

## **1. NAME OF THE MEDICINAL PRODUCT**

Econac XL 100 mg Tablets

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Diclofenac Sodium 100 mg

For excipients, see 6.1

## **3. PHARMACEUTICAL FORM**

Prolonged release tablet.

White, circular, biconvex, tablets engraved with “DSR” on one side. Diameter = 12.0 mm

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

In the management of chronic conditions, such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.

### **4.2 Posology and method of administration**

Dosage

Adults: One tablet daily, taken whole with liquid, to be taken preferably with or after food. The recommended maximum daily dose is 150mg.

Elderly: The pharmacokinetics of Econac XL 100 mg tablets are not impaired in elderly patients, and the standard adult dose may be used. Non-steroidal anti-inflammatory drugs should be used with caution in older patients who generally are more prone to adverse reactions. Elderly patients are to be treated with the lowest effective dose. If necessary a lower strength formulation is to be prescribed. The patient should be monitored for GI bleeding for 4 weeks following initiation of NSAID therapy.

Children: Econac XL 100 mg tablets are not recommended for use in children.

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

## Administration

For oral administration only.

The tablets should be swallowed whole with liquid, to be taken preferably with or after food.

### **4.3 Contraindications**

- Known 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 (see 4.6).
- Severe hepatic, renal or cardiac failure (see 4.4).
- 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 NSAIDs

### **4.4 Special warnings and precautions for use**

#### General

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see 4.2, and GI and cardiovascular risks below).

The concomitant use of Econac XL tablets 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

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

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

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

Diclofenac gastro-resistant tablets contain lactose and therefore are not recommended for patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.

*Gastro-intestinal effects:*

Gastrointestinal bleeding 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 gastrointestinal events. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving Econac XL tablets, the medicinal product should be withdrawn.

As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing Diclofenac in patients with symptoms indicative of gastrointestinal (GI) disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (see 4.8).

The risk of GI bleeding is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation. The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

To reduce the risk of GI toxicity in patient with a history of ulcer, particularly if complicated with haemorrhage or perforation and in the elderly, the treatment should be initiated and maintained at the lowest effective dose.

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 other medicinal products likely to increase gastrointestinal risk.

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding). 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-reuptake inhibitors (SSRIs) or anti-platelet agents such as acetylsalicylic acid (see 4.5).

Close medical surveillance and caution should also be exercised in patients with ulcerative colitis or Crohn's disease, as their condition may be exacerbated (see 4.8).

*Hepatic effects:*

Close medical surveillance is required when prescribing Diclofenac to patients with impaired 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. 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), Diclofenac should be discontinued. Hepatitis may occur with use of 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 NSAID 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 in those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery (see 4.3). Monitoring of renal function is recommended as a precautionary measure when using Diclofenac in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

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 XL tablets.

*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, (see 4.8). 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. Econac XL 100mg tablets should be discontinued at the first appearance of skin rash, mucosal lesions or any other signs of hypersensitivity.

*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 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).

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).

*Haematological effect:*

Use of Econac XL tablets is recommended only for short term treatment. 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 defects of haemostasis 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 (so-called intolerance to analgesics / analgesics-asthma), 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 and other NSAIDs can precipitate bronchospasm if administered to patients suffering from, or with a previous history of bronchial asthma.

*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 Undesirable effects).

Female fertility

The use of diclofenac 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 diclofenac should be considered (see section 4.6 Pregnancy and Lactation).

#### **4.5 Interaction with other medicinal products and other forms of interaction**

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

*Lithium:* If used concomitantly, diclofenac may raise plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

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

*Diuretics and antihypertensive agents:* Like other NSAIDs use of Econac XL tablets with diuretics or 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 and periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity. Concomitant treatment with potassium-sparing drugs may be associated with increased serum potassium levels, which should therefore be monitored frequently (see 4.4).

*Other NSAIDs and corticosteroids:* Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects (see 4.4).

*Anticoagulant and antiplatelet agents:* Caution is recommended since concomitant administration could increase the risk of bleeding (see 4.4). 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. As with other nonsteroidal anti-inflammatory agents, diclofenac in a high dose can reversibly inhibit platelet aggregation.

*Selective serotonin reuptake inhibitors (SSRIs):* Concomitant administration of systemic NSAIDs, including diclofenac, and SSRI may increase the risk of gastrointestinal bleeding (see 4.4).

*Antidiabetics:* Clinical studies have shown that Econac can be given together with oral antidiabetic agents without influencing their clinical effect. However there have been isolated reports of both hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, 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 or after treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased.

*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.

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

*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.

*Potent CYP2C9 inhibitors:* “Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as sulfinpyrazone and voriconazole), which could result in a significant increase in peak plasma concentration and exposure to diclofenac due to inhibition of diclofenac metabolism.

*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.

*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.

*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

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %.

The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality.

In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, Diclofenac Sodium should not be given unless clearly necessary. If Diclofenac Sodium is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Diclofenac Sodium is contraindicated during the third trimester of pregnancy.

### Lactation

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

### Fertility

As with other NSAIDs, the use of Diclofenac 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 Diclofenac should be considered.

#### 4.7 Effects on ability to drive and use machines

Patients experiencing visual disturbances, dizziness, vertigo, somnolence, central nervous system disturbances drowsiness or fatigue while taking Diclofenac, should refrain from driving or using machines.

#### 4.8 Undesirable effects

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common ( $>1/10$ ); common ( $\geq 1/100, <1/10$ ); uncommon ( $\geq 1/1,000, <1/100$ ); rare ( $\geq 1/10,000, <1/1,000$ ); very rare ( $<1/10,000$ ); Not known: cannot be estimated from the available data.

The following undesirable effects include those reported with either short-term or long-term use.

Table 1

Blood and lymphatic system disorders	
Very rare	Thrombocytopenia, leukopenia, anaemia (including haemolytic and aplastic anaemia), Agranulocytosis.
Immune system disorders	
Rare	Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).
Very rare	Angioneurotic oedema (including face oedema).
Psychiatric disorders	
Very rare	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.
Nervous system disorders	
Common	Headache, dizziness.
Rare	Somnolence, tiredness.
Very rare	Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident.
Unknown	Confusion, hallucinations, disturbances of sensation, malaise.
Eye disorders	
Very rare	Visual disturbance, vision blurred, diplopia.
Unknown	Optic neuritis.
Ear and labyrinth disorders	

Common	Vertigo.
Very rare	Tinnitus, hearing impaired.
Cardiac disorders	
Very rare	Palpitations, chest pain, cardiac failure, myocardial infarction.
Vascular disorders	
Very rare	Hypertension, hypotension, vasculitis.
Respiratory, thoracic and mediastinal disorders	
Rare	Asthma (including dyspnoea).
Very rare	Pneumonitis.
Gastrointestinal disorders	
Common	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia.
Rare	Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer with or without bleeding or perforation (sometimes fatal particularly in the elderly).
Very rare	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.
Hepatobiliary disorders	
Common	Transaminases increased.
Rare	Hepatitis, jaundice, liver disorder.
Very rare	Fulminant hepatitis, hepatic necrosis, hepatic failure.
Skin and subcutaneous tissue disorders	
Common	Rash.
Rare	Urticaria.
Very rare	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.
Renal and urinary disorders	
Very rare	Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis.
Reproductive system disorders	

Not known	Impotence.
General disorders	
Rare	Oedema

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 4.4).

## 4.9 Overdose

### 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 haemorrhage, diarrhoea, dizziness, disorientation, excitation, coma, drowsiness, tinnitus, fainting or convulsions. In the event of significant poisoning acute renal failure and liver damage are possible.

### *Therapeutic measures*

Management of acute poisoning with NSAIDs, including diclofenac, essentially consists of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.

Special measures such as forced diuresis, dialysis or haemo-perfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to the high protein binding and extensive metabolism

Activated charcoal may be considered after ingestion of a potentially toxic overdose, and gastric decontamination (e.g. vomiting, gastric lavage) after ingestion of a potentially life threatening overdose

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

The exact mechanism of action of diclofenac has not been clearly established, but many of the actions appear to be associated principally with the inhibition of prostaglandin synthesis. Diclofenac inhibits the synthesis of prostaglandins in body tissues by inhibiting cyclooxygenase, an enzyme that catalyses formation of prostaglandin precursors (endoperoxides) from arachidonic acid.

### 5.2 Pharmacokinetic properties

After ingestion of the diclofenac slow release tablet, the active principle is slowly released into the gastrointestinal contents. Once released from the tablet, diclofenac is rapidly absorbed from the gastrointestinal tract but is subject to first-pass metabolism. Peak plasma

concentrations occur about 6 - 8 hours after administration of the prolonged release tablets when taken with a meal. Food and antacids decrease the rate but not the extent of absorption of diclofenac. The active substance is 99.7% bound to plasma proteins, mainly albumin. Diclofenac enters the synovial fluid and peak synovial fluid concentrations at steady state exceed plasma concentrations. Furthermore, elimination from the synovial fluid is slower than from plasma. Diclofenac and its metabolites cross the placenta and traces of diclofenac have been found in the milk of lactating women. The half-life for the terminal elimination phase is 1-2 hours. Approximately 60% of the administered dose is excreted via the kidneys in the form of metabolites and less than 1% in unchanged form. About 30% of the dose is excreted via the bile in metabolised form. In patients with impaired renal function, accumulation of diclofenac sodium has not been reported. However, half-life of diclofenac may be prolonged in patients with severe renal impairment.

### **5.3 Preclinical safety data**

Multiple dose studies were performed in rats, dogs and monkeys. At toxic doses there were gastrointestinal ulcers and disorders in the blood picture in all species. Genetic toxicology studies with diclofenac sodium show that diclofenac is not a mutagen. Carcinogenicity studies have been conducted in mice and rats. No carcinogenic effect has been seen.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Lactose monohydrate  
Magnesium stearate  
Hydrogenated vegetable oil Type I  
Povidone K 30  
Talc

### **6.2 Incompatibilities**

None known.

### **6.3 Shelf life**

2 years.

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

Do not store above 25 °C.  
Store in the original package. (Blister packs)  
Keep the container tightly closed. (Bottles)

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

- |   |                            |
|---|----------------------------|
| 1. Blister packs (Al/PVC):              | 20, 21, 28, 30 tablets     |
| 2. PP-tubes with LDPE caps:             | 56, 100, 250 & 500 tablets |
| 3. HDPE-container with LDPE screw caps: | 56, 100, 250 & 500 tablets |

#### **6.6 Instructions for use and handling**

Not relevant.

### **7. MARKETING AUTHORISATION HOLDER**

Goldshield Pharmaceuticals Limited  
NLA Tower,  
12-16 Addiscombe Road,  
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CR0 0XT

### **8. MARKETING AUTHORISATION NUMBER**

PL 12762/0101

### **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

24/02/2009

### **10 DATE OF REVISION OF THE TEXT**

07/12/2011