Summary of Product Characteristics

1. Name of the Medicinal Product

1.1.Trade Name : **ETRICIB 60** (Etoricoxib Tablets 60 mg)

1.2.Strength : 60 mg

1.3.Pharmaceutical Form : Film Coated Tablets

2. Qualitative and Quantitative Composition

Each Film Coated Tablet Contains

Etoricoxib 60 mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

'Film Coated Tablets

White, Circular, slightly biconvex, film coated tablets plain on both sides.'

4. Clinical Particulars

4.1.Therapeutic indications

Etoricoxib is indicated in adults and adolescents 16 years of age and older for the symptomatic relief of osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis, and the pain and signs of inflammation associated with acute gouty arthritis. Etoricoxib is indicated in adults and adolescents 16 years of age and older for the short-term treatment of moderate pain associated with dental surgery.

The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks.

4.2.Posology and method of administration

Posology

As the cardiovascular risks of etoricoxib 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, especially in patients with osteoarthritis.

Osteoarthritis: The recommended dose is 30 mg once daily. In some patients with insufficient relief from symptoms, an increased dose of 60 mg once daily may increase efficacy. In the absence of an increase in therapeutic benefit, other therapeutic options should be considered.

***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 stabilized, 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 stabilized, 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 conditions: For acute pain conditions, etoricoxib should be used only for the acute symptomatic period.

Acute gouty arthritis: The recommended dose is 120 mg once daily. For acute gouty arthritis, Etoricoxib was given for 8 days.

Postoperative dental surgery pain: The recommended dose is 90 mg once daily, limited to a maximum of 3 days. Some patients may require other postoperative analgesia in addition to Etoricoxib during the three day treatment period.

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 and ankylosing spondylitis should not exceed 90 mg daily.

The dose for acute gout should not exceed 120 mg daily, limited to a maximum of 8 days treatment.

The dose for postoperative acute dental surgery pain should not exceed 90 mg daily, limited to a maximum of 3 days.

Special populations

Elderly patients: No dosage adjustment is necessary for elderly patients. As with other drugs, caution should be exercised in elderly patients.

Patients with hepatic impairment: Regardless of indication, in patients with mild hepatic dysfunction (Child-Pugh score 5-6) a dose of 60 mg once daily should not be exceeded. In patients with moderate hepatic dysfunction (Child-Pugh score 7-9), regardless of indication, the dose of 30 mg once daily should not be exceeded.

Patients with renal impairment: No dosage adjustment is necessary for patients with creatinine clearance ≥30 ml/min. The use of Etoricoxib in patients with creatinine clearance <30 ml/min is contra-indicated.

Paediatric population: Etoricoxib is contra-indicated in children and adolescents under 16 years of age.

Method of administration

Oral Administration

Etoricoxib tablet is administered orally and may be taken with or without food. The onset of the effect of the medicinal product may be faster when Etoricoxib is administered without food. This should be considered when rapid symptomatic relief is needed.

3. Contraindication

Etoricoxib is contraindicated

- Hypersensitivity to the Etoricoxib or to any of the excipients.
- Active peptic ulceration or active gastro-intestinal (GI) bleeding.
- Patients who, after taking acetylsalicylic acid 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.
- Patients with hypertension whose blood pressure is persistently elevated above 140/90 mmHg and has not been adequately controlled.

- Established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease.

4. Special warnings and special precautions for use

Gastrointestinal effects: Caution is advised with treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs; the elderly, patients using any other NSAID or acetylsalicylic acid concomitantly or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding.

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

COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of antiplatelet effect. Therefore antiplatelet therapies should not be discontinued.

Renal effects: 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.

Fluid retention, oedema and hypertension: Caution should be exercised in patients with a history of cardiac failure, left ventricular dysfunction, or hypertension and in patients with pre-existing oedema from any other reason. If there is clinical evidence of deterioration in the condition of these patients, appropriate measures including discontinuation of Etoricoxib should be taken.

Hypertension should be controlled before treatment with Etoricoxib and special attention should be paid to blood pressure monitoring during treatment with Etoricoxib. Blood pressure should be monitored within two weeks after initiation of treatment and periodically thereafter. If blood pressure rises significantly, alternative treatment should be considered.

Hepatic effects: If signs of hepatic insufficiency occur, or if persistently abnormal liver function tests (three times the upper limit of normal) are detected, Etoricoxib should be discontinued.

General: Medically appropriate supervision should be maintained when using Etoricoxib in the elderly and in patients with renal, hepatic, or cardiac dysfunction.

Caution should be used when initiating treatment with Etoricoxib in patients with dehydration. It is advisable to rehydrate patients prior to starting therapy with Etoricoxib.

Etoricoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Etoricoxib may mask fever and other signs of inflammation.

Caution should be exercised when co-administering Etoricoxib with warfarin or other oral anticoagulants.

The use of Etoricoxib, as with any medicinal product known to inhibit cyclooxygenase /prostaglandin synthesis, is not recommended in women attempting to conceive.

5. Interaction with other medicinal products and other forms of interaction

Oral anticoagulants: Patients receiving oral anticoagulants should be closely monitored for their prothrombin time International Normalized Ratio (INR), particularly in the first few days when therapy with Etoricoxib is initiated or the dose of Etoricoxib is changed.

Diuretics, ACE inhibitors and Angiotensin II Antagonists: The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Acetylsalicylic Acid: Concomitant administration of Etoricoxib with doses of acetylsalicylic acid above those for cardiovascular prophylaxis or with other NSAIDs is not recommended.

Cyclosporin and tacrolimus: Renal function should be monitored when Etoricoxib and either of these drugs is used in combination.

The effect of Etoricoxib on the pharmacokinetics of other drugs

Lithium: Monitor blood lithium closely and adjust the lithium dosage while the combination is being taken and when the NSAID is withdrawn.

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

Oral contraceptives: 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 (HRT): These increases in estrogenic concentration should be taken into consideration when selecting post-menopausal hormone therapy for use with Etoricoxib because the increase in oestrogen exposure might increase the risk of adverse events associated with HRT.

Digoxin: Patients at high risk of digoxin toxicity should be monitored for this when Etoricoxib and digoxin are administered concomitantly.

Effect of Etoricoxib on drugs metabolized by sulfotransferases: It may be prudent to exercise care when administering Etoricoxib concurrently with other drugs primarily metabolized by human sulfotransferases (e.g., oral salbutamol and Minoxidil).

Effects of other drugs on the pharmacokinetics of etoricoxib

The main pathway of etoricoxib metabolism is dependent on CYP enzymes. CYP3A4 appears to contribute to the metabolism of etoricoxib in vivo. In vitro studies indicate that CYP2D6, CYP2C9, CYP1A2 and CYP2C19 also can catalyse the main metabolic pathway, but their quantitative roles have not been studied in vivo.

Voriconazole and Miconazole: Co-administration of either oral Voriconazole or topical miconazole oral gel, strong CYP3A4 inhibitors, with etoricoxib caused a slight increase in exposure to etoricoxib, but is not considered to be clinically meaningful based on published data.

Rifampicin: Co-administration of etoricoxib with rifampicin, a potent inducer of CYP enzymes, produced a 65% decrease in etoricoxib plasma concentrations. This interaction may result in recurrence of symptoms when etoricoxib is coadministered with rifampicin. While this information may suggest an increase in dose, doses of etoricoxib greater than those listed for each indication have not been studied in combination with rifampicin and are therefore not recommended.

Antacids: Antacids do not affect the pharmacokinetics of etoricoxib to a clinically relevant extent.

6. Fertility, pregnancy and lactation

Pregnancy: The Etoricoxib is contraindicated in pregnancy. If a woman becomes pregnant during treatment, Etoricoxib must be discontinued.

Breast-feeding: 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.

7. 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.

8. Undesirable effects

The frequencies of adverse reactions are ranked according to the following convention. The frequency grouping is defined using the following convention: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000) and Not known.

***Very Common*:** Abdominal pain

***Common*:** Alveolar osteitis, oedema/fluid retention, dizziness, headache, palpitations, arrhythmia, hypertension, bronchospasm, Constipation, flatulence, gastritis, heartburn/acid reflux, diarrhea, dyspepsia/epigastric discomfort, nausea, vomiting, oesophagitis, oral ulcer, ALT increased, AST increased, ecchymosis, asthenia/fatigue, flu-like disease .

***Uncommon*:** Gastroenteritis, upper respiratory infection, urinary tract infection, anaemia, leukopenia, thrombocytopenia, hypersensitivity, appetite increase or decrease, weight gain,

anxiety, depression, mental acuity decreased, hallucinations, dysgeusia, insomnia, paresthaesia/hypaesthesia, somnolence, blurred vision, conjunctivitis, tinnitus, vertigo, atrial fibrillation, tachycardia, congestive heart failure, non-specific ECG changes, angina pectoris, myocardial infarction, flushing, cerebrovascular accident, transient ischaemic attack, hypertensive crisis, vasculitis, cough, dyspnoea, epistaxis, abdominal distention, bowel movement pattern change, dry mouth, gastroduodenal ulcer, peptic ulcers including gastrointestinal perforation and bleeding, irritable bowel syndrome, pancreatitis, facial oedema, pruritus, rash, erythema, urticaria, muscular cramp/spasm, musculoskeletal pain/ stiffness, proteinuria, serum creatinine increased, renal failure/renal insufficiency, chest pain, blood urea nitrogen increased, creatine phosphokinase increased, hyperkalaemia, uric acid increased.

***Rare*:** Blood sodium decreased, confusion, restlessness, hepatitis, hepatic failure, jaundice, Stevens-Johnson syndrome, toxic epidermal necrolysis.

9. Overdose

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 dialysable by haemodialysis; it is not known whether etoricoxib is dialysable by peritoneal dialysis.

5. Pharmacological Properties

5.1.Pharmacodynamics properties

Pharmacotherapeutic group:

Anti-inflammatory & Antirheumatics products, non-steroids, coxibs.

ATC code: M01 AH05

Mechanism of action: Etoricoxib is an oral, selective cyclo-oxygenase-2 (COX-2) inhibitor within the clinical dose range. Etoricoxib produced dose-dependent inhibition of COX-2

without inhibition of COX-1 at doses up to 150 mg daily. Etoricoxib did not inhibit gastric prostaglandin synthesis and had no effect on platelet function.

Cyclooxygenase is responsible for generation of prostaglandins. Two isoforms, COX-1 and COX-2, have been identified. COX-2 is the isoform of the enzyme that has been shown to be induced by pro-inflammatory stimuli and has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. COX-2 is also involved in ovulation, implantation and closure of the ductus arteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in man but its relevance to ulcer healing has not been established.

5.2.Pharmacokinetic Properties

Absorption: Orally administered Etoricoxib is well absorbed. The absolute bioavailability is approximately 100%. Dosing with food (a high-fat meal) had no effect on the extent of absorption of Etoricoxib after administration of a 120-mg dose. The rate of absorption was affected, resulting in a 36% decrease in C_{max} and an increase in T_{max} by 2 hours.

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 (Vdss) was approximately 1,20l in humans.

Biotransformation: Etoricoxib is extensively metabolised 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. CYP3A4 appears to contribute to the metabolism of etoricoxib in vivo. In vitro studies indicate that CYP2D6, CYP2C9, CYP1A2 and CYP2C19 also can catalyse the main metabolic pathway, but their quantitative roles in vivo have not been studied. 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.

5.3.Preclinical safety data

Etoricoxib has been demonstrated not to be genotoxic. Etoricoxib was not carcinogenic in mice. Rats developed hepatocellular and thyroid follicular cell adenomas at >2-times the daily human dose [90 mg] based on systemic exposure when dosed daily for approximately two years. Etoricoxib has not been shown to cause hepatic CYP3A enzyme induction in humans.

In the rat, gastrointestinal toxicity of etoricoxib increased with dose and exposure time.

Etoricoxib was not teratogenic in reproductive toxicity studies.

Etoricoxib is excreted in the milk of lactating rats at concentrations approximately two-fold those in plasma.

6. Pharmaceutical Particulars

6.1.List of excipients

Polyethylene Glycol 6000

Sodium Starch Glycolate (Type A)

Colloidal Anhydrous Silica

Magnesium Stearate

Purified Talc

Microcrystalline Cellulose

Opadry White (Polyvinyl Alcohol-Part Hydrolyzed, Titanium Dioxide, Talc, Macrogol/PEG & Lecithin)

6.2.Incompatibilities

None

6.3.Shelf life

36 Months from the date of manufacture.

6.4.Special precautions for storage

Store at a temperature not exceeding 30°C. Protect from light and moisture.

Keep out of reach and sight of children.

6.5.Nature and contents of container

3 × 10 Film Coated Tablets in Alu-Alu Blister Pack.

6.6. Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder

ZIM Laboratories Limited

B-21/22, MIDC Area,

Kalmeshwar, Nagpur 441 501,

Maharashtra State, India

Manufacturing Site Addresses:

B-21/22, MIDC Area,

Kalmeshwar, Nagpur 4401501,

Maharashtra State,

India.

8. Marketing Authorization Number

TAN 22 HM 0194

9. Date of First Registration / Renewal of the Registration

04th May, 2022

10. Date of Revision of the Text