Physician's Prescribing Information
Etopan XL 500
Extended Release Tablets

1. Name of the medicinal product

Etopan XL 500 mg Extended Release Tablets

2. Qualitative and quantitative composition

Each tablet of Etopan XL 500 mg contains 500 mg etodolac.

Excipient with known effect
Each Etopan XL 500 mg tablet contains 46.67 mg of lactose anhydrous.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Extended Release Tablets

4. Clinical particulars

4.1 Therapeutic indications

For the management of signs and symptoms of osteoarthritis and rheumatoid arthritis.

4.2 Posology and method of administration

500mg XL - one tablet once or twice daily

The total daily dose of Etopan XL should not exceed 1,200mg.

As with other NSAIDs, the lowest dose and longest interval should be sought for each patient. Therefore, after observing the response to initial therapy with Etopan XL, the dose and frequency should be adjusted to suit individual patient's needs (tolerance and response). In responsive patients, partial symptomatic relief of symptoms usually occurs within 1 or 2 weeks, although maximum effectiveness may occur only after several weeks of therapy.

During long-term administration the dose of Etopan XL may be adjusted, up or down, depending on the patient's clinical response (maximum dose 1200 mg/day).

As with other NSAIDs, Etopan XL is preferably taken after meals or with food or antacids to reduce gastrointestinal irritation, especially during chronic use.

However, for faster absorption when a rapid initial effect is required, the first 1 or 2 doses may be taken 30 minutes before meals or at least 2 hours after meals. If an antacid is taken concurrently, an aluminum and magnesium-containing formulation may be preferred. It is recommended to take Etopan XL tablets with a full glass of water and that the patient remains in an upright position for 15-30 minutes after administration. Patients should be advised to avoid alcoholic beverages while under treatment with this medicine.

4.3 Contraindications

- Hypersensitivity to etodolac or to any of the excipients listed in section 6.1.
- NSAIDs are contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) during therapy with ibuprofen, aspirin, or other non-steroidal anti-inflammatory drugs.
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- Active or history of recurrent peptic ulcer or a history of peptic ulcer disease (with two or more distinct episodes of proven ulceration or bleeding).
- 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

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

The use of etodolac 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).

Platelets

Although non-steroidal anti-inflammatory drugs do not have the same direct effects on platelets as does aspirin, all drugs which inhibitthe biosynthesis of prostaglandins may interfere, to some extent, with platelet function. Patients receiving etodolac who may be adversely affected by such actions should be carefully observed.

Cardiovascular, Renal and Hepatic Impairment

In patients with renal, cardiac or hepatic impairment especially those taking diuretics and the elderly, renal function should be monitored in these patients (see also section 4.3). Caution is required since the use of NSAIDs may result in a dose dependent reduction in prostaglandin formation and precipitate renal failure. The dose should be kept as low as possible. However, impairment of

renal or hepatic functions due to other causes may alter drug metabolism; patients receiving concomitant long term therapy, especially the elderly, should be observed for potential side effects and their drug doses adjusted as needed, or the drug discontinued.

Patients on long-term treatment with etodolac should be regularly reviewed as a precautionary measure e.g.for changes in renal function, haematological parameters, or hepatic function.

Cardiovascular and cerebrovascular effects

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

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for etodolac.

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

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 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. Etodolac should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Respiratory disorders

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

SLE and mixed connective tissue disease

In patients with systemic lupus erythematous (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see section 4.8).

Impaired female fertility

The use of etodolac 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 etodolac should be considered.

Gastrointestinal bleeding, ulceration and perforation:

Serious gastrointestinal adverse effects such as bleeding, ulceration and 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. If any sign of gastrointestinal bleeding occurs, etodolac should be stopped immediately.

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 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 etodolac, 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).

Patients with rare hereditary problems or galactose intolerance, the Lap lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4).

Since etodolac is extensively protein - bound, it may be necessary to modify the dosage of other highly protein-bound drugs.

Bilirubin tests can give a false positive result due to the presence of phenolic metabolites of etodolac in the urine.

Anti-hypertensives: Reduced anti-hypertensive effect

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

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).

Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

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

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

Lithium: Decreased elimination of lithium.

Methotrexate: Decreased elimination of methotrexate.

Cyclosporin: Increased risk of nephrotoxicity.

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

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 and ibuprofen.

4.6 Fertility, Pregnancy and lactation

Pregnancy

Drugs which inhibit prostaglandin biosynthesis may cause dystocia and delayed parturition as evidenced by studies in pregnant animals.

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. In view of the known effects of NSAIDs on the foetal cardiovascular system, some inhibitors of prostaglandin biosynthesis have been shown to interfere with the risk of closure of the ductus arteriosus, use in the last trimester of pregnancy is contraindicated. 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.

Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus:

Avoid use of NSAIDs, including ETOPAN XL, in pregnant women at about 28 weeks gestation and later. NSAIDs, including ETOPAN XL, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment:

Use of NSAIDs, including ETOPAN XL, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation.
Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.
If NSAID treatment is necessary between about 20 weeks and 28 weeks gestation, limit ETOPAN XL use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if ETOPAN XL treatment extends beyond 5 days. Discontinue ETOPAN XL if oligohydramnios occurs and follow up according to clinical practice.

Breast-feeding

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

Etodolac can cause dizziness, drowsiness, fatigue or abnormal vision. Patients need to be aware of how they react to this medicine before driving or operating machines.

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, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4), indigestion, heartburn, rectal bleeding have been reported following administration. Less frequently, gastritis has been observed. Pancreatitis has been reported very rarely.

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).

Cardiovascular and cerebrovascular

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

Clinical trial and epidemiological data suggests that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction of stroke) (see section4.4).

Other adverse reactions reported less commonly include:

Endocrine disorders:

Oedema, pyrexia

Musculoskeletal connective tissue and bone disorders:

Weakness/malaise

Respiratory, thoracic and mediastinal disorders:

Dyspnoea

Neurological and special senses:

Visual disturbances, 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, tremor, insomnia, and drowsiness.

Dermatological:

Bullous reactions including Stevens-Johnson syndrome, and Toxic Epidermal Necrolysis (very rare). Photosensitivity.

Haematological:

Thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia.

Hepatic:

Abnormal liver function, hepatitis and jaundice.

Renal:

Bilirubinuria, urinary frequency, dysuria, nephrotoxicity in various forms including interstitial nephritis, nephrotic syndrome and renal failure.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

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.
The standard practices of gastric lavage, activated charcoal administration and general supportive therapy should be undertaken.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-inflammatory and anti-rheumatic products, non-steroids, acetic acid derivatives and related substances, ATC code: M01A B08

Inhibition of prostaglandin synthesis and COX-2 selectivity
All non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to inhibit the formation of prostaglandins. It is this action which is responsible both for their therapeutic effects and some of their side effects. The inhibition of prostaglandin synthesis observed with etodolac differs from that of other NSAIDs. In an animal model at an established anti-inflammatory dose, cytoprotective PGE concentration in the gastric mucosa have been shown to be reduced to a lesser degree and for a shorter period than other NSAIDs. This finding is consistent with subsequent in-vitro studies which have found etodolac

to be selective for induced cyclo-oxygenase 2 (COX-2, associated with inflammation) over COX-1 (cytoprotective).

Furthermore, studies in human cell models have confirmed that etodolac is selective for the inhibition of COX-2.

The clinical benefit of preferential COX-2 inhibition over COX-1 has yet to be proven.

Anti-inflammatory effects

Experiments have shown etodolac to have marked anti-inflammatory activity, being more potent than several clinically established NSAIDs.

5.2 Pharmacokinetic properties

In man, etodolac is well absorbed following oral administration.

Etodolac is highly bound to serum proteins.

The elimination half-life averages seven hours in man. The primary route of excretion is in the urine, mostly in the form of metabolites.

In subjects receiving daily doses of etodolac 400 mg or 600 mg to steady state levels over a three day period, the peak plasma concentrations were 7.5 µg/ml at 7.9 hours and 11.9 µg/ml at 7.8 hours.

5.3 Preclinical safety data

Preclinical data reveal no special hazard based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline cellulose, Hypromellose, Lactose anhydrous, Povidone, Magnesium stearate, HPMC 2910, Polydextrose, PEG 8000, Titanium Dioxide, Triacetin, colors E132 and E172.

6.2 Incompatibilities

Not applicable

6.3 Expiry date

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store between 20°C - 25°C.

6.5 Nature and contents of container

Etopan XL 500 mg

Bottle in outer carton.

Available in pack size of 100 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Manufacturer and registration holder

Taro Pharmaceutical Industries Ltd., P.O., Haifa Bay 2624761

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