



For Medical Professional only

DIFAM IM (Intramuscular) IV (Infusion)

75mg/3ml Injection

(Diclofenac Sodium U.S.P.)

(Product specs.: M.S.)

د ائیفام
۲۵ ملی گرام / ۳ ملی لیتر بخشش

DESCRIPTION:

Diclofenac sodium, a nonsteroidal anti-inflammatory drug, is designated chemically as benzeneacetic acid, 2-[2,(6-dichlorophenyl)amino] monosodium salt, with a molecular formula of C₁₄H₁₀Cl₂NNaO₂. The molecular weight is 318.13.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties:

Pharmaco-therapeutic group: penicillins with extended spectrum; ATC code: J01CA04

Mechanism of action:

Difam is a nonsteroidal 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. When used concomitantly with opioids for the management of post-operative pain, Difam often reduces the need for opioids.

Pharmacokinetic properties:

Absorption

Intramuscular injection: After administration of 75mg diclofenac by intramuscular injection, absorption sets in immediately, and mean peak plasma concentrations of about $2.558 \pm 0.968 \mu\text{g}/\text{mL}$ ($2.5 \mu\text{g}/\text{mL} \equiv 8 \mu\text{mol}/\text{L}$) are reached after about 20 minutes. The amount absorbed is in linear proportion to the size of the dose.

Intravenous infusion: When 75mg diclofenac is administered as an intravenous infusion over 2 hours, mean peak plasma concentrations are about $1.875 \pm 0.436 \mu\text{g}/\text{mL}$ ($1.9 \mu\text{g}/\text{mL} \equiv 5.9 \mu\text{mol}/\text{L}$). Shorter infusions result in higher peak plasma concentrations, while longer infusions give plateau concentrations proportional to the infusion rate after 3 to 4 hours. 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 active substance is 99.7% protein bound, mainly to albumin (99.4%).

Diclofenac enters the synovial fluid, where maximum concentrations are measured 2-4 hours after the peak plasma values have been attained. The apparent half-life for elimination from the synovial fluid is 3-6 hours. 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.

Diclofenac was detected in a low concentration (100 ng/mL) in breast milk in one nursing mother. The estimated amount ingested by an infant consuming breast milk is equivalent to a 0.03 mg/kg/day dose.

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, 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 $263 \pm 56 \text{ mL}/\text{min}$ (mean value \pm SD). The terminal half-life in plasma is 1-2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1-3 hours.

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

Elderly

No relevant age-dependent differences in the drug's absorption, metabolism or excretion have been observed, other than the finding that

in five elderly patients, a 15 minute iv infusion resulted in 50% higher plasma concentrations than expected with young healthy subjects.

Renal impairment

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.

Hepatic impairment

In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

CLINICAL PARTICULARS:

Therapeutic Indications

Ampoules for Intra Muscular use:

The ampoules are effective in acute forms of pain, including renal colic, exacerbations of osteo- and rheumatoid arthritis, acute back pain, acute gout, acute trauma and fractures, and post-operative pain.

Ampoules used in intravenous infusion:

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

DOSAGE AND ADMINISTRATION

Adults

Difam ampoules (given IM or IV) should not be given for more than two days; if necessary, treatment can be continued with Difam tablets or suppositories.

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

One ampoule once (or in severe cases twice) daily intramuscularly by deep intragluteal injection into the upper outer quadrant. If two injections daily are required it is advised that the alternative buttock be used for the second injection.

Renal colic: One 75mg ampoule intramuscularly. A further ampoule may be administered after 30 minutes if necessary. The recommended maximum daily dose of Difam is 150mg.

Intravenous Infusion: Immediately before initiating an intravenous infusion, Difam must be diluted with 100-500ml of either sodium chloride solution (0.9%) or glucose solution (5%). Both solutions should be buffered with sodium bicarbonate solution (0.5ml 8.4% or 1ml 4.2%). Only clear solutions should be used.

Difam must not be given as an intravenous bolus injection.

Two alternative regimens are recommended:

For the treatment of moderate to severe post-operative pain, 75mg should be infused continuously over a period of 30 minutes to 2 hours.

If necessary, treatment may be repeated after 4-6 hours, not exceeding 150mg within any period of 24 hours.

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

Special populations

Elderly

Although the pharmacokinetics of Difam are not impaired to any clinically relevant extent in elderly patients, nonsteroidal anti-inflammatory drugs should be used with particular caution in such patients who generally are more prone to adverse reactions. In particular it is recommended that the lowest effective dosage be used in frail elderly patients or those with a low body weight (see also Precautions) and the patient should be monitored for GI bleeding during NSAID therapy.

Renal impairment

Diclofenac is contraindicated in patients with renal failure. 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 hepatic failure. 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.

Paediatric population

Difam ampoules are not recommended for use in children.

The recommended maximum daily dose of Difam is 150mg.

CONTRAINDICATION:

- Hypersensitivity to the active substance, or any of the excipients.
- Active, gastric or intestinal ulcer, bleeding or perforation
- History of gastrointestinal bleeding or perforation, relating 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
- Hepatic failure
- Renal 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, angioedema, urticaria or acute rhinitis are precipitated by ibuprofen, acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs.

Specifically for IV use.

- Concomitant NSAID or anticoagulant use (including low dose heparin).

- History of haemorrhagic diathesis, 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.

WARNINGS AND PRECAUTIONS

General

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms. The concomitant use of Difam 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.

As with other nonsteroidal anti-inflammatory drugs including diclofenac, allergic reactions, including anaphylactic/anaphylactoid reactions can also occur without earlier exposure to the drug. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to diclofenac, like other NSAIDs, diclofenac may mask the signs and symptoms of the infection due to its pharmacodynamic properties.

The instructions for intramuscular injection should be strictly followed in order to avoid adverse events at the injection site, which may result in muscle weakness, muscle paralysis, hypoesthesia and injection site necrosis.

Gastrointestinal effects:

Gastrointestinal bleeding (haematemesis, melaena), ulceration or perforation which can be fatal has been reported with all NSAIDs including diclofenac and may occur at any time during treatment, with or without warning symptoms or a previous history of serious GI events. They generally have more serious consequences in the elderly. The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses including diclofenac, and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation. The elderly have increased frequency of adverse reactions to NSAIDs especially gastro intestinal bleeding and perforation which may be fatal.

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

Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants such as warfarin, selective serotonin-re-uptake inhibitors (SSRIs) or anti-platelet agents such as acetylsalicylic acid. Close medical surveillance and caution should be exercised in patients with ulcerative colitis, or with Crohn's disease as these conditions may be exacerbated.

NSAIDs, including diclofenac, may be associated with increased risk of gastro-intestinal anastomotic leak. Close medical surveillance and caution are recommended when using diclofenac after gastro-intestinal surgery.

Hepatic effects:

Close medical surveillance is required when prescribing Difam to patients with impairment of 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, regular monitoring of hepatic function is indicated as a precautionary measure. Hepatitis may occur with diclofenac without prodromal symptoms. Caution is called for when using diclofenac in patients with hepatic porphyria, since it may trigger an attack.

Renal effects:

As fluid retention and oedema have been reported in association with NSAIDs 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 those patients with substantial extracellular volume depletion from any cause. Monitoring of renal function is recommended as a precautionary measure when using diclofenac in such cases. Discontinuation therapy is usually followed by recovery to the pre-treatment state.

Skin effects:

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, including Difam. Patients appear to be at the highest risk of 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. Difam should be discontinued at the first appearance of skin rash, mucosal lesions or any other signs of hypersensitivity.

SLE and mixed connective tissue disease:

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

Cardiovascular and cerebrovascular effects:

Patients with congestive heart failure (NYHA-I) or patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration.

Appropriate monitoring and advice are required for patients with a history of hypertension and congestive heart failure (NYHA-I) as fluid retention and oedema have been reported in association with NSAID therapy including diclofenac.

Patients should remain alert for the signs and symptoms of serious arteriothrombotic events (e.g. chest pain, shortness of breath, weakness, slurring of speech), which can occur without warnings. Patients should be instructed to see a physician immediately in case of

such an event.

Haematological effects:

During prolonged treatment with diclofenac, as with other NSAIDs, monitoring of the blood count is recommended. Difam may reversibly inhibit platelet aggregation. Patients with defects of haemostasis, bleeding diathesis or haematological abnormalities should be carefully monitored.

Pre-existing asthma:

In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions on NSAIDs like asthma exacerbations, 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.

Like other drugs that inhibit prostaglandin synthetase activity, diclofenac sodium and other NSAIDs can precipitate bronchospasm if administered to patients suffering from, or with a previous history of bronchial asthma.

Female fertility:

The use of Difam 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 Difam should be considered.

DRUG INTERACTIONS:

The following interactions include those observed with diclofenac gastro-resistant tablets and/or other pharmaceutical forms of diclofenac.

Lithium: If used concomitantly, Difam may increase plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

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

Diuretics and antihypertensive agents: Like other NSAIDs, concomitant use of Difam 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 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, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored.

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 has an influence on the effect of anticoagulants, there are reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulant concomitantly. Therefore, to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is required. As with other nonsteroidal anti-inflammatory agents, diclofenac in a high dose can reversibly inhibit platelet aggregation.

Other NSAIDs including cyclooxygenase-2 selective inhibitors and corticosteroids: Co-administration of diclofenac with other systemic NSAIDs or corticosteroids may increase the risk of gastrointestinal bleeding or ulceration. Avoid concomitant use of two or more NSAIDs

Antidiabetics: 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 hereby increasing methotrexate levels. Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased. Cases of serious toxicity have been reported when methotrexate and NSAIDs including diclofenac are given within 24 hours of each other.

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 antiprostaglandin 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 8-12 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.

USE IN PREGNANCY AND LACTATION:

Pregnancy: The risk is believed to increase with dose and duration of therapy. If Difam is used by a woman attempting to conceive, or during the 1st trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

Difam is contra-indicated during the third trimester of pregnancy.

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

ADVERSE EFFECTS:

Common: Headache, dizziness, Vertigo, Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia. Transaminases increased, Rash, Injection site reaction, injection site pain, injection site induration.

Uncommon: Myocardial infarction, cardiac failure, palpitations, chest pain.

Not known: Injection site necrosis. Confusion, hallucinations, disturbances of sensation, malaise, Optic neuritis. Kounis syndrome, Ischaemic colitis.

Rare: Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock). Somnolence, tiredness. Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer with or without bleeding or perforation (sometimes fatal particularly in the elderly), Hepatitis, jaundice, liver disorder, Urticaria. Oedema.

Very Rare: Thrombocytopenia, leucopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis, Angioneurotic oedema (including face oedema), Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder Paräesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident. Visual disturbance, vision blurred, diplopia. Tinnitus, hearing impaired. Hypertension, hypotension, vasculitis. Pneumonitis. Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis. Fulminant hepatitis, hepatic necrosis, hepatic failure. 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. Acute renal failure, haematuria, proteinuria, nephrotic syndrome,

interstitial nephritis, renal papillary necrosis.

OVERDOSEAGE:

Symptoms

There is no typical clinical picture resulting from diclofenac over dosage. Over dosage can cause symptoms such as headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, diarrhoea, dizziness, disorientation, excitation, coma, drowsiness, tinnitus, fainting or convulsions. In the case of significant poisoning acute renal failure and liver damage are possible.

Therapeutic measures

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

PHARMACEUTICAL PARTICULARS

INCOMPATIBILITIES

The ampoules used IM or IV as an infusion should not be mixed with other injection solutions.

PRESENTATION:

Difam IM (Intramuscular)/ IV (Infusion) injection: Each box containing 5x3ml ampoules

DIRECTIONS:

- Protect from light and moisture store at 15°C-25°C.
- Store in a cool and dry place
- The infusion solution should not be used if crystals or precipitates are observed.
- Keep out of the reach of children.
- For suspected adverse drug reaction for BOSCH products, report at ade@bosch-pharma.com

WARNING:

To be sold on the prescription of registered medical practitioner only.

مہلات :

ریٹن سے گھوٹکی اور بچ کے 15-25 گرامی میٹر پر جائز استعمال کیا جائے۔

کلکی لیتھی سے درست کیا جائے۔

ڈیکٹری پارکت کے طالعات تسلیم کیں۔

انجمن: حرف رجسٹریڈ نئی پکیٹ کے نئے پروڈکٹ کے لئے۔



For Medical Professional only

DIFAM IM (Intramuscular) IV (Infusion)

75mg/3ml Injection
(Diclofenac Sodium U.S.P.)
(Product specs.: M.S.)

ڈائیفام