PACKAGE INSERT TEMPLATE FOR ETORICOXIB TABLET

Brand or Product Name
[Product name] Tablet 30mg
[Product name] Tablet 60mg
[Product name] Tablet 90mg
[Product name] Tablet 120mg

Name and Strength of Active Substance(s)
Etoricoxib 30mg
Etoricoxib 60mg
Etoricoxib 90mg
Etoricoxib 120mg

Product Description
[Visual description of the appearance of the product (eg colour, markings etc)
eg White, circular flat beveled edge tablets marked '120' on one side]

Pharmacodynamics

Etoricoxib is a nonsteroidal anti-inflammatory agent (dipyridinyl derivative) for oral administration. It is a highly selective inhibitor of cyclooxygenase-2 (COX-2) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models.
Two isoforms of cyclooxygenase have been identified: cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2).
The COX-1 isoenzyme is constitutively expressed in most tissues, and is particularly involved in prostaglandin synthesis in kidneys, platelets, and gastric mucosa; products of COX-1 appear cytoprotective, and inhibition of this isoform has been associated with antiplatelet and gastrointestinal toxicity.
The inducible COX-2 isoform is expressed at sites of inflammation, and its inhibition is considered responsible for analgesic and anti-inflammatory properties of nonsteroidal anti-inflammatory agents.
The COX-1-sparing effects of selective COX-2 inhibitors suggest they may be as effective as nonselective inhibitors of both COX-1 and COX-2 (ie, naproxen, ibuprofen, ketorolac) in treating pain and inflammation with a reduced propensity for hematologic and gastrointestinal toxicity.

Pharmacokinetics
Absorption
Etoricoxib is well absorbed from the gastrointestinal tract after oral doses.
The mean oral bioavailability is approximately 100%.

Peak plasma concentrations occur in about 1 hour in fasted adults; food delays absorption by about 2 hours, although it has no effect on the extent of absorption.
Antacids (calcium carbonate, aluminum/magnesium hydroxide) do not significantly affect the absorption of etoricoxib.

Distribution
Plasma protein binding is about 92%.
Studies in animals suggest that etoricoxib may cross the placenta and that some is distributed into breast milk.
Volume of Distribution: 119 L at steady state.

Metabolism
Etoricoxib is extensively metabolized with <2% of a dose recovered in urine as the parent drug. The major route of metabolism is via cytochrome P450 isoenzymes including CYP3A4 to form the 6'-hydroxymethyl derivative of etoricoxib, which is then oxidised to the 6'-carboxylic acid derivative, the major metabolite.

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.
No metabolites are considered to contribute significantly to COX-2 (or COX-1) inhibition.

Elimination
Etoricoxib is excreted mainly via the urine (70%) with only 20% of a dose appearing in the faeces.
At steady state the half-life of etoricoxib is about 22 hours.

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 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.

Recommended Dosage
Arthritis
- *Osteoarthritis*
  The recommended dose is 30 mg or 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. Etoricoxib 120 mg should be used only for the acute symptomatic period, limited to a maximum of 8 days treatment.

Analgesia
- *Acute Pain and Primary Dysmenorrhea*
  The recommended dose is 120 mg once daily. Etoricoxib 120 mg should be used only for the acute symptomatic period, limited to a maximum of 8 days treatment.

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.

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 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).

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).

Safety and effectiveness of etoricoxib in pediatric patients have not been established.

Mode of Administration
Oral. Etoricoxib may be taken with or without food.

Contraindications
- 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)
- Pregnancy
- Patients with hypertension whose blood pressure has not been adequately controlled
- Renal impairment associated with a creatinine clearance of less than 30 mL/minute
- Patients with active gastrointestinal ulceration or bleeding
- Patients with a history of bronchospasm with rhinoconjunctivitis or urticaria/angioedema associated with aspirin or other nonsteroidal antiinflammatory agents (adult-onset asthma, chronic rhinitis, nasal polyps, and chronic urticaria/angioedema predispose to these reactions) (risk of anaphylactic-like reactions)
- Patients with inflammatory bowel disease
- Patients who have increased risk of cardiovascular disease (ischeamic heart disease and stroke)

Warnings and 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 Antiinflammatory 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 antiinflammatory 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 NSAID

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.

Interactions with Other Medicaments

Concurrent use of etoricoxib and warfarin may result in increased prothrombin time International Normalized Ratio (INR)

Concurrent use of etoricoxib and rifampicin may result in decreased plasma concentration of etoricoxib.

Concurrent use of etoricoxib and methotrexate may result in increased methotrexate plasma concentrations and toxicity.

Concurrent use of etoricoxib and diuretics (e.g. bumetanide, frusemide, hydrochlorothiazide) may result in decreased diuretic and antihypertensive efficacy.

Concurrent use of etoricoxib and the following may result in reduced diuretic effectiveness, hyperkalemia, or possible nephrotoxicity:

- **Amiloride**
- **Spironolactone**

Concurrent use of etoricoxib and angiotensin II antagonists (e.g. losartan, telmisartan, valsartan) may result in decreased antihypertensive effects and an increased risk of renal impairment.

Concurrent use of etoricoxib and beta-blockers (e.g. atenolol, bisoprolol, carvedilol) may result in decreased antihypertensive effect.

Concurrent use of etoricoxib and angiotensin converting enzyme inhibitors (ACEI e.g. captopril, enalapril, perindopril) may result in diminished antihypertensive effect of ACEI.

Concurrent use of etoricoxib and lithium may result in increased lithium plasma concentrations.

Concurrent use of etoricoxib and low-dose aspirin may result in increased rate of gastrointestinal ulceration or other complications.

Concurrent use of etoricoxib and ethinyl estradiol (Oral contraceptives) may result in increased plasma concentration of ethinyl estradiol.

Concurrent use of etoricoxib and conjugated estrogens or *Hormone Replacement Therapy* may result in increased conjugated estrogen exposure.

Concurrent use of etoricoxib and the following may result in increased risk of gastrointestinal bleeding:

- **Abciximab**
- **Dipyridamole**
- **Fondaparinux**
- **Heparin**
- **Ticlopidine**
- **Tirofiban**

Concurrent use of etoricoxib and the following may result in an increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect:

- **Amlodipine**
- **Verapamil**

Concurrent use of etoricoxib and the following may result in increased risk of bleeding:

- **Citalopram**
- **Clopidogrel**
- **Dabigatran Etexilate**
- **Duloxetine**
- **Enoxaparin**

- **Escitalopram**
- **Fluoxetine**
- **Ginkgo**
- **Paroxetine**
- **Pentoxifylline**
- **Prasugrel**
- **Rivaroxaban**
- **Tinzaparin**
- **Venlafaxine**

Concurrent use of etoricoxib and the following may result in an increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect:

- **Diltiazem**
- **Felodipine**
- **Flunarizine**
- **Nicardipine**
- **Nifedipine**
- **Nimodipine**

Concurrent use of etoricoxib and the following may result in an increased risk of seizures:

- **Levofloxacin**
- **Norfloxacin**
- **Ofloxacin**

Concurrent use of etoricoxib and the following may result in an increased risk of hypoglycemia:

- **Gliclazide**
- **Glimepiride**
- **Glipizide**

Concurrent use of etoricoxib and cyclosporine may result in an increased risk of cyclosporine nephrotoxicity.

Concurrent use of etoricoxib and ketorolac may result in enhanced gastrointestinal adverse effects (peptic ulcers, gastrointestinal bleeding and/or perforation).

Concurrent use of etoricoxib and minoxidil may result in increased exposure to minoxidil.

Concurrent use of etoricoxib and tacrolimus may result in acute renal failure.

Statement on Usage During Pregnancy and Lactation

Pregnancy
Etoricoxib is contraindicated during pregnancy. If pregnancy occurs during medication with etoricoxib, treatment should be withdrawn immediately. There is no clinical data on exposed pregnancies available. The potential risk for human in prenancy is unknown.

Lactation
It is not known whether etoricoxib is excreted in breast milk. 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.

Adverse Effects / Undesirable Effects

Blood and lymphatic system disorders: thrombocytopenia.

Immune system disorders: hypersensitivity reactions, anaphylactic/anaphylactoid reactions including shock.

Metabolism and nutrition disorders: hyperkalemia.

Psychiatric disorders: anxiety, insomnia, confusion, hallucinations, depression, restlessness.

Nervous system disorders: dysgeusia, somnolence.

Eye disorders: blurred vision.

Cardiac disorders: congestive heart failure, palpitations, angina, arrhythmia.

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, erythema, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria.

Renal and urinary disorders: renal insufficiency, including renal failure.

Overdose and Treatment
Symptoms
The most frequently observed adverse experience were consistent with the safety profile for etoricoxib. (e.g. gastrointestinal events, renovascular events).

Treatment
Treatment is symptomatic and supportive, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring.
Etoricoxib is not dialyzable by hemodialysis; it is not known whether etoricoxib is dialyzable by peritoneal dialysis.

Storage Conditions

Store below ….°C

Dosage Forms and Packaging Available
[Packaging type & pack size]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]