

Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

ETO MR -Etoricoxib 60mg and Thiocolchicoside 4mg tablets

2. Qualitative and quantitative composition

Each film coated tablet contains:

Etoricoxib 60 mg

Thiocolchicoside 4 mg

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Film-coated tablet

Yellow colour round shaped film coated tablet plain on both the sides.

4. Clinical particulars

4.1 Therapeutic indications

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

Etoricoxib is indicated in adults and adolescents 16 years of age and older for the short-term treatment of moderate pain associated with dental surgery.

Thiocolchicoside helps to reduce muscle spasm.

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 Etoricoxib during the three-day treatment period.

Doses greater than those recommended for each indication have either not demonstrated additional efficacy or have not been studied. Therefore, The dose for OA should not exceed 60 mg daily.

The dose for RA and ankylosing spondylitis should not exceed 90 mg daily.

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

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

Special populations

Elderly patients

No dosage adjustment is necessary for elderly patients. As with other drugs, caution should be exercised in elderly patients (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 ≥ 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 (see section 5.2). The use of ORICOX 120 in patients with creatinine clearance < 30 ml/min is contra-indicated.

Paediatric population

Etoricoxib is contraindicated in children and adolescents under 16 years of age.

Method of administration

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

Thiocolchicoside

Oral route: The recommended and maximal dose is 8 mg every 12 hours (i.e. 16 mg per day). The treatment duration is limited to 7 consecutive days. Intramuscular route: The recommended and maximal dose is 4 mg every 12 hours (i.e. 8 mg per day). The treatment duration is limited to 5 consecutive days.

Doses exceeding recommended doses or long-term use should be avoided (see Warnings). Not recommended for use in children below the age of 16 years

4.3 Contraindications

Hypersensitivity to Etoricoxib / Thiocolchicoside is a contraindication. In addition, Etoricoxib / Thiocolchicoside should not be used if you have the following conditions:

- Active peptic ulceration
- Allergic to Thiocolchicoside
- Breastfeeding
- Children and adolescents below 16 years
- Pregnant
- Severe congestive heart failure

4.4 Special warnings and precautions for use

Before using Etoricoxib / Thiocolchicoside, inform your doctor about your current list of medications, over the counter products (e.g. vitamins, herbal supplements, etc.), allergies, pre-existing diseases, and current health conditions (e.g. pregnancy, upcoming surgery, etc.). Some health conditions may make you more susceptible to the side-effects of the drug. Take as directed by your doctor or follow the direction printed on the product insert.

Dosage is based on your condition. Tell your doctor if your condition persists or worsens.

Important counseling points are listed below.

- Above 65 years of age
- Avoid driving or operating heavy machinery
- Avoid smoking
- Consult a doctor if you have allergic reactions
- Consult a doctor if you have an allergic disorders, coagulation defects, left ventricular dysfunction or hypertension
- Do not take for longer than what doctor instructed
- Limit alcoholic beverages
- May cause ulcers or bleeding
- May increase risk of heart attack and stroke
- Monitor blood pressure regularly

4.5 Interaction with other medicinal products and other forms of interaction

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 (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 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 (see sections 5.1 and 4.4.).

Ciclosporin and tacrolimus: Although this interaction has not been studied with etoricoxib, coadministration of ciclosporin or tacrolimus with any NSAID may increase the nephrotoxic effect of ciclosporin 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 AUC_{0-24hr} of EE by 37%. Etoricoxib 120 mg given with the same oral contraceptive concomitantly or separated by 12 hours, increased the steady state AUC_{0-24hr} 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 AUC_{0-24hr} of unconjugated estrone (41%), equilin (76%), and 17- β -estradiol (22%). The effect of the recommended chronic doses of etoricoxib (30, 60, and 90 mg) has not been studied. The effects of etoricoxib 120 mg on the exposure (AUC_{0-24hr}) 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 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 AUC_{0-24hr} or renal elimination of digoxin. There was an increase in digoxin C_{max} (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 ethinylestradiol. 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 relevant extent.

4.6 Fertility, pregnancy and Lactation

Pregnancy

No clinical data on exposed pregnancies are available for etoricoxib. Studies in animals have shown reproductive toxicity. 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.

Breastfeeding

It is not known whether etoricoxib is excreted in human milk. Etoricoxib is excreted in the milk of lactating rats. Women who use etoricoxib must not breast feed

Fertility

The use of etoricoxib, as with any drug substance known to inhibit COX2, is not recommended in women attempting to conceive.

Thiocolchicoside

Pregnancy and lactation the use of thiocolchicoside is contraindicated in pregnancy and in women of child bearing potential who are not using effective contraceptive. Contraindicated during breast feeding.

4.7 Effects on ability to drive and use machines

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

Thiocolchicoside

A vehicle or performing other hazardous tasks There is no data available on the effect on driving vehicles and using machines. Somnolence may occur commonly, and that has to be taken into account when driving vehicles and operating machines.

4.8 Undesirable effects

Summary of the safety profile

In clinical trials, etoricoxib was evaluated for safety in 9295 individuals, including 6757 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 for one year or longer.

In a clinical study for acute gouty arthritis, patients were treated with etoricoxib 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 (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 (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 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:

System Organ Class	Adverse Reactions	Frequency Category*
<i>Infections and infestations</i>	alveolar osteitis	Common
	gastroenteritis, upper respiratory infection, urinary tract infection	Uncommon
<i>Blood and lymphatic system disorders</i>	anaemia (primarily associated with gastrointestinal bleeding), leukopenia, thrombocytopenia	Uncommon
<i>Immune system disorders</i>	hypersensitivity [‡] [§]	Uncommon
	angioedema/anaphylactic/anaphylactoid reactions including shock [‡]	Rare
<i>Metabolism and nutrition disorders</i>	oedema/fluid retention	Common
	appetite increase or decrease, weight gain	Uncommon
<i>Psychiatric disorders</i>	anxiety, depression, mental acuity decreased, hallucinations [‡]	Uncommon
	confusion [‡] , restlessness [‡]	Rare

<i>Nervous system disorders</i>	dizziness, headache	Common
	dysgeusia, insomnia, paresthaesia/hypaesthesia, somnolence	Uncommon
<i>Eye disorders</i>	blurred vision, conjunctivitis	Uncommon
<i>Ear and labyrinth disorders</i>	tinnitus, vertigo	Uncommon
<i>Cardiac disorders</i>	palpitations, arrhythmia‡	Common
	atrial fibrillation, tachycardia‡, congestive heart failure, non-specific ECG changes, angina pectoris‡, myocardial infarction§	Uncommon
<i>Vascular disorders</i>	hypertension	Common
	flushing, cerebrovascular accident§, transient ischaemic attack, hypertensive crisis‡, vasculitis‡	Uncommon
<i>Respiratory, thoracic and mediastinal disorders</i>	bronchospasm‡	Common
	cough, dyspnoea, epistaxis	Uncommon
<i>Gastrointestinal disorders</i>	abdominal pain	Very common
	Constipation, flatulence, gastritis, heartburn/acid reflux, diarrhea, dyspepsia/epigastric discomfort, nausea, vomiting, oesophagitis, oral ulcer	Common
	abdominal distention, bowel	Uncommon
	movement pattern change, dry mouth, gastroduodenal ulcer, peptic ulcers including gastrointestinal perforation and bleeding, irritable bowel syndrome, pancreatitis‡	
<i>Hepatobiliary disorders</i>	ALT increased, AST increased	Common
	hepatitis‡	Rare
	hepatic failure‡, jaundice‡	Rare†
<i>Skin and subcutaneous tissue disorders</i>	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 [‡] (see section 4.4)	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 ($\geq 1/10$), Common ($\geq 1/100$ to $<1/10$), Uncommon ($\geq 1/1000$ to $<1/100$), Rare ($\geq 1/10,000$ to $<1/1000$), Very Rare ($<1/10,000$).

[‡] 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 Etoricoxib in the analysis of the Phase III data pooled by dose and indication (n=15,470).

[§] 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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Pharmacy and Poisons board Pharmacovigilance Electronic Reporting System (PvERS)

Website: <https://pv.pharmacyboardkenya.org>

4.9 Overdose

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

Pharmacotherapeutic group: NSIADS, Muscle relaxant

ATC code: Etoricoxib: M01AH05

Thiocolchicoside: M03BX05

Mechanism of Action

- Etoricoxib acts as NSAID & blocks site specific cyclooxygenase-2(COX-2) enzymes.
- By blocking Cox -2 enzymes, prostaglandins release is inhibited. Thereby, reduces pain & inflammation.
- Thiocolchicoside acts as muscle relaxant by inhibiting selective GABA A receptors (brain & spinal cord) therefore relieves muscle stiffness & act as potent muscle relaxant

5.2 Pharmacokinetic 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_{0-24hr}) 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 36% 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 range of concentrations of 0.05 to 5 µg/ml. The volume of distribution at steady state (V_{dss}) was approximately 120 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 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). (See sections 4.2 and 4.3.)

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). (See sections 4.3 and 4.4.)

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.

Thiocolchicoside

Absorption

After IM administration, thiocolchicoside C_{max} occur in 30 min and reaches values of 113 ng/mL after a 4 mg dose and 175 ng/mL after a 8 mg dose. The corresponding values of AUC are respectively 283 and 417 ng.h/mL. The pharmacologically active metabolite SL18.0740 is also observed at lower concentrations with a C_{max} of 11.7 ng/mL occurring 5 h post dose and an AUC of 83 ng.h/mL. No data are available for the inactive metabolite SL59.0955.

- After oral administration, no thiocolchicoside is detected in plasma. Only two metabolites are observed: The pharmacologically active metabolite SL18.0740 and an inactive metabolite SL59.0955. For both metabolites, maximum plasma concentrations occur 1 hour after thiocolchicoside administration. After a single oral dose of 8 mg of thiocolchicoside the C_{max} and AUC of SL18.0740 are about 60 ng/mL and 130 ng.h/mL respectively. For SL59.0955 these values are much lower: C_{max} around 13 ng/mL and AUC ranging from 15.5 ng.h/mL (until 3h) to 39.7 ng.h/mL (until 24h).

Distribution

The apparent volume of distribution of thiocolchicoside is estimated around 42.7 L after an IM administration of 8 mg. No data are available for both metabolites.

Biotransformation

After oral administration, thiocolchicoside is first metabolized in the aglycon 3demethylthiocolchicine or SL59.0955. This step mainly occurs by intestinal metabolism explaining the lack of circulating unchanged thiocolchicoside by this route of administration. SL59.0955 is then glucuroconjugated into SL18.0740 which has equipotent pharmacological activity to thiocolchicoside and thus supports the pharmacological activity after oral administration of thiocolchicoside. SL59.0955 is also demethylated into didemethyl-thiocolchicine.

Elimination

- After IM administration the apparent $t_{1/2}$ of thiocolchicoside is 1.5h and the plasma clearance 19.2 L/h. - After oral administration, total radioactivity is mainly excreted in feces (79%) while urinary excretion represents only 20%. No unchanged thiocolchicoside is excreted either in urine or feces. SL18.0740 and SL59.0955 are found in urine and feces while the didemethyl-thiocolchicine is only recovered in feces. After oral administration of thiocolchicoside, the SL18.0740 metabolite is eliminated with an apparent $t_{1/2}$ ranging from 3.2 to 7 hours and the metabolite SL59.0955 has a $t_{1/2}$ averaging 0.8h.

5.3 Preclinical safety data

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

In the rat, gastro-intestinal toxicity of etoricoxib increased with dose and exposure time. In the 14-week toxicity study, etoricoxib caused gastro-intestinal ulcers at exposures greater than those seen in man at the therapeutic dose. In the 53- and 106- week toxicity study, gastro-intestinal ulcers were also seen at exposures comparable to those seen in man at the therapeutic dose. In dogs, renal and gastro-intestinal abnormalities were seen at high exposures.

Etoricoxib 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 (90mg). 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 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 during lactation.

Thiocolchicoside

Thiocolchicoside profile has been assessed in vitro, and in vivo following parenteral and oral administration. Thiocolchicoside was well tolerated following oral administration for periods of up to 6 months in both the rat and the non-human primate when administered at repeated doses of less than or equal to 2 mg/kg/day in the rat and less or equal to 2.5 mg/kg/day in non-human primate, and by the intramuscular route in the primate at repeated doses up to 0.5 mg/kg/day for 4 weeks. At high doses, thiocolchicoside induced emesis in dog, diarrhoea in rat and convulsions in both rodents and non-rodents after acute administration by oral route. After repeated administration, thiocolchicoside induced gastro-intestinal disorders (enteritis, emesis) by oral route and emesis by IM route. Thiocolchicoside itself did not induce gene mutation in bacteria (Ames test), in vitro chromosomal damage (chromosome aberration test in human lymphocytes) and in vivo chromosomal damage (in vivo micronucleus in mouse bone marrow administered intraperitoneally). The major glucuro-conjugated metabolite SL18.0740 did not induce gene mutation in bacteria (Ames test); however it induced in vitro chromosomal damage (in vitro micronucleus test on human lymphocytes) and in vivo chromosomal damage (in vivo micronucleus test in mouse bone marrow administered orally). The micronuclei predominantly resulted from chromosome loss (centromere positive micronuclei after FISH centromere staining), suggesting aneugenic properties. The aneugenic effect of SL18.0740 was observed at concentrations in the in vitro test and at AUC plasma exposures in the in vivo test higher (more than 10 fold based on AUC) than those observed in human plasma at therapeutic doses. The aglycon metabolite (3-demethylthiocolchicine-SL59.0955) formed mainly after oral administration induced in vitro chromosomal damage (in vitro micronucleus test on human lymphocytes) and in vivo chromosomal damage (in vivo oral micronucleus test in rat bone marrow administered orally). The micronuclei predominantly resulted from chromosome loss

(centromere positive micronuclei after FISH or CREST centromere staining), suggesting aneugenic properties. The aneugenic effect of SL59.0955 was observed at concentrations in the in vitro test and at exposures in the in vivo test close to those observed in human plasma at therapeutic doses of 8 mg twice daily per os. Aneugenic effect in dividing cells may result in aneuploid cells. Aneuploidy is a modification in the number of chromosomes and loss of heterozygosity, which is recognized as a risk factor for teratogenicity, embryotoxicity/ spontaneous abortion, impaired male fertility, when impacting germ cells and a potential risk factor for cancer when impacting somatic cells. The presence of the aglycon metabolite (3-demethylthiocolchicine-SL59.0955) after intramuscular administration has never been assessed, therefore its formation using this route of administration can not be excluded. In the rat, an oral dose of 12 mg/kg/day of thiocolchicoside caused major malformations along with foetotoxicity (retarded growth, embryo death, impairment of sex distribution rate). The dose without toxic effect was 3 mg/kg/day. In the rabbit, thiocolchicoside showed maternotoxicity starting from 24 mg/kg/day. Furthermore, minor abnormalities have been observed (supernumerary ribs, retarded ossification). In a fertility study performed in rats, no impairment of fertility was seen at doses up to 12 mg/kg/day, i.e. at dose levels inducing no clinical effect. Thiocolchicoside and its metabolites exert aneugenic activity at different concentration levels, which is recognised as a risk factor for impairment of human fertility. The carcinogenic potential was not evaluated.

6. Pharmaceutical Particulars

6.1 List of Excipients

Maize Starch, lactose, Micro crystalline Cellulose, Cross Carmellose Sodium, Sodium Benzoate, Purified Talc, Magnesium Stearate Colloidal Silicon Dioxide, Isopropyl Alcohol, Methylene Dichloride, & Titanium Dioxide & Tartrazine

6.2 Incompatibilities

Not applicable

6.3 Shelf-Life

36 Months

6.4 Special Precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and Content of container

Aluminum-Aluminum Blister Pack

10 Tablets are blister packed with Aluminum-Aluminum foil; such 3-blister packed in one carton pack.

Pack size: 3 x 10 Tablets in one carton box along with a packing leaflet.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

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

7. Marketing Authorization Holder

MARS REMEDIES LTD.

635, GIDC Estate, Waghodia-391760, Vadodara, GUJARAT

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8. Marketing Authorization Number

CTD10280

9. Date of first authorization/renewal of the authorization

09/08/2023

10. Date of revision of the text

11/05/2025