SUMMARY OF PRODUCT CHARACTERISTICS
(Product Data Sheet)

1. Name of the Medical Product

1.1 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

1.2 Pharmaceutical Dosage Form : Tablets

2. Qualitative & Quantitative Composition:

RALEF 60

Sr. No.	Ingredients	Theoretical Quantity per tablet (mg)	Reason for inclusion
	Active ingredient		
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

Sr. No.	Ingredients	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

Sr. No.	Ingredients	Theoretical Quantity per tablet (mg)	Reason for inclusion
	Active ingredient		
1	Etoricoxib IH	120.000	Active ingredient
	Excipient for Granulation		
2	Anhydrous Dibasic Calcium Phosphate USP (A-TAB)	40.000	Diluent
3	Microcrystalline Cellulose BP (Avicel PH 101)	214.500	Diluent
4	Croscarmellose sodium BP (Ac-Di-Sol)	7.500	Disintegrant
5	Povidone BP (Kollidone 30)	5.000	Binder
6	Purified Water	q.s	Solvent
	Excipients for Lubrication		
7	Croscarmellose sodium BP (Ac-Di-Sol)	7.500	Disintegrant
8	Magnesium Stearate BP	6.000	Lubricant
	Excipients for Coating		
9	Instacoat Aqua III IH A03R00290 (Green)	12.000	Coating material
10	Purified Water #	q.s	Solvent

	# Purified water confirms to the specification of IP/BP/USP/Ph.Eur./IH BP : British Pharmacopoeia IH : In-house specification. USP : United States Pharmacopeia Ph.Eur. : European Pharmacopoeia IH : In-house specification
3.	**Pharmaceutical Form:** 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: 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 pain and signs of inflammation associated with acute gouty arthritis. RALEF 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 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 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 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.
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 ≥10); therefore, its use is contra-indicated in these patients.

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
RALEF is administered orally and may be taken with or without food. The onset of the effect of the medicinal product may be faster when RALEF 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.
- ❖ 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 (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.

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 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.

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 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.

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 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, can be associated with new onset or recurrent congestive heart failure. For information regarding a dose related response for etoricoxib. 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 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 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
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 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 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 therapy should be considered. 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.

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. 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. 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 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. RALEF 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 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 is initiated or the dose of etoricoxib is changed.

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 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 120 mg once 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 low-dose acetylsalicylic acid with etoricoxib may result in an increased rate of GI ulceration or 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, coadministration 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 to 20 mg for rheumatoid arthritis. Etoricoxib at 60 and 90 mg had no effect on methotrexate plasma concentrations or renal clearance. In one study, etoricoxib 120 mg had no effect, but in the other study, etoricoxib 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 and methotrexate are administered concomitantly.

Oral contraceptives: Etoricoxib 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 AUC0-24hr of EE by 37%. Etoricoxib 120 mg given with the same oral contraceptive concomitantly or separated by 12 hours, increased the steady state AUC0-24hr 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 120 mg with hormone replacement therapy consisting of conjugated estrogens (0.625 mg PREMARINTM) for 28 days, increased the mean steady state AUC0-24hr of unconjugated estrone (41%), equilin (76%), and 17-β-estradiol (22%). 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.

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

Digoxin: Etoricoxib 120 mg administered once daily for 10 days to healthy volunteers did not alter the steady-state plasma AUC0-24hr or renal elimination of digoxin. There was an increase in digoxin Cmax (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 and digoxin are administered concomitantly.

Effect of etoricoxib on drugs metabolised by sulfotransferases
Etoricoxib 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 concurrently with other drugs primarily metabolised by human sulfotransferases (e.g., oral salbutamol and minoxidil).

Effect of etoricoxib on drugs metabolised by CYP isoenzymes
Based on in vitro studies, etoricoxib 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 120 mg did not alter hepatic CYP3A4 activity as assessed by the erythromycin breath test.

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.

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 (43% increase in AUC).

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 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.

Antacids: Antacids do not affect the pharmacokinetics of etoricoxib to a clinically re

4.6 Pregnancy and Lactation:

Pregnancy

No clinical data on exposed pregnancies are available for etoricoxib. The potential for human risk in pregnancy is unknown. Etoricoxib, as with other medicinal products inhibiting 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 must 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 clinical 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 gastrointestinal bleeding), leukopenia, thrombocytopenia	Uncommon
Immune system disorders	hypersensitivity‡ ß	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 disorders	tinnitus, vertigo	Uncommon
Cardiac disorders	palpitations, arrhythmia‡	Common
	atrial fibrillation, tachycardia‡, congestive heart failure, non-specific ECG changes, angina pectoris‡, myocardial infarction§	Uncommon
Vascular disorders	hypertension	Common
	flushing, cerebrovascular accident§, transient ischaemic attack, hypertensive crisis‡, 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/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‡	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‡	Rare†
Musculoskeletal and connective tissue disorders	muscular cramp/spasm, musculoskeletal pain/stiffness	Uncommon
Renal and urinary disorders	proteinuria, serum creatinine increased, renal failure/renal insufficiency	Uncommon
General disorders and administration site conditions	asthenia/fatigue, flu-like disease	Common
	chest pain	Uncommon
Investigations	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 (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1000 to <1/100), Rare (≥1/10,000 to <1/1000), Very Rare (<1/10,000).

‡ 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.

†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 RALEF in the analysis of the Phase III data pooled by dose and indication (n=15,470).

ß Hypersensitivity includes the terms "allergy", "drug allergy", "drug hypersensitivity", "hypersensitivity", "hypersensitivity NOS", "hypersensitivity reaction" and "nonspecific allergy".

§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).

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 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., 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 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 is well absorbed. The absolute bioavailability is approximately 100%. Following 120 mg once-daily dosing to steady state, the peak plasma concentration (geometric mean Cmax = 3.6 µg/ml) was observed at approximately 1 hour (Tmax) after administration to fasted adults. The geometric mean area under the curve (AUC0-24hr) was 37.8 µg•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 36% decrease in Cmax and an increase in Tmax 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 range of concentrations of 0.05 to 5 µg/ml. The volume of distribution at steady state (Vdss) was approximately 1,20l 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 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 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, mostly as 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 once daily administration of 120 mg, with an accumulation ratio of approximately 2, corresponding to a half-life of approximately 22 hours. The plasma clearance after a 25-mg intravenous dose is estimated to be approximately 50 ml/min. Characteristics in patients Elderly patients: Pharmacokinetics in the elderly (65 years of age and older) are similar to those in the young. Gender: The pharmacokinetics of etoricoxib are similar between men and women. Hepatic impairment: Patients with mild hepatic dysfunction (Child-Pugh score 5-6) administered etoricoxib 60 mg once daily had an approximately 16% higher mean AUC as compared to healthy subjects given the same regimen. Patients with moderate hepatic dysfunction (Child-Pugh score 7-9) administered etoricoxib 60 mg every other day had similar mean AUC to the healthy subjects given etoricoxib 60 mg once daily; etoricoxib 30 mg once daily has not been studied in this population. There are no clinical or pharmacokinetic data in patients with severe hepatic dysfunction (Child-Pugh score ≥10). Renal impairment: The pharmacokinetics of a single dose of etoricoxib 120 mg in patients with moderate to severe renal insufficiency and patients with end-stage renal disease on haemodialysis were not significantly different from those in healthy subjects. Haemodialysis contributed negligibly to elimination (dialysis clearance approximately 50 ml/min). Paediatric patients: The pharmacokinetics of etoricoxib in paediatric patients (<12 years old) have not been studied. In a pharmacokinetic study (n=16) conducted in adolescents (aged 12 to 17) the pharmacokinetics in adolescents weighing 40 to 60 kg given etoricoxib 60 mg once daily and adolescents >60 kg given etoricoxib 90 mg once daily were similar to the pharmacokinetics in adults given etoricoxib 90 mg once daily. Safety and effectiveness of etoricoxib in paediatric patients have not been established.
6.	**Pharmaceutical particulars**
	6.1 List of Excipients: **RALEF 60** Anhydrous Dibasic Calcium Phosphate USP (A-TAB), Microcrystalline Cellulose BP (Avicel PH 101)**,** Croscarmellose sodium BP (Ac-Di-Sol)**,** Povidone BP (Kollidone 30), Purified Water, Magnesium Stearate BP, Instacoat Aqua III IH A03R00286 (Green). **RALEF 90** Anhydrous Dibasic Calcium Phosphate USP (A-TAB), Microcrystalline Cellulose BP (Avicel PH 101)**,** Croscarmellose sodium BP (Ac-Di-Sol)**,** Povidone BP (Kollidone 30), Purified Water, Magnesium Stearate BP, Instacoat Aqua III IH A03R10311 (White) **RALEF 120** Anhydrous Dibasic Calcium Phosphate USP (A-TAB), Microcrystalline Cellulose BP (Avicel PH 101)**,** Croscarmellose sodium BP (Ac-Di-Sol)**,** Povidone BP (Kollidone 30), Purified Water,

	Magnesium Stearate BP, Instacoat Aqua III IH A03R00290 (Green).
	6.2 Incompatibilities: Not applicable
	6.3 Shelf life: 24 months from the date of manufacturer
	6.4 Special Precautions for storage: Store below 30°C. Protect from moisture
	6.5 Nature and contents of container: **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. **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. **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.
	6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product, if appropriate : Not applicable
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) :** Not Applicable
9.	**Date of first registration/ re-registration:** Not Applicable
10.	**Date of revision of the SPC's text :** Not applicable