EBERIL 60
EBERIL 90
EBERIL 120

Each film coated tablet contains:
Etoricoxib 60 mg
Etoricoxib 90 mg
Etoricoxib 120 mg

☸ PRODUCT DESCRIPTION:

60 mg: Green, apple-shaped, biconvex, film coated tablet with engraved 60 on one side and plain on the other side
90 mg: White, apple-shaped, biconvex, film coated tablet with engraved 90 on one side and scored on the other side
120 mg: Pale-green, apple-shaped, biconvex, film coated tablet with engraved 120 on one side and scored on the other side

☸ MECHANISM OF ACTION:

Pharmacology

Etoricoxib is a non-steroidal 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 cyclo-oxygenase 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.

Etoricoxib produces dose-dependent inhibition of COX-2 without inhibition of COX-1 at doses up to 150 mg daily.

Platelet Function

Multiple doses of Etoricoxib up to 150 mg administered daily up to nine days have no effect on bleeding time. There is 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 absolute bioavailability is approximately 100%. The pharmacokinetics of Etoricoxib are linear across the clinical dose range.

A standard meal had no clinically meaningful effect on the extent or rate of absorption of a dose of Etoricoxib 120 mg. Etoricoxib can be administered without regard to food.

Distribution

Etoricoxib is approximately 92% bound to human plasma protein over the range of concentrations of 0.05 to 5 µg/mL. The volume of distribution at steady state (V_{dss}) was approximately 120 L in humans.

Etoricoxib crosses the placenta in rats and rabbits and the blood barrier in rats.

Biotransformation

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 CYP enzymes.

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 inhibit COX-1.

Elimination

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 a half-life of approximately 22 hours.

The plasma clearance after a 25-mg intravenous dose is estimated to be approximately 50 mL/min.

Characteristics in patients

Elderly patients

Pharmacokinetics in the elderly (65 years of age and older) are similar to those in the young.

Gender

The pharmacokinetics of Etoricoxib are similar between men and women.

Hepatic impairment

Patients with mild hepatic dysfunction (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 dysfunction (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; Etoricoxib 30 mg once daily has not been studied in this population. There are no clinical or pharmacokinetic data in patients with severe hepatic dysfunction (Child-Pugh score $\geq$ 10).

Renal impairment

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).

Pediatric patients

The pharmacokinetics of Etoricoxib in pediatric patients (< 12 years old) have not been studied.

Pharmacokinetics of adolescents (aged 12 to 17) weighing 40 to 60 kg given Etoricoxib 60 mg once daily and 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 pediatric patients have not been established.

☸ INDICATION:

Etoricoxib is indicated for:

- Acute and chronic treatment of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA)
- Treatment of ankylosing spondylitis (AS)
- Treatment of acute gouty arthritis
- Treatment of acute pain, including that related to primary dysmenorrhea 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 (see Warnings and Precautions).

☸ 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.

Osteoarthritis

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

Rheumatoid Arthritis

The recommended dose is 60 mg once daily. In some patients with insufficient relief from symptoms, an increased dose of 90 mg once daily may increase efficacy. Once the patient is clinically stabilised, down-titration to a 60 mg 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 60 mg once daily. In some patients with insufficient relief from symptoms, an increased dose of 90 mg once daily may increase efficacy. Once the patient is clinically stabilised, down-titration to a 60 mg 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 120 mg once daily.
- Primary Dysmenorrhea: The recommended dose is 120 mg once daily.
- Minor Dental Procedures: The recommended dose is 90 mg once daily. Oral

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 and primary dysmenorrhea should not exceed 120 mg daily.
- The dose for minor dental procedures should not exceed 90 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. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically (see Warnings and Precautions).

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 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, administration of 30 mg once daily can also be considered. There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score > 9). (see Warnings and Precautions).

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). (see Warnings and Precautions).

Given the association between cardiovascular risk and exposure to COX-2 Inhibitors, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment

☸ WARNING AND PRECAUTION:

Selective COX-2 inhibitor class of drugs may be associated with an increased risk of thrombotic events (especially MI and stroke), relative to placebo and some NSAIDs (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. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.

Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidemia, diabetes mellitus, smoking) should only be treated with Etoricoxib after careful consideration.

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 a further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) for Etoricoxib, other selective COX-2 inhibitors and NSAIDs, when taken concomitantly with Acetylsalicylic acid (even at low doses). The relative difference in gastrointestinal safety between selective COX-2 inhibitors + Acetylsalicylic acid vs. NSAIDs + Acetylsalicylic acid has not been adequately evaluated.

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 NSAIDs 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.

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 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 Non-steroidal Anti-inflammatory Drugs (NSAIDs), including Etoricoxib, can be associated with new onset or recurrent congestive heart failure. (see Side Effects.). Etoricoxib may be associated with more frequent and severe hypertension than some other NSAIDs and selective COX-2 inhibitors, particularly at high doses. Therefore, special attention should be paid to blood pressure monitoring during treatment with Etoricoxib. If blood pressure rises significantly, alternative treatment should be considered.

Physicians should be aware that individual patients may develop upper gastrointestinal (GI) ulcers/ulcer complications irrespective of treatment. Although the risk of GI toxicity is not eliminated with Etoricoxib, the risk of GI toxicity with Etoricoxib 60 mg or 90 mg once daily is significantly less than with Diclofenac 150 mg daily. 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.

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 cyclo-oxygenase 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, includes exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis in association with the use of NSAIDs and some selective COX-2 inhibitors. 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 (see Side Effects).
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.
Warning:
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 NSAIDs 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.

Caution should be exercised 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.

❁ PREGNANCY AND LACTATION:

Pregnancy

No clinical data on exposed pregnancies are available for Etoricoxib. 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.

Breastfeeding

It is not known whether Etoricoxib is excreted in human milk. Women who use Etoricoxib must not breastfeed.

Fertility

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

❁ SIDE EFFECT:

The adverse event profile of Etoricoxib was similar in patients with OA, RA, chronic low back pain, acute gouty arthritis or in patients with patients with acute postoperative dental pain following surgery.
The following undesirable effects were reported with Etoricoxib.

System Organ Class	Adverse Reactions	Frequency category
Infections and infestations	Alveolar osteitis	Common
	Gastroenteritis, upper respiratory infection, urinary tract infection	Uncommon
Blood and lymphatic system disorders	Anemia (primarily associated with gastrointestinal bleeding), leukopenia, thrombocytopenia	Uncommon
Immune system disorders	Hypersensitivity	Uncommon
	Angioedema/ anaphylactic/ anaphylactoid reactions including shock	Rare
Metabolism and nutrition disorders	Edema/ fluid retention	Common
	Appetite increase or decrease, weight gain	Uncommon
Psychiatric disorders	Anxiety, depression, mental acuity decreased, hallucinations	Uncommon
	Confusion, restlessness	Rare

Nervous system disorders	Dizziness, headache	Common
	Dysgeusia, insomnia, paresthesia/ hypaesthesia, somnolence	Uncommon
Eye disorders	Blurred vision, conjunctivitis	Uncommon
Ear and labyrinth disorders	Tinnitus, vertigo	Uncommon
Cardiac disorders	Palpitations, arrhythmia	Common
	Atrial fibrillation, tachycardia, congestive heart failure, non-specific ECG changes, angina pectoris, myocardial infarction	Uncommon
Vascular disorders	Hypertension	Common
	Flushing, cerebrovascular accident, transient ischemic attack, hypertensive crisis, vasculitis	Uncommon
Respiratory, thoracic and mediastinal disorders	Bronchospasm	Common
	Cough, dyspnea, epistaxis	Uncommon
Gastrointestinal disorders	Abdominal pain	Very common
	Constipation, flatulence, gastritis, heartburn/acid reflux, diarrhea, dyspepsia/epigastric discomfort, nausea, vomiting, esophagitis, oral ulcer	Common
	Abdominal distention, bowel movement pattern change, dry mouth, gastroduodenal ulcer, peptic ulcers including gastrointestinal perforation and bleeding, irritable bowel syndrome, pancreatitis	Uncommon
Hepatobiliary disorders	ALT increased, AST increased	Common
	Hepatitis	Rare
	Hepatic failure, jaundice	Rare
Skin and subcutaneous tissue disorders	Ecchymosis	Common
	Facial edema, pruritus, rash, erythema, urticaria	Uncommon
	Stevens-Johnson syndrome, toxic epidermal necrolysis, fixed drug eruption	Rare
Musculoskeletal and connective tissue disorders	Muscular cramp/spasm, musculoskeletal pain/stiffness	Uncommon
Renal and urinary disorders	Proteinuria, serum creatinine increased, renal failure/ renal insufficiency	Uncommon
General disorders and administration site conditions	Asthenia/fatigue, flu-like disease	Common
	Chest pain	Uncommon
Investigations	Blood urea nitrogen increased, creatine phosphokinase increased, hyperkalemia, uric acid increased	Uncommon
	Blood sodium decreased	Rare

Hypersensitivity includes the terms "allergy", "drug allergy", "drug hypersensitivity", "hypersensitivity", "hypersensitivity NOS", "hypersensitivity reaction" and "nonspecific allergy". Selective COX-2 inhibitors have been reported to be associated with an increased risk of serious thrombotic arterial events, including myocardial infarction and stroke.

The following serious undesirable effects have been reported in association with the use of NSAIDs and cannot be ruled out for Etoricoxib: Nephrotoxicity including interstitial nephritis and nephrotic syndrome.

☸ EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Patients who experience dizziness, vertigo or somnolence while taking Etoricoxib should refrain from driving or operating machinery.

☸ CONTRAINDICATION:

Etoricoxib is contraindicated in patients with:

- Hypersensitivity to any component of this product
- Congestive heart failure (NYHA II-IV)
- Established ischemic heart disease, 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 is not under control.
- Pregnancy

- Patients who have increased risk of cardiovascular disease (ischemic heart disease and stroke).

☸ DRUG INTERACTION:

Warfarin

In an individual 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

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 NSAIDs 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 acute 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 NSAIDs and selective COX-2 inhibitors may increase plasma Lithium levels. This interaction should be given consideration in patients taking Etoricoxib concomitantly with Lithium.

Aspirin

Etoricoxib can be used concomitantly with low-dose Aspirin at doses for cardiovascular prophylaxis. At steady state, Etoricoxib 120 mg once daily had no effect on the anti-platelet activity of low-dose aspirin (81 mg once daily). However, concomitant administration of low-dose Aspirin with Etoricoxib increases the rate of GI ulceration or other complications compared to use of Etoricoxib alone. (see Warnings and Precautions).

Oral Contraceptives

Etoricoxib 60 mg given concomitantly with an oral contraceptive containing 35 mcg Ethinyl estradiol (EE) and 0.5 to 1 mg Norethindrone for 21 days increased the steady state AUC 0-24hr of EE by 37%. A Etoricoxib 120 mg given with the same oral contraceptive either concomitantly or separated by 12 hours, increased the steady state AUC0-24hr 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 (0.625 mg PREMARIN®†) for 28 days, increased the mean steady state $AUC_{0\text{-}24hr}$ of unconjugated estrone (41%), equilin (76%) and 17-ß-estradiol (22%). The effect of the recommended chronic doses of Etoricoxib (30, 60 and 90 mg) has not been studied. The effects of Etoricoxib 120 mg on the exposure ($AUC_{0\text{-}24hr}$) to these estrogenic components of PREMARIN®† were less than half of those observed when PREMARIN®† was 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 PREMARIN®† 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

Etoricoxib did not have clinically important effects on the pharmacokinetics of Prednisone/Prednisolone or Digoxin.

Antacids and Ketoconazole (a potent inhibitor of CYP3A4) do not have clinically important effects on the pharmacokinetics of Etoricoxib.

☸ OVERDOSE 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, cardiorenal 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 dialyzable by hemodialysis; it is not known whether Etoricoxib is dialyzable by peritoneal dialysis.

☸ STORAGE:

Store at temperature of not more than 30°C.

☸ DOSAGE FORM AND PACKAGING AVAILABLE:

60 mg Tablet, Blister 3x10's and 10x10's
90 mg Tablet, Blister 3x10's and 10x10's
120 mg Tablet, Blister 3x10's and 10x10's

☸ DATE OF REVISION:

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