15-04-2022
1st Copy

Change of Pack Size

210mm

Dicloran® Tablets/Injection
(Diclofenac Sodium)

CARDIOVASCULAR RISK: NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.
Diclofenac sodium is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.

GASTROINTESTINAL RISK: NSAIDs cause an increased risk of serious gastrointestinal adverse events including inflammation, bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

QUALITATIVE AND QUANTITATIVE COMPOSITION

Dicloran® 50mg Tablets
Each enteric coated tablet contains:
Diclofenac Sodium BP.....50mg

Dicloran® Disperlet Tablets
Each dispersible tablet contains:
Diclofenac Acid MS eq. to
Diclofenac Sodium BP.....50mg

Dicloran® SR 100 Tablets
Each sustained release film coated tablet contains:
Diclofenac Sodium BP.....100mg

Dicloran® 75mg Injection
Each 3ml contains:
Diclofenac Sodium BP.....75mg

PHARMACEUTICAL FORM
Tablet / Injection

CLINICAL PARTICULARS
THERAPEUTIC INDICATIONS:
Adults and Elderly: Relief of all grades of pain and inflammation in a wide range of conditions, including:
- Arthritic conditions: rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout.
- Acute musculo-skeletal disorders such as peri-arthritis (for example frozen shoulder), tendinitis, tenosynovitis, bursitis.
- Other painful conditions resulting from trauma, including fracture, low back pain, sprains, strains, dislocations, orthopedic, dental and other minor surgery.

Children: Diclofenac sodium 50mg tablets are not suitable for children.
Injection: Ampoules for IM use: 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.
Ampoules used in intravenous infusion: For treatment or prevention of post-operative pain in the hospital setting.

POSOLOGY AND METHOD OF ADMINISTRATION:
Posology: Dicloran® should only be prescribed when the benefits are considered to outweigh the potential risks. After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used.
Dicloran® 50mg Tablets: ***Adults:*** 75mg to 150mg daily in two or three divided doses. The recommended maximum daily dose of diclofenac sodium is 150mg.
Dicloran® Disperlet Tablets: The recommended initial daily dose is 2 to 3 **Dicloran®** Disperlet tablets or as prescribed by the physician.
In milder cases, 2 **Dicloran®** Disperlet tablets daily are usually sufficient. The total daily dose should generally be divided into 2 to 3 separate doses or as prescribed by the physician.
In primary dysmenorrhea, the daily dose should be individually adjusted and is generally 1 to 2 **Dicloran®** Disperlet tablets. A dose of 1 to 2 tablets should be given initially and, if necessary, increased over the course of several menstrual cycles up to a maximum of 4 tablets daily or as prescribed by the physician.
Dicloran® SR 100mg Tablet: ***Adults:*** One **Dicloran®** SR 100mg tablet or as prescribed by the physician. In milder cases and for long-term therapy, one tablet per day is normally sufficient.
Injection: Dicloran® injection (IM or IV) should not be given for more than two days or as prescribed by the physician; if necessary, treatment can be continued with tablets.
Intramuscular injection: 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. One ampoule once as prescribed by the physician (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 alternative buttock be used for the second injection. Alternatively, one ampoule of 75mg can be combined with other dosage forms of **Dicloran®** up to the maximum daily dosage of 150mg.
Renal colic: One 75mg ampoule intramuscularly. A further ampoule may be administered after 30 minutes if necessary. The recommended maximum daily dose of **Dicloran®** is 150mg.
Intravenous Infusion: Diclofenac sodium should be used upon physician's advice in their presence. Immediately before initiating an intravenous infusion, **Dicloran®** 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%). Only clear solutions should be used. Diclofenac sodium must not be given as an intravenous bolus injection.
Two alternative regimens are recommended: For the treatment of moderate to severe post-operative pain, 75mg should be infused continuously over a period of 30 minutes to 2 hours. If necessary, treatment may be repeated after 4-6 hours, not exceeding 150mg within any period of 24 hours.
For the prevention of post-operative pain, a loading dose of 25mg-50mg should be infused after surgery over 15 minutes to 1 hour, followed by a continuous infusion of approx. 5mg per hour up to a maximum daily dosage of 150mg.

Special Populations: ***Elderly:*** In particular, it is recommended that the lowest effective dosage be used in frail elderly patients or those with a low body weight and the patient should be monitored for GI bleeding during NSAID therapy. ***Cardiovascular and significant cardiovascular risk factors:*** Contraindicated in patients with established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease. The lowest effective daily dose should be used and for the shortest duration possible. ***Renal & Hepatic impairment:*** Contraindicated in patients with renal & hepatic failure. Caution is advised when administering to patients with mild to moderate renal and hepatic impairment. ***Paediatric population:*** Diclofenac sodium is not recommended for use in children.

Directions for use: Dicloran® ***50mg and*** **Dicloran®** ***SR 100mg Tablet:*** For oral use only. To be taken whole with liquid, preferably with or after food.
Dicloran® Disperlet tablets should preferably be taken before meals. Tablets should be dropped into a glass of water and the liquid stirred to aid dispersion before swallowing. Since a proportion of the active substance may remain in the glass after swallowing, it is advisable to rinse the glass with a small amount of water and swallow again. The dispersible tablets must not be divided or chewed.

CONTRAINDICATIONS:
- Hypersensitivity to the active substance.
- Active, gastric or intestinal ulcer, bleeding or perforation.
- History of gastrointestinal bleeding or perforation, relating to previous NSAIDs therapy.
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Last trimester of pregnancy.
- Hepatic failure and renal failure.
- Established congestive heart failure (NYHA-II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- Contraindicated in patients in whom attacks of asthma, angioedema, urticaria or acute rhinitis are precipitated by ibuprofen, acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs.

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

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
General: Undesirable effects may be minimized by using the lowest effective dose for the shortest duration. In particular, elderly patients or those with a low body weight. Diclofenac cause allergic reactions, including anaphylactic reactions, can also occur without earlier exposure to the drug. Hypersensitivity reactions can also progress to Kumis syndrome, a serious allergic reaction that can result in myocardial infarction. The instructions for intramuscular injection should be strictly followed in order to avoid adverse events at the injection site, which may result in muscle weakness, muscle paralysis, hypoesthesia and injection site necrosis. **Gastrointestinal effects:** GI bleeding (haematemesis, melena), 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 gastrointestinal (GI) events. If GI bleeding occurs diclofenac should be withdrawn. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant use of medicinal products containing low dose acetylsalicylic acid (ASA/ aspirin), or other medicinal products likely to increase gastrointestinal risk. 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, selective serotonin-reuptake inhibitors (SSRIs) or anti-platelet agents such as acetylsalicylic acid. Caution should also be exercised 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. Caution are recommended when using diclofenac after gastro-intestinal surgery. **Hepatic impairment:** Close medical surveillance required when prescribing diclofenac to patients with hepatic impairment. Hepatitis may occur with diclofenac without prodromal symptoms. Caution is advised for when using diclofenac in patients with hepatic porphyria, since it may trigger an attack. **Renal impairment:** Monitoring of renal function is recommended as a precautionary measure when using diclofenac in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state. **Skin effects:** Serious skin reactions including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs, including diclofenac. Diclofenac sodium should be discontinued at the first appearance of skin rash, mucosal lesions or any other signs of hypersensitivity. **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. **Cardiovascular and cerebrovascular effects:** Patients with congestive heart failure (NYHA-I) or patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration. Patients should remain alert for the signs and symptoms of serious arterio-thrombotic events (e.g. chest pain, shortness of breath, weakness, slurring of speech), which can occur without warnings. **Haematological effects:** Diclofenac may reversibly inhibit platelet aggregation. Patients with defects of haemostasis, bleeding diathesis or haematological abnormalities should

120mm

210mm

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. Quincke's edema or urticaria are more frequent than in other patients. Therefore, special precaution is recommended in such patients. Diclofenac sodium and other NSAIDs can precipitate bronchospasm if administered to patients suffering from, or with a previous history of bronchial asthma. ***Female fertility:*** The use of Diclofenac may impair female fertility and is not recommended in women attempting to conceive.
Tablet: ***Lactose:*** This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine. ***Sodium:*** This medicine contains less than 1 mmol sodium (23mg) per tablet, that is to say essentially 'sodium-free'. The sodium metabisulphite present in solution for injection may rarely cause severe hypersensitivity reactions and bronchospasm. This medicine contains less than 1mmol sodium (23mg) per 3ml ampoule, that is to say essentially 'sodium-free'.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS:
Lithium & Digoxin: If used concomitantly, diclofenac may raise plasma concentrations of lithium and digoxin. Monitoring is recommended. **Diuretics and Anti-hypertensive 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. **Drugs known to cause hyperkalemia:** Concomitant treatment with potassium-sparing diuretics, cyclosporin, 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. No change in anticoagulant dosage is required, close monitoring of such patients is required. Co-administration of diclofenac and 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 SSRIs may increase the risk of gastrointestinal bleeding. **Antidiabetics:** Monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy. **Methotrexate:** Caution is recommended 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 increased. **Cyclosporin and Tacrolimus:** Diclofenac, like other NSAIDs, may increase the nephrotoxicity due to the effect on renal prostaglandins. Therefore, it should be avoided. **Quinolone antimicrobials:** Convulsions may occur due to an interaction between quinolones and NSAIDs. Caution should be exercised when considering the use of a quinolone in patients who are receiving NSAID. **Phenytoin:** When using phenytoin concomitantly, 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. 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. **Potent CYP2C9 inhibitors:** Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as voriconazole).

FERTILITY, PREGNANCY AND LACTATION:
Fertility: The use of diclofenac may impair female fertility and is not recommended in women attempting to conceive. **Pregnancy:** If diclofenac is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Diclofenac sodium tablets are contraindicated during the third trimester of pregnancy. **Breast-feeding:** Like other NSAIDs, diclofenac passes into the breast milk in small amounts. Therefore, diclofenac should not be administered during breast feeding.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
Patients who experience visual disturbances, dizziness, vertigo, somnolence, central nervous system disturbances, drowsiness or fatigue while taking NSAIDs should refrain from driving or operate machinery.

UNDESIRABLE EFFECTS:
Blood and lymphatic system disorders: ***Very rare:*** Thrombocytopenia, leucopoenia, anaemia (including hemolytic and aplastic anemia), agranulocytosis. **Immune system disorders:** ***Rare:*** Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock). ***Very rare:*** Angioneurotic edema (including face edema). **Psychiatric disorders:** V***ery rare:*** Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder. **Nervous system disorders:** ***Common:*** Headache, dizziness. ***Rare:*** Somnolence, tiredness. ***Very rare:*** Paresthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident. ***Unknown:*** Confusion, hallucinations, disturbances of sensation, malaise. **Eye disorders:** ***Very rare:*** Visual disturbance, blurred vision, diplopia. ***Unknown:*** Optic neuritis. **Ear and labyrinth disorders:** ***Common:*** Vertigo. ***Very rare:*** Tinnitus, hearing impaired. **Cardiac disorders:** ***Uncommon**:*** Myocardial infarction, cardiac failure, palpitations, chest pain. ***Unknown:*** Kounis syndrome. **Vascular disorders:** ***Very Rare:*** Hypertension, hypotension, vasculitis. **Respiratory, thoracic and mediastinal disorder:** ***Rare:*** Asthma (including dyspnea). ***Very rare:*** Pneumonitis. **Gastrointestinal disorders:** ***Common:*** Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia. ***Rare:*** Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melena, gastrointestinal ulcer with or without bleeding or perforation (sometimes fatal particularly in the elderly). ***Very rare:*** Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, esophageal disorder, diaphragm-like intestinal strictures, pancreatitis. ***Unknown:*** Ischemic colitis. **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 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 and urinary disorders:** ***Very rare:*** Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis. **Reproductive system and breast disorders:** ***Very rare:*** Impotence. **General disorders and administration site conditions:** ***Common:*** Injection site reaction, injection site pain, injection site induration. ***Rare:*** Edema.
* The frequency reflects data from long-term treatment with a high dose (150mg/day).

OVERDOSE:
Over dosage can cause symptoms such as headache, nausea, vomiting, epigastric pain, gastrointestinal haemorrhage, diarrhoea, dizziness, disorientation, excitation, coma, drowsiness, tinnitus, fainting or convulsions. In the case of significant poisoning acute renal failure and liver damage are possible. Activated charcoal may be considered after ingestion of a potentially toxic overdose, and gastric decontamination (e.g. vomiting, gastric lavage) after ingestion of a potentially life threatening overdose.

PHARMACOLOGICAL PROPERTIES
PHARMACODYNAMIC PROPERTIES: Pharmacotherapeutic group: Acetic acid derivatives and related substances. **ATC code:** M01AB05.

PHARMACOKINETIC PROPERTIES:
Absorption: ***Oral Enteric Coated Tablet:*** The mean peak plasma diclofenac concentration reached at about 2 hours (50mg dose produces 1511± 466 ng/ml). ***Sustained Release Tablet:*** On average the systemic bioavailability of diclofenac is approximately 82% of that attained with the same dose administered in the form of diclofenac gastro-resistant tablets. Mean peak plasma concentrations of 0.5 µg/ml are attained on average 4 hours after administration of 100 tablet. Ingestion of 100mg once daily produces trough plasma levels of approximately 22 ng/ml. ***Dispersible Tablets:*** Absorption of diclofenac from dispersible tablets sets in immediately after administration, the bioavailability of diclofenac being 82% of that achieved with gastro-resistant tablets. ***Injection:*** 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. ***Bioavailability:*** About half of the administered diclofenac is metabolised during its first passage through the liver. 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 maximum concentrations 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. **Metabolism:** Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation. 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% is excreted as unchanged substance. The rest of the dose is eliminated as metabolites through the bile in the faeces.

SHELF LIFE
See expiry on the pack.

AVAILABILITY
Dicloran® 50mg tablets in a pack of 30's
Dicloran® Disperlet tablets in a pack of 20's
Dicloran® SR 100 tablets in a pack of 30's
Dicloran® 75mg injection in a pack of 5's

INSTRUCTIONS
Dosage: As advised by the physician. To be sold on the prescription of registered medical practitioner. Keep out of reach of children.
Avoid exposure to heat, light, humidity and freezing. Store between 15 to 30°C. Improper storage may deteriorate the medicine.

Injection should not be used if container is leaking, solution is cloudy or it contains undissolved particle(s).

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com
Mfg. Lic. No. 000072

ڈکلوران ٹیبلٹ/انجکشن
(ڈکلوفینک سوڈیم)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔
دوا کو گرمی، روشنی، نمی اور منجمد ہونے سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی۔
انجکشن کے لیک ہونے، دُھندلا ہونے یا اس میں کوئی غیر حل پذیر شے نظر آنے کی صورت میں ہرگز استعمال نہ کریں۔

120mm