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Physician's Prescribing Information

Etopan 400, 500, 600 mg XL Tablets

Composition:

Etopan XL 400	Etopan XL 500	Etopan XL 600
Each Extended Release	Each Extended Release	Each Extended Release
Tablet contains:	Tablet contains:	Tablet contains:
Etodolac 400 mg	Etodolac 500 mg	Etodolac 600 mg

Therapeutic class

Etodolac is a non steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, antirheumatic and analgesic activities.

Reported to be a preferential inhibitor of Cyclo-oxygenase 2 (COX-2).

Dosage form

Tablets

Mechanism of action

Non steroidal anti-inflammatory drugs inhibit the activity of the enzyme cyclo-oxygenase, resulting in decreased formation of precursors of prostaglandins and thromboxanes from arachidonic acid. Although the resultant decrease in prostaglandin synthesis and activity in various tissues may be responsible for many of the therapeutic effects of NSAIDs, other actions may also contribute significantly to the therapeutic effects of these medications.

Antirheumatic - act via analgesic and anti-inflammatory mechanisms.

Analgesic - may block pain impulse generation via a peripheral action that may involve reduction of the activity of prostaglandins, and possibly inhibition of the synthesis or actions of other substances that sensitize pain receptors to mechanical or chemical stimulation.

Antigout agent - act via analgesic and anti-inflammatory mechanisms.

Vascular headache suppressant - analgesic action may be involved in relief of headache. Also, by reducing prostaglandin activity, may directly prevent or relieve certain types of headaches thought to be caused by prostaglandin-induced dilation or constriction of cerebral blood vessels.

Anti-inflammatory - exact mechanism have not been determined. May act peripherally in inflamed tissue, probably by reducing prostaglandin activity in these tissues and possibly by inhibiting the synthesis and/ or action of other local mediators of the inflammatory response. Inhibition of leukocyte migration, inhibition of the release and / or actions of

lysosomal enzymes, and action on other cellular and immunological processes in mesenchymal and connective tissue may be involved.

Pharmacokinetics

Etodolac is well absorbed from the gastrointestinal tract. The systemic availability of etodolac is at least 80%, and etodolac does not undergo significant first-pass metabolism following oral administration. The dose-proportionality based on AUC is linear following doses up to 600mg every 12 hours. Peak concentrations are dose-proportional for both total and free etodolac following doses up to 400mg every 12 hours, but following a 600mg dose, the peak is about 20% higher than predicted on the basis of lower doses. Etodolac plasma concentrations, after multiple-dose administration, are slightly higher than after single doses, as predicted, indicating no change in pharmacokinetics with multiple-dose use.

Etodolac is more than 99% bound to plasma proteins. Etodolac when administered orally, exhibits characteristics which are well described by a two-compartment model with first order absorption. Mean peak plasma concentrations range from approximately 14 ± 4 to $37 \pm 9 \mu\text{g/ml}$ after 200 to 600mg single doses and are reached in 80 ± 30 minutes. The mean plasma clearance of etodolac is $47 \pm 16 \text{ml/h/kg}$, and terminal disposition half life is 7.3 ± 4 hours. Etodolac is extensively metabolised in the liver, with renal elimination of etodolac and its metabolites being the primary route of excretion. Approximately 72% of the administered dose is recovered in the urine (1% etodolac unchanged). Fecal excretion accounted for 16% of the dose. Therefore, enterohepatic circulation, if present, is not extensive. The extent of absorption of etodolac is not affected when administered after a meal or with an antacid. Food intake, however, reduces the peak concentration reached by approximately one half, and increases the time to peak concentration by 1.4 to 3.8 hours. Coadministration with an antacid decreases the peak concentration reached by about 15-20%, with no measurable effect on time to peak. In studies in the elderly, age was found to have no effect on etodolac $t_{1/2}$ or protein binding, and there was no accumulation. No dosage adjustment is generally necessary in the elderly on the basis of pharmacokinetics (due to small reduction, 15%, in clearance) but rather on the basis of body size, and they may be more sensitive to antiprostaglandin effects than younger patients. Etodolac is not dialyzable. No adjustment of dosage is generally required in patients with mild to moderate renal impairment, however, etodolac should be used with caution in such patients because, as with other NSAIDs, it may further decrease renal function in some patients with impaired renal function. No dosage adjustment is generally required in patients with compensated hepatic cirrhosis, but since etodolac clearance is dependent on hepatic function it could be reduced in patients with severe hepatic failure. NSAIDs enter the synovial fluid and several hours after administration of a single dose, synovial fluid concentrations equal or exceed the simultaneously measured plasma concentration.

Indications

Etodolac is indicated for the management of sign and symptoms of osteoarthritis and rheumatoid arthritis.

Contraindications

Etodolac is contraindicated in patients with known severe allergic reaction, such as anaphylaxis or angioedema and nasal polyps associated with bronchospasm induced by acetylsalicylic acid or other NSAIDs.

The drug is also contra-indicated in patients with active peptic ulceration or with a history of peptic ulcer disease.

Warnings

Risk benefit should be considered in patients with: A history of mild allergic reaction, such as allergic rhinitis, urticaria or skin rash, induced by aspirin or other NSAIDs. Inflammatory or ulcerative disease of the upper or lower gastrointestinal tract, including Crohn's disease, diverticulitis, peptic ulcer disease, active or history ulcerative colitis. Hemophilia or other bleeding problems including coagulation or platelet function disorders. Renal function impairment. Stomatitis.

Patient monitoring: Hematological determinations should be performed if symptoms of blood dyscrasias occur. Chronically treated patients should be observed for the signs and symptoms of GI ulceration and bleeding which may occur without warning symptoms.

Caution is required if Etodolac is administered to patients suffering from or with a previous history of bronchial asthma.

Etodolac should be used with caution in patients with fluid retention, hypertension or heart failure.

Use in Pregnancy

There are no adequate or well controlled studies in pregnant women. Etodolac should be used during pregnancy only if the potential benefits justifies the potential risk for the fetus.

During first trimester: Alterations of limb development was demonstrated in animal studies, but drug or dose-response relationship not established.

During second and third trimesters: Because of the known effects of NSAIDs on parturition and on the human fetal cardiovascular system with respect to closure of the ductus arterious, use during late pregnancy should be avoided.

Use in Lactation

Problems in humans have not been documented with most of the NSAIDs. It is not known whether etodolac is distributed into breast milk.

Use in Pediatrics

This medicine is not usually recommended for administration to children / infants.

Adverse Reactions

Etodolac is well tolerated.

Medical attention needed only if continuing or are bothersome:

Incidence more frequent (3-9%) - Dizziness, mild to moderate headache, unusual weakness with no other signs or symptoms, abdominal cramps, mild to moderate abdominal pain or discomfort, bloated feeling or gas, diarrhea, indigestion, nausea.

Incidence less frequent (1-3%): nervousness or irritability, constipation.

Medical attention needed:

Incidence less frequent (1-3%) - *Central nervous system effects* mental depression. *Dermatological effects* itching, skin rash. *Digestive system effects* gastritis (burning feeling in chest or stomach, indigestion, tenderness in stomach area), gastrointestinal bleeding or hemorrhage, melena (bloody stools), hematemesis (vomiting blood or material that looks like coffee grounds), gastrointestinal ulceration (severe pain, cramping or burning; bloody or black tarry stools, vomiting of blood or material that looks like coffee grounds, severe and continuing nausea, heartburn and / or indigestion. *Genitourinary*

effects dysuria (burning, painful or difficult urination), frequent urge to urinate. *Hypersensitivity reactions* fever with or without chills. *Ocular effects* blurred or double vision or any change in vision. *Otic effects* ringing or buzzing in ears.

Incidence rare (<1%): *Cardiovascular effects* congestive heart failure or exacerbation of, increased blood pressure (cardiac arrhythmias - has been reported but a causal relationship has not been established). *Central nervous system effects* syncope (fainting), (confusion - has been reported but a causal relationship has not been established). *Dermatological effects* bullous eruption / blisters, hives, Stevens-Johnson syndrome (desquamation has been reported but a causal relationship has not been established). *Digestive system effects* (colitis or exacerbation of, esophagitis - has been reported but a causal relationship has not been established). *Genitourinary effects* (bleeding from vagina, unexplained / unexpected / unusually heavy menstrual, blood in urine, crystalluria, cystitis - has been reported but a causal relationship has not been established). *Hematological effects* anemia, bruising, thrombocytopenia with or without purpura (leukopenia - has been reported but a causal relationship has not been established). *Hepatic effects* cholestatic hepatitis or jaundice, toxic hepatitis or jaundice. *Hypersensitivity reactions* vasculitis, angioedema, bronchospastic allergic reactions. *Ocular effects* (conjunctivitis - has been reported but a causal relationship has not been established). *Oral/perioral effects* stomatitis, aphthous. *Renal effects* fluid retention / edema, (intestinal nephritis - has been reported but a causal relationship has not been established). *Otic effects* (decreased hearing or any change in hearing - has been reported but a causal relationship has not been established). Shortness of breath or troubled breathing - has been reported but a causal relationship has not been established. *Continuing thirst*.

Drug Interactions

The following drug interactions and / or related problems have been reported: *Anticoagulants, coumarin or indandione-derivative or heparin or thrombolytic agents* - etodolac has been reported to potentiate the effects of coumarin or indandione-derivative anticoagulants that may result from displacement of the anticoagulant from protein binding sites. Inhibition of platelet aggregation by NSAIDs, and the possibility of NSAID-induced gastrointestinal ulceration or bleeding, may be hazardous to patients receiving anticoagulant or thrombolytic therapy. *Acetyl salicylic acid or two or more NSAIDs concurrently* - alteration of pharmacokinetic profile of at least one of the medications, may alter the therapeutic effect and/ or increase the risk of adverse effects - may increase the risk of gastrointestinal toxicity, ulceration or hemorrhage, bleeding. *Cefamandole, cefoperazone, cefotetan, plicamycin, valproic acid* - may cause hypoprothrombinemia, in addition plicamycin or valproic acid may inhibit platelet aggregation. Concurrent use with a NSAID may increase the risk of bleeding because of additive interferences with platelet function and/ or potential occurrence of NSAID-induced GI ulceration or hemorrhage. *Cyclosporine, digitalis glycosides, methotrexate, lithium* - etodolac, like other NSAIDs, through effects on renal prostaglandins, may cause changes in the elimination of these drugs leading to elevated serum levels and increased toxicity. Nephrotoxicity associated with cyclosporine may also be enhanced. Patients receiving these drugs who are given etodolac or any other NSAID and particularly those patients with altered renal function, should be observed for the development of the specific toxicities of these drugs. *Diuretics* - etodolac should be used with caution in patients receiving diuretics, who have cardiac, renal or hepatic failure. *Probenecid* may decrease excretion and increase serum concentrations of NSAIDs, possibly enhancing effectiveness and/ or increasing the

potential for toxicity; a decrease in dosage of the NSAID may be necessary if adverse effects occur.

Corticosteroids oral glucocorticoid or Corticotropin (chronic therapeutic use) may increase risk of gastrointestinal side effects, including ulceration or hemorrhage; however, concurrent use in the treatment of arthritis may provide additional therapeutic benefit and permit reduction of glucocorticoid or corticotropin dosage¹.

Precautions

The antipyretic, analgesic and anti-inflammatory actions of NSAIDs may mask symptoms of the occurrence or worsening of infections. Renal effect - renal toxicity encountered with etodolac, as with other NSAIDs, is seen in patients with conditions in which renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of NSAIDs therapy is usually followed by recovery to the pretreatment state. Etodolac metabolites are eliminated primarily by the kidneys. The extent to which the inactive glucuronide metabolites may accumulate in patients with renal failure has not been studied. As with other drugs whose metabolites are excreted by the kidney, the possibility that adverse reactions may be attributable to these metabolites should be considered. About 10% of patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthmas has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, etodolac should not be administered to patients with this form of aspirin-sensitive and should be used with caution in all patients with pre-existing asthma. Hepatic effects - As with all NSAIDs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may disappear, remain essentially unchanged or progress with continued therapy. A patient with symptoms and/ or signs suggesting liver dysfunction or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with etodolac. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop or if systemic manifestations occur (e.g. eosinophilia, rash), etodolac should be discontinued. Hematological effects - anemia is sometimes seen in patients receiving etodolac or other NSAIDs. This may be due to fluid retention, gastrointestinal blood loss, or an incompletely described effect upon erythropoiesis. Patients on long term treatment with NSAIDs, including etodolac, should have their hemoglobin or hematocrit checked if they develop signs or symptoms of anemia. All drugs which inhibit the biosynthesis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding. Patients receiving etodolac who may be adversely affected by such actions should be carefully observed. Fluid retention - fluid retention and edema have been observed in some patients taking etodolac. Therefore, as with other NSAIDs, etodolac should be used with caution in patients with fluid retention, hypertension or heart failure. GI ulceration, bleeding and perforation - physicians should be alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous

GI tract symptoms. Prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc. have been associated with increased incidence of these side effects. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in this population. High doses of any NSAIDs probably carry a greater risk of these reactions, thus sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity when considering use of relatively large doses (within recommended dosage range).

Dosage and Administration

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

600mg 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 remain in an upright position for 15-30 minutes after administration. Patients should be advised to avoid alcoholic beverages while under treatment with this medicine.

Overdosage

Signs and symptoms following acute NSAIDs overdose are usually limited to: lethargy, drowsiness, nausea, vomiting and epigastric pain, which are generally reversible with supportive care. Hypotension, acute renal failure and respiratory depression may occur but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs and may occur following overdose.

Treatment There are no specific antidotes.

1. Emptying the stomach via induction of emesis (in alert patients only, syrup ipecac is not recommended) or gastric lavage.
2. Administering activated charcoal (preferably within 2 hours following overdose ingestion or repeatedly).
3. Administering antacids.
4. Instituting symptomatic and other supportive treatment as necessary (certain adverse reactions may respond to glucocorticoid administration).
5. Administering as required: plasma volume expanders for severe hypotension, diazepam/ other appropriate benzodiazepine anti convulsant for convulsions, vitamin K₁ for hypoprothrombinemia and/ or dopamine plus dobutamine I.V., to prevent or reverse early indications of renal failure. Patients being discharged after initial treatment should be

informed of possible presenting symptoms and advised to seek immediate treatment if they occur.

Diagnostic Interference

Phenolic metabolites of etodolac may cause false-positive results in urine bilirubin determination. False-positive test results may occur with dipstick method of urine ketones determinations.

Storage

Store in a cool and dry place.

Manufacturer

Taro Pharmaceutical Industries Ltd., Haifa Bay 26110

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