

SUMMARY OF PRODUCT CHARACTERISTICS
(Product Data Sheet)

1.	Name of the Medical Product
	1. Product Name: RALEF 60 (Etoricoxib Tablets 60mg) RALEF 90 (Etoricoxib Tablets 90mg) RALEF 120 (Etoricoxib Tablets 120mg)
	1.2 Strength : Etoricoxib 60 mg Etoricoxib 90mg Etoricoxib 120mg
2.	Pharmaceutical Dosage Form : Tablets

2. Qualitative & Quantitative Composition:

RALEF 60

No.	Ingredients	Sr.	Theoretical Quantity per tablet (mg)	Reason for inclusion
1	Etoricoxib IH	60.000	Active ingredient	
Excipient for Granulation				
2	Anhydrous Dibasic Calcium Phosphate USP (A-TAB)	20.00	Diluent	
3	Microcrystalline Cellulose BP (Avicel PH 101)	107.00	Diluent	
4	Croscarmellose sodium BP (Ac-Di-Sol)	3.750	Disintegrant	
5	Povidone BP (Kollidone 30)	2.500	Binder	
6	Purified Water	q.s	Solvent	
Excipients for Lubrication				
7	Croscarmellose sodium BP (Ac-Di-Sol)	3.750	Disintegrant	
8	Magnesium Stearate BP	3.000	Lubricant	
Excipients for Coating				
9	Instacoat Aqua III IH A03R00286 (Green)	6.000	Coating material	
10	Purified Water #	q.s	Solvent	

RALEF 90

No.	Ingredients	Sr.	Theoretical Quantity per tablet (mg)	Reason for inclusion
Active ingredient				
1	Etoricoxib IH	90.000	Active ingredient	
Excipient for Granulation				
2	Anhydrous Dibasic Calcium Phosphate USP (A-TAB)	30.000	Diluent	
3	Microcrystalline Cellulose BP (Avicel PH 101)	160.500	Diluent	
4	Croscarmellose sodium BP (Ac-Di-Sol)	5.620	Disintegrant	
5	Povidone BP (Kollidone 30)	3.750	Binder	
6	Purified Water	q.s	Solvent	
Excipients for Lubrication				
7	Croscarmellose sodium BP (Ac-Di-Sol)	5.630	Disintegrant	
8	Magnesium Stearate BP	4.500	Lubricant	
Excipients for Coating				
9	Instacoat Aqua III IH A03R10311 (White)	9.000	Coating material	
10	Purified Water #	q.s	Solvent	

RALEF 120

<p>3.</p>	<p>Pharmaceutical Form:</p> <p>RALEF 60 Light green to green coloured, circular, biconvex, film coated tablets, plain on both sides.</p> <p>RALEF 90 White coloured, circular, biconvex, film coated tablets, plain on both sides.</p> <p>RALEF 120 Pale green coloured, circular, biconvex, film coated tablets, plain on both sides.</p>
<p>4.</p>	<p>Clinical Particulars</p> <p>4.1 Therapeutic Indications:</p> <p>RALEF 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 signs of inflammation associated with acute gouty arthritis.</p> <p>RALEF is indicated in adults and adolescents 16 years of age and older for the symptomatic treatment of moderate pain associated with dental surgery.</p> <p>The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks.</p>

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 should be re-evaluated periodically 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 of 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 of 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 of 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 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 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 RALEF 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 of 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

4.3 Contraindications:

- ❖ Hypersensitivity to the active substance or to any of the excipients.
- ❖ Active peptic ulceration or active gastro-intestinal (GI) bleeding.
- ❖ Patients who, after taking acetylsalicylic acid or NSAIDs including (cyclooxygenase-2) inhibitors, experience bronchospasm, acute rhinitis, nasal angioneurotic oedema, urticaria, or allergic-type reactions.
- ❖ Pregnancy and lactation.
- ❖ Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score \geq 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 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 resulting in fatal outcome, have occurred in patients treated with etoricoxib.

Caution is advised with treatment of patients most at risk of developing a gastro 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 ulcer or GI bleeding.

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

Cardiovascular effects

Clinical trials suggest that the selective COX-2 inhibitor class of drugs may be associated with an increased risk of thrombotic events (especially myocardial infarction (MI) and stroke), relative to some NSAIDs. As the cardiovascular risks of etoricoxib may increase with 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 evaluated periodically, especially in patients with osteoarthritis.

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

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 may 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 Non-steroidal Anti-inflammatory Drugs (NSAIDs), including etoricoxib, can be associated with new-onset or recurrent congestive heart failure. For information regarding a dose related response to etoricoxib. Caution should be exercised in patients with a history of cardiac failure, ventricular dysfunction, or hypertension and in patients with pre-existing oedema for 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.

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 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 of therapy with etoricoxib is initiated or the dose of etoricoxib is changed.

Diuretics, ACE inhibitors and Angiotensin II Antagonists: NSAIDs may reduce the effectiveness 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 concomitant administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclooxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients receiving etoricoxib concomitantly with ACE inhibitors or angiotensin II antagonists. This 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 at the initiation of concomitant therapy, and periodically thereafter.

Acetylsalicylic Acid: In a study in healthy subjects, at steady state, etoricoxib 120 mg daily had no effect on the anti-platelet activity of acetylsalicylic acid (81 mg once daily). Etoricoxib can be used concomitantly with acetylsalicylic acid at doses used for cardiovascular prophylaxis (low-dose acetylsalicylic acid). However, concomitant administration of etoricoxib with acetylsalicylic acid may result in an increased rate of GI ulceration and other complications compared to use of etoricoxib alone. Concomitant administration of etoricoxib with doses of acetylsalicylic acid above those for cardiovascular prophylaxis or with other NSAIDs is not recommended.

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

Pharmacokinetic interactions

The effect of etoricoxib 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 60, 90 or 120 mg administered once daily for seven days in patients receiving once-weekly methotrexate doses of 7.5 mg for rheumatoid arthritis. Etoricoxib at 60 and 90 mg had no effect on methotrexate

4.6 Pregnancy and Lactation:**Pregnancy**

No clinical data on exposed pregnancies are available for etoricoxib. The potential for risk in pregnancy is unknown. Etoricoxib, as with other medicinal products that inhibit prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus during the last trimester. Etoricoxib is contraindicated in pregnancy. If a woman becomes pregnant during treatment, etoricoxib must be discontinued.

Lactation

It is not known whether etoricoxib is excreted in human milk. Women who use etoricoxib should not breast feed.

4.7 Effects on ability to drive and use machine:

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

4.8 Undesirable Effects:

The following undesirable effects were reported at an incidence greater than placebo in trials in patients with OA, RA, chronic low back pain or ankylosing spondylitis treated with etoricoxib 60 mg or 90 mg up to the recommended dose for up to 12 weeks.

System Organ Class Adverse Reactions Frequency Category*

Infections and infestations	alveolar osteitis	Common
	gastroenteritis, upper respiratory infection, urinary tract infection	Uncommon
Blood and lymphatic system disorders	anaemia (primarily associated with gastro-bleeding), leukopenia, thrombocytopenia	Uncommon
Immune system disorders	hypersensitivity [‡] ^β	Uncommon
	angioedema/anaphylactic /anaphylactoid reactions including shock [‡]	Rare
Metabolism and nutrition disorders	oedema/fluid retention	Common
	appetite increase or decrease, weight gain	Uncommon
Psychiatric disorders	anxiety, depression, mental acuity decreased, hallucinations	Uncommon
	confusion [‡] , restlessness [‡]	Rare
Nervous system disorders	dizziness, headache	Common
	dysgeusia, insomnia, paresthaesia/hypaesthesia, somnolence	Uncommon
Eye disorders	blurred vision, conjunctivitis	Uncommon
Ear and labyrinth disorder	tinnitus, vertigo	Uncommon
Cardiac disorders	palpitations, arrhythmia [‡]	Common
	atrial fibrillation, tachycardia [‡] , congestive heart failure, non-specific ECG angina pectoris [‡] , myocardial infarction [§]	Uncommon
Vascular disorders	hypertension	Common
	flushing, cerebrovascular accident [§] , transient ischaemic attack, hypercalcaemia [‡] , vasculitis [‡]	Uncommon
Respiratory, thoracic and mediastinal disorders	bronchospasm [‡]	Common
	cough, dyspnoea, epistaxis	Uncommon
Gastrointestinal disorders	abdominal pain	Very common
	Constipation, flatulence, gastritis, heartburn/acid reflux, diarrhea, dyspepsia/epididymitis, discomfort, nausea, vomiting, oesophagitis, oral ulcer	Common
	abdominal distention, bowel movement pattern change, dry mouth, gastro-ulcer, peptic ulcers including gastrointestinal perforation and bleeding, irritable bowel syndrome, pancreatitis [‡]	Uncommon
Hepatobiliary disorders	ALT increased, AST increased	Common
	hepatitis [‡]	Rare
	hepatic failure [‡] , jaundice [‡]	Rare [†]
Skin and subcutaneous tissue disorders	ecchymosis	Common
	facial oedema, pruritus, rash, erythema [‡] , urticaria [‡]	Uncommon
	Stevens-Johnson syndrome [‡] , toxic epidermal necrolysis [‡] , fixed drug eruption [‡]	
Musculoskeletal and connective tissue disorders	muscular cramp/spasm, muscular pain/stiffness	Uncommon
Renal and urinary disorders	proteinuria, serum creatinine increased, renal failure	Uncommon
General disorders and administration site conditions	asthenia/fatigue, flu-like disorders	Common

4.9 Overdosage:

In clinical studies, administration of single doses of etoricoxib up to 500 mg and multiple doses up to 150 mg/day for 21 days did not result in significant toxicity. There have been no reports of acute overdosage with etoricoxib, although adverse experiences were not reported in the majority of cases. The most frequently observed adverse experiences were consistent with the safety profile for etoricoxib (e.g. gastrointestinal events, cardiorenal events).

In the event of overdose, it is reasonable to employ the usual supportive measures, e.g. to 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 Pharmacodynamic Properties:

Mechanism of Action

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

Across clinical pharmacology studies, RALEF produced dose-dependent inhibition of COX-2 without inhibition of COX-1 at doses up to 150 mg daily. Etoricoxib did not inhibit 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). COX-2 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 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_{max} = 3.6 $\mu\text{g/ml}$) was observed at approximately 1 hour (T_{max}) after administration to fasted adults. The geometric mean area under the curve (AUC_{0-24}) was 37.8 $\mu\text{g}\cdot\text{hr/ml}$. The pharmacokinetics of etoricoxib are linear across the clinical dose range. 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 decrease in C_{max} and an increase in T_{max} by 2 hours. These data are not considered clinically significant. In clinical trials, etoricoxib was administered without regard to food intake.

Distribution

Etoricoxib is approximately 92% bound to human plasma protein over the therapeutic concentrations of 0.05 to 5 $\mu\text{g/ml}$. The volume of distribution at steady state (V_{ss}) is approximately 1,200 l in humans.

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

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 CYP3A4 enzymes. CYP3A4 appears to contribute to the metabolism of etoricoxib in vivo. Other studies indicate that CYP2D6, CYP2C9, CYP1A2 and CYP2C19 also can catalyse the 6'-hydroxymethyl 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'-carboxymethyl derivative of etoricoxib formed by further oxidation of the 6'-hydroxymethyl derivative. The other principal metabolites either demonstrate no measurable activity or are only weakly active COX-2 inhibitors. None of these metabolites inhibit COX-1.

Elimination

Following administration of a single 25-mg radiolabeled intravenous dose of etoricoxib to healthy subjects, 70% of radioactivity was recovered in urine and 20% in faeces, as parent drug and metabolites. Less than 2% was recovered as unchanged drug.

Elimination of etoricoxib occurs almost exclusively through metabolism followed by renal excretion. Steady state concentrations of etoricoxib are reached within seven days of oral 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.

<p>6. Pharmaceutical particulars</p>	<p>6.1 List of Excipients:</p> <p>RALEF 60 Anhydrous Dibasic Calcium Phosphate USP (A-TAB), Microcrystalline Cellulose BP (PH 101), Croscarmellose sodium BP (Ac-Di-Sol), Povidone BP (Kollidone 30), Purified Magnesium Stearate BP, Instacoat Aqua III IH A03R00286 (Green).</p> <p>RALEF 90 Anhydrous Dibasic Calcium Phosphate USP (A-TAB), Microcrystalline Cellulose BP (PH 101), Croscarmellose sodium BP (Ac-Di-Sol), Povidone BP (Kollidone 30), Purified Magnesium Stearate BP, Instacoat Aqua III IH A03R10311 (White)</p> <p>RALEF 120 Anhydrous Dibasic Calcium Phosphate USP (A-TAB), Microcrystalline Cellulose BP (PH 101), Croscarmellose sodium BP (Ac-Di-Sol), Povidone BP (Kollidone 30), Purified Magnesium Stearate BP, Instacoat Aqua III IH A03R00290 (Green).</p>
	<p>6.2 Incompatibilities: Not applicable</p>
	<p>6.3 Shelf life: 24 months from the date of manufacturer</p>
	<p>6.4 Special Precautions for storage: Store below 30°C. Protect from moisture</p>
	<p>6.5 Nature and contents of container:</p> <p>RALEF 60 The tablets are provided in Alu-Alu blister. Each blister contains 7 tablets and it is packed in a carton along with pack insert.</p> <p>RALEF 90 The tablets are provided in Alu-Alu blister. Each blister contains 7 tablets and it is packed in a carton along with pack insert.</p> <p>RALEF 120 The tablets are provided in Alu-Alu blister. Each blister contains 7 tablets and it is packed in a carton along with pack insert.</p>
	<p>6.6 Special precautions for disposal of a used medicinal product or waste materials from such medicinal product, if appropriate: Not applicable</p>

7.	Registration Certificate Holder: Ajanta Pharma Ltd. Ajanta House, Charkop Kandivli (West) Mumbai - 400 067 India. Tel : +91-22-6606 1000 Fax : +91-22-6606 1200 Email : info@ajantapharma.com
8.	Registration certificate number(s): TAN 22 HM 0172
9.	Date of first registration/ re-registration: 04 th May, 2022
10.	Date of revision of the SPC's text: