Axcel®

ETORICOXIB-120mg
TABLET

MAL15045074AZ

COMPOSITION:
Each tablet contains:
Etoricoxib 120mg

PRESENTATION:
Green coloured, round shape with 9.8mm diameter, biconvex, embossed with 'Kotra' logo on one side and breakline on the other side.

INDICATIONS:
For acute and chronic treatment of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA). Treatment of ankylosing spondylitis (AS), acute gouty arthritis, and acute pain, including that related to primary dysmenorrhoea and minor dental procedures. The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks.

PHARMACOLOGY:
Mechanism of Action:
Etoricoxib is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. Etoricoxib is a potent, orally active, highly selective cyclooxygenase-2 (COX-2) inhibitor within and above the clinical dose range. Two isoforms of cyclooxygenase have been identified: cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 is responsible for prostaglandin-mediated normal physiologic functions such as gastric cytoprotection and platelet aggregation. Inhibition of COX-1 by nonselective NSAIDs has been associated with gastric damage and platelet inhibition. COX-2 has been shown to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. Selective inhibition of COX-2 by etoricoxib decreases these clinical signs and symptoms with decreased GI toxicity and without effects on platelet function.

Pharmacokinetics:
Absorption:
In studies specifically designated to measure the onset of action of etoricoxib, the onset of action occurred as early as 24 minutes after dosing. Orally administered etoricoxib is well absorbed. The mean oral bioavailability is approximately 100%. Following 120mg once-daily dosing to steady state, the peak plasma concentration (geometric mean C_{max} = 3.6mcg/mL) was observed at approximately 1 hour (T_{max}) after administration to fasted adults. The geometric mean $AUC_{0\text{-}24hr}$ was 37.8mcg*hr/mL. The pharmacokinetics of etoricoxib are linear across the clinical dose range. A standard meal had no effect on the extent or rate of absorption of etoricoxib after administration of a 120mg dose. In clinical trials, etoricoxib was administered without regard to food.

Distribution:
Etoricoxib is approximately 92% bound to plasma protein over the range of concentration of 0.05 to 5mcg/mL. The volume of distribution of steady state (V_{dss}) is approximately 120L in humans.

Metabolism:
Etoricoxib is extensively metabolized with <1% of a dose recovered in urine as the parent drug. The major route of metabolism to form the 6'-hydroxymethyl derivative is catalyzed by cytochrome P450 (CYP) enzymes. CYP3A4 appears to contribute to the metabolism of etoricoxib *in vivo*. Five metabolites have been identified in man. The principal metabolites either demonstrate no measurable activity or are only weakly active as COX-2 inhibitors. None of these metabolites inhibit COX-1.

Elimination:
Following administration of a single 25mg radiolabeled intravenous dose of etoricoxib to healthy subjects, 70% of radioactivity was recovered in urine and 20% in feces, mostly as metabolites. Less than 2% was recovered as unchanged drug. Elimination of etoricoxib occurs almost exclusively through metabolism followed by renal excretion. Steady state concentrations of etoricoxib are reached within seven days of once-daily administration of 120mg, with an accumulation ratio of approximately 2, corresponding to a half-life of approximately 22 hours. The plasma clearance after a 25mg intravenous dose is estimated to be approximately 50ml/min.

DOSAGE AND ADMINISTRATION:
Etoricoxib is administered orally. Etoricoxib may be taken with or without food. Etoricoxib should be administered for the shortest duration possible and the lowest effective daily dose should be used. The tablets can be divided into equal doses.

Osteoarthritis:
The recommended dose is 30mg or 60mg once daily.

Rheumatoid Arthritis:
The recommended dose is 60mg once daily. In some patients with insufficient relief from symptoms, an increased dose of 90mg once daily may increase efficacy. Once the patient is clinically stabilised, down-titration to a 60mg once daily dose may be appropriate. In the absence of an increase in therapeutic benefit, other therapeutic options should be considered.

Ankylosing Spondylitis:
The recommended dose is 60mg once daily. In some patients with insufficient relief from symptoms, an increased dose of 90mg once daily may increase efficacy. Once the patient is clinically stabilised, down-titration to a 60mg once daily dose may be appropriate. In the absence of an increase in therapeutic benefit, other therapeutic options should be considered.

Acute Pain:
In the following acute painful conditions, Etoricoxib should be used only for the acute symptomatic period, limited to a maximum of 8 days treatment :

Acute Gouty Arthritis:
The recommended dose is 120mg once daily.

Primary Dysmenorrhea:
The recommended dose is 120mg once daily.

Minor Dental Procedures:
The recommended dose is 90mg once daily.

Doses greater than those recommended for each indication have either not demonstrated additional efficacy or have not been studied. Therefore:
The dose for osteoarthritis should not exceed 60mg daily.
The dose for rheumatoid arthritis should not exceed 90mg daily.
The dose for ankylosing spondylitis should not exceed 90mg daily.
The dose for acute gout should not exceed 120mg daily.
The dose for acute pain and primary dysmenorrhea should not exceed 120mg daily.
The dose for minor dental procedures should not exceed 90mg daily.

As the cardiovascular risks of selective COX-2 inhibitors may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.

Elderly, Gender, Race:
No dosage adjustment in Etoricoxib is necessary for the elderly or based on gender or race.

Hepatic Insufficiency:
In patients with mild hepatic insufficiency (Child-Pugh score 5-6), a dose of 60mg once daily should not be exceeded. In patients with moderate hepatic insufficiency (Child-Pugh score 7-9), the dose should be reduced; a dose of 60mg every other day should not be exceeded, administration of 30mg once daily can also be considered. There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9).

Renal Insufficiency:
In patients with advanced renal disease (creatinine clearance <30 mL/min), treatment with Etoricoxib is not recommended. No dosage adjustment is necessary for patients with lesser degrees of renal insufficiency (creatinine clearance ≥30 mL/min).

CONTRAINDICATIONS:
Contraindicated in patient with : Hypersensitivity to the active substance or to any of the excipients; Congestive heart failure (NYHA II-IV); Increased risk of cardiovascular disease (Ischaemic heart disease and stroke); Peripheral arterial disease, and / or cerebrovascular disease (including patients who have recently undergone coronary artery bypass graft surgery or angioplasty); Patients with hypertension whose blood pressure has not been adequately controlled; Pregnancy; Active peptic ulceration or active gastro-intestinal (GI) bleeding; Severe hepatic dysfunction (serum albumin <25g/l or Child-Pugh score ≥10); Estimated renal creatinine clearance <30ml/min; Children and adolescents under 16 years of age; Inflammatory bowel disease.

WARNING & PRECAUTIONS:
Etoricoxib may be associated with an increased risk of thrombotic events (especially MI and stroke). As the cardiovascular risks of selective COX-2 inhibitors may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. Etoricoxib should not be used in patients with ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease. It should be used with caution in patients with significant risk factors for cardiovascular disease such as hypertension, hyperlipidaemia, and diabetes mellitus.

Warning to prescriber when prescribing COX-2 Inhibitors to patients with risk factors of heart disease, hypertension (high blood pressure), hyperlipidemia, diabetes, smoking patient and patient with peripheral arterial disease. Selective COX-2 inhibitors are not a substitute for aspirin for cardiovascular prophylaxis because of their lack of effect on platelets. Hence, antiplatelet therapies should not be discontinued. There is a further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) for etoricoxib when taken concomitantly with acetylsalicylic acid (even at low doses).

In patients with advanced renal disease, treatment with etoricoxib is not recommended. If therapy with etoricoxib must be initiated in such patients, renal function should be monitored closely. Long-term use of NSAIDs has resulted in renal papillary necrosis and other renal injury. Monitoring of renal function should be considered for those with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis. Caution should be used when initiating treatment with etoricoxib in patients with considerable dehydration. It is advisable to rehydrate patients prior to starting therapy with etoricoxib.

The possibility of fluid retention, edema or hypertension should be taken into consideration when etoricoxib is used in patients with pre-existing edema, hypertension, or heart failure. All Nonsteroidal Anti-inflammatory Drugs (NSAIDs), including etoricoxib, can be associated with new onset or recurrent congestive heart failure. Etoricoxib, particularly at high doses, may be associated with more frequent and severe hypertension compared with other NSAIDs and selective cyclo-oxygenase-2 (COX-2) inhibitors; blood pressure monitoring during etoricoxib treatment is recommended. Etoricoxib should not be used in patients with hypertension whose blood pressure is not controlled.

Conditions predisposing to gastrointestinal events (eg, history of peptic ulcer, upper gastrointestinal disease, ulcerative colitis, smoking, advancing age, concurrent aspirin or corticosteroids, alcohol abuse, stress). A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for persistently abnormal liver function tests. If persistently abnormal liver function tests (three times the

upper limit of normal) are detected, etoricoxib should be discontinued. Etoricoxib should be used with caution in patients with history of acute asthmatic attacks, urticaria, or rhinitis, which were caused by salicylates or non-selective cyclooxygenase inhibitors.

When using etoricoxib in the elderly and in patients with renal, hepatic, or cardiac dysfunction, medically appropriate supervision should be maintained. If these patients deteriorate during treatment, appropriate measures should be taken, including discontinuation of therapy. It should be avoided in patients with severe hepatic impairment (Child-Pugh score of 10 or more). Therapy should be stopped if persistently abnormal liver enzyme values are seen. Use of etoricoxib is associated with very rare occurrence of serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis. These serious events may occur without warning and patients are at highest risk for these reactions early in the course of therapy.

Patients with history of mild allergic phenomena related to ingestion of other nonsteroidal anti-inflammatory drugs (eg, rash) should be treated with caution. Etoricoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. Etoricoxib may mask fever, which is a sign of infection.

Risk of GI Ulceration, Bleeding and Perforation with NSAIDs:
Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAID therapy. Although minor upper GI problems (e.g. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms. Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious GI events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking, and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.

Use In Pregnancy:
No clinical data on exposed pregnancies are available for etoricoxib. Studies in animals have shown reproductive toxicity. The potential for human risk in pregnancy is unknown. Etoricoxib, as with other medicinal products inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus during the last trimester. Etoricoxib is contraindicated in pregnancy. If a woman becomes pregnant during treatment, etoricoxib must be discontinued.

Use In Lactation:
It is not known whether etoricoxib is excreted in human milk. Etoricoxib is excreted in the milk of lactating rats. Women who use etoricoxib must not breast feed.

Fertility:
The use of etoricoxib, as with any drug substance known to inhibit COX-2, is not recommended in women attempting to conceive.

SIDE EFFECTS:
Post-Marketing Experience:
The following adverse reactions have been reported in post-marketing experience:

Blood and Lymphatic System Disorders: Thrombocytopenia.
Immune System Disorders: Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions including shock.
Psychiatric Disorders: Anxiety, insomnia, confusion, hallucinations.
Nervous System Disorders: Dysgeusia, somnolence.
Eye Disorders: Blurred vision.
Cardiac Disorders: Congestive heart failure, palpitations, angina.
Vascular Disorders: Hypertensive crisis.
Respiratory, Thoracic and Mediastinal Disorders: Bronchospasm.
Gastrointestinal Disorders: Abdominal pain, oral ulcers, peptic ulcers including perforation and bleeding (mainly in elderly patients), vomiting, diarrhea.
Hepatobiliary Disorders: Hepatitis, jaundice.
Skin and Subcutaneous Tissue Disorders: Angioedema, pruritus, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria.
Renal and Urinary Disorders: Renal insufficiency, including renal failure, usually reversible upon discontinuation of therapy (see Precautions).

DRUG INTERACTIONS:
Warfarin:
Patients receiving oral anticoagulants should be closely monitored for their prothrombin time International Normalised Ratio (INR), particularly when therapy with etoricoxib is initiated or the dose of etoricoxib is changed.

Rifampicin:
Co-administration of etoricoxib with rifampicin, a potent inducer of CYP enzymes, produced a 65% decrease in etoricoxib plasma concentrations.

Methotrexate:
Adequate monitoring for methotrexate-related toxicity is recommended when etoricoxib and methotrexate are administered concomitantly.

Diuretics, Angiotensin Converting Enzyme (ACE) Inhibitors & Angiotensin II Antagonists (AIIAs):
NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly.

Lithium:
NSAIDs decrease lithium renal excretion and therefore increase lithium plasma levels. If necessary, monitor blood lithium closely and adjust the lithium dosage while the combination is being taken and when the NSAID is withdrawn.

Aspirin:
Etoricoxib can be used concomitantly with acetylsalicylic acid at doses used for cardiovascular prophylaxis. However, concomitant administration of low-dose acetylsalicylic acid with etoricoxib may result in an increased rate of GI ulceration or other complications compared to use of etoricoxib alone.

OVERDOSAGE AND TREATMENT:
There have been reports of acute overdosage with etoricoxib, although adverse experiences were not reported in the majority of cases. The most frequently observed adverse experiences were consistent with the safety profile for etoricoxib (e.g., gastrointestinal events, renovascular events). In the event of overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the GI tract, employ clinical monitoring, and institute supportive therapy, if required. Etoricoxib is not dialysable by haemodialysis; it is not known whether etoricoxib is dialysable by peritoneal dialysis.

STORAGE:
Store below 30^{O}C. Protect from moisture and light.

KEEP OUT OF REACH OF CHILDREN
JAUHI DARI KANAK-KANAK

PACK QUANTITIES:
Available in blister pack of 3 x 10's and 10 x 10's.
Not all pack sizes may be marketed.

Further information can be obtained from pharmacist, physician or the manufacturer.

Product Registration Holder & Manufactured By :
Kotra Pharma (M) Sdn. Bhd. (90082-V)
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75250 Melaka, Malaysia.

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