

**1. NAME OF THE MEDICINAL PRODUCT**

Econac 100 mg suppositories

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

One suppository contains 100 mg diclofenac sodium

**3. PHARMACEUTICAL FORM**

Suppositories for rectal use

**4. CLINICAL PARTICULARS**

**4.1. Therapeutic indications**

Relief of all grades of pain and inflammation in a wide range of conditions, including:

- arthritic conditions: rheumatoid arthritis, osteo-arthritis, ankylosing spondylitis, acute gout,
- acute musculo-skeletal disorders such as peri-arthritis (for example frozen shoulder), tendinitis, tenosynovitis, bursitis,
- other painful conditions resulting from trauma, including fracture, low back pain, sprains, strains, dislocations, orthopaedic, dental and other minor surgery.

**4.2 Posology and Method of Administration**

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

Adults:

One 100mg suppository may be given as a once daily treatment usually at night.

Where necessary therapy may be combined with tablets up to a total maximum dose of 150mg diclofenac per day.

Elderly:

Although the pharmacokinetics of Econac are not impaired to any clinically relevant extent in elderly patients, non-steroidal 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).

Children (aged 1 - 12 years):

Econac 100 mg suppositories are not suitable for children.

### **4.3 Contraindications**

- Active or suspected peptic ulcer or gastro-intestinal bleeding
- Previous sensitivity to diclofenac
- Patients in whom attacks of asthma, urticaria or acute rhinitis are precipitated by aspirin or other non-steroidal anti-inflammatory agents
- In ulcerative or acute inflammatory conditions of the anus, rectum (proctitis) and sigmoid colon.

Severe heart failure.

### **4.4 Special Warnings and Special Precautions for Use**

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).

*Warnings:*

Close medical surveillance is imperative in patients with symptoms indicative of gastrointestinal disorders, with a history suggestive of gastric or intestinal ulceration, with ulcerative colitis, or with Crohn's disease.

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 100 mg suppositories the drug should be withdrawn.

*Hepatic:* Close medical surveillance is also imperative in patients suffering from severe impairment of hepatic function.

*Hypersensitivity reactions:* As with other nonsteroidal anti-inflammatory drugs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug.

*Cardiovascular and cerebrovascular effects*

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of diclofenac, particularly at high dose (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).

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with diclofenac after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

*Precautions:*

*Renal:* Patients with renal, cardiac or hepatic impairment and the elderly should be kept under surveillance, since the use of NSAIDS may result in deterioration of renal function. The lowest effective dose should be used and renal function monitored.

The importance of prostaglandins in maintaining renal blood flow should be taken into account in patients with impaired cardiac or renal function, those being treated with diuretics or recovering from major surgery. Effects on renal function are usually reversible on withdrawal of Econac 100 mg suppositories.

*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 100 mg suppositories should be discontinued. Hepatitis may occur without prodromal symptoms. Use of Econac 100 mg suppositories in patients with hepatic porphyria may trigger an attack.

*Haematological:* Econac 100 mg suppositories may reversibly inhibit platelet aggregation (see anticoagulants in 'Drug Interactions'). Patients with defects of

haemostasis, bleeding diathesis or haematological abnormalities should be carefully monitored.

*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.

#### **4.5 Interactions with Other Medicaments and Other Forms of Interaction**

*Drug interactions:* Lithium and digoxin: Econac 100 mg suppositories may increase plasma concentrations of lithium and digoxin.

**Anticoagulants:** Although clinical investigations do not appear to indicate that Econac 100 mg suppositories 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.

**Antidiabetic agents:** Clinical studies have shown that Econac 100 mg suppositories 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:** Cases of nephrotoxicity have been reported in patients receiving concomitant cyclosporin and NSAIDS, including Econac 100 mg suppositories. This might be mediated through combined renal antiprostaglandin effects of both the NSAID and cyclosporin.

**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:** 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.

Other NSAIDS and steroids: Co-administration of Econac 100 mg suppositories 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.

Diuretics: 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.

#### **4.6 Pregnancy and lactation**

Econac 100 mg suppositories should not be prescribed during pregnancy, unless there are compelling reasons for doing so. The lowest effective dosage should be used.

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.

Following oral doses of 150 mg/day, traces of diclofenac have been detected in breast milk, but in quantities so small that no undesirable effects on the infant are to be expected.

#### **4.7 Effect on ability to drive and use machines**

Patients who experience dizziness or other central nervous system disturbances while taking NSAIDS should refrain from driving or operating machinery.

#### **4.8 Undesired Effects**

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

Clinical trial and epidemiological data suggest that use of diclofenac, particularly at high doses (150 mg 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).

If serious side-effects occur, Econac should be withdrawn

Frequency estimate: frequent: >10%, occasional: >1-10%, rare: >0.001-1%, isolated cases: <0.001%.

*Gastrointestinal Tract:*

*Occasional:* Epigastric pain, other gastro-intestinal disorders (e.g. nausea, vomiting, diarrhoea, abdominal cramps, dyspepsia, flatulence, anorexia).

*Rare:* Gastro-intestinal bleeding (haematemesis, melaena, bloody diarrhoea), gastro-intestinal ulcers with or without bleeding or perforation.

*Isolated cases:* Aphthous stomatitis, glossitis, oesophageal lesions, lower gut disorders (e.g. non-specific haemorrhagic colitis and exacerbations of ulcerative colitis or Crohn's proctocolitis, colonic damage and stricture formation), pancreatitis, constipation.

*Suppositories only:*

*Occasional:* Local reactions (e.g. itching, burning and increased bowel movement).

*Isolated cases:* exacerbation of haemorrhoids.

*Central Nervous System:*

*Occasional:* Headache, dizziness or vertigo.

*Rare:* drowsiness, tiredness.

*Isolated cases:* Disturbances of sensation, paraesthesia, memory disturbance, disorientation, insomnia, irritability, convulsions, depression, anxiety, nightmares, tremor, psychotic reactions aseptic meningitis.

*Special senses:*

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

*Skin:*

*Occasional:* Rashes or skin eruptions.

*Rare:* Urticaria.

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

*Kidney:*

*Rare:* Oedema.

*Isolated cases:* Acute renal insufficiency, urinary abnormalities (e.g. haematuria, proteinuria), interstitial nephritis, nephrotic syndrome, papillary necrosis.

*Liver:*

*Occasional:* Elevation of serum aminotransferase enzymes (ALT, AST).  
*Rare:* Liver function disorders including hepatitis (in isolated cases fulminant) with or without jaundice.

*Blood:*

*Isolated cases:* Thrombocytopenia, leucopenia, agranulocytosis, haemolytic anaemia, aplastic anaemia.

*Hypersensitivity:*

*Rare:* Hypersensitivity reactions (e.g. bronchospasm, anaphylactic/anaphylactoid systemic reactions including hypotension).

*Isolated cases:* Vasculitis, pneumonitis.

*Cardiovascular system:*

*Isolated cases:* Palpitations, chest pain, hypertension, congestive heart failure.

## **4.9 Overdose**

Management of acute poisoning with NSAIDS essentially consists of supportive and symptomatic measures. There is no typical clinical picture resulting from Econac overdose. The therapeutic measures to be taken are: Supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, 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.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1. Pharmacodynamic properties**

Econac 100 mg suppositories are 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 rapidly and efficiently absorbed after conventional oral, rectal or intramuscular administration.

Maximal plasma concentrations after rectal administration are attained after approximately thirty minutes. Peak plasma concentrations and area under the plasma concentration-time curve (AUC) are linearly related to a dose over the range of 25 - 150 mg, regardless of administration route; after oral, rectal or intramuscular doses no accumulation occurred after repeated doses.

In elderly patients of more than 62 years of age and patients aged 2 - 7 years with juvenile rheumatoid arthritis peak plasma concentrations, time to peak plasma concentrations (t<sub>max</sub>) and AUC values are similar to those produced in adult patients without arthritic conditions.

### *Distribution*

Highest concentrations of Diclofenac are found in descending order in the liver, bile, kidneys, blood, heart and lungs.

Diclofenac passes into the synovial fluid of patients with osteoarthritis and rheumatoid arthritis, where higher concentrations are maintained compared with plasma concentrations.

Even though Diclofenac has a relatively short elimination half-life in plasma (1.5 hours), the drug persists in synovial fluid.

Diclofenac, like all NSAIDs, is  $\geq 99.5$  % bound to human serum proteins, specifically to albumin. The volume of distribution of diclofenac in healthy subjects is 0.12 to 0.17 L/kg and that of the central compartment 0.04 L/kg.

### *Metabolism*

Diclofenac is metabolized in the liver by conjugation. The principal metabolite in humans, 4'-hydroxydiclofenac, which has about 1/40 of the activity of the parent compound against adjuvant-induced arthritis.

5'-hydroxydiclofenac and 4', 5'-dihydroxydiclofenac do not have any pharmacologic activity. Drug disposition in patients with hepatic impairment is comparable to that in normal subjects.

### *Elimination*

Diclofenac is eliminated by urinary and biliary excretion of glucuronide and sulfate conjugates of the metabolites.

Urinary excretion of 4'-hydroxydiclofenac accounts for 20 % to 30 % of the dose. Biliary excretion of this metabolite accounts for 10 % to 20 %. The other metabolites excreted in urine each account for 10 % to 20 % of the dose; smaller amounts are excreted in the bile.

Approximately 90 % of an oral dose of diclofenac is excreted within 96 hours. The mean elimination half-life of the unchanged drug is 1.2 to 1.8 hours. 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*

The relative bioavailability of the suppositories compared to the reference product is 96.4 %.

The 90 % confidence intervals are for:

-	AUC <sub>0-∞</sub> :	90.5 - 102.7
-	C <sub>max</sub> :	77.0 - 93.4

### **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 Carcinogenic 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**

Hard fat

### **6.2. Incompatibilities**

Not applicable.

### **6.3. Shelf life**

3 years

### **6.4. Special precautions for storage**

Do not store above 25°C.

### **6.5. Nature and contents of container**

PVC strips with 10 suppositories

### **6.6. Special precautions for disposal and other handling**

See 4.2

**7 Marketing Authorisation Holder**

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