

1. NAME OF THE MEDICINAL PRODUCT

Diclofenac injection 75 mg / 3 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ampoule contains 75 mg diclofenac sodium in 3 ml injectable solution

For excipients see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Injections

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ampoules for Intramuscular use-

Diclofenac ampoules are indicated in

- acute forms of pain, including renal colic
- exacerbations of osteo- and rheumatoid arthritis
- acute back pain
- acute gout
- acute trauma and fracture
- post operative pain

Ampoules for Intravenous use-

For the treatment or prevention of post-operative pain in the hospital setting.

4.2 Posology and method of administration

Adults

Ampoules for Intramuscular use:

The following directions for intramuscular injection must be adhered to in order to avoid damage to a nerve or other tissue at the injection site.

Adults:

One ampoule once (or in severe cases twice) daily intramuscularly by deep intragluteal injection into the upper outer quadrant. If two injections daily are required it is advised that the alternate buttock be used for the second injection. Diclofenac injection 75 mg / 3 ml (given i.m. or i.v.) should not be given for more than 2 days; if necessary, treatment can be continued with tablets or suppositories.

Combinations with other dosage forms of Diclofenac (tablets or suppositories) can be used up to the maximum daily dosage of 150mg.

Renal colic: One 75 mg ampoule intramuscularly.

A further ampoule may be administered after 30 minutes if necessary.

The recommended maximum daily dose of 150 mg in any combination of the three formulations of Diclofenac should not be exceeded.

“Diclofenac Injection can also be given by an intravenous infusion, never as a bolus.”

Ampoules for intravenous use:

Prior to infusion it must be diluted with 100-500ml of either sodium chloride solution (0.9%) or glucose solution (5%). Both solutions should be buffered with sodium bicarbonate solution (0.5ml 8.4% or 1ml 4.2%).

For the treatment of moderate to severe post-operative pain, 75mg should be infused over a period of 30 minutes to 2 hours. This can be repeated after 4-6 hours, without exceeding 150mg within any 24-hour period.

For the prevention of post-operative pain, a loading dose of 25mg-50mg should be infused after surgery over 15 minutes to an hour, followed by a continuous infusion of around 5mg per hour up to a maximum of 150mg daily.

Elderly:

The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest dose should be used and the patient should be monitored for GI bleeding during NSAID therapy. To be taken preferably with or after food.

Children (aged 1 - 12 years):

Diclofenac injection 75 mg/3 ml is not suitable for children.

Advice:

For intramuscular injections, the following directions must be adhered to in order to prevent damage to a nerve or other tissue at the injection site:

The solution should be injected slowly and securely intramuscularly after a control aspiration. A depot into the vicinity of nerves should be avoided. If more severe pain or malaise occurs during the injection, the procedure should be discontinued.

Diclofenac ampoules are friable ampoules with a break under a blue point. The coloured rings at the neck of the ampoules are of significance to the company as they are necessary for identification of ampoules before labelling.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control the symptoms (see section 4.4).

4.3 Contraindications

Hypersensitivity to diclofenac or to any of the excipients- mannitol, propylene glycol, benzyl alcohol, sodium metabisulphite, sodium hydroxide.

-NSAIDs should not be administered to patients with active or a history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

-NSAIDs are contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin or other nonsteroidal anti-inflammatory drugs.

Specifically for intravenous use.

-Concomitant NSAID or anticoagulant use (including low dose heparin). History of haemorrhagic diathesis, a history of confirmed or suspected cerebrovascular bleeding.

-Operations associated with a risk of haemorrhage.

-A history of asthma.

-Hypovolaemia or dehydration from any cause.

Severe heart failure, hepatic failure and renal failure. (see section 4.4).

During the last trimester of pregnancy.(See section 4.6).

History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

4.4 Special warnings and precautions for use

Warnings:

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

Like other NSAIDs, Diclofenac may mask the signs and symptoms of infection due to its pharmacodynamic properties.

Concomitant use of NSAIDs with intravenous diclofenac is contraindicated (see Section 4.3)

Cardiovascular, Renal and Hepatic impairment

The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see also section 4.3).

Gastro-intestinal: Close medical surveillance is imperative in patients with symptoms indicative of gastrointestinal disorders, with a history suggestive of gastro-intestinal ulceration, with ulcerative colitis, Crohn's disease, or haematological abnormalities.

Gastrointestinal bleeding, ulceration and perforation:

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

Gastro-intestinal bleeding or ulcerative/perforation, haematemesis and melaena have in general more serious consequences in the elderly. They can occur at any time during treatment with or without warning symptoms

or a previous history. In the rare instances where gastro-intestinal bleeding or ulceration occurs in patients receiving Diclofenac injection, the drug should be withdrawn.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk. (See below and section 4.5).

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, selective serotonin-reuptake inhibitors and anti-platelet agents. Concomitant use of anticoagulants with intravenous diclofenac is contraindicated (see Section 4.3 and 4.5).

When GI bleeding or ulceration occurs in patients receiving diclofenac, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).

Hepatic: Close medical surveillance is also imperative in patients suffering from severe impairment of hepatic function.

SLE and mixed connective tissue disease.

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see section 4.8).

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 (see section 4.8). Patients appear to be at high risk for these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Diclofenac injection should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Hypersensitivity reactions: As with other nonsteroidal anti-inflammatory drugs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug.

Precautions:

Cardiovascular and cerebrovascular effects:

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of diclofenac, particularly at high doses (150mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with diclofenac after careful consideration. Similar consideration should be made before initiating longer term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Renal: Patients with renal, cardiac or hepatic impairment and the elderly should be kept under surveillance, since the use of NSAIDs may result in deterioration of renal function. The lowest effective dose should be used and renal function monitored.

The importance of prostaglandins in maintaining renal blood flow should be taken into account in patients with impaired cardiac or renal function, those being treated with diuretics or recovering from major surgery. Effects on renal function are usually reversible on withdrawal of Diclofenac injection.

Respiratory disorders:

Use of intravenous diclofenac is contraindicated in patients with a history of asthma.

Hepatic: If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), Diclofenac injection should be discontinued. Hepatitis may occur without prodromal symptoms. Use of Diclofenac injection in patients with hepatic porphyria may trigger an attack.

Haematological: Diclofenac injection may reversibly inhibit platelet aggregation (see anticoagulants in 'drug interactions'). Patients with defects of haemostasis, bleeding diathesis or haematological abnormalities should be carefully monitored.

The elderly: The elderly are at increased risk of the consequences of adverse reactions.

Caution is required in patients with a history of heart failure or hypertension since oedema has been reported in association with NSAIDs.

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal. (See section 4.2).

Long-term treatment: All patients who are receiving non-steroidal anti-inflammatory agents should be monitored as a precautionary measure e.g. renal function, hepatic function (elevation of liver enzymes may occur) and blood counts. This is particularly important in the elderly.

Impaired female fertility

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

4.5 Interaction with other medicinal products and other forms of interaction

Care should be taken in patients treated with any of the following drugs as interactions have been reported in some patients.

Antihypertensives: reduced antihypertensive effect.

Diuretics: reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

Lithium: Decreased elimination of lithium.

Methotrexate: Decreased elimination of methotrexate.

Ciclosporin: Increased risk of nephrotoxicity.

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Other analgesics: Concomitant use of NSAIDs with intravenous diclofenac is contraindicated (see Section 4.3)

Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see sec 4.4).

Anticoagulants: NSAIDs may enhance the effects of anti-coagulants such as warfarin. Concomitant use of anticoagulants with intravenous diclofenac is contraindicated (see section 4.3)

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see section 4.4)

Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine.

4.6 Pregnancy and lactation

Whilst no teratogenic effects have been demonstrated in animal toxicology studies, the use of NSAIDs during pregnancy should if possible be avoided during the first two trimester of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus. Congenital abnormalities have been reported in association with NSAID administration in man; however, these are low in frequency and do not appear to follow any discernible pattern. In view of the known effects of NSAIDs on the foetal cardiovascular system (a closure of the ductus arteriosus), use in the last trimester of pregnancy is contraindicated. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child (see section 4.3) NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

Lactation:

In the limited studies so far available, NSAIDs can appear in breast milk in very low concentrations NSAIDs should, if possible, be avoided when breastfeeding. See sec 4.4 Special warnings and precautions for use, regarding female fertility.

4.7 Effects on ability to drive and use machines

Dizziness, drowsiness, visual disturbances or headaches are possible undesirable effects after taking NSAIDs, if affected, patients should not drive or operate machinery.

4.8 Undesirable effects

If serious side-effects occur, Diclofenac should be withdrawn.

Frequency estimate:

Frequent: >10%

Occasional: >1-10%

Rare >0.001-1%

Isolated cases: <0.001%

Gastrointestinal: The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (See section 4.4) and have been reported following administration. Less frequently, gastritis has been observed. Pancreatitis has been reported very rarely.

Hypersensitivity: Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of a) non-specific allergic reactions and anaphylaxis b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea or c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and less commonly, bullous dermatoses (including epidermal necrolysis, erythema multiforme and exfoliative dermatitis).

Cardiovascular: Oedema has been reported in association with NSAID treatment.

Other adverse events reported less commonly include:

Renal: Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome and renal failure.

Hepatic: Abnormal liver function, hepatitis and jaundice.

Neurological & special senses: Visual disturbances, optic neuritis, headaches, paraesthesia, reports of aseptic meningitis (especially in patients with existing auto immune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation (See section 4.4) depression, confusion, hallucinations, tinnitus, vertigo, dizziness, malaise, fatigue and drowsiness.

Haematological: Thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia.

Dermatological: Bullous reactions including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis (very rare) Photosensitivity.

Clinical trial and epidemiological data suggest that use of diclofenac, particularly at high doses (150mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

4.9 Overdose

a) Symptoms

Symptoms of overdose include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, fainting occasionally convulsions. In cases of significant poisoning acute renal failure and liver damage are possible.

b) Therapeutic measure

Patients should be treated symptomatically as required.

Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

Good urine output should be ensured.

Renal and liver function should be closely monitored.

Patients should be observed for at least four hours after ingestion of potentially toxic amounts.

Frequent or prolonged convulsions should be treated with Intravenous diazepam. Other measures may be indicated by the patient's clinical condition.

Supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, gastro-intestinal irritation, and respiratory depression; specific therapies such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Diclofenac injection 75 mg/3 ml is a non-steroidal agent with marked analgesic/anti-inflammatory properties. It is an inhibitor of prostaglandin synthetase, (cyclo-oxygenase). Diclofenac sodium *in vitro* does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in human beings.

5.2 Pharmacokinetic properties

Absorption

Diclofenac is absorbed after all forms of administration. The plasma concentrations of the agent is linearly proportional to the administered dose.

After an intramuscular injection of 75 mg of diclofenac a plasma maximum of 2.5 µg/ml (8µmol/l) will be achieved after approximately 20 minutes. The area under the plasma concentration curve (AUC) after i.m. injection is approximately the double of that after oral or rectal administration of the same dose, because approximately half of the active substance is metabolized (first pass effect) in the first passage in the liver.

Distribution

Diclofenac is 99.7 % bound to serum proteins mainly albumin (99.4 %).

Diclofenac passes into the synovial fluid. Here maximum concentrations are measured 2 - 4 hours after maximal plasma values have been reached. The elimination half-life of the synovial fluid is 3 - 6 hours. Therefore the concentrations of the active substance are higher 4 - 6 hours after administration than in the plasma and remain at this level for up to 12 hours after administration.

Metabolism

The metabolism of diclofenac occurs quickly and almost completely. The metabolites are

known. The biotransformation occurs for a small part by glucuronidation of the unchanged molecule, by mainly a simple or multiple hydroxylation which leads to a formation of several phenolic metabolites (3'-hydroxy-, 4'-hydroxy-, 5'-hydroxy-, 4',5'-dihydroxy- and 3'-hydroxy-4'-methoxydiclofenac), which are then extensively conjugated to glucuronic acid.

Elimination

The elimination of the active substance out of the plasma occurs with a systemic clearance of 263 ± 56 ml/min.

The terminal half-life is 1 - 2 hours.

Less than 1 % of the active substance is renally eliminated in its unchanged form. 60 % of the administered amount are renally eliminated as metabolites, the rest is eliminated with the feces.

The pharmacokinetics of diclofenac also remain unchanged after repeated administration.

No cumulation is to be expected, if the recommended dosage is observed. No relevant differences of absorption, metabolism and elimination caused by the age of the patients have been observed.

In patients with impaired renal function, no accumulation of diclofenac has been reported.

Elimination rates in renally impaired patients are comparable to those in other patients. The steady state concentrations of the total metabolites in patients with severe renal impairment are four times higher than in subjects with normal renal function, but exert no additional pharmacological effects.

Bioavailability

Bioavailability studies are not necessary because it is an injection solution.

5.3 Preclinical safety data

Acute Toxicity

The study of acute toxicity in various animal models did not reveal any special sensitivity.

Chronic Toxicity

The chronic toxicity was examined in rats, dogs and monkeys. Ulceration in the gastrointestinal tract was observed and produced complications, i.e. peritonitis, anaemia and leucocytosis.

Mutagenic and Carcinogenic Potential

A mutagenic effect of diclofenac seems to be excluded by the results of in-vitro and in-vivo tests. Studies on carcinogenicity in rats did not show any evidence of tumour-developing activities.

Reproduction Toxicology

The embryotoxic potential of diclofenac was studied in 3 animal models (rat, mouse and rabbit). Fetal death and retardation of growth resulted in doses in the toxic range. Malformations have not been observed. The gestation period and duration of parturition were prolonged by diclofenac. The effect on fertility was not examined. Doses below the maternal-toxic range did not reveal any influence on the postnatal development of the descendants.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, propylene glycol, benzyl alcohol, sodium metabisulphite, sodium hydroxide, water for injections

6.2 Incompatibilities

Diclofenac ampoules for intramuscular or intravenous use should not be mixed with other solutions for injections, other than those for diluting as directed in Instructions for use and handling section 6.6.

6.3 Shelf life

For sales pack- 2 years.
For diluted product- Use immediately.

6.4 Special precautions for storage

Do not store above 25°C.
Keep the container in the outer carton.

6.5 Nature and contents of container

3 ml Type I glass ampoules.
10 ampoules per carton.

6.6 Instructions for use and handling (and disposal)

When used intravenously, Diclofenac Injection should be given as an intravenous infusion, never as bolus. Prior to infusion it must be diluted with 100-500ml of either sodium chloride solution(0.9%) or glucose solution (5%). Both solutions should be buffered with sodium bicarbonate solution (0.5ml 8.4% or 1ml 4.2%). Intravenous infusions should be freshly made up and used immediately. Only clear solution should be used.

7 MARKETING AUTHORISATION HOLDER

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