

Product Summary

1. Trade Name of the Medicinal Product

Econac injection 75 mg / 3 ml

2. Qualitative and Quantitative Composition

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

3. Pharmaceutical Form

Solution for Injections

Clinical Particulars

4.1 Therapeutic Indications

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 fractures
- post-operative pain

4.2 Posology and method of administration

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. Econac injection 75 mg / 3 ml should not be given for more than 2 days; if necessary, treatment can be continued with tablets or suppositories.

Econac injection 75 mg / 3 ml should not be administered by intravenous injection.

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 Econac should not be exceeded.

Elderly:

The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dosage be used and for the shortest possible duration The patient should be monitored regularly for GI bleeding during NSAID therapy.

Children (aged 1 - 12 years):

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

Advice:

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 any of the excipients mannitol, propylene glycol, benzyl alcohol, sodium metabisulphite, sodium hydroxide.

- Active or history of recurrent peptic ulcer /haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- History of gastro-intestinal bleeding or perforation, related to previous NSAIDs therapy
- Previous sensitivity to diclofenac
- NSAIDs are contraindicated in patients who have previously shown hypersensitivity reactions (e g attacks of asthma, urticaria , angioedema or acute rhinitis) in response to ibuprofen, aspirin or other non-steroidal anti-inflammatory drugs.
- Severe heart failure, hepatic failure and renal failure (see section 4.4).
- During the last trimester of pregnancy (see section 4 6)

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).

The use of Econac injection with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

Elderly:

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

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 or recovering from major surgery and the elderly. Renal function should be monitored in these patients (see also section 4.3). The lowest effective dose should be used. Effects on renal function are usually reversible on withdrawal of Econac injection 75 mg/3 ml.

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 or with Crohn's disease, bleeding diathesis 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 Econac injection 75 mg/3 ml 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, Anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents; such as aspirin (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving Econac injection, 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 highest 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. Econac 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:

Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention, hypertension 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).

Respiratory disorders:

Caution is required if administered to patients suffering from, or with a previous history of bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients

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), Econac injection 75mg/3 ml should be discontinued. Hepatitis may occur without prodromal symptoms. Use of Econac injection 75 mg/3 ml in patients with hepatic porphyria may trigger an attack.

Haematological: Econac injection 75mg/3 ml may reversibly inhibit platelet aggregation (see anticoagulants in ‘drug interactions’).

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 Econac 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 Econac injection should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Drug interactions: digoxin: Econac injection 75 mg/3 ml may increase plasma concentrations of digoxin.

Lithium: Decreased elimination of lithium

Anticoagulants: NSAIDs may enhance the effects of anti-coagulants such as warfarin (see section 4.4). Although clinical investigations do not appear to indicate that Econac injection 75 mg/3 ml has an influence on the effect of anticoagulants, there are isolated reports of an increased risk of haemorrhage with the combined use of diclofenac and anticoagulant therapy. Therefore, to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is required. As with other non-steroidal anti-inflammatory agents, diclofenac in high dose can reversibly inhibit platelet aggregation.

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

Antidiabetic agents: Clinical studies have shown that Econac injection 75 mg/3 ml can be given together with oral antidiabetic agents without influencing their clinical effect. However there have been isolated reports of hypoglycaemic and

hyperglycaemic effects which have required adjustment to the dosage of hypoglycaemic agents.

Cyclosporin: Increased risk of nephrotoxicity. Cases of nephrotoxicity have been reported in patients receiving concomitant cyclosporin and NSAIDs, including Econac injection 75 mg/3 ml. This might be mediated through combined renal antiprostaglandin effects of both the NSAID and cyclosporin.

Methotrexate: Decreased elimination of methotrexate. Cases of serious toxicity have been reported when methotrexate and NSAIDs are given within 24 hours of each other. This interaction is mediated through accumulation of methotrexate resulting from impairment of renal excretion in the presence of the NSAID.

Quinolone antimicrobials: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. 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. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving an NSAID.

Other analgesics including cyclooxygenase—2 selective inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects (see section 4. 4)

Other NSAIDs and steroids: Co-administration of Econac injection 75 mg/3 ml with other systemic NSAIDs and steroids may increase the frequency of unwanted effects.

Concomitant therapy with aspirin lowers the plasma levels of each, although no clinical significance is known.

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

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

Various NSAIDs are liable to inhibit the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels, hence serum potassium should be monitored

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

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

Anti-hypertensives: Reduced anti-hypertensive effect

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

Pregnancy:

Econac injection 75 mg/3 ml should not be prescribed during pregnancy, unless there are compelling reasons for doing so. The lowest effective dosage should be used. 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. Use of prostaglandin synthetase inhibitors may result in premature closure of the ductus arteriosus or uterine inertia, such drugs are therefore not recommended during the last trimester of pregnancy. 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 limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breastfeeding.

See section 4.4 Special warnings and precautions for use, regarding female fertility.

4.7 Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

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 (approximately 6 - 14 % of patients), flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (See section 4.4) have been reported following administration. Also minor gastrointestinal blood loss which in exceptional cases may cause anaemia. Occasionally intestinal cramps, anorexia as well as or intestinal ulcer may occur, possibly with haemorrhagic diarrhoea. Less frequently, gastritis has been observed. Pancreatitis has been reported very rarely. In isolated cases, glossitis, oesophageal lesions may occur.

Other adverse reactions reported less commonly include:

Neurological and special senses:

Visual disturbances (diplopia or blurred vision), 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.

Central nervous disturbances, e.g. excitation, irritability, insomnia, and giddiness may occasionally be expected. In individual cases disturbances of sensibility have been observed, impairment of taste, or reversible defective hearing, impaired memory, cramps, anxiety, nightmares, trembling or psychotic reactions.

Dermatological: Bullous reactions including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis (very rare) Photosensitivity. Occasionally hypersensitivity reactions, i.e. skin eruptions and itching have been observed, seldom urticaria or alopecia, rash with bullous eruptions, eczema, erythema, purpura, including allergic purpura occurred in individual cases.

Renal: Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome and renal failure. Individual cases of acute renal insufficiency (proteinuria, hematuria) or necrosis of renal papillae have been reported.

Hepatic: abnormal liver function, hepatitis and jaundice.
Occasionally elevation of serum aminotransferase enzymes (ALT, AST).

Pancreas:

Individual cases of pancreatitis have been reported.

Haematological: thrombocytopenia, neutropenia, agranulocytosis, hemolytic and aplastic anemia. During long-term therapy haematological parameters should be monitored regularly. Intramuscular diclofenac is not recommended for long term use.

Other Organs:

Peripheral oedema rarely occurred especially in patients with hypertension.

Rarely hypersensitivity reactions may occur with symptoms of facial oedema, swelling of the tongue or larynx with restriction of the respiratory tract, dyspnoea and asthma attacks, tachycardia, hypotension including hypotensive shock. If any of these symptoms occur, rapid medical assistance is necessary. Individual cases of palpitations and chest pain or hypertension have been reported.

Rarely injection site disorders e.g. local pain and indurations; in isolated cases: abscesses and local necrosis.

Cardiovascular and Cerebrovascular:

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.

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, angiodema and, more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

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 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.

Pharmacological Properties

5.1 Pharmacodynamic Properties

Econac 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 intramuscular injection of 75 mg 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, anemia and leucocytosis.

Mutagenic and Cancerogenic 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.

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 use should not be mixed with other solutions for injections.

6.3 Shelf Life

2 years.

6.4 Special Precautions for Storage

Do not store above 25°C.
Store in the original outer carton.

6.5 Nature and Contents of Container

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

6.6 Instructions for Use/Handling

See 4.2.

Administrative Data

7. Marketing Authorisation Holder

GOLDSHIELD GROUP LIMITED
(trading as Goldshield Pharmaceuticals)
NLA TOWER
12-16 ADDISCOMBE ROAD
CROYDON
SURREY
CR0 0XT

8. Marketing Authorisation Number

PL 10972/0070

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10 DATE OF REVISION OF THE TEXT

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