

# **PACKAGE INSERT TEMPLATE FOR DICLOFENAC SODIUM SOLUTION FOR INJECTION**

## **Brand or Product Name**

*[Product name]* Solution for Injection 75mg/3ml

## **Name and Strength of Active Substance(s)**

Diclofenac sodium 75mg/3ml

## **Product Description**

*[Visual description of the appearance of the product (eg colour, odour etc)  
eg :Clear, colorless liquid ]*

## **Pharmacodynamics**

### *Mechanism of action*

Diclofenac sodium is a non-steroidal compound with pronounced antirheumatic, anti-inflammatory, analgesic and antipyretic properties. Inhibition of prostaglandin biosynthesis, which has been demonstrated in experiments, is considered fundamental to its mechanism of action. Prostaglandins play a major role in causing inflammation, pain and fever. Diclofenac sodium in vitro does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to those reached in humans.

### *Pharmacodynamic effects*

In rheumatic diseases, the anti-inflammatory and analgesic properties of diclofenac sodium elicit a clinical response characterised by marked relief from signs and symptoms such as pain at rest, pain on movement, morning stiffness, and swelling of the joints, as well as by an improvement in function.

Diclofenac sodium has also been found to exert a pronounced analgesic effect in moderate and severe pain of non-rheumatic origin, an effect which sets in within 15 to 30 minutes.

Diclofenac sodium has also been shown to have a beneficial effect in migraine attacks.

In post-traumatic and post-operative inflammatory conditions, diclofenac sodium rapidly relieves both spontaneous pain and pain on movement and reduces inflammatory swelling and wound oedema.

When used concomitantly with opioids for the management of post-operative pain, diclofenac sodium significantly reduces the need for opioids.

Diclofenac sodium injection are particularly suitable for initial treatment of inflammatory and degenerative rheumatic diseases, and of painful conditions due to inflammation of non-rheumatic origin.

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## Pharmacokinetics

### *Absorption*

After administration of 75 mg diclofenac by intramuscular injection, absorption sets in immediately, and mean peak plasma concentrations of about 2.5 micrograms/mL (8 micromol/L) are reached after about 20 minutes. The amount absorbed is in linear proportion to the size of the dose.

When 75 mg diclofenac is administered as an intravenous infusion over 2 hours, mean peak plasma concentrations are about 1.9 micrograms/mL (5.9 micromol/L). Shorter infusions result in higher peak plasma concentrations, while longer infusions give plateau concentrations proportional to the infusion rate after 3 to 4 hours. In contrast, plasma concentrations decline rapidly once peak levels have been reached following intramuscular injection or administration of gastro-resistant tablets or suppositories.

The area under the concentration curve (AUC) after intramuscular or intravenous administration is about twice as large as it is following oral or rectal administration, because about half the active substance is metabolised during its first passage through the liver ("first pass" effect) when administered via the oral or rectal routes. Pharmacokinetic behaviour does not change after repeated administration. No accumulation occurs provided the recommended dosage intervals are observed.

### *Distribution*

99.7% of diclofenac is bound to serum proteins, mainly to albumin (99.4%). The apparent volume of distribution calculated is 0.12 to 0.17 L/kg. Diclofenac enters the synovial fluid, where maximum concentrations are measured 2 to 4 hours after peak plasma values have been attained. The apparent half-life for elimination from the synovial fluid is 3 to 6 hours. Two hours after reaching peak plasma values, concentrations of the active substance are already higher in the synovial fluid than in the plasma, and they remain higher for up to 12 hours.

### *Biotransformation*

Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites (3'-hydroxy-,4'-hydroxy-,5-hydroxy-,4',5-dihydroxy- and 3'-hydroxy-4'-methoxy-diclofenac), most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active, but to a much smaller extent than diclofenac.

### *Elimination*

Total systemic clearance of diclofenac from plasma is  $263 \pm 56$  mL/min (mean value  $\pm$ SD). The terminal half-life in plasma is 1 to 2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1 to 3 hours. One metabolite, 3'-hydroxy-4'-methoxy-diclofenac has a much longer plasma half-life. However, this metabolite is virtually inactive.

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About 60% of the administered dose is excreted in the urine as the glucuronide conjugate of the intact molecule and as metabolites, most of which are also converted to glucuronide conjugates. Less than 1% is excreted as unchanged substance. The rest of the dose is eliminated as metabolites through the bile in the faeces.

#### *Characteristics in patients*

No relevant age-dependent differences in the drug's absorption, metabolism or excretion have been observed. In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule. At a creatinine clearance of <10 mL/min, the calculated steady-state plasma levels of the hydroxy metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile. In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

### **Indication**

#### *Intramuscular injection*

Treatment of:

- Exacerbations of inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, spondylarthritis, painful syndromes of the vertebral column, non-articular rheumatism.
- Acute attacks of gout.
- Renal colic and biliary colic.
- Post-traumatic and post-operative pain, inflammation and swelling.

#### *Intravenous infusion*

- Treatment or prevention of post-operative pain in a hospital setting.

### **Recommended Dosage**

As a general recommendation, the dose should be individually adjusted and the lowest effective dose given for the shortest possible duration.

#### Adults

Diclofenac sodium solution for injection should not be given for more than 2 days; if necessary, treatment can be continued with diclofenac sodium tablets or suppositories.

#### *Intramuscular injection*

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

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The dose is generally one 75 mg ampoule daily, given by deep intragluteal injection into the upper outer quadrant. In severe cases (e.g. colic), the daily dose can exceptionally be increased to two injections of 75 mg, separated by an interval of a few hours (one into each buttock). Alternatively, one ampoule of 75 mg can be combined with other pharmaceutical forms of diclofenac sodium (e.g. tablets, suppositories) up to a total maximum daily dose of 150 mg.

#### *Intravenous infusion*

Diclofenac sodium solution for injection must not be given as an intravenous bolus injection. Immediately before starting an intravenous infusion, diclofenac sodium solution for injection must be diluted with saline 0.9% or glucose 5% infusion solution buffered with sodium bicarbonate according to the instructions given in section Instructions for Use.

Two alternative dosage regimens of diclofenac sodium solution for injection are recommended. For the treatment of moderate to severe post-operative pain, 75 mg should be infused continuously over a period of 30 minutes to 2 hours. If necessary, treatment may be repeated after a few hours, but the dose should not exceed 150 mg within any period of 24 hours.

For the prevention of post-operative pain, a loading dose of 25 mg to 50 mg should be infused after surgery over 15 minutes to 1 hour, followed by a continuous infusion of about 5 mg per hour up to a maximum daily dose of 150 mg.

#### Children and adolescents

Because of their dosage strength, the ampoules of diclofenac sodium solution for injection are not suitable for children and adolescents.

#### **Mode of Administration**

Intravenous infusion

Intramuscular injection

#### **Contraindications**

- Known hypersensitivity to the active substance or to any of the excipients.
- Active gastric or intestinal ulcer, bleeding or perforation.
- Last trimester of pregnancy
- Severe hepatic, renal or cardiac failure
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac sodium is also contraindicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs.

#### **Warnings and Precautions**

*Updated August 2011*

*[Specific package insert requirement for diclofenac sodium]*

**PRECAUTION:**

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.

*[Specific package insert requirement for NSAID]*

**WARNING**

**RISK OF GI ULCERATION, BLEEDING AND PERFORATION WITH NSAID**

Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAID therapy. Although minor upper GI problems (e.g. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious GI events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking, and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.

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 sodium may mask the signs and symptoms of infection due to its pharmacodynamic properties.

The concomitant use of diclofenac sodium with systemic NSAIDs including cyclooxygenase-2 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 basic 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.

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### *Pre-existing asthma*

In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions on NSAIDs like asthma exacerbations (so-called intolerance to analgesics / analgesics-asthma), Quincke's oedema or urticaria are more frequent than in other patients. Therefore, special precaution is recommended in such patients (readiness for emergency). This is applicable as well for patients who are allergic to other substances, e.g. with skin reactions, pruritus or urticaria.

Special caution is recommended when diclofenac sodium is used parenterally in patients with bronchial asthma because symptoms may be exacerbated.

### *Gastrointestinal effects*

To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly, the treatment should be initiated and maintained at the lowest effective dose.

Combination therapy with protective agents (e.g. proton pump inhibitors or misoprostol) should be considered for these patients, and also for patients requiring concomitant use of medicinal products containing low-dose acetylsalicylic acid (ASA)/aspirin or other medicinal products likely to increase gastrointestinal risk.

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding). Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, anti-platelet agents or selective serotonin-reuptake inhibitors.

Close medical surveillance and caution should also be exercised in patients with ulcerative colitis or Crohn's disease, as their condition may be exacerbated.

### *Hepatic effects*

Close medical surveillance is required when prescribing diclofenac sodium to patients with impaired hepatic function, as their condition may be exacerbated.

As with other NSAIDs, including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with diclofenac sodium, regular monitoring of hepatic function is indicated as a precautionary measure. If abnormal liver function tests persist or worsen, if clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (e.g. eosinophilia, rash), diclofenac sodium should be discontinued. Hepatitis may occur with use of diclofenac without prodromal symptoms.

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Caution is called for when using diclofenac sodium in patients with hepatic porphyria, since it may trigger an attack.

#### *Renal effects*

As fluid retention and oedema have been reported in association with NSAID therapy, including diclofenac particular caution is called for in patients with impaired cardiac or renal function, history of hypertension, the elderly, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and in those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery. Monitoring of renal function is recommended as a precautionary measure when using diclofenac sodium in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

#### *Haematological effects*

During prolonged treatment with diclofenac sodium, as with other NSAIDs, monitoring of the blood count is recommended. Like other NSAIDs, diclofenac sodium may temporarily inhibit platelet aggregation. Patients with defects of haemostasis should be carefully monitored.

#### *Effects on ability to drive and use machines*

Patients experiencing visual disturbances, dizziness, vertigo, somnolence or other central nervous system disturbances while taking diclofenac sodium should refrain from driving or using machines.

### **Interactions with Other Medicaments**

The following interactions include those observed with diclofenac sodium enteric-coated tablets and/or other pharmaceutical forms of diclofenac.

#### *Lithium*

If used concomitantly, diclofenac may raise plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

#### *Digoxin*

If used concomitantly, diclofenac may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

#### *Diuretics and antihypertensive agents*

Like other NSAIDs, concomitant use of diclofenac with diuretics or antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect. Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function

*Updated August 2011*

after initiation of concomitant therapy and periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity. Concomitant treatment with potassium-sparing drugs may be associated with increased serum potassium levels, which should therefore be monitored frequently.

#### *Other NSAIDs and corticosteroids*

Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects.

#### *Anticoagulants and anti-platelet agents*

Caution is recommended since concomitant administration could increase the risk of bleeding. Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are isolated reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

#### *Selective serotonin reuptake inhibitors (SSRIs)*

Concomitant administration of systemic NSAIDs, including diclofenac, and SSRIs may increase the risk of gastrointestinal bleeding.

#### *Antidiabetics*

Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of both hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

#### *Methotrexate*

Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before or after treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased.

#### *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.

#### *Quinolone antibacterials*

There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs.

*Updated August 2011*

## **Statement on Usage During Pregnancy and Lactation**

### *Pregnancy*

The use of diclofenac in pregnant women has not been studied. Therefore, diclofenac sodium should not be used during the first two trimesters of pregnancy unless the potential benefit to the mother outweighs the risk to the foetus. As with other NSAIDs, use of diclofenac during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia and/or premature closure of the ductus arteriosus. Animal studies have not shown any directly or indirectly harmful effects on pregnancy, embryonal/foetal development, parturition or postnatal development.

### *Lactation*

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

### *Fertility*

As with other NSAIDs, the use of diclofenac sodium 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 sodium should be considered.

## **Adverse Effects / Undesirable Effects**

*[Specific package insert requirement for diclofenac sodium]*

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 experiencing visual disturbances, dizziness, vertigo, somnolence or other central nervous system disturbances while taking diclofenac sodium, should refrain from driving or using machines.

The following undesirable effects include those reported with diclofenac sodium injection and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.

### *Infections and infestations*

Very rare: Injection site abscess.

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*Blood and lymphatic system disorders*

Very rare: Thrombocytopenia, leukopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis.

*Immune system disorders*

Rare: Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).

Very rare: Angioneurotic oedema (including face oedema).

*Psychiatric disorders*

Very rare: Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.

*Nervous system disorders*

Common: Headache, dizziness.

Rare: Somnolence.

Very rare: Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident.

*Eye disorders*

Very rare: Visual disturbance, vision blurred, diplopia.

*Ear and labyrinth disorders*

Common: Vertigo.

Very rare: Tinnitus, hearing impaired.

*Cardiac disorders*

Very rare: Palpitations, chest pain, cardiac failure, myocardial infarction.

*Vascular disorders*

Very rare: Hypertension, vasculitis.

*Respiratory, thoracic and mediastinal disorders*

Rare: Asthma (including dyspnoea).

Very rare: Pneumonitis.

*Gastrointestinal disorders*

Common: Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia.

Rare: Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer (with or without bleeding or perforation).

Very rare: Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis.

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### *Hepatobiliary disorders*

Common: Transaminases increased.

Rare: Hepatitis, jaundice, liver disorder.

Very rare: Fulminant hepatitis

### *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.

### *General disorders and administration site conditions*

Common: Injection site reaction, injection site pain, injection site induration.

Rare: Oedema, injection site necrosis.

## **Overdose and Treatment**

### *Symptoms*

There is no typical clinical picture resulting from diclofenac overdose. Overdose can cause symptoms such as vomiting, gastrointestinal haemorrhage, diarrhoea, dizziness, tinnitus or convulsions. In the event of significant poisoning, acute renal failure and liver damage are possible.

### *Therapeutic measures*

Management of acute poisoning with NSAIDs, including diclofenac essentially consists of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.

Special measures such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to the high protein binding and extensive metabolism.

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## **Incompatibilities**

As a rule, diclofenac sodium solution for injection should not be mixed with other injection solutions.

Infusion solutions of sodium chloride 0.9% or glucose 5% without sodium bicarbonate as an additive present a risk of supersaturation, possibly leading to formation of crystals or precipitates. Infusion solutions other than those recommended should not be used.

## **Instructions for Use**

To be injected either intramuscularly by deep intragluteal injection into the upper outer quadrant, or intravenously by slow infusion after dilution in accordance with the following instructions.

Depending on the intended duration of infusion, mix 100 to 500 mL of isotonic saline (sodium chloride 0.9% solution) or glucose 5% solution buffered with sodium bicarbonate injectable solution (0.5 mL of 8.4% or 1 mL of 4.2% or a corresponding volume of a different concentration) taken from a freshly opened container; add the contents of one diclofenac sodium injection ampoule to this solution. Only clear solutions should be used. If crystals or precipitates are observed, the infusion solution should not be used.

## **Storage Conditions**

Finished product - Store below ....°C

Each ampoule is for single use only. The solution should be used immediately after opening. Any unused contents should be discarded.

Diluted product (if applicable) - Store below ....°C for .... hours.

\* If not, please include this statement – The diluted product is for single use only. Discard any unused portion after dilution

## **Dosage Forms and Packaging Available**

*[ Packaging type & pack size eg*

*3 ml type I clear glass ampoule, capped with a butyl rubber stopper X 5s/box]*

## **Name and Address of Manufacturer**

*[ Name & full address of manufacturer ]*

## **Name and Address of Marketing Authorization Holder**

*[ Name & full address of marketing authorization holder ]*

## **Date of Revision of Package Insert**

*[ day/month/year ]*

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