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For the use only of a Registered Medical Practitioner or Hospital or a Laboratory

DICLOMAX

(Diclofenac Sodium Injection I.P.)

Anti-inflammatory, Analgesic (Non-steroidal anti-inflammatory drug).

Composition and form of issue

Active ingredient is sodium-[o-[(2, 6-dichlorophenyl)-amino]-phenyl]-acetate (= diclofenac sodium).

Each ml contains :

Diclofenac sodium I.P.	25 mg
Benzyl alcohol I.P.	4 % w/v
Water for injection I.P.	q.s.

Therapeutic Indications

Intramuscular injection

Treatment of :

- Exacerbation of inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, ankylosing spondylitis and osteoarthritis
- Acute attacks of gout
- Renal colic
- Post-traumatic and postoperative pain, inflammation and swelling
- Pain following dental surgery
- Painful inflammatory conditions in gynaecology

Intravenous infusion

Treatment or prevention of postoperative pain in a hospital setting.

Dosage and directions for use:

Adults

Diclomax injection should not be given for more than 2 days; if necessary, treatment can be continued with Diclofenac tablets.

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.

The dosage is generally 75 mg 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, 75 mg can be combined with other analgesics.

Intravenous Injection

Diclomax must not be given as an intravenous bolus injection.

Immediately before starting an intravenous infusion Diclomax 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 Diclomax are recommended.

For the *treatment* of moderate to severe postoperative pain, 3 ml 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 dosage should not exceed 150 mg within any period of 24 hours.

For the *prevention* of postoperative pain, a loading dose of 1 ml - 2 ml 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 dosage of 150 mg.

Children

Diclomax injection is not recommended for use in children.

Not to be used in newly born or premature infants.

Contraindications

Gastric or intestinal ulcer.

Known hypersensitivity to the active substance and other excipients. 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 drugs with prostaglandin-synthetase inhibiting activity.

Special Warnings and Special Precautions for Use

Warnings

Gastrointestinal bleeding or ulceration/perforation can occur at any time during treatment, with or without warning symptoms or a previous history. They generally have more serious consequences in the elderly. In the rare cases where gastrointestinal bleeding or ulceration occurs in patients receiving Diclofenac, the drug should be withdrawn.

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases without earlier exposure to the drug.

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

Precautions

Close medical surveillance is imperative in patients with symptoms indicative of gastrointestinal disorders or a history suggestive of gastric or intestinal ulcer, patients with ulcerative colitis or Crohn's disease and in patients suffering from impaired hepatic function.

As with other NSAIDs, values of one or more liver enzymes may increase. During prolonged treatment with Diclofenac (e.g. in the form of tablets or suppositories), 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, etc.), Diclofenac should be discontinued. Hepatitis may occur without prodromal symptoms.

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

Owing to the importance of prostaglandins in maintaining renal blood flow, particular caution is called for in patients with impaired cardiac or renal function, the elderly, patients being treated with diuretics, and patients with substantial extracellular volume depletion of any cause, e.g. before or after major surgery. Monitoring of renal function is recommended as a precautionary measure when using Diclofenac in such cases. Discontinuation of therapy is normally followed by a return to the pretreatment state.

During prolonged treatment with Diclofenac - as with other NSAIDs - monitoring of the blood count is recommended.

Like other NSAIDs, Diclofenac may temporarily inhibit platelet aggregation. Patients with haemostatic disorders should be carefully monitored.

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

Caution is indicated in the elderly on basic medical grounds. In particular it is recommended that the lowest effective dosage should be used in frail elderly patients or those with a low body-weight.

Interactions with Other Drugs and Other Types of Interactions

(Including interactions observed with other pharmaceutical forms of Diclofenac)

Lithium, digoxin: Diclofenac may raise plasma concentrations of lithium and digoxin.

Diuretics: Like other NSAIDs, Diclofenac may decrease the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels, which should therefore be monitored.

NSAIDs: Concomitant administration of systemic NSAIDs may increase the frequency of side effects.

Anticoagulants: 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.

Antidiabetics: Clinical studies have shown that Diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, isolated cases have been reported of both hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of hypoglycaemic agents during treatment with Diclofenac.

Methotrexate: Caution is called for if NSAIDs 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.

Cyclosporin: The effects of NSAIDs on renal prostaglandins may increase the nephrotoxicity of cyclosporin.

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

Pregnancy and Lactation

Because of insufficient data, administration of Diclofenac injection during pregnancy and lactation is not recommended.

Effects on Ability to Drive and Use Machines

Patients experiencing dizziness or other central nervous disturbances, including visual disturbances, should not drive or operate machinery.

Undesirable Effects

The undesirable effects including with other dosage forms of Diclofenac either in short term or long term use the following frequency were used: frequent > 10 %, occasional > 1 - 10 %, rare > 0.001 - 1 %, isolated cases < 0.001 %.

Gastrointestinal tract

Occasional: epigastric pain; other gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal cramps, dyspepsia, flatulence, anorexia.

Rare: gastrointestinal bleeding, gastric or intestinal ulcer with or without bleeding or perforation.

Isolated cases: aphthous stomatitis, glossitis, oesophageal lesions, diaphragm-like intestinal strictures, lower gut disorders such as non-specific haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease, constipation, pancreatitis.

Central nervous system

Occasional: headache, dizziness, vertigo.

Rare: drowsiness.

Isolated cases: sensory disturbances, including paraesthesias, memory disturbances, disorientation, insomnia, irritability, convulsions, depression, anxiety, nightmares, tremor, psychotic reactions, aseptic meningitis.

Special senses

Isolated cases: blurred vision, diplopia, impaired hearing, tinnitus, taste disturbances.

Skin

Occasional: rashes or skin eruptions.

Rare: urticaria

Isolated cases: bullous eruptions, eczema, erythema multiforme, Stevens-Johnson syndrome, acute toxic epidermolysis, exfoliative dermatitis, loss of hair, photosensitivity reactions; purpura, including allergic purpura.

Kidney

Rare: oedema.

Isolated cases: acute renal failure, urinary abnormalities such as haematuria and proteinuria, interstitial nephritis, nephrotic syndrome, papillary necrosis.

Liver

Occasional: elevation of serum aminotransferase values.

Rare: hepatitis with or without jaundice.

Isolated cases: fulminant hepatitis.

Blood

Isolated cases: thrombocytopenia, leucopenia, haemolytic anaemia, aplastic anaemia, agranulocytosis.

Hypersensitivity

Rare: hypersensitivity reactions such as asthma, systemic anaphylactic/anaphylactoid reactions including hypotension.

Isolated cases: vasculitis, pneumonitis.

Cardiovascular system

Isolated cases: palpitation, chest pain, hypertension, congestive heart failure.

Other organ systems

Occasional: intramuscular injection site reactions such as local pain and induration.

Isolated cases: local abscesses and necrosis at the intramuscular injection site.

Over dosage

Management of acute poisoning with NSAIDs consists essentially of supportive and symptomatic measures. There is no typical clinical picture associated with an overdosage of diclofenac.

The following therapeutic measures should be taken in cases of overdosage:

Supportive and symptomatic treatments are indicated for complications such as hypotension, renal failure, convulsions, gastrointestinal irritation, and respiratory depression.

Specific measures such as forced diuresis, dialysis, or haemoperfusion are unlikely to be helpful in eliminating NSAIDs because of their high protein-binding rate and extensive metabolism.

Pharmacological Properties

Mechanism of action

Diclomax contains diclofenac sodium, 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 to be fundamental to its mechanism of action. Prostaglandins play an important role in causing inflammation, pain and fever.

Diclofenac sodium in vitro does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in humans.

Pharmacodynamic effects

In rheumatic diseases, the anti-inflammatory and analgesic properties of Diclofenac 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 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 15-30 minutes. Diclofenac has also been shown to have a beneficial effect in migraine attacks.

In post-traumatic and postoperative inflammatory conditions, Diclofenac 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 significantly reduces the need for opioids.

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

Pharmacokinetic Properties

Absorption

After administration of 3 ml Diclofenac by intramuscular injection, absorption sets in immediately, and mean peak plasma concentrations of about 2.5 mcg/ml (8 micromol/L) are reached after about 20 minutes. The amount absorbed is in linear proportion to the size of the dose.

When 3 ml Diclofenac is administered as an intravenous infusion over 2 hours, mean peak plasma concentrations are about 1.9 mcg/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 binds to serum proteins, mainly to albumin (99.4%). The apparent volume of distribution calculated is 0.12-0.17 L/kg.

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

Elimination

Total systemic clearance of Diclofenac from plasma is 263 ± 56 ml/min (mean value ± 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. One metabolite, 3'-hydroxy-4'-methoxy-diclofenac, has a much longer plasma half-life. However, this metabolite is virtually inactive.

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 after oral administration. However, in a few elderly patients a 15-minutes intravenous infusion resulted in 50% higher plasma concentrations than expected from the data on young healthy subjects.

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 less than 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.

Preclinical Safety Data

Diclofenac did not influence fertility of the parent animals (rats) nor the pre-, peri-, and postnatal development of the offspring. No teratogenic effects were detected in mice, rats and rabbits. No mutagenic effects could be demonstrated in various in vitro and in vivo experiments, and no carcinogenic potential was detected in long-term studies in rats and mice.

Storage

Store below 30^{O}C, protected from light.

Keep out of reach of children.

Instructions for Use / Handling

Diclomax solution for injection should not be mixed with other injection solutions.

Diclofenac injection can be given either intramuscularly by deep intragluteal injection into the upper outer quadrant, or intravenously by slow infusion after dilution as per following instructions.

Depending on the intended duration of infusion (Refer "Dosage and method of administration"), mix 100-500 ml of isotonic saline (sodium chloride 0.9 % solution) or glucose 5 % solution with sodium bicarbonate injectable solution (0.5 ml of 8.4 % or 1 ml of 4.2 % or 0.56 ml of 7.5 % or a corresponding volume of a different concentration) taken from a freshly opened container; add the contents of one Diclomax injection to this solution.

Only clear solutions should be used. If crystals or precipitates are observed, the infusion solution should not be used.

Once punctured the content of the vial should be used within 15 days of opening.

Discard the content if any particulate matter or discoloration is found during the use.

Intravenous infusions should be initiated immediately after preparing the infusion. The infusion solutions should not be stored.

WARNING : " NOT FOR VETERINARY USE "

Expiry Date

Do not use later than the date of expiry.

Presentation

DICLOMAX is available as 30 ml vial.

torrent

Manufactured by :
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