Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Diclofenac Injection IP

(Brand Name: DICLOTAL® Injection)

WARNING: Not for veterinary use

2. Qualitative and Quantitative Composition

Each ml contains

Diclofenac Sodium IP ……. …… 25 mg

Benzyl Alcohol IP (as preservative) …… 4% w/v

Water for Injection IP …..……..…… q.s.

3. Dosage Form and Strength

Dosage Form: Injection.

Dosage Strength: Diclofenac Sodium 75 mg per 3 ml ampoule.

4. Clinical Particulars

4.1 Therapeutic Indication

Diclofenac injection is indicated for the treatment of acute pain, including renal colic, exacerbations of osteo- and rheumatoid arthritis, acute back pain, acute gout, trauma and fractures, and post-operative pain.

4.2Posology and Method of Administration

For intramuscular (I.M.) or intravenous (I.V.) infusion use in adults only.

I.M. Injection: The usual dose is 75 mg of diclofenac once daily (or, in severe cases twice daily), given by deep intra-gluteal injection into the upper outer quadrant. If more than one injection needs to be given, the other buttock should be used.

Renal colic: 75 mg of diclofenac to be administered by I.M. route. If necessary, a further dose of 75 mg may be administered after 30 minutes (not more than 150 mg/day).

I.V. Infusion (in hospital setting): Immediately before initiating an I.V. infusion, diclofenac injection must be diluted with 100 to 500 ml of either sodium chloride solution (0.9%) or dextrose solution (5%). Both solutions should be buffered with sodium bicarbonate solution (0.5 ml of 8.4% strength or 1 ml of 4.2% strength). The I.V. infusion should be administered over a period of 30 to 60 minutes.

Two alternative regimens are also recommended as follows:

- **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 to 6 hours, not exceeding 150 mg within 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 approximately 5 mg per hour up to a maximum daily dosage of 150 mg.

Diclofenac injection must not be given as an I.V. bolus injection.
Treatment with diclofenac injection should not be given for more than 2 days; if necessary, treatment can be continued with diclofenac tablets or suppositories. The maximum daily dose of diclofenac injection should not exceed 150 mg.
Or, as prescribed by Physician.

Stability and Handling
Each ampoule is for single use only. The solution should be used immediately after opening. The unused portion, if any, should be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if solution is not clear or has suspended matter.
After dilution (for I.V. infusion use), do not use diclofenac injection beyond 24 hours. The infusion solution should not be used if crystals or precipitates are observed. Only clear form of diluted solution should be used for I.V. infusion purpose.

4.3Contraindications

DICLOTAL Injection is contraindicated in the following:

- Known hypersensitivity to diclofenac or to any component of this formulation.
- Active gastric or intestinal ulcer, bleeding or perforation.
- History of gastrointestinal (GI) bleeding or perforation, relating to previous non-steroidal anti-inflammatory (NSAID) therapy.
- Last trimester of pregnancy.
- Neonates or premature infants.
- In the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.
- Severe hepatic, renal, and cardiac failure.
- Patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by aspirin or other NSAIDs.

Contraindications Specifically for I.V. infusion 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.
- A history of asthma.
- Moderate or severe renal impairment (serum creatinine >160 µmol/l).
- Hypovolaemia or dehydration from any cause.

4.4Special Warnings and Precautions for Use

Test Dose: Before therapy with DICLOTAL Injection is instituted, a test dose is recommended to ascertain possibility of hypersensitivity to ingredients of DICLOTAL Injection. Serious acute hypersensitivity reactions may require the use of subcutaneous epinephrine and other emergency measures.

Cardiovascular (CV) Risk: NSAIDs may increase the risk of serious cardiovascular thrombotic events, myocardial infarction (MI), and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease (CVD) or risk factors for CVD may be at greater risk.

Gastrointestinal (GI) Bleeding, Ulceration and Perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs. They can occur at any time during treatment, with or without warning symptoms. Risk is higher with increasing NSAID doses and in patients with previous history of ulceration. The drug should be withdrawn if GI bleeding or ulceration occurs.

Hepatic Effects: Close medical surveillance is required when prescribing diclofenac to patients with impairment of hepatic function as their condition may be exacerbated. 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 should be discontinued.

Renal Effects: As fluid retention and edema have been reported in association with NSAIDs therapy, including diclofenac, particular caution is required 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 those patients with substantial extracellular volume depletion from any cause, e.g., before or after major surgery. Monitoring of renal function is recommended as a precautionary measure when using diclofenac in such cases.

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.

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 or those recovering from major surgery and the elderly. Renal function should be monitored in these patients.

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 edema have been reported in association with NSAID therapy including diclofenac.
Respiratory Disorders: Caution is required if administered to patients suffering from, or with a previous history of bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.
Haematological: Diclofenac injection may reversibly inhibit platelet aggregation. Patients with defect of hemostasis, bleeding diathesis or hematological abnormalities should be carefully monitored.
Female Fertility: 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.

4.5Drug Interactions

The following interactions include those observed with diclofenac injection and other forms of diclofenac.
Lithium: If used concomitantly, diclofenac injection may increase plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.
Digoxin: If used concomitantly, diclofenac injection 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 injection 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 and 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, cyclosporine, 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.
Other NSAIDs including cyclooxygenase-2 selective inhibitors and corticosteroids: Co-administration of diclofenac with other systemic NSAIDs or corticosteroids may increase the risk of GI 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 GI bleeding.

Anti-diabetics: 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 thereby increasing methotrexate levels. Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before treatment with methotrexate, since blood concentration of methotrexate may rise which further increases the risk of methotrexate toxicity.

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 GFR, and increase plasma glycoside levels.

Mifepristone: NSAIDs should not be used for 8 to 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), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism.

4.6Use in Special Populations

Pregnant Women

Pregnancy Category C prior to 30 weeks of gestation; Pregnancy Category D starting at 30 weeks of gestation. NSAIDs including diclofenac should not be used during the first two trimesters of pregnancy or labor unless the potential benefit to the patient outweighs the potential risk to the fetus. Use of diclofenac in the last trimester of pregnancy is contraindicated as premature closure of the ductus arteriosus in the fetus may occur.

Lactating Women

Like other NSAIDs, diclofenac passes into breast milk in small amounts. Therefore, diclofenac should not be administered in breastfeeding mothers in order to avoid undesirable effects in the infant.

Pediatric Patients
DICLOTAL Injection is not recommended for use in children. Also, use of diclofenac injection is contraindicated in new born and infants.

Geriatric Patients
Diclofenac injection should be used with caution in elderly patients who generally are more prone to adverse reactions. Generally, dosage adjustment is not required in elderly people with normal body functions. It is recommended to use the lowest effective dosage in weak elderly patients or those with a low body weight; further, these patients should be monitored for GI bleeding during NSAID therapy.

Renal and Hepatic Impairment Patients
Diclofenac is contraindicated in patients with severe renal and/or hepatic impairment. Caution is advised when administering diclofenac to patients with mild to moderate renal and/or hepatic impairment.

4.7Effect on Ability to Drive and Use Machines
Patients experiencing visual disturbances, dizziness, vertigo, fatigue, or somnolence while taking this medicine, should refrain from driving or using machines.

4.8Undesirable Effects
The following terminologies have been used in order to classify the occurrence of undesirable effects. Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon/occasional (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000).
Adverse reactions reported in clinical trials and/or spontaneous reports of diclofenac or other NSAIDs or literature reports are as follows:
Blood and lymphatic system disorders: Very rare: Thrombocytopenia, leucopoenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis.
Immune system disorders: Rare: Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock); Very rare: Angioneurotic edema (including face edema).
Eye disorders: Very rare: Visual disturbance, vision blurred, diplopia.
Ear and labyrinth disorders: Common: Vertigo; Very rare: Tinnitus, impaired hearing.
Cardiac disorders: Very rare: Palpitations, chest pain, cardiac failure, myocardial infarction.
Vascular disorders: Very rare: Hypertension, hypotension, vasculitis.
Respiratory, thoracic and mediastinal disorders: Rare: Asthma (including dyspnoea); Very rare: Pneumonitis.

Renal and urinary disorders: Very rare: Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis.
Hepatobiliary disorders: Common: Increased transaminases; Rare: Hepatitis, jaundice, liver disorder; Very rare: Fulminant hepatitis, hepatic necrosis, hepatic failure.
Gastrointestinal tract: Occasional: Epigastric pain, other GI disorders (e.g., nausea, vomiting, diarrhoea, dyspepsia, flatulence, anorexia); Rare: GI bleeding, abdominal pain/tenderness, GI ulcers with or without bleeding or perforation, mouth ulcerations, tooth and tongue disorders or dysphagia.
Central nervous system: Occasional: Headache, dizziness or vertigo; Rare: Drowsiness, tiredness, dysgeusia, paraesthesia, balance impairment, aponia, hypoaesthesia, migraine, speech disorder, or trismus.
Musculoskeletal and connective tissue disorders: Occasional: Pain in jaw; Rare: Facial pain, joint stiffness, myalgia, back pain, chest wall pain, neck pain, muscle cramp, or muscle tightness.
Skin: Occasional: Rashes or skin eruptions; Rare: Urticaria, pruritus, or increased sweating.
Laboratory abnormalities: Rare: Elevated creatine phosphokinase, ketonuria, haematuria, or bilirubin in urine.
Arteriothrombotic events: Meta-analysis suggests a small increased risk of arteriothrombotic events (e.g., myocardial infarction) associated with the use of diclofenac, particularly at a high dose (150 mg daily) and during long-term treatment.
Administration site reactions
Nicolau's Syndrome as an adverse drug reaction reported with the use of diclofenac injection.

- **Reactions to I.M. injection:** Common: Injection site reaction, injection site pain, injection site induration, injection site abscesses; Rare: Injection site necrosis, edema.
- **Reaction to I.V. injection:** Rare: Thrombophlebitis, cannula site reaction, infusion site discomfort or burning, injection site stinging, or pyrexia.

4.9Overdose

Symptoms: There are no typical symptoms observed with diclofenac overdose. Overdose can cause symptoms such as vomiting, GI hemorrhage, diarrhoea, dizziness, tinnitus or convulsions. In the event of significant poisoning, acute renal failure and liver damage are possible.
Treatment: 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, GI disorder, and respiratory depression. Special measures such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to the high protein binding and extensive metabolism.

5. Pharmacological Properties

5.1 Mechanism of Action

Anti-inflammatory action of diclofenac is mainly due to its effect on cyclooxygenase (COX) enzyme. Cyclooxygenase is a key enzyme required for synthesis of prostaglandins (PGs) from arachidonic acid. Arachidonic acid is produced from the phospholipids of damaged cell membrane. Prostaglandins play an important role in causing inflammation, pain, and fever.

Diclofenac inhibits COX enzyme and thereby inhibit synthesis of PGs. This action of diclofenac is mainly responsible for its anti-inflammatory and analgesic effects.

5.2Pharmacodynamic Properties

Diclofenac sodium is a non-steroidal compound with pronounced antirheumatic, anti-inflammatory, analgesic, and antipyretic properties. When used concomitantly with opioids for the management of post-operative pain, diclofenac often reduces the need for opioids.

5.3Pharmacokinetic Properties

Absorption:

- **Intramuscular (I.M.) Route:** After administration of 75 mg diclofenac by I.M. injection, absorption sets in immediately, and mean peak plasma concentrations of about 2.558 µg/ml are reached after about 20 minutes. The amount absorbed is in linear proportion to the size of the dose. The area under the concentration curve (AUC) after I.M. administration is about twice as large as it is following oral or rectal administration as this route avoids "first-pass" metabolism.
- **Intravenous (I.V.) Infusion:** When 75 mg diclofenac is administered as an I.V. infusion over 2 hours, mean peak plasma concentrations are about 1.875 µg/ml. Shorter infusions result in higher peak plasma concentrations, while longer infusions give plateau concentrations proportional to the infusion rate after 3 to 4 hours. This is in contrast to the rapid decline in plasma concentrations seen after peak levels have been achieved with oral, rectal or I.M. administration.

Distribution: The plasma protein binding of diclofenac is about 99.7%, mainly to albumin (99.4%). Diclofenac enters the synovial fluid, where maximum concentrations are measured 2 to 4 hours after the peak plasma values have been reached. At this time, concentration of diclofenac is higher in the synovial fluid than in the plasma and remains higher for up to 12 hours.

Metabolism: Metabolism of diclofenac takes place partly by glucuronidation, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites, most of which are converted to glucuronide conjugates. Two phenolic metabolites are biologically active, but to a much lesser extent than diclofenac.

Excretion: Total systemic clearance of diclofenac in plasma is about 263 ml/min. 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. 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.

6. Nonclinical Properties

6.1 Animal Toxicology

Carcinogenesis: Long-term carcinogenicity studies in rats given diclofenac sodium up to 2 mg/kg/day (approximately 0.13 times the maximum recommended human dose [MRHD] based on mg/m² body surface area [BSA] comparison) have revealed no significant increase in tumor incidence. A 2-year carcinogenicity study conducted in mice employing diclofenac sodium at doses up to 0.3 mg/kg/day (approximately 0.01 times the MRHD based on BSA comparison) in males and 1 mg/kg/day (approximately 0.04 times the MRHD based on BSA comparison) in females did not reveal any oncogenic potential.

Mutagenesis: Diclofenac sodium did not show mutagenic activity in *in vitro* point mutation assays in mammalian (mouse lymphoma) and microbial (yeast, Ames) test systems and was nonmutagenic in several mammalian *in vitro* and *in vivo* tests, including dominant lethal and male germinal epithelial chromosomal aberration studies in Chinese hamsters.

Impairment of Fertility: Diclofenac sodium administered to male and female rats at 4 mg/kg/day (approximately 0.3 times the MRHD based on BSA comparison) did not affect fertility.

Reproductive and developmental toxicity: Reproductive and developmental studies in animals demonstrated that diclofenac sodium 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 (approximately 0.7 times the MRHD based on BSA comparison), and in rats and rabbits at oral doses up to 10 mg/kg/day (approximately 0.7 and 1.3 times, respectively, the MRHD based on BSA comparison). In rats, maternally toxic doses were associated with dystocia, prolonged gestation, reduced fetal weights and growth, and reduced fetal survival. Diclofenac has been shown to cross the placental barrier in mice, rats, and humans.

7. Description

DICLOTAL Injection is clear colourless to yellowish liquid filled in 3 ml clear glass ampoules with blue colour snap off ring.

Each 3 ml ampoule contains 75 mg of diclofenac sodium for I.M. or I.V. infusion use.

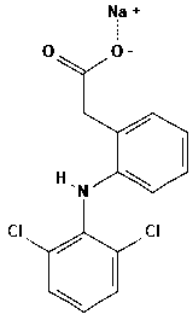
Diclofenac sodium is the sodium salt form of diclofenac, a benzene acetic acid derivate and non-steroidal anti-inflammatory drug (NSAID) with analgesic, antipyretic and anti-inflammatory activity. Diclofenac sodium is a white to off-white, virtually odorless, crystalline powder which is sparingly soluble in water.

Molecular Weight: 318.14 g/mol.

Molecular Formula: C14H10Cl2NNaO2.

Chemical Name: 2-[(2,6-dichlorophenyl) amino] benzeneacetic acid, monosodium salt.

Structural Formula:



Inactive ingredients (excipients) of DICLOTAL Injection contain EDTA Sodium, Sodium Metabisulphite, Propylene Glycol, Benzyl Alcohol, and Sodium Hydroxide Pellets.

8. Pharmaceutical Particulars

8.1 Incompatibilities

DICLOTAL Injection should not be mixed with other injection solutions.

8.2Shelf-life

24 months.

After dilution (for I.V. infusion use), injection should be used within 24 hours.

8.3Packaging Information

3 ml glass ampoule.

8.4Storage and Handling Instructions

Store at a temperature not exceeding 30°C. Protected from light.

Keep out of reach of the children.

9. Patient Counseling Information

Administration Instructions

- Instruct patient to take medicine as advised and not to exceed the recommended dose.
- Inform patients about the signs of hypersensitivity/allergic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur.
- Advise patients to stop medicine immediately if they develop any type of rash, and contact their healthcare provider as soon as possible.
- Advise females of reproductive potential who desire pregnancy that NSAIDs may be associated with a reversible delay in ovulation.
- Instruct patients that this medicine is not advised in children, pregnant women (in the last trimester), and in breastfeeding mothers.

- Advise patients to report symptoms of ulcerations and GI bleeding, including epigastric pain, dyspepsia, and hematemesis to their health care provider.
- Inform patients that the concomitant use of DICLOTAL Injection with other NSAIDs or salicylates (including oral OTC preparations containing NSAID) is not recommended due to the increased risk of GI toxicity, and little or no increase in efficacy.
- Inform patients not to use low-dose aspirin concomitantly unless advised by their healthcare provider.

10.Details of Manufacturer

Nitin Lifesciences Ltd.,
Rampur Road, Paonta Sahib, Dist. Sirmour,
Himachal Pradesh – 173 025, India.

11. Details of Permission or License Number with Date

DCG(I) approval date: June 1987.
Manufacturing license No. MB/05/209 dated 22/04/2016.

12. Date of Revision

January 2021.

Marketed by:
BLUE CROSS LABORATORIES PVT LTD.
A-12, M.I.D.C., NASHIK-422 010.
Regd. Off.: Peninsula Chambers, G. K. Marg, Mumbai-400 013.