**SUMMARY OF PRODUCT CHARACTERISTICS**
**(Product Data Sheet)**

| | |
|---|---|
| **1.** | **Name of the Medical Product** |
| | **1. Product Name: RALEF 60**<br>**(Etoricoxib Tablets 60mg)**<br><br>**RALEF 90**<br>**(Etoricoxib Tablets 90mg)**<br><br>**RALEF 120**<br>**(Etoricoxib Tablets 120mg)** |
| | **1.2 Strength :** Etoricoxib 60 mg<br>Etoricoxib 90mg<br>Etoricoxib 120mg |
| | 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**

| | |
|---|---|
| **3.** | **Pharmaceutical Form:**<br>RALEF 60<br>Light green to green coloured, circular, biconvex, film coated tablets, plain on both side<br><br>RALEF 90<br>White coloured, circular, biconvex, film coated tablets, plain on both sides.<br><br>RALEF 120<br>Pale green coloured, circular, biconvex, film coated tablets, plain on both sides. |
| **4.** | **Clinical Particulars** |
| | **4.1 Therapeutic Indications:**<br>RALEF is indicated in adults and adolescents 16 years of age and older for the sym relief of osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis, and the signs of inflammation associated with acute gouty arthritis.<br><br>RALEF is indicated in adults and adolescents 16 years of age and older for the sl treatment of moderate pain associated with dental surgery.<br>The decision to prescribe a selective COX-2 inhibitor should be based on an assessme 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 expo
shortest duration possible and the lowest effective daily dose should be used. The patie
for symptomatic relief and response to therapy should be re-evaluated periodically, esp
patients with osteoarthritis.

Osteoarthritis

The recommended dose is 30 mg once daily. In some patients with insufficient re
symptoms, an increased dose of 60 mg once daily may increase efficacy. In the abse
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 re
symptoms, an increased dose of 90 mg once daily may increase efficacy. Once the
clinically stabilised, down-titration to a 60 mg once daily dose may be appropriat
absence of an increase in therapeutic benefit, other therapeutic options should be consid

Ankylosing spondylitis

The recommended dose is 60 mg once daily. In some patients with insufficient re
symptoms, an increased dose of 90 mg once daily may increase efficacy. Once the
clinically stabilised, down-titration to a 60 mg once daily dose may be appropriat
absence of an increase in therapeutic benefit, other therapeutic options should be consid

Acute pain conditions

For acute pain conditions, etoricoxib should be used only for the acute symptomatic per

Acute gouty arthritis

The recommended dose is 120 mg once daily. In clinical trials for acute gouty
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
may require other postoperative analgesia in addition to RALEF during the three day t
period.

Doses greater than those recommended for each indication have either not dem
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 o
treatment.

The dose for postoperative acute dental surgery pain should not exceed 90 mg daily, lin
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 ≥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 abov mmHg and has not been adequately controlled.
- Established ischaemic heart disease, peripheral arterial disease, and/or cerebr 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 acetylsalic concomitantly or patients with a prior history of gastrointestinal disease, such as ulcer GI bleeding.
There is a further increase in the risk of gastrointestinal adverse effects (gastro ulceration or other gastrointestinal complications) when etoricoxib is taken concomita acetylsalicylic acid (even at low doses). A significant difference in GI safety between COX-2 inhibitors + acetylsalicylic acid vs. NSAIDs + acetylsalicylic acid has demonstrated in long-term clinical trials.

Cardiovascular effects
Clinical trials suggest that the selective COX-2 inhibitor class of drugs may be associat risk of thrombotic events (especially myocardial infarction (MI) and stroke), relative to and some NSAIDs. As the cardiovascular risks of etoricoxib may increase with duration of exposure, the shortest duration possible and the lowest effective daily dos be used. The patient's need for symptomatic relief and response to therapy shoul evaluated periodically, especially in patients with osteoarthritis.
Patients with significant risk factors for cardiovascular events (e.g. hype hyperlipidaemia, diabetes mellitus, and smoking) should only be treated with etorico careful consideration.
COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for proph cardiovascular thrombo-embolic diseases because of their lack of antiplatelet effect. T antiplatelet therapies should not be discontinued.

Renal effects
Renal prostaglandins may play a compensatory role in the maintenance of renal p Therefore, under conditions of compromised renal perfusion, administration of etoric cause a reduction in prostaglandin formation and, secondarily, in renal blood flow, an impair renal function. Patients at greatest risk of this response are those with pre significantly impaired renal function, uncompensated heart failure, or cirrhosis. Moni renal function in such patients should be considered.

Fluid retention, oedema and hypertension
As with other medicinal products known to inhibit prostaglandin synthesis, fluid oedema and hypertension have been observed in patients taking etoricoxib. All Non Anti-inflammatory Drugs (NSAIDs), including etoricoxib, can be associated with new recurrent congestive heart failure. For information regarding a dose related resp etoricoxib. Caution should be exercised in patients with a history of cardiac fai ventricular dysfunction, or hypertension and in patients with pre-existing oedema other reason. If there is clinical evidence of deterioration in the condition of these 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 administ etoricoxib 120 mg daily was associated with an approximate 13% increase in prothrom International Normalised Ratio (INR). Therefore, patients receiving oral anticoagulan be closely monitored for their prothrombin time INR, particularly in the first few da therapy with etoricoxib is initiated or the dose of etoricoxib is changed.

Diuretics, ACE inhibitors and Angiotensin II Antagonists: NSAIDs may reduce the diuretics and other antihypertensive drugs. In some patients with compromised renal (e.g. dehydrated patients or elderly patients with compromised renal function) administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhib oxygenase may result in further deterioration of renal function, including possible ac failure, which is usually reversible. These interactions should be considered in patien etoricoxib concomitantly with ACE inhibitors or angiotensin II antagonists. There combination should be administered with caution, especially in the elderly. Patients s adequately hydrated and consideration should be given to monitoring of renal funct initiation of concomitant therapy, and periodically thereafter.

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

Cyclosporin and tacrolimus: Although this interaction has not been studied with et coadministration of cyclosporin or tacrolimus with any NSAID may increase the nep effect of cyclosporin or tacrolimus. Renal function should be monitored when etoric 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 plasm If necessary, monitor blood lithium closely and adjust the lithium dosage while the con is being taken and when the NSAID is withdrawn.

Methotrexate: Two studies investigated the effects of etoricoxib 60, 90 or 120 mg adm once daily for seven days in patients receiving once-weekly methotrexate doses of 7.5 for rheumatoid arthritis. Etoricoxib at 60 and 90 mg had no effect on methotrexat

**4.6 Pregnancy and Lactation:**

**Pregnancy**

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

**Lactation**

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

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

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

**4.8 Undesirable Effects:**

The following undesirable effects were reported at an incidence greater than placebo i trials in patients with OA, RA, chronic low back pain or ankylosing spondylitis trea 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‡ 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, hallucinatio | 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 angina pectoris‡, myocardial infarction§ | Uncommon |
| **Vascular disorders** | hypertension | Common |
| | flushing, cerebrovascular accident§, transient ischaemic attack, hype 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/e discomfort, nausea, vomiting, oesophagitis, oral ulcer | Common |
| | abdominal distention, bowel movement pattern change, dry mouth, gastro ulcer, peptic ulcers including gastrointestinal perforation and bleeding, irritabl 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, muscul pain/stiffness | Uncommon |
| **Renal and urinary disorders** | proteinuria, serum creatinine increased, renal fail insufficiency | Uncommon |
| **General disorders and administration site conditions** | asthenia/fatigue, flu-like dis | Common |

| | |
|---|---|
| | **4.9 Overdosage:**<br>In clinical studies, administration of single doses of etoricoxib up to 500 mg and multi up to 150 mg/day for 21 days did not result in significant toxicity. There have been r acute overdosage with etoricoxib, although adverse experiences were not reporte majority of cases. The most frequently observed adverse experiences were consistent safety profile for etoricoxib (e.g. gastrointestinal events, cardiorenal events).<br><br>In the event of overdose, it is reasonable to employ the usual supportive measures, e.g. unabsorbed material from the GI tract, employ clinical monitoring, and institute su therapy, if required.<br><br>Etoricoxib is not dialysable by haemodialysis; it is not known whether etoricoxib is d by peritoneal dialysis. |
| **5.** | **Pharmacological properties** |
| | **5.1 Pharmacodynamic Properties:**<br>Mechanism of Action<br>Etoricoxib is an oral, selective cyclo-oxygenase-2 (COX-2) inhibitor within the clin range.<br>Across clinical pharmacology studies, RALEF produced dose-dependent inhibition o without inhibition of COX-1 at doses up to 150 mg daily. Etoricoxib did not inhib prostaglandin synthesis and had no effect on platelet function.<br><br>Cyclooxygenase is responsible for generation of prostaglandins. Two isoforms, CO COX-2, have been identified. COX-2 is the isoform of the enzyme that has been sho induced by pro-inflammatory stimuli and has been postulated to be primarily responsib synthesis of prostanoid mediators of pain, inflammation, and fever. COX-2 is also inv ovulation, implantation and closure of the ductus arteriosus, regulation of renal func central nervous system functions (fever induction, pain perception and cognitive fun may also play a role in ulcer healing. COX-2 has been identified in tissue around gast 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 appro
100%. Following 120 mg once-daily dosing to steady state, the peak plasma conc
(geometric mean Cmax = 3.6 µg/ml) was observed at approximately 1 hour (Tm
administration to fasted adults. The geometric mean area under the curve (AUC0-2
37.8 µg•hr/ml. The pharmacokinetics of etoricoxib are linear across the clinical dose ra
Dosing with food (a high-fat meal) had no effect on the extent of absorption of etoric
administration of a 120-mg dose. The rate of absorption was affected, resulting i
decrease in Cmax and an increase in Tmax by 2 hours. These data are not considered
significant. In clinical trials, etoricoxib was administered without regard to food intake.

Distribution

Etoricoxib is approximately 92% bound to human plasma protein over the
concentrations of 0.05 to 5 µg/ml. The volume of distribution at steady state (V
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 par
The major route of metabolism to form the 6'-hydroxymethyl derivative is catalyzed
enzymes. CYP3A4 appears to contribute to the metabolism of etoricoxib in vivo.
studies indicate that CYP2D6, CYP2C9, CYP1A2 and CYP2C19 also can catalyse
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'-carbox
derivative of etoricoxib formed by further oxidation of the 6'-hydroxymethyl derivativ
principal metabolites either demonstrate no measurable activity or are only weakly
COX-2 inhibitors. None of these metabolites inhibit COX-1.

Elimination

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

Elimination of etoricoxib occurs almost exclusively through metabolism followed
excretion. Steady state concentrations of etoricoxib are reached within seven days of o
administration of 120 mg, with an accumulation ratio of approximately 2, correspon
half-life of approximately 22 hours. The plasma clearance after a 25-mg intravenou
estimated to be approximately 50 ml/min.

Characteristics in patients

Elderly patients: Pharmacokinetics in the elderly (65 years of age and older) are simila
in the young.

| | |
|---|---|
| **6.** | **Pharmaceutical particulars** |
| | **6.1 List of Excipients:**<br>**RALEF 60**<br>Anhydrous Dibasic Calcium Phosphate USP (A-TAB), Microcrystalline Cellulose BP (A PH 101)**,** Croscarmellose sodium BP (Ac-Di-Sol)**,** Povidone BP (Kollidone 30), Purifie Magnesium Stearate BP, Instacoat Aqua III IH A03R00286 (Green).<br>**RALEF 90**<br>Anhydrous Dibasic Calcium Phosphate USP (A-TAB), Microcrystalline Cellulose BP (A PH 101)**,** Croscarmellose sodium BP (Ac-Di-Sol)**,** Povidone BP (Kollidone 30), Purifie Magnesium Stearate BP, Instacoat Aqua III IH A03R10311 (White)<br>**RALEF 120**<br>Anhydrous Dibasic Calcium Phosphate USP (A-TAB), Microcrystalline Cellulose BP (A PH 101)**,** Croscarmellose sodium BP (Ac-Di-Sol)**,** Povidone BP (Kollidone 30), Purifie 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:**<br>**RALEF 60**<br>The tablets are provided in Alu-Alu blister.<br>Each blister contains 7 tablets and it is packed in a carton along with pack insert.<br><br>**RALEF 90**<br>The tablets are provided in Alu-Alu blister.<br>Each blister contains 7 tablets and it is packed in a carton along with pack insert.<br><br>**RALEF 120**<br>The tablets are provided in Alu-Alu blister.<br>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 from such medicinal product, if appropriate :** Not applicable |

| | |
|---|---|
| **7.** | **Registration Certificate Holder:**<br>Ajanta Pharma Ltd.<br>Ajanta House, Charkop<br>Kandivli (West)<br>Mumbai - 400 067<br>India.<br>Tel : +91-22-6606 1000<br>Fax : +91-22-6606 1200<br>Email : info@ajantapharma.com |
| **8.** | **Registration certificate number(s): TAN 22 HM 0174** |
| **9.** | **Date of first registration/ re-registration:** 04th May 2022 |
| **10.** | **Date of revision of the SPC's text**: |