

## Summary of Product Characteristics

### 1. Name of the Medical Product

#### 1.1 Product Name:

RALEF 60 (Etoricoxib Tablets 60 mg)

RALEF 90 (Etoricoxib Tablets 90 mg)

RALEF 120 (Etoricoxib Tablets 120 mg)

#### 1.2 Strength:

Each film coated tablet contains:

Etoricoxib ..... 60 mg

Colour: Lake of Indigo Carmine, Yellow Oxide of Iron and Titanium Dioxide.

Each film coated tablet contains:

Etoricoxib ..... 90 mg

Colour: Titanium Dioxide.

Each film coated tablet contains:

Etoricoxib ..... 120 mg

Colour: Lake of Indigo Carmine, Yellow Oxide of Iron and Titanium Dioxide

#### 1.3 Pharmaceutical Dosage Form:

Film-coated tablets

### 2. Qualitative & Quantitative Composition:

Each film coated tablet contains:

Etoricoxib ..... 60 mg

Colour: Lake of Indigo Carmine, Yellow Oxide of Iron and Titanium Dioxide.

Each film coated tablet contains:

Etoricoxib ..... 90 mg

Colour: Titanium Dioxide.

Each film coated tablet contains:

Etoricoxib ..... 120 mg

Colour: Lake of Indigo Carmine, Yellow Oxide of Iron and Titanium Dioxide

For full list of excipients, see section 6.1 of SmPC

### 3. Pharmaceutical Form:

Film-coated tablets

**Ralef 60:** Light green to green coloured, circular, biconvex, film coated tablets, plain on both sides.

**Ralef 90:** White coloured, circular, biconvex, film coated tablets, plain on both sides.

**Ralef 120:** Pale green coloured, circular, biconvex, film coated tablets, plain on both sides.

#### **4. Clinical Particulars:**

##### **4.1 Therapeutic Indications:**

Etoricoxib Tablets 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 Tablets 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 (see sections 4.3, 4.4).

##### **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 (see sections 4.3, 4.4, 4.8 and 5.1).

###### 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 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 conditions

For acute pain conditions, Etoricoxib Tablets should be used only for the acute symptomatic period.

###### Acute gouty arthritis

The recommended dose is 120 mg once daily. In clinical trials for acute gouty arthritis, Etoricoxib Tablets 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 Tablets 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 (see section 4.4).

#### *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.

Clinical experience is limited particularly in patients with moderate hepatic dysfunction and caution is advised. There is no clinical experience in patients with severe hepatic dysfunction (Child-Pugh score  $\geq 10$ ); therefore, its use is contraindicated in these patients (see sections 4.3, 4.4 and 5.2).

#### *Patients with renal impairment*

No dosage adjustment is necessary for patients with creatinine clearance  $\geq 30$  ml/min (see section 5.2). The use of Etoricoxib Tablets in patients with creatinine clearance  $< 30$  ml/min is contra-indicated (see sections 4.3 and 4.4).

#### *Paediatric population*

Etoricoxib Tablets is contra-indicated in children and adolescents under 16 years of age (see section 4.3).

### **Method of administration**

Etoricoxib Tablets 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 Tablets is administered without food. This should be considered when rapid symptomatic relief is needed.

### **4.3 Contraindications:**

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- 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 (see sections 4.6 and 5.3).

- 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 140/90 mmHg and has not been adequately controlled.
- Established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease.

#### **4.4 Special warning and precautions for use\*:**

##### *Gastrointestinal effects*

Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], some of them resulting in fatal outcome, have occurred in patients treated with etoricoxib tablets.

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.

There is a further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) when Etoricoxib Tablets is taken concomitantly with acetylsalicylic acid (even at low doses). A significant difference in GI safety between selective COX-2 inhibitors + acetylsalicylic acid *vs.* NSAIDs + acetylsalicylic acid has not been demonstrated in long-term clinical trials (see section 5.1).

##### *Cardiovascular effects*

Clinical trials suggest that the selective COX-2 inhibitor class of drugs may be associated with a risk of thrombotic events (especially myocardial infarction (MI) and stroke), relative to placebo and some NSAIDs. As the cardiovascular risks of Etoricoxib Tablets 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 (see sections 4.2, 4.3, 4.8 and 5.1).

Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with Etoricoxib Tablets after careful consideration (see section 5.1).

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 (see sections above, 4.5 and 5.1.).

##### *Renal effects*

Renal prostaglandins may play a compensatory role in the maintenance of renal perfusion. Therefore, under conditions of compromised renal perfusion, administration of Etoricoxib Tablets 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*

As with other medicinal products known to inhibit prostaglandin synthesis, fluid retention, oedema and hypertension have been observed in patients taking etoricoxib. All Nonsteroidal Anti-inflammatory Drugs (NSAIDs), including Etoricoxib Tablets, can be associated with new onset or recurrent congestive heart failure. For information regarding a dose related response for Etoricoxib Tablets see section 5.1. 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.

Etoricoxib Tablets may be associated with more frequent and severe hypertension than some other NSAIDs and selective COX-2 inhibitors, particularly at high doses. Therefore, hypertension should be controlled before treatment with Etoricoxib Tablets (see section 4.3) and special attention should be paid to blood pressure monitoring during treatment with Etoricoxib Tablets. 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*

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 Tablets 30, 60 and 90 mg daily.

Any patients with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be monitored. If signs of hepatic insufficiency occur, or if persistently abnormal liver function tests (three times the upper limit of normal) are detected, Etoricoxib Tablets should be discontinued.

### *General*

If during treatment, patients deteriorate in any of the organ system functions described above, appropriate measures should be taken and discontinuation of Etoricoxib Tablets therapy should be considered. Medically appropriate supervision should be maintained when using Etoricoxib Tablets in the elderly and in patients with renal, hepatic, or cardiac dysfunction.

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

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 NSAIDs and some selective COX-2 inhibitors during post-marketing surveillance (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy with 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 Tablets (see section 4.8). 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 Tablets should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Etoricoxib Tablets may mask fever and other signs of inflammation.

Caution should be exercised when co-administering etoricoxib tablets with warfarin or other oral anticoagulants (see section 4.5).

The use of Etoricoxib Tablets, as with any medicinal product known to inhibit cyclooxygenase / prostaglandin synthesis, is not recommended in women attempting to conceive (see sections 4.6, 5.1, and 5.3).

Etoricoxib Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

#### **4.5 Interactions with other medicinal products and other forms of Interactions\*:**

##### *Pharmacodynamic interactions*

**Oral anticoagulants:** In subjects stabilised on chronic warfarin therapy, the administration of Etoricoxib Tablets 120 mg daily was associated with an approximate 13% increase in prothrombin time International Normalised Ratio (INR). Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR, particularly in the first few days when therapy with Etoricoxib Tablets is initiated or the dose of Etoricoxib Tablets is changed (see section 4.4).

**Diuretics, ACE inhibitors and Angiotensin II Antagonists:** NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking Etoricoxib Tablets concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, 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:** In a study in healthy subjects, at steady state, Etoricoxib Tablets 120 mg once daily had no effect on the anti-platelet activity of acetylsalicylic acid (81 mg once daily). Etoricoxib Tablets can be used concomitantly with acetylsalicylic acid at doses used for cardiovascular prophylaxis (low-dose acetylsalicylic acid). However, concomitant administration of low-dose acetylsalicylic acid with Etoricoxib Tablets may result in an increased rate of GI ulceration or other complications compared to use of Etoricoxib Tablets. Concomitant administration of Etoricoxib Tablets with doses of acetylsalicylic acid above those for cardiovascular prophylaxis or with other NSAIDs is not recommended (see sections 5.1 and 4.4.).

**Cyclosporin and tacrolimus:** Although this interaction has not been studied with Etoricoxib Tablets, coadministration of cyclosporin or tacrolimus with any NSAID may increase the nephrotoxic effect of cyclosporin or tacrolimus. Renal function should be monitored when Etoricoxib Tablets and either of these drugs is used in combination.

##### *Pharmacokinetic interactions*

##### *The effect of etoricoxib tablets on the pharmacokinetics of other drugs*

**Lithium:** NSAIDs decrease lithium renal excretion and therefore increase lithium plasma levels. If necessary, monitor blood lithium closely and adjust the lithium dosage while the combination is being taken and when the NSAID is withdrawn.

**Methotrexate:** Two studies investigated the effects of Etoricoxib Tablets 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 Tablets at 60 and 90 mg had no effect on methotrexate plasma concentrations or renal clearance. In one study, Etoricoxib Tablets 120 mg had no effect, but in the other study, Etoricoxib Tablets 120 mg increased methotrexate plasma concentrations by 28% and reduced renal clearance of methotrexate by 13%. Adequate monitoring for methotrexate-related toxicity is recommended when Etoricoxib Tablets and methotrexate are administered concomitantly.

*Oral contraceptives:* Etoricoxib Tablets 60 mg given concomitantly with an oral contraceptive containing 35 micrograms ethinyl estradiol (EE) and 0.5 to 1 mg norethindrone for 21 days increased the steady state AUC<sub>0-24hr</sub> of EE by 37%. Etoricoxib Tablets 120 mg given with the same oral contraceptive concomitantly or separated by 12 hours, increased the steady state AUC<sub>0-24hr</sub> of EE by 50 to 60%. This increase in EE concentration should be considered when selecting an 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 (HRT):* Administration of Etoricoxib Tablets 120 mg with hormone replacement therapy consisting of conjugated estrogens (0.625 mg PREMARIN<sup>TM</sup>) for 28 days, increased the mean steady state AUC<sub>0-24hr</sub> of unconjugated estrone (41%), equilin (76%), and 17- $\beta$ -estradiol (22%). The effect of the recommended chronic doses of Etoricoxib Tablets (30, 60, and 90 mg) has not been studied. The effects of Etoricoxib Tablets 120 mg on the exposure (AUC<sub>0-24hr</sub>) 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 Tablets because the increase in oestrogen exposure might increase the risk of adverse events associated with HRT.

*Prednisone/prednisolone:* In drug-interaction studies, Etoricoxib Tablets did not have clinically important effects on the pharmacokinetics of prednisone/prednisolone.

*Digoxin:* Etoricoxib tablets 120 mg administered once daily for 10 days to healthy volunteers did not alter the steady-state plasma AUC<sub>0-24hr</sub> or renal elimination of digoxin. There was an increase in digoxin C<sub>max</sub> (approximately 33%). This increase is not generally important for most patients. However, patients at high risk of digoxin toxicity should be monitored for this when Etoricoxib Tablets and digoxin are administered concomitantly.

#### *Effect of Etoricoxib Tablets on drugs metabolised by sulfotransferases*

Etoricoxib Tablets is an inhibitor of human sulfotransferase activity, particularly SULT1E1, and has been shown to increase the serum concentrations of ethinyl estradiol. While knowledge about effects of multiple sulfotransferases is presently limited and the clinical consequences for many drugs are still being examined, it may be prudent to exercise care when administering Etoricoxib Tablets concurrently with other drugs primarily metabolised by human sulfotransferases (e.g., oral salbutamol and minoxidil).

#### *Effect of Etoricoxib Tablets on drugs metabolised by CYP isoenzymes*

Based on *in vitro* studies, Etoricoxib Tablets is not expected to inhibit cytochromes P450 (CYP) 1A2, 2C9, 2C19, 2D6, 2E1 or 3A4. In a study in healthy subjects, daily

administration of Etoricoxib Tablets 120 mg did not alter hepatic CYP3A4 activity as assessed by the erythromycin breath test.

#### *Effects of other drugs on the pharmacokinetics of Etoricoxib Tablets*

The main pathway of Etoricoxib Tablets 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*.

**Ketoconazole:** Ketoconazole, a potent inhibitor of CYP3A4, dosed at 400 mg once a day for 11 days to healthy volunteers, did not have any clinically important effect on the single-dose pharmacokinetics of 60 mg Etoricoxib Tablets (43% increase in AUC).

**Voriconazole and Miconazole:** Co-administration of either oral voriconazole or topical miconazole oral gel, strong CYP3A4 inhibitors, with Etoricoxib Tablets 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 Tablets with rifampicin, a potent inducer of CYP enzymes, produced a 65% decrease in Etoricoxib Tablets plasma concentrations. This interaction may result in recurrence of symptoms when Etoricoxib Tablets is co-administered 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 (see section 4.2).

**Antacids:** Antacids do not affect the pharmacokinetics of Etoricoxib Tablets to a clinically relevant extent.

### **4.6 Pregnancy and Lactation\*:**

#### **Pregnancy**

No clinical data on exposed pregnancies are available for Etoricoxib Tablets. Studies in animals have shown reproductive toxicity (see section 5.3). The potential for human risk in pregnancy is unknown. Etoricoxib Tablets, as with other medicinal products inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus during the last trimester. Etoricoxib Tablets is contraindicated in pregnancy (see section 4.3). If a woman becomes pregnant during treatment, etoricoxib must be discontinued.

#### **Lactation**

It is not known whether Etoricoxib Tablets is excreted in human milk. Etoricoxib Tablets is excreted in the milk of lactating rats. Women who use etoricoxib must not breast feed (see sections 4.3 and 5.3).

### **Females and Males of Reproductive Potential**

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

### **4.7 Effects on ability to drive and use machine\*:**

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

### **4.8 Undesirable Effects\*:**

*Summary of the safety profile*

In clinical trials, Etoricoxib Tablets was evaluated for safety in 9,295 individuals, including 6,757 patients with OA, RA, chronic low back pain or ankylosing spondylitis (approximately 600 patients with OA or RA were treated for one year or longer).

In clinical studies, the undesirable effects profile was similar in patients with OA or RA treated with Etoricoxib Tablets for one year or longer.

In a clinical study for acute gouty arthritis, patients were treated with Etoricoxib Tablets 120 mg once daily for eight days. The adverse experience profile in this study was generally similar to that reported in the combined OA, RA, and chronic low back pain studies.

In a cardiovascular safety outcomes programme of pooled data from three active comparator-controlled trials, 17, 412 patients with OA or RA were treated with Etoricoxib Tablets (60 mg or 90 mg) for a mean duration of approximately 18 months. The safety data and details from this programme are presented in section 5.1.

In clinical studies for acute postoperative dental pain following surgery including 614 patients treated with Etoricoxib Tablets (90 mg or 120 mg), the adverse experience profile in these studies was generally similar to that reported in the combined OA, RA, and chronic low back pain studies.

#### *Tabulated list of adverse reactions*

The following undesirable effects were reported at an incidence greater than placebo in clinical trials in patients with OA, RA, chronic low back pain or ankylosing spondylitis treated with Etoricoxib Tablets 30 mg, 60 mg or 90 mg up to the recommended dose for up to 12 weeks; in the MEDAL Programme studies for up to 3½ years; in short term acute pain studies for up to 7 days; or in post-marketing experience (see Table 1):

**Table 1:**

| <b>System Organ Class</b>                   | <b>Adverse Reactions</b>                                                                    | <b>Frequency Category*</b> |
|---------------------------------------------|---------------------------------------------------------------------------------------------|----------------------------|
| <b>Infections and infestations</b>          | alveolar osteitis                                                                           | Common                     |
|                                             | gastroenteritis, upper respiratory infection, urinary tract infection                       | Uncommon                   |
| <b>Blood and lymphatic system disorders</b> | anaemia (primarily associated with gastrointestinal bleeding), leukopenia, thrombocytopenia | Uncommon                   |
| <b>Immune system disorders</b>              | hypersensitivity <sup>‡</sup> <sup>§</sup>                                                  | Uncommon                   |
|                                             | angioedema/anaphylactic reactions including shock <sup>‡</sup> /anaphylactoid               | Rare                       |
| <b>Metabolism and nutrition disorders</b>   | oedema/fluid retention                                                                      | Common                     |
|                                             | appetite increase or decrease, weight gain                                                  | Uncommon                   |
| <b>Psychiatric disorders</b>                | anxiety, depression, mental acuity decreased, hallucinations <sup>‡</sup>                   | Uncommon                   |
|                                             | confusion <sup>‡</sup> , restlessness <sup>‡</sup>                                          | Rare                       |
| <b>Nervous system disorders</b>             | dizziness, headache                                                                         | Common                     |
|                                             | dysgeusia, insomnia, paraesthesia/hypaesthesia, somnolence                                  | Uncommon                   |
| <b>Eye disorders</b>                        | blurred vision, conjunctivitis                                                              | Uncommon                   |
| <b>Ear and labyrinth disorders</b>          | tinnitus, vertigo                                                                           | Uncommon                   |

|                                                             |                                                                                                                                                                                                              |                   |
|-------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| <b>Cardiac disorders</b>                                    | palpitations, arrhythmia <sup>‡</sup>                                                                                                                                                                        | Common            |
|                                                             | atrial fibrillation, tachycardia <sup>‡</sup> , congestive heart failure, non-specific ECG changes, angina pectoris <sup>‡</sup> , myocardial infarction <sup>§</sup>                                        | Uncommon          |
| <b>Vascular disorders</b>                                   | Hypertension                                                                                                                                                                                                 | Common            |
|                                                             | flushing, cerebrovascular accident <sup>§</sup> , transient ischaemic attack, hypertensive crisis <sup>‡</sup> , vasculitis <sup>‡</sup>                                                                     | Uncommon          |
| <b>Respiratory, thoracic and mediastinal disorders</b>      | bronchospasm <sup>‡</sup>                                                                                                                                                                                    | Common            |
|                                                             | cough, dyspnoea, epistaxis                                                                                                                                                                                   | Uncommon          |
| <b>Gastrointestinal disorders</b>                           | abdominal pain                                                                                                                                                                                               | Very common       |
|                                                             | Constipation, flatulence, gastritis, heartburn/acid reflux, diarrhoea, dyspepsia/epigastric discomfort, nausea, vomiting, oesophagitis, oral ulcer                                                           | Common            |
|                                                             | abdominal distention, bowel movement pattern change, dry mouth, gastroduodenal ulcer, peptic ulcers including gastrointestinal perforation and bleeding, irritable bowel syndrome, pancreatitis <sup>‡</sup> | Uncommon          |
| <b>Hepatobiliary disorders</b>                              | ALT increased, AST increased                                                                                                                                                                                 | Common            |
|                                                             | hepatitis <sup>‡</sup>                                                                                                                                                                                       | Rare              |
|                                                             | hepatic failure <sup>‡</sup> , jaundice <sup>‡</sup>                                                                                                                                                         | Rare <sup>†</sup> |
| <b>Skin and subcutaneous tissue disorders</b>               | ecchymosis                                                                                                                                                                                                   | Common            |
|                                                             | facial oedema, pruritus, rash, erythema <sup>‡</sup> , urticaria <sup>‡</sup>                                                                                                                                | Uncommon          |
|                                                             | Stevens-Johnson syndrome <sup>‡</sup> , toxic epidermal necrolysis <sup>‡</sup> , fixed drug eruption <sup>‡</sup>                                                                                           | Rare <sup>†</sup> |
| <b>Musculoskeletal and connective tissue disorders</b>      | muscular cramp/spasm, musculoskeletal pain/stiffness                                                                                                                                                         | Uncommon          |
| <b>Renal and urinary disorders</b>                          | proteinuria, serum creatinine increased, renal failure/renal insufficiency <sup>‡</sup> (see section 4.4)                                                                                                    | Uncommon          |
| <b>General disorders and administration site conditions</b> | asthenia/fatigue, flu-like disease                                                                                                                                                                           | Common            |
|                                                             | chest pain                                                                                                                                                                                                   | Uncommon          |
| <b>Investigations</b>                                       | blood urea nitrogen increased, creatine phosphokinase increased, hyperkalaemia, uric acid increased                                                                                                          | Uncommon          |
|                                                             | blood sodium decreased                                                                                                                                                                                       | Rare              |

\*Frequency Category: Defined for each Adverse Experience Term by the incidence reported in the clinical trials data base: Very Common ( $\geq 1/10$ ), Common ( $\geq 1/100$  to  $< 1/10$ ), Uncommon ( $\geq 1/1000$  to  $< 1/100$ ), Rare ( $\geq 1/10,000$  to  $< 1/1000$ ), Very Rare ( $< 1/10,000$ ).

<sup>‡</sup>This adverse reaction was identified through post-marketing surveillance. Its reported frequency has been estimated based upon the highest frequency observed across clinical trial data pooled by indication and approved dose.

<sup>†</sup>The frequency category of "Rare" was defined per the Summary of Product Characteristics (SmPC) guidance (rev.2, Sept 2009) on the basis of an estimated upper bound of the 95% confidence interval for 0 events given the number of subjects treated with Etoricoxib Tablets in the analysis of the Phase III data pooled by dose and indication (n=15,470).

<sup>§</sup>Hypersensitivity includes the terms "allergy", "drug allergy", "drug hypersensitivity", "hypersensitivity", "hypersensitivity NOS", "hypersensitivity reaction" and nonspecific allergy".

<sup>§</sup>Based on analyses of long-term placebo and active controlled clinical trials, selective COX-2 inhibitors have been associated with an increased risk of serious thrombotic arterial events, including myocardial infarction and stroke. The absolute risk increase for such events is unlikely to exceed 1% per year based on existing data (uncommon).

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

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>.

#### **4.9 Overdose:**

In clinical studies, administration of single doses of Etoricoxib Tablets up to 500 mg and multiple doses up to 150 mg/day for 21 days did not result in significant toxicity. There have been reports of acute overdosage with Etoricoxib Tablets, 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 Tablets (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 Tablets is not dialyzable by haemodialysis; it is not known whether Etoricoxib Tablets is dialyzable by peritoneal dialysis.

### **5. Pharmacological properties:**

#### **5.1 Pharmacodynamic Properties:**

**Pharmacotherapeutic group:** *Anti-inflammatory and antirheumatic products, non-steroids, coxibs*

**ATC-code:** *M01AH05*

#### **Mechanism of Action**

Please note: Ajanta Pharma being a generic pharma company has not conducted clinical trials, all the clinical studies/trials data presented in this SPC is from published data.

Etoricoxib is an oral, selective cyclo-oxygenase-2 (COX-2) inhibitor within the clinical dose range.

Across clinical pharmacology studies, 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 Pharmacokinetics Properties\*:**

*Absorption*

Orally administered Etoricoxib Tablets is well absorbed. The absolute bioavailability is approximately 100%. Following 120 mg once-daily dosing to steady state, the peak plasma concentration (geometric mean C<sub>max</sub> = 3.6 µg/ml) was observed at approximately 1 hour (T<sub>max</sub>) after administration to fasted adults. The geometric mean area under the curve (AUC<sub>0-24hr</sub>) was 37.8 µg•hr/ml. The pharmacokinetics of Etoricoxib Tablets are linear across the clinical dose range.

Dosing with food (a high-fat meal) had no effect on the extent of absorption of Etoricoxib Tablets after administration of a 120-mg dose. The rate of absorption was affected, resulting in a 36% decrease in C<sub>max</sub> and an increase in T<sub>max</sub> by 2 hours. These data are not considered clinically significant. In clinical trials, Etoricoxib Tablets was administered without regard to food intake.

#### *Distribution*

Etoricoxib Tablets 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<sub>dss</sub>) was approximately 1,20l in humans.

Etoricoxib Tablets crosses the placenta in rats and rabbits, and the blood-brain barrier in rats.

#### *Biotransformation*

Etoricoxib Tablets 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 catalysed 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 Tablets 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*

Following administration of a single 25-mg radiolabelled intravenous dose of etoricoxib tablets 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 Tablets occurs almost exclusively through metabolism followed by renal excretion. Steady state concentrations Etoricoxib Tablets 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**

In preclinical studies, etoricoxib has been demonstrated not to be genotoxic. Etoricoxib tablets 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. Hepatocellular and thyroid follicular cell adenomas observed in rats are considered to be a consequence

of rat-specific mechanism related to hepatic CYP enzyme induction. Etoricoxib Tablets has not been shown to cause hepatic CYP3A enzyme induction in humans. In the rat, gastrointestinal toxicity of Etoricoxib Tablets increased with dose and exposure time. In the 14-week toxicity study Etoricoxib Tablets caused gastrointestinal ulcers at exposures greater than those seen in man at the therapeutic dose. In the 53- and 106-week toxicity study, gastrointestinal ulcers were also seen at exposures comparable to those seen in man at the therapeutic dose. In dogs, renal and gastrointestinal abnormalities were seen at high exposures.

Etoricoxib Tablets was not teratogenic in reproductive toxicity studies conducted in rats at 15 mg/kg/day (this represents approximately 1.5 times the daily human dose [90 mg] based on systemic exposure). In rabbits, a treatment related increase in cardiovascular malformations was observed at exposure levels below the clinical exposure at the daily human dose (90 mg). However, no treatment-related external or skeletal foetal malformations were observed. In rats and rabbits, there was a dose dependent increase in post implantation loss at exposures greater than or equal to 1.5 times the human exposure (see sections 4.3 and 4.6).

Etoricoxib Tablets is excreted in the milk of lactating rats at concentrations approximately two-fold those in plasma. There was a decrease in pup body weight following exposure of pups to milk from dams administered Etoricoxib Tablets during lactation.

*\* Data represented based on published literatures.*

## **6. Pharmaceutical particulars:**

### **6.1 List of Excipients:**

**For Ralef 60:** Anhydrous Dibasic Calcium Phosphate, Microcrystalline Cellulose, Povidone, Croscarmellose sodium (Ac-Di-Sol), Magnesium Stearate, Instacoat Aqua III A03R00286 (Green), Purified Water

**For 90:** Anhydrous Dibasic Calcium Phosphate, Microcrystalline, Cellulose, Povidone, Croscarmellose sodium (Ac-Di-Sol), Magnesium Stearate, Instacoat Aqua III A03R10311 White, Purified Water

**For Ralef 120:** Anhydrous Dibasic Calcium Phosphate, Microcrystalline Cellulose, Povidone, Croscarmellose sodium (Ac-Di-Sol), Magnesium Stearate, Instacoat Aqua III A03R00290 Green, Purified Water

### **6.2 Incompatibilities:**

Not applicable

### **6.3 Shelf life:**

24 months

### **6.4 Special Precautions for storage:**

Store below 30°C. Protect from moisture.

### **6.5 Nature and contents of container:**

7 tablets in Alu-Alu blister pack, 1 such blister in a printed carton along with Pack Insert.

### **6.6 Special precautions for disposal:**

Not applicable

**7. Marketing Authorization Holder:**

Ajanta Pharma Limited  
Ajanta Tower, 54-A, M VasANJI Road,  
Chakala, Andheri (E),  
Mumbai 400 093,  
India.

**Manufacturing Site Address:**

Ajanta Pharma Limited  
Plot no B-4/5/6, MIDC Area Paithan,  
Chhatrapati Sambhajanagar-431148  
Maharashtra, India.

**8. Marketing Authorization Numbers:**

H2021/CTD8501/18447

**9. Date of first registration /renewal of the registration:**

Sep 01, 2021

**10. Date of revision of text:**

Mar 19, 2026