

EBERIL 30

EBERIL 60

EBERIL 90

EBERIL 120

Each film coated tablet contains:

Etoricoxib 30 mg

Etoricoxib 60 mg

Etoricoxib 90 mg

Etoricoxib 120 mg

PRODUCT DESCRIPTION:

30 mg: Light green, apple-shaped, biconvex, film coated tablet with engraved 30 on one side and plain on the other side

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_{ss}*) 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 ≥ 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
- Chronic low back pain (30 mg and 60 mg only)
- 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 Warning and Precaution).



DOSAGE AND ADMINISTRATION:

Oral

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.

Chronic low back pain

The recommended dose is 60 mg once daily.

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 Warning and Precaution).

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 Warning and Precaution).

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 Warning and Precaution).

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.

20 cm.

Product	Code No.	Dimension	Packaging Type	Thickness
EBERIL 30	IEMY 0051	W 26.5 x L 20 cm.	Wood Free Paper (गुणवत्तापूर्ण)	60 g (0.08 mm.)
PM Specification				
Designed by: I (PDM, ASPD, PDC-M, PDC-A, PDQ-M, PDO-A)		Checked by: (PDM/ASPD)		
Approved by: PLC: (Date)		Approved by: (M/D (Only Pattern and Color))		
		LRA: (Date)		
		GCC-PM: (Date)		
		CUSTOMER(SALES DEPT.): (Date)		

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