TERICOX

Tablets

Composition
Each film-coated tablet contains 60, 90, or 120 mg of Etoricoxib.

Action
Etoricoxib is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. Tericox 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 NSAID's 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.

Across clinical pharmacology studies, Etoricoxib produced dose-dependent inhibition of COX-2 without inhibition of COX-1 at doses up to 150 mg daily.

The influence on gastro-protective COX-1 activity was also assessed in a clinical study where prostaglandin synthesis was measured in gastric biopsy samples from subjects administered either Etoricoxib 120 mg daily, naproxen 500 mg twice daily, or placebo. Etoricoxib did not inhibit gastric prostaglandin synthesis as compared to placebo. In contrast, naproxen inhibited gastric prostaglandin synthesis by approximately 80% compared with placebo. These data further support the COX-2 selectivity of Etoricoxib.

Platelet Function
Multiple doses of Etoricoxib up to 150 mg administered daily up to nine days had no effect on bleeding time relative to placebo. Similarly, bleeding time was not altered in a single dose study with Etoricoxib 250 or 500 mg. There was no inhibition of *ex vivo* arachidonic acid or collagen induced platelet aggregation at steady state with doses of Etoricoxib up to 150 mg. These findings are consistent with the COX-2 selectivity of Etoricoxib.

Pharmacokinetics
Absorption
Orally administered Etoricoxib is well absorbed. The mean oral bioavailability is approximately 100%. Following 120 mg once daily dosing to steady state, the peak plasma concentration (geometric mean C_{max} = 3.6 mcg/ml) was observed at approximately 1 hour (T_{max}) after administration to fasted adults. The geometric mean $AUC_{0\text{-}24\ hr}$ was 37.8 mcg hr/ml. The pharmacokinetics of Etoricoxib is linear across the clinical dose range.
In studies specifically designed to measure the onset of action of Etoricoxib, the onset of action occurred as early as 24 minutes after dosing.

A standard meal had no clinically meaningful effect on the extent or rate of absorption of a dose of Etoricoxib 120 mg. In clinical trials, Etoricoxib was administered without regard to food.
The pharmacokinetics of Etoricoxib in 12 healthy subjects were similar (comparable AUC, C_{max} within approximately 20%) when administered alone, with a magnesium/aluminum hydroxide antacid, or a calcium carbonate antacid (approximately 50 meq acid-neutralizing capacity).

Distribution
Etoricoxib is approximately 92% bound to human plasma protein over the range of concentrations of 0.05 to 5 mcg/ml. The volume of distribution at steady state (V_{dss}) is approximately 120 L in humans. Etoricoxib crosses the placenta in rats and rabbits, and the blood-brain barrier in rats.

Metabolism

Etoricoxib is extensively metabolized with <1% of a dose recovered in urine as the parent drug. Cytochrome P450 (CYP) enzymes catalyze the major route of metabolism to form the 6'-hydroxymethyl derivative.
Five metabolites have been identified in man. The principal metabolite is the 6'-carboxylic acid derivative of Etoricoxib formed by further oxidation of the 6'-hydroxymethyl derivative. These principal metabolites either demonstrate no measurable activity or are only weakly active as COX-2 inhibitors. None of these metabolites inhibits COX-1.

Elimination
Following administration of a single 25 mg radiolabeled intravenous dose of Etoricoxib to healthy subjects, 70% of radioactivity was recovered in urine and 20% in faeces, 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 120 mg, with an accumulation ratio of approximately 2, corresponding to an accumulation half-life of approximately 22 hours. The plasma clearance is estimated to be approximately 50 ml/min.

Characteristics in Patients
Gender
The pharmacokinetics of Etoricoxib is similar between men and women.

Elderly
Pharmacokinetics in the elderly (65 years of age and older) are similar to those in the young. No dosage adjustment is necessary for elderly patients.

Race
There is no clinically important effect of race on the pharmacokinetics of Etoricoxib.

Hepatic Insufficiency
Patients with mild hepatic insufficiency (Child-Pugh score 5-6) administered Etoricoxib 60 mg once daily had an approximately 16% higher mean AUC as compared to healthy subjects given the same regimen. Patients with moderate hepatic insufficiency (Child-Pugh score 7-9) administered Etoricoxib 60 mg ***every other day*** had similar mean AUC to the healthy subjects given Etoricoxib 60 mg once daily. There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9). (See Dosage and Administration, *Hepatic Insufficiency.*)

Renal Insufficiency
The pharmacokinetics of a single dose of Etoricoxib 120 mg in patients with moderate to severe renal insufficiency and patients with end-stage renal disease on hemodialysis were not significantly different from those in healthy subjects. Hemodialysis contributed negligibly to elimination (dialysis clearance approximately 50 ml/min).

Paediatric Patients
The pharmacokinetics of Etoricoxib in paediatric patients (<12 years of age) have not been studied. In a pharmacokinetic study (N=16) conducted in adolescents (aged 12 to 17) the pharmacokinetics in adolescents weighing 40 to 60 kg given Etoricoxib 60 mg once daily and in adolescents >60 kg given Etoricoxib 90 mg once daily were similar to the pharmacokinetics in adults given Etoricoxib 90 mg once daily. Safety and effectiveness of Etoricoxib in paediatric patients have not been established.

Indications
Tericox is indicated for:
- Acute and chronic treatment of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA)
- The management of ankylosing spondylitis (AS)
- Treatment of acute gouty arthritis

- Relief of acute pain
- Relief of chronic musculoskeletal pain

Contraindications

Etoricoxib is contraindicated in patients with:

- Active peptic ulceration or active gastro-intestinal (GI) bleeding.
- Patients who, after taking acetylsalicylic or NSAIDs including COX-2 (cyclooxygenase-2) inhibitors, experience bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria, or allergic-type reactions.
- Pregnancy and lactation.
- Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score ≥10).
- Estimated renal creatinine clearance <30 ml/min.
- Children and adolescents under 16 years of age.
- Inflammatory bowel disease.
- Congestive heart failure (NYHA II-IV).
- Patients with hypertension whose blood pressure is persistently elevated above 140/90mmHg and has not been adequately controlled.
- Established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular dis

Warnings and Precautions

Cardiovascular effect

Clinical trials suggest that the selective COX-2 inhibitor class of drugs (of which Etoricoxib is one) may be associated with an increased risk of thrombotic events (especially MI and stroke), relative to placebo and some NSAID's (naproxen). 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. Patients on long-term treatment should be reviewed regularly, such as every three months, concerning efficacy, risk factors, and ongoing need for treatment.
Prescribers should inform the individual patient of the increased risk when prescribing Etoricoxib to patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidemia, diabetes mellitus, and smoking).

Two large, controlled clinical trials of a different COX-2 selective inhibitor for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. In the absence of comparable data with Etoricoxib, it may be assumed that patients at high risk of cardiovascular disease (including patients with diabetes, hyperlipidemia, hypertension, or smokers) who are undergoing any major surgery may face an increased risk of developing a cardiovascular event. Patients with significant risk factors for cardiovascular events should only be treated with Etoricoxib after careful consideration of the patient's overall risk and the potential risks and benefits of alternative analgesic therapies.

Selective COX-2 inhibitors are not a substitute for aspirin for cardiovascular prophylaxis because of their lack of effect on platelets. Because Etoricoxib, a member of this class, does not inhibit platelet aggregation, antiplatelet therapies should not be discontinued. There is no evidence that concurrent use of aspirin decreases the risk of cardiovascular adverse events associated with COX-2 inhibitors, including Etoricoxib.

Gastrointestinal effect

There is a further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) for Etoricoxib, other selective COX-2 inhibitors and NSAID's, when taken concomitantly with acetylsalicylic acid (even at low doses). The relative difference in gastrointestinal safety between selective COX-2 inhibitors + acetylsalicylic acid *vs*. NSAID's + acetylsalicylic acid has not been adequately evaluated in long-term clinical trials.

Physicians should be aware that individual patients might develop upper gastrointestinal (GI) ulcers/ulcer complications irrespective of treatment. In clinical studies, the risk of endoscopically detected upper GI ulcers was lower in patients treated with Etoricoxib 120 mg once daily than in

patients treated with non-selective NSAID's. While the risk of endoscopically detected ulcers was low in patients treated with Etoricoxib 120 mg it was higher than in patients treated with placebo. Upper GI ulcers/ulcer complications have occurred in patients treated with Etoricoxib. These events can occur at any time during use and without warning symptoms. Independent of treatment, patients with a prior history of GI perforation, ulcers, and bleeding (PUB) and patients greater than 65 years of age are known to be at a higher risk for a PUB.

Renal effects
In patients with advanced renal disease, treatment with Etoricoxib is not recommended. Clinical experience in patients with estimated creatinine clearance of <30 ml/min is very limited. If therapy with Etoricoxib must be initiated in such patients, close monitoring of the patient's renal function is advisable.

Long-term administration of NSAID's has resulted in renal papillary necrosis and other renal injury. Renal prostaglandins may play a compensatory role in the maintenance of renal perfusion. Therefore, under conditions of compromised renal perfusion, administration of Etoricoxib may cause a reduction in prostaglandin formation and, secondarily, in renal blood flow, and thereby impair renal function. Patients at greatest risk of this response are those with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis. Monitoring of renal function in such patients should be considered. As with other drugs known to inhibit prostaglandin synthesis, discontinuation of therapy with Etoricoxib would be expected to be followed by recovery to the pre-treatment state.

Fluid retention, edema, and hypertension
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.
As with other drugs known to inhibit prostaglandin synthesis, fluid retention, edema, and hypertension have been observed in some patients taking Etoricoxib. The possibility of exacerbating fluid retention, edema, or hypertension should be taken into consideration when Etoricoxib is used in patients with pre-existing edema, hypertension, or heart failure. Close monitoring is essential.

All patients prescribed Etoricoxib should have their blood pressure monitored regularly while taking this medication. Etoricoxib should be stopped if the patient's blood pressure is persistently raised.

Hepatic effects
Elevations of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials treated for up to one year with Etoricoxib 60 and 90 mg daily. In active comparator portions of clinical trials, the incidence of elevated AST and/or ALT in patients treated with Etoricoxib 60 and 90 mg daily was similar to that of patients treated with naproxen, but notably less than the incidence in the diclofenac group. These elevations resolved in patients treated with Etoricoxib, with approximately half resolving while patients remained on therapy.

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 who have previously experienced acute asthmatic attacks, urticaria, or rhinitis, which were precipitated by salicylates or non-selective cyclooxygenase inhibitors. Since the pathophysiology of these reactions is unknown, physicians should weigh the potential benefits of prescribing Etoricoxib versus the potential risks.
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.

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 NSAID's and some selective COX-2 inhibitors during post-marketing surveillance. These serious events may occur without warning. 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. Serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving Etoricoxib. Some selective COX-2 inhibitors have been associated with an increased risk of skin reactions in patients with a history of any drug allergy. 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. The physician should be aware of this when using Etoricoxib in patients being treated for infection.

Pregnancy
Category D
There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Nursing Mothers
It is unknown whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the possible adverse effects of drugs that inhibit prostaglandin synthesis on nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Paediatric Use
Safety and effectiveness of Etoricoxib in paediatric patients have not been established.

Elderly Use
Pharmacokinetics in the elderly (65 years of age and older) are similar to those in the young. In clinical studies, no overall differences in safety or effectiveness were observed between elderly and younger patients.

Adverse Reactions
The following drug-related adverse experiences were reported in clinical studies in patients with OA, RA, or chronic low back pain treated for up to 12 weeks. These occurred in ≥1% of patients treated with Etoricoxib and at an incidence greater than placebo: asthenia/fatigue, dizziness, lower extremity edema, hypertension, dyspepsia, heartburn, nausea, headache, ALT increased, AST increased. The adverse experience profile was similar in patients with OA or RA treated with Etoricoxib for one year or longer.

Post-marketing Experience
The following adverse reactions have been reported in post-marketing experience:
Immune system disorders: hypersensitivity reactions, anaphylactic/anaphylactoid reactions including shock.

Psychiatric disorders: anxiety, insomnia, confusion, hallucinations

Nervous system disorders: dysgeusia, somnolence

Cardiac disorders: congestive heart failure

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

Skin and subcutaneous tissue disorders: angioedema, rash, Stevens-Johnson syndrome pruritus, urticaria.

Renal and urinary disorders: renal insufficiency, including renal failure, usually reversible upon discontinuation of therapy

Drug Interactions

Warfarin
In subjects stabilized on chronic warfarin therapy, the administration of Etoricoxib 120 mg daily was associated with an approximate 13% increase in prothrombin time International Normalized Ratio (INR). Standard monitoring of INR values should be conducted when therapy with Etoricoxib is initiated or changed, particularly in the first few days, in patients receiving warfarin or similar agents.

Rifampin
Co-administration of Etoricoxib with Rifampin, a potent inducer of hepatic metabolism, produced a 65% decrease in Etoricoxib plasma area under the curve (AUC). This interaction should be considered when Etoricoxib is co-administered with Rifampin.

Methotrexate
Two studies investigated the effects of Etoricoxib 60, 90 or 120 mg administered once daily for seven days in patients receiving once-weekly methotrexate doses of 7.5 to 20 mg for rheumatoid arthritis. Etoricoxib at 60 and 90 mg had no effect on methotrexate plasma concentrations (as measured by AUC) or renal clearance. In one study, Etoricoxib 120 mg had no effect on methotrexate plasma concentrations (as measured by AUC) or renal clearance. In the other study, Etoricoxib 120 mg increased methotrexate plasma concentrations by 28% (as measured by AUC) and reduced renal clearance of methotrexate by 13%. Monitoring for methotrexate-related toxicity should be considered when Etoricoxib at doses greater than 90 mg daily and methotrexate are administered concomitantly.

Diuretics
Angiotensin Converting Enzyme (ACE) Inhibitors and Angiotensin II Antagonists (AIIAs): Reports suggest that NSAID's including selective COX-2 inhibitors may diminish the antihypertensive effect of diuretics, ACE inhibitors and AIIAs. This interaction should be given consideration in patients taking Etoricoxib concomitantly with these products.
In some patients with compromised renal function (e.g., elderly patients or patients who are volume-depleted, including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory drugs, including selective COX-2 inhibitors, the co-administration of ACE inhibitors or AIIAs may result in a further deterioration of renal function, including possible renal failure. These effects are usually reversible. Therefore, the combination should be administered with caution, especially in the elderly.

Lithium
Reports suggest that non-selective NSAID's and selective COX-2 inhibitors may increase plasma lithium levels. This interaction should be given consideration in patients taking Etoricoxib concomitantly with lithium.

Aspirin
There is no evidence that concurrent use of aspirin decreases the risk of cardiovascular adverse events associated with COX-2 inhibitors, including Etoricoxib. However, concomitant administration of low-dose aspirin with Etoricoxib results in an increased rate of GI ulceration or other complications compared to use of Etoricoxib alone. At steady state, Etoricoxib 120 mg once daily had no effect on the anti-platelet activity of low-dose aspirin (81 mg once daily).

Oral Contraceptives
Etoricoxib 60 mg given concomitantly with an oral contraceptive containing 35mcg ethinyl estradiol (EE) and 0.5 to 1 mg norethindrone for 21 days increased the steady state AUC0-24 hr of EE by 37%. Etoricoxib 120 mg either given with the same oral contraceptive, concomitantly or separated by 12 hours increased the steady state AUC0-24 hr of EE by 50 to 60%. This increase in EE concentration should be considered when selecting an appropriate oral contraceptive for use with Etoricoxib. An increase in EE exposure can increase the incidence of adverse events associated with oral contraceptives (e.g., venous thrombo-embolic events in women at risk).

Hormone Replacement Therapy
Administration of Etoricoxib 120 mg with hormone replacement therapy consisting of conjugated estrogens for 28 days increased the mean steady state AUC0-24 hr of unconjugated estrone (41%), equilin (76%), and 17-β-estradiol (22%). The effect of the recommended chronic doses of Etoricoxib (60 and 90 mg) has not been studied. The effects of Etoricoxib 120 mg on the exposure (AUC0-24 hr) to these estrogenic components were less than half of those observed when conjugated estrogens were administered alone and the dose was increased from 0.625 to 1.25 mg. The clinical significance of these increases is unknown, and higher doses of conjugated estrogens were not studied in combination with Etoricoxib. These increases in estrogenic concentration should be taken into consideration when selecting post-menopausal hormone therapy for use with Etoricoxib

Other
In drug-interaction studies, Etoricoxib did not have clinically important effects on the pharmacokinetics of Prednisone/Prednisolone or digoxin.
Antacids and ketoconazole (a potent inhibitor of CYP3A4) did not have clinically important effects on the pharmacokinetics of Etoricoxib.

Dosage and Administration
Tericox is administered orally. Tericox may be taken with or without food.

Arthritis
Osteoarthritis: The recommended dose is 60 mg once daily.
Rheumatoid Arthritis: The recommended dose is 90 mg once daily.
Ankylosing Spondylitis: The recommended dose is 90 mg once daily
Acute Gouty Arthritis: The recommended dose is 120 mg once daily. Tericox 120 mg should be used only for the acute symptomatic period, limited to a maximum of 8 days treatment.

Analgesia
Acute Pain: The recommended dose is 120 mg once daily. Tericox 120 mg should be used only for the acute symptomatic period, limited to a maximum of 8 days treatment.
Chronic Musculoskeletal Pain: The recommended dose is 60 mg 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 OA should not exceed 60 mg daily.
The dose for RA should not exceed 90 mg daily.
The dose for ankylosing spondylitis should not exceed 90 mg daily.
The dose for acute gout should not exceed 120 mg daily.
The dose for acute pain should not exceed 120 mg daily.
The dose for chronic pain should not exceed 60 mg 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. Patients on long-term treatment should be reviewed regularly, such as every three months, concerning efficacy, risk factors, and ongoing need for treatment.

Elderly, Gender, Race

No dosage adjustment in Tericox 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 60 mg 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 60 mg ***every other day*** should not be exceeded. 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 Tericox is not recommended. No dosage adjustment is necessary for patients with lesser degrees of renal insufficiency (creatinine clearance ≥30 ml/min).

Over Dosage
No overdoses of Etoricoxib were reported during clinical trials.
In clinical studies, administration of single doses of Etoricoxib up to 500 mg and multiple doses up to 150 mg/day for 21 days did not result in significant toxicity.
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 dialyzable by hemodialysis; it is not known whether Etoricoxib is dialyzable by peritoneal dialysis.

Presentation
Tericox 60
Box of 10 tablets

Tericox 90
Box of 10 tablets

Tericox 120
Box of 7 tablets