For the use of Registered Medical Practitioner, Hospital or a Laboratory Only.

# DICLOTROY AQ

Diclofenac Sodium Injection 75 mg/ml

**COMPOSITION:**
Each ml contains:
Diclofenac Sodium BP 75 mg.
Water for Injections BP q.s.

**DESCRIPTION:**
Diclotroy AQ (Diclofenac Sodium Injection 75mg/ml) is Clear, colorless to yellowish liquid filled in 1 ml flint ampoule with blue OPC, together Pack 5 filled labeled ampoules in a plastic ampoule tray and 1 plastic ampoule tray in a carton with one pack insert.

**PHARMACOLOGICAL PROPERTIES AND EFFECTS:**
**Mechanism of action**
Diclofenac is a non-steroidal agent with marked analgesic/anti-inflammatory properties. It is an inhibitor of prostaglandin synthetase (cyclo-oxygenase). Diclofenac in vitro does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in human beings. When used concomitantly with opioids for the management of post-operative pain, diclofenac sodium often reduces the need for opioids.
**Pharmacodynamics Properties:**
Diclofenac sodium is a benzene-acetic acid derivative. Diclofenac sodium is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities. The mechanism of action of diclofenac, like that of other NSAIDs may be related to prostaglandin synthetase inhibition.
**Pharmacokinetic Properties:**
**Absorption**
After administration of DICLOTROY AQ (75mg/ml) by intragluteal and intradeltoid, mean peak plasma concentrations of 2.14 ± 0.75 µg/ml and 1.95 ± 0.08 µg/ml, are reached after about 29 minutes and 23 minutes respectively. The mean $AUC_{0-t}$ and $AUC_{0-\infty}$ by intragluteal is 3.79 ± 0.96 µg.h/ml, and 4.03 ± 0.99 µg.h/ml and by intradeltoid is 3.37 ± 0.13 µg.h/ml and 3.57 ± 0.13 µg.h/ml respectively.
**Distribution:**
Diclofenac is more than 99% bound to human serum proteins, primarily to albumin. 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. Two hours after reaching the peak plasma values, concentrations of the active substance are already higher in the synovial fluid than they are in the plasma and remain higher for up to 12 hours.
**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, most of which are converted to glucuronide conjugates. Two phenolic metabolites are biologically active, but to a much lesser extent than diclofenac.
**Elimination**
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. The terminal half-life in plasma is 1-2 hours.

**INDICATION AND USAGE:**
**Intramuscular Injection/Intragluteal and Intradeltoid:**
DICLOTROY AQ is indicated as initial therapy for inflammatory and degenerative rheumatic diseases as well as for the treatment of painful conditions due to inflammation of non-rheumatic origin.
**Intravenous bolus Injection and Infusion**
For treatment or prevention of post-operative pain
**Recommended Dose**
**Dosage and Administration:**
As a general recommendation, the dose should be individually adjusted and the lowest effective dose should be given for the shortest possible duration. The recommended maximum daily dose of Diclofenac Sodium Injection is 150 mg. Diclotroy AQ solution for injection should not be given for more than two days.
***Intramuscular Injection:***
For adults the dosage is generally 1 diclofenac injection of 75mg daily injected intramuscularly (intradeltoid or deep intragluteal injection into the upper outer quadrant) twice daily, for a maximum of 2 days.
***Intravenous use:***
Diclotroy AQ solution for injection can be given as an intravenous bolus injection or intravenous infusion.
**By intravenous bolus:**
For moderate to severe post-operative pain, 75 mg should be injected intravenously as a bolus injection over 5 to 60 seconds. If necessary, treatment may be repeated twice daily which can be divided to maximum interval of 12 hours between two doses, not exceeding 150 mg within any period of 24 hours.
**By Intravenous Infusion:** By intravenous infusion (in hospital settings) – continuous or intermittent in glucose 5% or sodium chloride 0.9% - dilute 75mg diclofenac with 100-500 ml infusion fluid; 75mg given over 30-120 minutes repeated if necessary after 4-6 hours for maximum 2 days.
I.V. infusion is given in prevention of post-operative pain, initially after surgery 25-50 mg over 15-60 minutes then 5 mg per hour for maximum 2 days.

**USE IN SPECIAL POPULATION:**
**Elderly**
The elderly are at increased risk of serious adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy. The recommended maximum daily dose of Diclotroy AQ is 150 mg.

**Renal impairment**
Diclofenac is contraindicated in patients with severe renal impairment. 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 diclofenac to patients with mild to moderate renal impairment.
**Hepatic impairment**
Diclofenac is contraindicated in patients with severe hepatic impairment. 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 diclofenac to patients with mild to moderate hepatic impairment.
**Paediatric population**
DICLOTROY AQ is not recommended for use in children.
**Route of Administration**
Intradeltoid, Interagluteal, IV Infusion, IV Bolus

**CONTRAINDICATION:**
- Known hypersensitivity to the active substance or to any of the excipients.
- Active gastric or intestinal ulcer, bleeding or perforation
- History of gastrointestinal bleeding or perforation related to previous NSAID therapy.
- Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Last trimester of pregnancy
- Severe hepatic renal or cardiac failure
- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac is also contraindicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs.
- Haemostasis disorders or current anticoagulant treatment (for intramuscular route of administration only).

***Specifically for i.v. use:***
- Concomitant NSAID or anticoagulant use (including low dose heparin).
- History of haemorragic 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.

**WARNING AND PRECAUTIONS:**
***General***
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.
The concomitant use of Diclofenac with systemic NSAIDs including cyclooxygenase selective inhibitors should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects.
Caution is indicated in the elderly on the basis of medical grounds. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight.
As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases with diclofenac without earlier exposure to the drug.
Like other NSAIDs, Diclofenac may mask the signs and symptoms of infection due to its pharmacodynamic properties.
The sodium metabisulphite present in solution for injection can also lead to isolated severe hypersensitivity reactions and bronchospasm.
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, hypoaesthesia and injection site necrosis.
**Cardiovascular Events:**
**Cardiovascular Thrombotic Events:**
All NSAIDs. Both COX-2 selective and nonselective may have a similar risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.
**Hypertension:**
NSAIDs, including diclofenac, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIOs. NSAIOs, including diclofenac, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.
**Congestive Heart Failure and Edema Renal Effects:**
Fluid retention and edema have been observed in some patients taking NSAIDs. Diclofenac should be used with caution in patients with fluid retention or heart failure.
**Gastrointestinal Effects-Risk of Ulceration, Bleeding, and Perforation:**
NSAIDs, including diclofenac, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic.
NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment ii a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out.

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**Renal Effects:**
Caution should be used when initiating treatment with diclofenac in patients with considerable dehydration.
Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow. Which may precipitate overt renal decomposition. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.
**Advanced Renal Disease:**
Treatment with diclofenac is not recommended in patients with advanced renal disease. If diclofenac therapy must be initiated, close monitoring of the patient's renal function is advisable.
**Anaphylactoid Reactions:**
As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to diclofenac. Diclofenac should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs. Emergency help should be sought in cases where an anaphylactoid reaction occurs.
**Skin Reactions:**
NSAIDs including diclofenac can cause serious skin adverse events such as exfoliative dermatitis, Stevens - Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.
**Pregnancy:**
In late pregnancy, as with other NSAIDs, diclofenac should be avoided because it may cause premature closure of the ductus arteriosus.

**PRECAUTIONS:**
**General**
Diclofenac sodium cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.
Severe cutaneous reactions, including Stevens - Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome), have been reported with diclofenac sodium. Patients treated with diclofenac sodium should be closely monitored for signs of hypersensitivity reactions. Discontinue diclofenac sodium immediately if rash occurs.
**Hepatic Effects:**
Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including diclofenac. In patients on chronic treatment with diclofenac, periodic monitoring of transaminases is recommended. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.
A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred. Should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with diclofenac. If clinical signs and symptoms consistent with liver disease develop or if systemic manifestations occur (e.g eosinophilia, rash, etc.), diclofenac should be discontinued.
**Hematological Effects:**
Anemia is sometimes seen in patients receiving NSAIDs, including diclofenac. This may be due to fluid retention, occult or gross GI loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including diclofenac, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.
NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Patients receiving diclofenac who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.
**Preexisting Asthma:**
Diclofenac should not be administered to patients with aspirin sensitively and should be used with caution in patients with preexisting asthma.
**Pregnancy:**
Diclofenac should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.
**Nonteratogenic Effects:**
Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.
**Labor and Delivery:**
The effects of diclofenac on labor and delivery in pregnant women are unknown.
**Nursing Mothers:**
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from diclofenac, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
**Pediatric Use:**
Not indicated in children under the age of 14 years.
**Geriatric Use**
As with any NSAIDs, caution should be exercised in treating the elderly (65 years and older).

**INTERACTION OF OTHER MEDICAMENTS:**
**Drug Interactions:**
**Aspirin:** When diclofenac is administered with aspirin, its protein binding is reduced. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of diclofenac and aspirin is not generally recommended because of the potential of increased adverse effects.
**Methotrexate:** NSAIDs could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.
**Cyclosporine:** Diclofenac, like other NSAIDs may increase cyclosporine's nephrotoxicity. Caution should be used when diclofenac is administered concomitantly with cyclosporine.
**ACE-inhibitors:** Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors.
**Diuretics:** Diclofenac can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure, as well as to assure diuretic efficacy.
**Lithium:** NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.
**Warfarin:** The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.
**Preclinical safety data:**
Preclinical data from acute and repeated dose toxicity studies in healthy Albino rabbits and Healthy wistar rats, revealed no specific hazards for humans at the intended therapeutic doses. However in larger doses diclofenac may produce liver and kidney toxicity.
**Incompatibility**
Diclofenac Sodium for injection should not be mixed with other injection solutions. Infusion solutions other than those recommended should not be used.

**ADVERSE EFFECTS:**
**Dermatological:** Occasional - rashes or skin eruptions, cases of hair loss, bullous eruptions, erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), and photosensitivity reactions have been reported. Patients may complain of nausea and diarrhea, headache, tinnitus or dizziness. Peripheral oedema and skin reactions, such as drug rash and eczema, have also been encountered.
Central nervous system side-effects, such as tiredness, insomnia, nervousness. Depression or irritability, have occurred. Blurred vision and other ocular reactions. Sensitivity reactions (e.g. bronchospasm, anaphylactic/anaphylactoid systemic reactions), elevated transaminase levels, jaundice, hepatitis, renal failure and nephritic syndrome, may occur. Oyshaemopoiesis (leucopenia, thrombocytopenia, aplastic anemia) and erythema multiforme have been observed. Agranulocytosis and haemolytic anemia have been observed. Abscesses and local necrosis have also occurred, particularly in elderly diabetics.
**Effect on platelets:** Diclofenac sodium 75mg by infusion to arthritic patients may significantly inhibit platelet aggregation. Diclofenac sodium I.V. may increase mean bleeding time. But some studies show that I.V. infusion of Diclofenac sodium 75mg/hour up to a total dose of 212 mg did not significantly alter platelet counts, prothrombin time. Partial thromboplastin time and bleeding time in patients undergoing general anesthesia.

**SYMPTOMS AND TREATMENT OF OVERDOSE:**
Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose. Patients should be managed by symptomatic and supportive care following a NSAID overdose. There are no specific antidotes. Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

**EXCIPIENTS:**
Potassium dihydrogen phosphate, Benzyl Alcohol, Sodium metabisulphite, Sodium hydroxide pellets, Glycofurol (stabilizer 1)

**STORAGE CONDITION:**
Store below 30°C.
Do not refrigerate.

Dilutions of Diclotroy AQ injection in compatible intravenous infusion fluids are stable under ambient temperature upto 12 hours with 0.9% Sodium chloride Intravenous Infusion and 5% Dextrose Intravenous Infusion.

**SHELF LIFE:**
36 months (unopened).

**DATE OF REVISION:**
15/05/2024

**PRODUCT REGISTRATION HOLDER/IMPORTED BY:**
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