Physician's Prescribing Information
Etopan XL 400
Etopan XL 600
Extended Release Tablets

1. Name of the medicinal product

Etopan XL 400

Etopan XL 600

2. Qualitative and quantitative composition

Each tablet of Etopan XL 400 mg contains 400 mg etodolac.

Each tablet of Etopan XL 600 mg contains 600 mg etodolac.

Excipients with known effect

Each Etopan XL 400 mg tablet contains 37.33 mg of lactose anhydrous.
Each Etopan XL 600 mg tablet contains 56 mg of lactose anhydrous.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Extended release tablets

Etopan XL 400: pink, round, bi-convex, film coated tablet. One side is engraved with 'T400', other side is plain.

Etopan XL 600: gray, oval, bi-convex, film coated tablets. One side is engraved with 'T600', other side is plain.

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

400 mg XL - One to two tablets twice daily but no more than three tablets a day.

600 mg XL - One tablet once or twice daily.

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

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 the active substance or to any of the excipients listed in section 6.1.
- Etopan XL should not be used in patients with active or history of recurrent peptic ulceration or a history of peptic ulcer disease (with two or more distinct episodes of proven ulceration or bleeding).
- 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.
- Severe heart failure, hepatic failure and renal failure (see section 4.4).
- During the last trimester of pregnancy (see section 4.6).
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

4.4 Special warnings and 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).

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

Elderly

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

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 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 longer term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

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.

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.

Gastrointestinal bleeding, ulceration and perforation

Serious gastrointestinal adverse effects such as bleeding, ulceration and perforation, which can be fatal, has been reported and can occur at any time with or without warning symptoms in patient treated with NSAIDs or a previous history of serious GI events. If any sign of gastrointestinal bleeding occurs, etodolac should be stopped immediately.

Platelets

Although non-steroidal anti-inflammatory drugs do not have the same direct effects on platelets as does aspirin, all drugs which inhibit the 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.

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.

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 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).

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).

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

Lactose

Etopan XL contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium

This medicinal product contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially ‘sodium-free’.

4.5 Interactions with other medicinal products and other forms of interaction

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

Other analgesics including cyclooxygenase-2 selective inhibitor: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects (see section 4.4).

Anti-hypertensives: Reduced anti-hypertensive effect
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.

Ciclosporin: Increased risk of nephrotoxicity.

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

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.

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

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

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (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.

4.6 Fertility, pregnancy and lactation

Fertility

The use of Etopan XL 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 Etopan XL should be considered.

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).

From the 20th week of pregnancy onward, etodolac use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, etodolac should not be given unless clearly necessary. If etodolac 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. Antenatal monitoring (by ultrasound screening) for oligohydramnios and ductus arteriosus constriction should be considered after exposure to etodolac in its therapeutic dose for more than five days from gestational week 20 onward. Etodolac should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

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

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);

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, etodolac is contraindicated during the third trimester of pregnancy (see section 4.3).

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.

4.7 Effects on ability to drive and use machines

Etopan XL 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

Oedema, hypertension and cardiac failure, have been reported in association with NSAID treatment. Clinical trial and epidemiological data suggest 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 or stroke) (see section 4.4).

Gastrointestinal

Reported side effects include nausea, epigastric pain, diarrhoea, indigestion, heartburn, flatulence, abdominal pain, constipation, vomiting, ulcerative stomatitis, dyspepsia, haematemesis, melaena, rectal bleeding, exacerbation of colitis, vasculitis, Stevens-Johnson syndrome and Crohn's disease (see section 4.4) 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, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Cardiovascular and cerebrovascular

Palpitations, vasculitis, oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest 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 or stroke) (see section4.4).

Renal

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

Hepatic:

Abnormal liver function, hepatitis and jaundice.

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 and drowsiness, tremor, insomnia.

Haematological:

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

Dermatological:

Bullous reactions including Stevens-Johnson syndrome, and toxic epidermal necrolysis (very rare), photosensitivity, vasculitis.

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 has 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 XL 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

Nothing of note to the prescriber.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline cellulose, hypromellose, lactose anhydrous, povidone, magnesium stearate.

Coating: HPMC 2910, titanium dioxide, polydextrose, triacetin, macrogol, FD&C Red #40 Aluminium Lake (E129), FD&C Yellow #6 Aluminium Lake (E110)

In addition each Etopan XL 600 mg tablet contains FD&C Blue #2 Aluminium Lake (E132), Black iron oxide (E172), Yellow iron oxide (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 below 25°C.

6.5 Nature and contents of container

Etopan XL 400 mg

PVC/PVDC/Aluminium blister packs in outer cardboard cartons.

Available in pack sizes of 20 and 30 tablets.

Etopan XL 600 mg

PVC/PVDC/Aluminium blister packs in outer cardboard cartons.

Available in pack sizes of 10, 12, 18, 20 and 24 tablets.

White round HDPE container with PP safety cap with aluminium foil inner seal and purified cotton fill.

Available in pack sizes of 30, 100 and 1,000 tablets.

Not all packs may be marketed.

6.6 Special precautions for disposal and other handling

None.

7. Manufacturer and registration holder

Taro Pharmaceutical Industries Ltd., 14 Hakitor Street, Haifa Bay 2624761

8. Marketing authorisation numbers

Etopan 400 XL: 13003.30728
Etopan 600 XL: 12259.30274

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