DECLOPHEN
Ampoules

Solution for
I.M. Injection & I.V. infusion

This product contains benzyl alcohol, not for use in neonates and infants.

Composition : Each ampoule (3 ml) contains:
Active Ingredient : Diclofenac sodium 75 mg
Inactive Ingredients : Sodium metabisulphite, Disodium edetate, Sodium hydroxide, Benzyl alcohol, Propylene glycol, Ethyl alcohol, Nicotinamide, Water for injection.

Properties/effects

Mechanism of action : Declophen ampoules contain diclofenac sodium, a non-steroidal compound with pronounced antirheumatic, anti-inflammatory, 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.

Therapeutic effect

In rheumatic diseases, the anti-inflammatory and analgesic properties of **Declophen** elicit a clinical response characterized 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. In post-traumatic and postoperative inflammatory conditions, **Declophen** rapidly relieves both spontaneous pain and pain on movement and reduces inflammatory swelling and wound oedema. When used concomitantly with opoids for the management of postoperative pain, **Declophen** significantly reduces the need for opoids. In clinical trials, the pronounced analgesic effect has also been demonstrated in moderate and severe pain of non-rheumatic origin, an effect which sets in within 15 – 30 minutes. **Declophen** has also been shown to have a beneficial effect in migraine attacks. **Declophen** ampoules are particularly suitable for initial treatment of inflammatory and degenerative rheumatic diseases and of painful conditions due to inflammation of non-rheumatic origin.

Pharmacokinetics :

Absorption : After administration of 75 mg diclofenac by intramuscular injection, mean peak plasma concentrations of about 2.5 µg/ml (8 µmol/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 infusion over 2 hours, mean peak plasma concentrations are about 1.9 µg/mL (5.9 µmol/L). Shorter infusions result in higher peak plasma concentrations, while longer infusions give plateau concentrations proportional to the 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 route. Pharmacokinetic behavior does not change after repeated administration .

No accumulation occurs provided the recommended dosage intervals are observed.

Distribution : Altogether 99.7 % of diclofenac binds to serum protein, 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.

Metabolism : Biotransformation of diclofenac takes place partly glucuronidation the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites (3'-hydroxy-4 methoxy,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 in the form of metabolites. Less than 1% is excreted as unchanged substance. The rest of the dose is eliminated as metabolites through the bile in the faeces.

Kinetics in special clinical situations.

No relevant age-dependent differences in the drug's absorption, metabolism, or excretion have been observed after oral administration.

However, in elderly patients a 15-minute 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 healthy subjects. However, the metabolites are ultimately cleared through the bile. In patients with impaired liver function (chronic hepatitis or non-decompensated cirrhosis), the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

Indications : Intramuscular injection initial 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.
- Severe migraine attacks.

Intravenous Infusion : Treatment or prevention of postoperative pain in a hospital setting

Dosage/administration

Adults : Declophen ampoules should not be given for more than 2 days; if necessary, treatment can be continued with **Declophen** tablets or suppositories.

Intramuscular injection : The following directions for intramuscular injection must be followed in order to avoid damage to nerve or other tissue at the injection site. The dosage 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 dosage forms of **Declophen** (tablets, suppositories) up to a maximum daily dosage of 150 mg. In migraine attacks, clinical experience is limited to initial use of 1 ampoule of 75 mg administered as soon as possible, followed by suppositories up to 100 mg on the same day if required. The total dosage should not exceed 175 mg on the first day. No data are available on the use of **Declophen** to treat migraine for more than one day. Should it be necessary to continue treatment on the following days, the maximum daily dose is to be limited to 150 mg (given in divided doses in the form of suppositories).

Intravenous Injection : Declophen must not be given as an intravenous bolus injection. Immediately before starting an intravenous infusion, **Declophen** must be diluted with saline 0.9% or glucose 5% infusion solution buffered with sodium bicarbonate (see in instructions for use/handling). Two alternative dosage regimens of **Declophen** are recommended. For the treatment of moderate to severe postoperative 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 dosage should not exceed 150 mg within any period of 24 hours. For the prevention of post-operative pain, a loading dose of 25 – 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 dosage of 150 mg.

Children : Declophen ampoules are contraindicated in children.

Instructions for use/handling

Declophen ampoules can be given 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 – 500 mL of isotonic saline (sodium chloride 0.9% solution) or glucose 5% with sodium bicarbonate injectable solution (0.5 mL of 8.4 mL or 1 mL of 4.2% solution, or a corresponding volume of sponding volume of solution in different concentration) taken from a freshly opened container, add the contents of one **Declophen** ampoules to this solution. Only clear solutions should be used. If crystals or precipitates are observed, the infusion solution should not be used.

Restrictions for use : Contraindications

- Gastric or intestinal ulcer.
- Known hypersensitivity to the active substance or any of the excipients.
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), **Declophen** is also contraindicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other drugs with prostaglandin synthesase inhibiting activity. Nasal polyps, angioedema, bronchospasm, or asthma, liver & kidney diseases, hypovolaemia, or dehydration. Patients at high risk for postoperative bleeding or incomplete haemostasis, haematopoietic disorders, or cerebrovascular bleeding.

Declophen must not be used together with high doses of anticoagulants or with other anti-inflammatory agents. **Declophen** ampoules must not be used in children, since there is no experience of such use.

Pregnancy, Nursing Mothers & Pediatric use : Do not administer injections preserved with benzyl alcohol to neonates, infants, pregnant women or nursing mothers. Benzyl alcohol has been associated with serious adverse events & death, particularly in pediatric patients. Injections preservative free should be used in these populations.

Warnings : Cardiovascular Risk* : NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

NSAIDs is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

Gastrointestinal Risk* : NSAIDs cause an increased risk of serious gastrointestinal adverse events including inflammation, bleeding, ulceration, and perforation of the stomach or intestine, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal.

* This product contains benzyl alcohol which is potentially toxic when administered locally to neural tissue.

* This product is contraindicated for use in premature infants because the formulation contains benzyl alcohol.

Precautions : Careful diagnosis and close medical surveillance are imperative in patients with symptoms indicative of gastrointestinal disorders or a history suggestive of gastric or intestinal ulcer, in patients with ulcerative colitis or Crohn's diseases, and in patients suffering from impaired hepatic function.

In the rare cases where gastrointestinal bleeding or ulceration occurs in patients receiving **Declophen**, the drug should be withdrawn.

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

As with other NSAIDs, value of one or more liver enzymes may increase during prolonged treatment with **Declophen**. This was observed in clinical studies of diclofenac and may occur in 15% of patients, but is rarely accompanied by clinical symptoms. The clinical relevance of this phenomenon is not known. In most cases the increases were borderline. Occasionally (in 2.5%) moderate increases were observed (> 3 to < 8 times the upper limit of normal). While the incidence of marked increases (> 8 times the upper limit of normal) remained at about 1%. If the above-mentioned studies, clinical signs of liver damage were reported along with the elevations of liver enzyme activity in 0.5% of cases. The increased enzyme activity was generally reversible after withdrawal of the preparation. As with other NSAIDs, the liver values should be monitored regularly during long-term therapy with **Declophen**. If impairment of hepatic function persists or worsens, and if clinical signs or symptoms of liver disease (e.g. hepatitis or other manifestations e.g. eosinophilia, rash, etc.) occur, **Declophen** should be discontinued. In addition to increased liver enzyme values, rare cases of severe hepatic reactions, including jaundice and, in isolated cases, fulminant hepatitis with fatal outcome, have been reported. Hepatitis may occur without prodromal symptoms. Caution is called for when using **Declophen** in patients with hepatic porphyria, since **Declophen** may trigger an attack. During prolonged treatment with **Declophen** – as with other NSAIDs monitoring of the blood count is recommended. Like other NSAIDs, **Declophen** may temporarily inhibit platelet aggregation. Patients with haemostatic disorders should be carefully monitored. Special caution is recommended when **Declophen** is used parenterally in patients with bronchial asthma because symptoms may be exacerbated. As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases without earlier exposure to drug.

The sodium metabisulphite in the ampoules can also lead to isolated hypersensitivity reactions. Like other NSAIDs, **Declophen** may mask the signs and symptoms of infection due to its pharmacodynamic properties.

Pregnancy : Declophen Ampoules should not be used in pregnancy.

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

Adverse reactions : (including undesirable effects observed with other pharmaceutical forms of **Declophen**).

Gastrointestinal tract :

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

Rare: gastrointestinal bleeding (haemat-emesis, malaena, bloody diarrhoea), 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 (and peripheral) nervous system

Occasional: headache, dizziness, vertigo.

Rare : drowsiness.

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

Special senses : Isolated cases : disturbances of vision (blurred vision, diplopia), impaired hearing, tinnitus, taste disturbances.

Skin : Occasion: rashes or skin eruptions. **Rare :** urticaria.

Isolated cases : bullous eruptions, eczema, erythema, multiforme, Stevens-Johnson syndrome, Lyell's syndrome (acute toxic epidemolysis), erythroderma (exfoliative dermatitis), loss of hair, photosensitivity reactions, purpura, including allergic purpura.

Kidney : Rare : oedema

Isolated cases : acute renal failure, haematuria, proteinuria, interstitial nephritis, nephritic syndrome, papillary necrosis.

Liver : Frequent : elevation of serum aminotransferase values (SGOT, SGPT), Occasionally to a moderate (> 3 times higher than upper limit of normal) or a marked degree (> 8 times higher than upper limit of normal).

Rare : hepatitis with or without jaundice.

In isolated cases : fulminant hepatitis.

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

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.

Interactions : (including interactions observed with other pharmaceutical forms of **Declophen**).

Lithium, digoxin: Declophen may raise plasma concentration of lithium and digoxin.

Diuretics : Like other NSAIDs, **Declophen** 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 sodium affects the action of anticoagulants, there are isolated reports of increased risk of haemorrhage in patients receiving **Declophen** and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

Antidiabetics : Clinical studies have shown that **Declophen** 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 hypo-glycaemic agents during treatment with **Declophen**.

Methotrexate : Caution is called if NSAIDs are administered less than 24 hours before or after treatment with 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 NASIDs.

Overdosage : 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 treatment are indicated for constipations such as hypotension, renal failure, convulsions, gastrointestinal irritation, and repiratory depression. Specific measures such as forced diuresis, dialysis or hemoperfusion are unlikely to be helpful in eliminating NSAIDs because of their protein-binding rate and extensive metabolism.

Other information :

Note : As a rule **Declophen** 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 additive, present a risk of super-saturation, possibly leading to information of crystals or precipitates. Infusion solutions other than those recommended should not be used.

Packing :

A carton box containing 3 or 6 Printed transparent glass type (I) ampoules 3 ml each and an inner pamphlet.

Storage :

Store at temperature not exceeding 30 ^{o} C.

Keep out of the reach of children.

Pharco Pharmaceuticals

Issue date : 18 / 8 / 2015

Made in Egypt
PHARCO
PHARMACEUTICALS
Alexandria