal ductus arteriosus and fetal renal impairment leading to oligohydramnios.
Because of these risks, Dicloran should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the fetus.
In addition, Dicloran should not be used during the third trimester of pregnancy.
In animal reproduction studies, no evidence of teratogenicity was observed in mice, rats, or rabbits given diclofenac daily during the period of organogenesis at doses up to approximately 0.41, 0.41, and 0.81 times, respectively, the maximum recommended human dose (MRHD) of Dicloran, despite the presence of maternal and fetal toxicity (see Animal data).
Clinical considerations
Fetal Adverse Drug Reactions
Premature Closure of Fetal Ductus Arteriosus
As with other NSAIDs, use of diclofenac during the third trimester of pregnancy is contraindicated owing to the possibility of premature closure of the fetal ductus arteriosus.
Oligohydramnios/Fetal Renal Impairment
Risk of fetal renal impairment with subsequent oligohydramnios has been observed when NSAIDs (including diclofenac) were used from the 20th week of pregnancy onwards.
If an NSAID is necessary from the 20th week gestation to the end of the 2nd trimester, limit the use to the lowest effective dose and shortest duration possible. If Dicloran treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue Dicloran and follow up according to clinical practice.
Labor or Delivery
There are no studies on the effects of Dicloran during labor or delivery. As with other NSAIDs, use of diclofenac during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia. In animal studies, NSAIDS, including diclofenac, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.
Data
Human Data
Premature Closure of Fetal Ductus Arteriosus
Published literature reports that the use of NSAIDs during the third trimester of pregnancy may cause premature closure of the fetal ductus arteriosus.
Oligohydramnios/Fetal Renal Impairment
Published studies and post-marketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal impairment leading to oligohydramnios. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug.
Animal Data
Reproductive and developmental studies in animals demonstrated that diclofenac administration during organogenesis did not produce teratogenicity despite the induction of maternal toxicity and fetal toxicity in mice at oral doses up to 20 mg/kg/day (0.41 times the maximum recommended human dose [MRHD] of Dicloran, 200 mg/day, based on body surface area (BSA) comparison), and in rats and rabbits at oral doses up to 10 mg/kg/day (0.41 and 0.81 times, respectively, the MRHD based on BSA comparison).
In a study in which pregnant rats were orally administered 2 or 4 mg/kg diclofenac (0.08 and 0.16 times the MRHD based on BSA) from Gestation Day 15 through Lactation Day 21, significant maternal mortality (caused by gastrointestinal ulceration and peritonitis) was noted. These maternally toxic doses were associated with dystocia, prolonged gestation, intrauterine growth retardation, and decreased fetal survival.
Administration of NSAIDs (including diclofenac) inhibited ovulation in the rabbit and implantation and placentation in the rat, and led to premature closure of the fetal ductus arteriosus.
Lactation
Risk Summary
Like other NSAIDs, diclofenac passes into the breast milk in small amounts. Therefore, Dicloran should not be administered during breast feeding in order to avoid undesirable effects in the infant.
Human Data
Diclofenac was detected in a low concentration (100 ng/mL) in breast milk in one nursing mother treated orally with a diclofenac salt of 150 mg/day. The estimated dose ingested by an infant consuming breast milk is equivalent to 0.03 mg/kg/day.
Females and males of reproductive potential
Female fertility
As with other NSAIDs, the use of Dicloran 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 Dicloran should be considered.
Male fertility
There is no human data on the effect of Dicloran on male fertility.
Diclofenac administered to male and female rats at 4 mg/kg/day (approximately 0.16 times the MRHD based on BSA comparison) did not affect fertility.

SYMPTOMS AND TREATMENT OF OVERDOSE
Symptoms
There is no typical clinical picture resulting from diclofenac overdosage. Overdosage can cause symptoms such as vomiting, gastrointestinal hemorrhage, diarrhea, dizziness, tinnitus or convulsions. In the event of significant poisoning, acute renal failure and liver damage are possible.
Therapeutic measures
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, due to the high protein binding and extensive metabolism.

INSTRUCTIONS FOR USE AND HANDLING
The following directions for intramuscular injection must be followed in order to avoid damage to a nerve or other tissue at the injection site.
To be injected either intramuscularly by deep intragluteal injection into the upper outer quadrant using aseptic technique, or intravenously by slow infusion after dilution in accordance with the following instructions. Each ampoule is for single use only. The solution should be used immediately after opening. Any unused contents should be discarded.
Appropriate injection technique and length of the needle (considering the thickness of the patient's gluteal fat) should be used to avoid inadvertent subcutaneous administration of Dicloran injection.
Depending on the intended duration of infusion, mix 100 to 500 mL of isotonic saline (sodium chloride 0.9% solution) or glucose 5% solution with the contents of one Dicloran ampoule. Both solutions should be buffered with sodium bicarbonate injectable solution (0.5 mL of 8.4% or 1 mL of 4.2% or a corresponding volume of a different concentration) taken from a freshly opened container. Only clear solutions should be used. If crystals or precipitates are observed, the infusion solution should not be used.

WARNINGS
RISK OF GI ULCERATION, BLEEDING, AND PERFORATION WITH NSAID
Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAID therapy. Although minor upper GI problems (e.g. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms.
Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious adverse events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneously reports for fatal GI events.

INCOMPATIBILITIES
As a rule, Diclofenac solution for injection should not be mixed with other injection solutions.
Infusion solutions of sodium chloride 0.9% or glucose 5% without sodium bicarbonate as an additive present a risk of supersaturation, possibly leading to formation of crystals or precipitates. Infusion solutions other than those recommended should not be used.

STORAGE CONDITION : Store below 30°C. Do not freeze. Protect from light

SHELF-LIFE : 30 months from the date of manufacture

PRESENTATION : Ampoule of 3mL & Box of 5

MANUFACTURED BY
UNIQUE PHARMACEUTICAL LABORATORIES.
(A Div. of J.B.Chemicals & Pharmaceuticals Ltd.)
Plot No.4, Phase IV, GIDC Industrial Area,
Panoli-394 116, India.

Imported & Distributed by:
UNIMED SDN BHD
53, Jalan Tembaga SD 5/2B,
Bandar Sri Damansara 52200,
Kuala Lumpur, Malaysia.

XXXXXX

DATE OF REVISION:
August 2024.

490mm

140mm

X:\Artworks\Mahesh\Malaysia\Dicloran Injection\Open File\XXXXXX Dicloran Injection Leaflet.indd