For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

ETOXIB MR

1. Generic Name

Etoricoxib & Thiocolchicoside Tablets

2. Qualitative and quantitative composition

Each film coated tablet contains:

Etoricoxib I.P. ……60 mg

Thiocolchicoside I.P. ……...4 mg

Excipients ……...q.s.

Colours: Tartrazine Lake & Titanium Dioxide I.P.

The excipients used are Lactose, Microcrystalline Cellulose, Croscarmellose Sodium, Maize Starch, PVPK-30, Purified Talc, Magnesium Stearate, Colloidal Silicon Dioxide, Instacoat ICS 6046 White, Tartrazine Lake, Isopropyl Alcohol and Methylene Chloride.

3. Dosage form and strength

Dosage form: Film Coated Tablets

Strength: Etoricoxib - 60 mg, Thiocolchicoside - 4 mg

4. Clinical particulars

4.1 Therapeutic indication

For the acute treatment of inflammatory musculoskeletal disorders associated with painful muscle spasm in adults.

4.2 Posology and method of administration

Dose: As directed by physician.

4.3 Contraindications

Etoricoxib

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- Active peptic ulceration or active gastro-intestinal (GI) bleeding.
- Patients who, after taking acetylsalicylic acid or NSAIDs including COX-2 (cyclooxygenase-2) inhibitors, experience bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria, or allergic-type reactions.
- Pregnancy and lactation (see sections 4.6 and 5.3).
- Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score ≥10).

- Estimated renal creatinine clearance <30 ml/min.
- Children and adolescents under 16 years of age.
- Inflammatory bowel disease.
- Congestive heart failure (NYHA II-IV).
- Patients with hypertension whose blood pressure is persistently elevated above 140/90 mmHg and has not been adequately controlled.
- Established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease.

Thiocolchicoside

Thiocolchicoside must not be used

- In patients hypersensitive to the active substance or to any of the excipients.
- In patients with flaccid paralysis, hypotone muscle.
- During the entire pregnancy period
- During lactation
- In women of childbearing potential not using contraception.

4.4 Special warnings and precautions for use

Etoricoxib

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 (see section 5.1).

Cardiovascular effects

Clinical trials suggest that the selective COX-2 inhibitor class of drugs may be associated with a risk of thrombotic events (especially myocardial infarction (MI) and stroke), relative to placebo and some NSAIDs. As the cardiovascular risks of etoricoxib 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 see section 5.1. Caution should be exercised in patients with a history of cardiac failure, left ventricular dysfunction, or hypertension and in patients with pre-existing oedema from any other reason. If there is clinical evidence of deterioration in the condition of these patients, appropriate measures including discontinuation of etoricoxib should be taken.

Etoricoxib 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 (see section 4.3) 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 30, 60 and 90 mg daily.

Any patients with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be monitored. If signs of hepatic

insufficiency occur, or if persistently abnormal liver function tests (three times the upper limit of normal) are detected, etoricoxib 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 (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy with the onset of the reaction occurring in the majority of cases within the first month of treatment. Serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving etoricoxib (see section 4.8). Some selective COX-2 inhibitors have been associated with an increased risk of skin reactions in patients with a history of any drug allergy. Etoricoxib 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 (see section 4.5).

The use of etoricoxib, as with any medicinal product known to inhibit cyclooxygenase / prostaglandin synthesis, is not recommended in women attempting to conceive.

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

Thiocolcoside

The dose must be reduced in case of presence of diarrhoea following oral administration.
After administration by intramuscular route episodes were observed of vasovagal syncope, thus the patient has to be monitored after being injected
Post marketing cases of cytolytic hepatitis and cholestatic were reported with Thiocolchicoside.
The serious cases (for example fulminant hepatitis) were observed in patients that had taken FANS or paracetamol at the same time. The patients have to be informed to report any sign of hepatic toxicity
Thiocolchicoside may precipitate seizures especially in epileptic patients or those at risk of convulsions (see paragraph 4.8).

The maximum daily oral dose of 16mg must not be exceeded and must be split in two doses at 12-hour interval.
In case you forget to take a dose take the next dose avoiding taking doses close to each other.
Preclinical studies showed that one of Thiocolcoside metabolites (SL59.0955) induced aneuploidy (i.e. alterations in the number of chromosomes in dividing cells) at concentrations close to human exposure observed at doses 8 mg twice daily per os (see section 5.3). Aneuploidy is considered as a risk factor for teratogenicity, embryo/foeto-toxicity, spontaneous abortion, and impaired male fertility and a potential risk factor for cancer. As a precautionary measure, use of the product at doses exceeding the recommended dose or long-term use should be avoided
Patients should be carefully informed about the potential risk of a possible pregnancy and about effective contraception measures to be followed.

4.5 Drugs interactions

Etoricoxib

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.

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 $AUC_{0\text{-}24hr}$ of EE by 37%. Etoricoxib 120 mg given with the same oral contraceptive concomitantly or separated by 12 hours, increased the steady state $AUC_{0\text{-}24hr}$ 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 PREMARIN™) for 28 days, increased the mean steady state $AUC_{0\text{-}24hr}$ 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 ($AUC_{0\text{-}24hr}$) 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 $AUC_{0\text{-}24hr}$ 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 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 (see section 4.2)

Antacids: Antacids do not affect the pharmacokinetics of etoricoxib to a clinically relevant extent.

Thiocolchicoside

No studies on interactions were carried out

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Etoricoxib

Pregnancy

No clinical data on exposed pregnancies are available for etoricoxib. Studies in animals have shown reproductive toxicity (see section 5.3). 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 COX-2, is not recommended in women attempting to conceive.

Thiocolchicoside

Pregnancy
There are limited data on the use of Thiocolchicoside in pregnant women. Therefore, the potential hazards for the embryo and foetus are unknown.
Studies in animals have shown teratogenic effects.
ETOXIB MR is contraindicated during pregnancy and in women of childbearing potential not using contraception
Breastfeeding
Since it passes into the mother’s milk, the use of Thiocolchicoside is contraindicated during breastfeeding.
Fertility
In a fertility study performed in rats, no impairment of fertility was seen at doses up to 12 mg/kg, i.e. at dose levels inducing no clinical effect. Thiocolchicoside and its metabolites exert aneugenic activity at different concentration levels, which is a risk factor for impairment of human fertility.

4.7 Effects on ability to drive and use machines

Etoricoxib

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

Thiocolchicoside

No studies were carried out on the ability to drive or use of machinery. So if drowsiness is a common occurrence, this must be taken in account when driving or using machinery.

4.8 Undesirable effects

Etoricoxib

Summary of the safety profile

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

In clinical studies, the undesirable effects profile was similar in patients with OA or RA treated with etoricoxib 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*
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‡(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 (≥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 ETOXIB MR 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).

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

Thiocolchicoside

Disturbances in immunity system

Anaphylactic reactions:

Uncommon: pruritis,

Rare: urticarial

Very rare: hypotension

Not noted: angiooedema and anaphylactic shock after intramuscular administration.

Pathology of the nervous system

Common: drowsiness (see paragraph 4.7)

Rare: agitation and clouding

Not noted: malaise associated or to a lesser extent vasovagal syncope in the minutes following intramuscular administration, convulsions (see paragraph 4.4).

Gastrointestinal pathology

Common: diarrhoea (see paragraph 4.4), stomach pain

Uncommon: nausea, vomiting

Rare: heartburn after oral administration

Hepatobiliary pathology

Not noted: cytolytic hepatitis and cholestatic (see paragraph 4.4).

Pathology of the skin and subcutaneous tissue

Uncommon: allergic skin reactions

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting. By reporting side effects, you can help provide more information on the safety of this medicine

4.9 Overdose

Etoricoxib

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, cardio renal 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.

Thiocolchicoside

Overdosage was not noted or reported in any literature.

In case of overdosage it is recommended to get medical attention and implement symptomatic measures.

5. Pharmacological properties

5.1 Mechanism of Action

Etoricoxib

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

Thiocolchicoside

Thiocolchicoside binds to GABA-A and strychnine sensitive glycine receptors. Thiocolchicoside acting as a GABA-A receptor antagonist, its myorelaxant effects could be exerted at the supra-spinal level, via complex regulatory mechanisms, although a glycinergic mechanism of action cannot be excluded. The characteristics of the interaction of Thiocolchicoside with GABA-A receptors are qualitatively and quantitatively shared by its main circulating metabolite, the glucuronidated Derivative

5.2 Pharmacodynamic properties

Etoricoxib

Pharmacotherapeutic group: Anti-inflammatory and ant rheumatic products, non-steroids, coins, ATC code: M01 AH05

Clinical efficacy and safety

Efficacy

In patients with osteoarthritis (OA), etoricoxib 60 mg once daily provided significant improvements in pain and patient assessments of disease status. These beneficial effects were observed as early as the second day of therapy and maintained for up to 52 weeks. Studies with etoricoxib 30 mg once daily demonstrated efficacy superior to placebo over a 12-week treatment period (using similar assessments as the above studies). In a dose ranging study, etoricoxib 60 mg demonstrated significantly greater improvement than 30 mg for all 3 primary endpoints over 6 weeks of treatment. The 30 mg dose has not been studied in osteoarthritis of hands.

In patients with rheumatoid arthritis (RA), etoricoxib 60 mg and 90 mg once daily both provided significant improvements in pain, inflammation, and mobility. In studies evaluating the 60 mg and 90 mg dose, these beneficial effects were maintained over the 12-week treatment periods. In a study evaluating the 60 mg dose compared to the 90 mg dose, etoricoxib 60 mg once daily and 90 mg once daily were both more effective than placebo. The 90 mg dose was superior to the 60 mg dose for Patient Global Assessment of Pain (0-100mm visual analogue scale), with an average improvement of -2.71 mm (95% CI: -4.98 mm, -0.45 mm).

In patients experiencing attacks of acute gouty arthritis, etoricoxib 120 mg once daily over an eight-day treatment period, relieved moderate to extreme joint pain and inflammation comparable to indomethacin 50 mg three times daily. Pain relief was observed as early as four hours after initiation of treatment.

In patients with ankylosing spondylitis, etoricoxib 90 mg once daily provided significant improvements in spine pain, inflammation, stiffness and function. The clinical benefit of etoricoxib was observed as early as the second day of therapy after initiation of treatment

and was maintained throughout the 52-week treatment period. In a second study evaluating the 60 mg dose compared to the 90 mg dose, etoricoxib 60 mg daily and 90 mg daily demonstrated similar efficacy compared to naproxen 1,000 mg daily. Among inadequate responders to 60 mg daily for 6 weeks, dose escalation to 90 mg daily improved spinal pain intensity score (0-100 mm visual analogue scale) compared to continuing on 60 mg daily, with an average improvement of -2.70 mm (95% CI: -4.88 mm, -0.52 mm).

In a clinical study evaluating postoperative dental pain, etoricoxib 90 mg was administered once daily for up to three days. In the subgroup of patients with moderate pain at baseline, etoricoxib 90 mg demonstrated a similar analgesic effect to that of ibuprofen 600 mg (16.11 vs. 16.39; P=0.722), and greater than that of paracetamol/codeine 600 mg/60 mg (11.00; P<0.001) and placebo (6.84; P<0.001) as measured by total pain relief over the first 6 hours (TOPAR6). The proportion of patients reporting rescue medication usage within the first 24 hours of dosing was 40.8% for etoricoxib 90 mg, 25.5% for ibuprofen 600 mg Q6h, and 46.7% for paracetamol/codeine 600 mg/60 mg Q6h compared to 76.2% for placebo. In this study, the median onset of action (perceptible pain relief) of 90 mg etoricoxib was 28 minutes after dosing.

Safety

Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) Programme

The MEDAL Programme was a prospectively designed Cardiovascular (CV) Safety Outcomes Programme of pooled data from three randomized, double-blind active comparator controlled trials, the MEDAL study, EDGE II and EDGE.

The MEDAL Study, was an endpoint driven CV Outcomes study in 17,804 OA and 5,700 RA patients treated with etoricoxib 60 (OA) or 90 mg (OA and RA) or diclofenac 150 mg daily for a mean period of 20.3 months (maximum of 42.3 months, median 21.3 months). In this trial, only serious adverse events and discontinuations due to any adverse events were recorded.

The EDGE and EDGE II studies compared the gastrointestinal tolerability of etoricoxib versus diclofenac. The EDGE study included 7,111 OA patients treated with a dose of etoricoxib 90 mg daily (1.5 times the dose recommended for OA) or diclofenac 150 mg daily for a mean period of 9.1 months (maximum 16.6 months, median 11.4 months). The EDGE II study included 4,086 RA patients treated with etoricoxib 90 mg daily or diclofenac 150 mg daily for a mean period of 19.2 months (maximum 33.1 months, median 24 months).

In the pooled MEDAL Programme, 34,701 patients with OA or RA were treated for a mean duration of 17.9 months (maximum 42.3 months, median 16.3 months) with approximately 12,800 patients receiving treatment for more than 24 months. Patients enrolled in the Programme had a wide range of cardiovascular and gastrointestinal risk factors at baseline. Patients with a recent history of myocardial infarction, coronary artery bypass grafting or percutaneous coronary intervention within 6 months preceding

enrollment were excluded. Use of gastro protective agents and low dose aspirin were permitted in the studies.

Overall Safety:

There was no significant difference between etoricoxib and diclofenac in the rate of cardiovascular thrombotic events. Cardio renal adverse events were observed more frequently with etoricoxib than with diclofenac, and this effect was dose-dependent (see specific results below). Gastrointestinal and hepatic adverse events were observed significantly more frequently with diclofenac than etoricoxib. The incidence of adverse experiences in EDGE and EDGE II and of adverse experiences considered serious or resulting in discontinuation in the MEDAL study was higher with etoricoxib than diclofenac.

Cardiovascular safety results:

The rate of confirmed thrombotic cardiovascular serious adverse events (consisting of cardiac, cerebrovascular, and peripheral vascular events) was comparable between etoricoxib and diclofenac, and data are summarized in the table below. There were no statistically significant differences in thrombotic event rates between etoricoxib and diclofenac across all subgroups analysed including patient categories across a range of baseline cardiovascular risk. When considered separately, the relative risks for confirmed thrombotic cardiovascular serious adverse events with etoricoxib 60 mg or 90 mg compared with diclofenac 150 mg were similar.

Table 2: Rates of Confirmed Thrombotic CV Events (Pooled MEDAL Programme)

	Etoricoxib (N=16,819) 25,836 Patient-Years	**Diclofenac (N=16,483) 24,766 Patient-Years**	**Between Treatment Comparison**
	Rate† (95% CI)	**Rate† (95% CI)**	**Relative Risk (95% CI)**
Confirmed Thrombotic Cardiovascular Serious Adverse Events			
Per-protocol	1.24 (1.11, 1.38)	1.30 (1.17, 1.45)	0.95 (0.81, 1.11)
Intent-to-treat	1.25 (1.14, 1.36)	1.19 (1.08, 1.30)	1.05 (0.93, 1.19)
Confirmed Cardiac Events			
Per-protocol	0.71 (0.61, 0.82)	0.78 (0.68, 0.90)	0.90 (0.74, 1.10)
Intent-to-treat	0.69 (0.61, 0.78)	0.70 (0.62, 0.79)	0.99 (0.84, 1.17)
Confirmed Cerebrovascular Events			
Per-protocol	0.34 (0.28, 0.42)	0.32 (0.25, 0.40)	1.08 (0.80, 1.46)
Intent-to-treat	0.33 (0.28, 0.39)	0.29 (0.24, 0.35)	1.12 (0.87, 1.44)
Confirmed Peripheral Vascular Events			
Per-protocol	0.20 (0.15, 0.27)	0.22 (0.17, 0.29)	0.92 (0.63, 1.35)

Intent-to-treat	0.24 (0.20, 0.30)	0.23 (0.18, 0.28)	1.08 (0.81, 1.44)
†Events per 100 Patient-Years; CI=confidence interval N=total number of patients included in Per-protocol population Per-protocol: all events on study therapy or within 14 days of discontinuation (excluded: patients who took < 75% of their study medication or took non-study NSAIDs >10% of the time). Intent-to-treat: all confirmed events up to the end of the trial (included patients potentially exposed to non-study interventions following discontinuation of study medication). Total number of patients randomised, n= 17,412 on etoricoxib and 17,289 on diclofenac.			

CV mortality, as well as overall mortality, was similar between the etoricoxib and diclofenac treatment groups.

Cardio renal Events:

Approximately 50% of patients enrolled in the MEDAL study had a history of hypertension at baseline. In the study, the incidence of discontinuations due to hypertension-related adverse events was statistically significantly higher for etoricoxib than for diclofenac. The incidence of congestive heart failure adverse events (discontinuations and serious events) occurred at similar rates on etoricoxib 60 mg compared to diclofenac 150 mg but was higher for etoricoxib 90 mg compared to diclofenac 150 mg (statistically significant for 90 mg etoricoxib vs. 150 mg diclofenac in MEDAL OA cohort). The incidence of confirmed congestive heart failure adverse events (events that were serious and resulted in hospitalisation or a visit to an emergency department) was non-significantly higher with etoricoxib than diclofenac 150 mg, and this effect was dose-dependent. The incidence of discontinuations due to oedema-related adverse events was higher for etoricoxib than diclofenac 150 mg, and this effect was dose-dependent (statistically significant for etoricoxib 90 mg, but not for etoricoxib 60 mg).

The cardio renal results for EDGE and EDGE II were consistent with those described for the MEDAL Study.

In the individual MEDAL Programme studies, for etoricoxib (60 mg or 90 mg), the absolute incidence of discontinuation in any treatment group was up to 2.6% for hypertension, up to 1.9% for oedema, and up to 1.1% for congestive heart failure, with higher rates of discontinuation observed with etoricoxib 90 mg than etoricoxib 60 mg.

MEDAL Programme Gastrointestinal Tolerability Results:

A significantly lower rate of discontinuations of treatment for any clinical (e.g., dyspepsia, abdominal pain, ulcer) GI adverse event was observed with etoricoxib compared with diclofenac within each of the three component studies of the MEDAL Programme. The rates of discontinuations due to adverse clinical GI events per hundred patient-years over the entire period of study were as follows: 3.23 for etoricoxib and 4.96 for diclofenac in the MEDAL Study; 9.12 with etoricoxib and 12.28 with

diclofenac in the EDGE study; and 3.71 with etoricoxib and 4.81 with diclofenac in the EDGE II study.

MEDAL Programme Gastrointestinal Safety Results:

Overall upper GI events were defined as perforations, ulcers and bleeds. The subset of overall upper GI events considered complicated included perforations, obstructions, and complicated bleeding; the subset of upper GI events considered uncomplicated included uncomplicated bleeds and uncomplicated ulcers. A significantly lower rate of overall upper GI events was observed with etoricoxib compared to diclofenac. There was no significant difference between etoricoxib and diclofenac in the rate of complicated events. For the subset of upper GI haemorrhage events (complicated and uncomplicated combined), there was no significant difference between etoricoxib and diclofenac. The upper GI benefit for etoricoxib compared with diclofenac was not statistically significant in patients taking concomitant low-dose aspirin (approximately 33% of patients).

The rates per hundred patient-years of confirmed complicated and uncomplicated upper GI clinical events (perforations, ulcers and bleeds (PUBs)) were 0.67 (95% CI 0.57, 0.77) with etoricoxib and 0.97 (95% CI 0.85, 1.10) with diclofenac, yielding a relative risk of 0.69 (95% CI 0.57, 0.83).

The rate for confirmed upper GI events in elderly patients was evaluated and the largest reduction was observed in patients ≥ 75 years of age (1.35 [95% CI 0.94, 1.87] vs. 2.78 [95% CI 2.14, 3.56] events per hundred patient-years for etoricoxib and diclofenac, respectively.

The rates of confirmed lower GI clinical events (small or large bowel perforation, obstruction, or haemorrhage, (POBs)) were not significantly different between etoricoxib and diclofenac.

MEDAL Programme Hepatic Safety Results:

Etoricoxib was associated with a statistically significantly lower rate of discontinuations due to hepatic-related adverse experiences than diclofenac. In the pooled MEDAL Programme, 0.3% of patients on etoricoxib and 2.7% of patients on diclofenac discontinued due to hepatic-related adverse experiences. The rate per hundred patient-years was 0.22 on etoricoxib and 1.84 for diclofenac (p-value was <0.001 for etoricoxib vs. diclofenac). However, most hepatic adverse experiences in the MEDAL Programme were non-serious.

Additional Thrombotic Cardiovascular Safety Data

In clinical studies excluding the MEDAL Programme Studies, approximately 3,100 patients were treated with etoricoxib ≥60 mg daily for 12 weeks or longer. There was no discernible difference in the rate of confirmed serious thrombotic cardiovascular events between patients receiving etoricoxib ≥60 mg, placebo, or non-naproxen NSAIDs. However, the rate of these events was higher in patients receiving etoricoxib compared with those receiving naproxen 500 mg twice daily. The difference in

antiplatelet activity between some COX-1 inhibiting NSAIDs and selective COX-2 inhibitors may be of clinical significance in patients at risk of Thrombo-embolic events. Selective COX-2 inhibitors reduce the formation of systemic (and therefore possibly endothelial) prostacyclin without affecting platelet thromboxane. The clinical relevance of these observations has not been established.

Additional Gastrointestinal Safety Data

In two 12-week double-blind endoscopy studies, the cumulative incidence of gastroduodenal ulceration was significantly lower in patients treated with etoricoxib 120 mg once daily than in patients treated with either naproxen 500 mg twice daily or ibuprofen 800 mg three times daily. Etoricoxib had a higher incidence of ulceration as compared to placebo.

Renal Function Study in the Elderly

A randomized, double-blind, placebo-controlled, parallel-group study evaluated the effects of 15 days of treatment of etoricoxib (90 mg), celecoxib (200 mg bid), naproxen (500 mg bid) and placebo on urinary sodium excretion, blood pressure, and other renal function parameters in subjects 60 to 85 years of age on a 200-mEq/day sodium diet. Etoricoxib, celecoxib, and naproxen had similar effects on urinary sodium excretion over the 2 weeks of treatment. All active comparators showed an increase relative to placebo with respect to systolic blood pressures; however, etoricoxib was associated with a statistically significant increase at Day 14 when compared to celecoxib and naproxen (mean change from baseline for systolic blood pressure: etoricoxib 7.7 mmHg, celecoxib 2.4 mmHg, naproxen 3.6 mmHg).

Thiocolchicoside

Pharmacotherapeutic category: Other muscle relaxant with central action

ATC code: M03BX05

Thiocolchicoside is a semisynthetic sulphide derivative of colchicoside, showing muscle relaxant pharmacological activity.

In vitro thiocolchicoside binds solely with GABA receptors and glycinergic stricnine sensitive. From the moment that thiocolchicoside acts as an antagonist of the GABA receptors, its muscle relaxant effect may be exercised to a supraspinal level, through a regulatory mechanism even though the glycinergic mechanism of action cannot be excluded. The characteristics of interaction with the GABA receptors are qualitative and quantitative divided between thiocolchicoside and its main circulating metabolite, the derivative glucuronidated

In vivo the muscle relaxant properties of thiocolchicoside and its main metabolite have been shown in various predictive models of rat and rabbit.

The lack of muscle relaxant effect of thiocolchicoside in spineless rat suggests a predominant supraspinal activity.

Also electrocephalographic studies have shown that thiocolchicoside and its main metabolite are devoid of any sedative effect.

5.3 Pharmacokinetic properties

Etoricoxib

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 µg/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 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 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 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 radiolabelled 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). (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 Cmax occur in 30 min and. reach 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 Cmax 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 SL59.0955.22

- 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 1hour after thiocolchicoside administration. After a single oral dose of 8 mg of thiocolchicoside the Cmax and AUC of SL18.0740 are about 60 ng/mL and 130 ng.h/mL respectively. For SL59.0955 these values are much lower: Cmax 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 3-demethyltiocolchicine 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 t1/2 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 metabolites is eliminated with an apparent t1/2 ranging from 3.2 to 7 hours and the metabolite SL59.0955 has a t 1/2 averaging 0.8h.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Etoricoxib

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

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

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

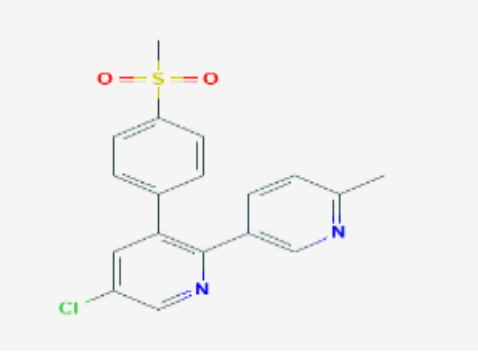
Thiocolchicoside profile has been assessed in vitro, and in vivo following parenteral and oral administration. Thiocolchicoside was well tolerated following oral administration for periods of up to 6 months in both the rat and the non-human primate when administered at repeated doses of less than or 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 no 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 (3-23 demethylthiocolchicine-SL59.0955) after intramuscular administration has never been assessed, therefore its formation using this route of administration cannot be excluded. In the rat, an oral dose of 12 mg/kg/day of thiocolchicoside caused major malformations along with fetotoxicity (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.

7. Description

Etoricoxib

Etoricoxib is 5-chloro-2-(6-methyl-3-pyridinyl)-3-(4-methylsufonylphenyl) pyridine having molecular weight of 358.5 and molecular formula is $C_{18}H_{15}ClN_2O_2S$ and chemical structure is:



Etoricoxib is an off-white to creamish coloured powder which is freely soluble in tetrahydrofuran, dimethylsulphoxide and in dimethylformamide, soluble in methanol and in acetone, sparingly soluble in ethanol.

Thiocolchicoside

Thiocolchicoside is chemically N-[(7S)-1,2-dimethoxy-10-methylsulfanyl-9-oxo-3-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-6,7-dihydro-5H-

benzo[a]heptalen-7-yl]acetamide having molecular weight of 563.6 g/mol and molecular formula is $C_{27}H_{33}NO_{10}S$ with the chemical structure as below:

Etoricoxib & Thiocolchicoside Tablets are yellow coloured, circular shaped, biconvex, film coated tablets having both sides plain. The excipients used are Lactose, Microcrystalline Cellulose, Croscarmellose Sodium, Maize Starch, PVPK-30, Purified Talc, Magnesium Stearate, Colloidal Silicon Dioxide, Instacoat ICS 6046 White, Tartrazine Lake, Isopropyl Alcohol and Methylene Chloride.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

ETOXIB MR is available in blister strip of 10 tablets.

8.4 Storage and handing instructions

Store below 30°C. Protect from light & moisture.

Keep all medicine out of reach of children.

9. Patient Counselling Information

Package leaflet: Information for the user

Etoricoxib 60 mg film-coated tablets

Thiocolchicoside 4 mg

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them even if their signs of illness are the same as yours.

- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet?

9.1 What ETOXIB MR is and what it is used for

What is ETOXIB MR?

ETOXIB MR is combination of active substance etoricoxib and Thiocolchicoside (muscle relaxant). ETOXIB MR is one of a group of medicines called selective COX-2 inhibitors. These belong to a family of medicines called non-steroidal anti-inflammatory drugs (NSAIDs)

What is ETOXIB MR used for?

For the acute treatment of inflammatory musculoskeletal disorders associated with painful muscle spasm in adults.

9.2 What you need to know before you take ETOXIB MR

Do not take ETOXIB MR:

- If you are allergic (hypersensitive) to etoricoxib or any of the other ingredients of this medicine
- If you are allergic to non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin and COX-2 inhibitors (see Possible Side Effects, section 4)
- If you have a current stomach ulcer or bleeding in your stomach or intestines
- If you have serious liver disease
- If you have serious kidney disease
- If you are or could be pregnant or are breast-feeding (see 'Pregnancy, breast feeding, and fertility')
- If you are under 16 years of age
- If you have inflammatory bowel disease, such as Crohn's Disease, Ulcerative Colitis, or Colitis
- If you have high blood pressure that has not been controlled by treatment (check with your doctor or nurse if you are not sure whether your blood pressure is adequately controlled)
- If your doctor has diagnosed heart problems including heart failure (moderate or severe types), angina (chest pain)
- If you have had a heart attack, bypass surgery, peripheral arterial disease (poor circulation in legs or feet due to narrow or blocked arteries)

- If you have had any kind of stroke (including mini-stroke, transient ischaemic attack or TIA).

Etoricoxib may slightly increase your risk of heart attack and stroke and this is why it should not be used in those who have already had heart problems or stroke.

If you think any of these are relevant to you, do not take the tablets until you have consulted your doctor.

Warnings and precautions

Talk to your doctor or pharmacist before taking ETOXIB MR if:

- You have a history of stomach bleeding or ulcers.
- You are dehydrated, for example by a prolonged bout of vomiting or diarrhoea.
- You have swelling due to fluid retention.
- You have a history of heart failure, or any other form of heart disease.
- You have a history of high blood pressure. ETOXIB MR can increase blood pressure in some people, especially in high doses, and your doctor will want to check your blood pressure from time to time.
- You have any history of liver or kidney disease.
- You are being treated for an infection. ETOXIB MR can mask or hide a fever, which is a sign of infection.
- You have diabetes, high cholesterol, or are a smoker. These can increase your risk of heart disease.
- You are a woman trying to become pregnant.
- You are over 65 years of age.

If you are not sure if any of the above apply to you, talk to your doctor before taking ETOXIB MR to see if this medicine is suitable for you.

ETOXIB MR works equally well in older and younger adult patients. If you are over 65 years of age, your doctor will want to appropriately keep a check on you. No dosage adjustment is necessary for patients over 65 years of age.

Children and adolescents

Do not give this medicine to children and adolescents under 16 years of age.

Other medicines and ETOXIB MR

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

In particular, if you are taking any of the following medicines, your doctor may want to monitor you to check that your medicines are working properly, once you start taking ETOXIB MR:

- Medicines that thin your blood (anticoagulants), such as warfarin
- Rifampicin (an antibiotic)
- Methotrexate (a drug used for suppressing the immune system, and often used in rheumatoid arthritis)

- Ciclosporin or tacrolimus (drugs used for suppressing the immune system)
- Lithium (a medicine used to treat some types of depression)
- medicines used to help control high blood pressure and heart failure called ACE inhibitors and angiotensin receptor blockers, examples include enalapril and ramipril, and losartan and valsartan
- Diuretics (water tablets)
- Digoxin (a medicine for heart failure and irregular heart rhythm)
- Minoxidil (a drug used to treat high blood pressure)
- Salbutamol tablets or oral solution (a medicine for asthma)
- Birth control pills (the combination may increase your risk of side effects)
- Hormone replacement therapy (the combination may increase your risk of side effects)
- Aspirin, the risk of stomach ulcers is greater if you take ETOXIB MR with aspirin.

- Aspirin for prevention of heart attacks or stroke:

ETOXIB MR can be taken with low-dose aspirin. If you are currently taking low-dose aspirin to prevent heart attacks or stroke, you should not stop taking aspirin until you talk to your doctor - aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs): do not take high dose aspirin or other anti-inflammatory medicines while taking ETOXIB MR.

The dose must be reduced in case of presence of diarrhoea following oral administration.
After administration by intramuscular route episodes were observed of vasovagal syncope, thus the patient has to be monitored after being injected
Post marketing cases of cytolytic hepatitis and cholestatic were reported with Thiocolchicoside.
The serious cases (for example fulminant hepatitis) were observed in patients that had taken FANS or paracetamol at the same time. The patients have to be informed to report any sign of hepatic toxicity.
Thiocolchicoside may precipitate seizures especially in epileptic patients or those at risk of convulsions.
The maximum daily oral dose of 16mg must not be exceeded and must be split in two doses at 12-hour interval.
In case you forget to take a dose take the next dose avoiding taking doses close to each other.
Preclinical studies showed that one of Thiocolcoside metabolites (SL59.0955) induced aneuploidy (i.e. alterations in the number of chromosomes in dividing cells) at concentrations close to human exposure observed at doses 8 mg twice daily per os (see section 5.3). Aneuploidy is considered as a risk factor for teratogenicity, embryo/foeto-toxicity, spontaneous abortion, and impaired male fertility and a potential risk factor for cancer. As a precautionary measure, use of the product at doses exceeding the recommended dose or long-term use should be avoided. Patients should be carefully informed about the potential risk of a possible pregnancy and about effective contraception measures to be followed.

ETOXIB MR with food and drink

The onset of the effect of ETOXIB MR may be faster when taken without food.

Pregnancy, breast-feeding, and fertility

Pregnancy

ETOXIB MR Tablets must not be taken during pregnancy. If you are pregnant or think you could be pregnant, or if you are planning to become pregnant, do not take the tablets. If you become pregnant, stop taking the tablets and consult your doctor. Consult your doctor if you are unsure or need more advice.

Breast-feeding

It is not known if ETOXIB MR is excreted in human milk. If you are breast-feeding, or planning to breast-feed, consult your doctor before taking ETOXIB MR. If you are using ETOXIB MR, you must not breast-feed.

Fertility

ETOXIB MR is not recommended in women attempting to become pregnant.

Driving and using machines

Dizziness and sleepiness have been reported in some patients taking ETOXIB MR.

Do not drive if you experience dizziness or sleepiness.

Do not use any tools or machines if you experience dizziness or sleepiness.

9.3 How to take ETOXIB MR

Always take this medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Do not take more than the recommended dose for your condition. Your doctor will want to discuss your treatment from time to time. It is important that you use the lowest dose that controls your pain and you should not take ETOXIB MR for longer than necessary. This is because the risk of heart attacks and strokes might increase after prolonged treatment, especially with high doses.

There are different strengths available for this medicinal product and depending on your disease your, doctor will prescribe the tablet strength that is appropriate for you.

The recommended dose is:

Take the medicine exactly as suggested by physician.

If you take more ETOXIB MR than you should

You should never take more tablets than the doctor recommends. If you do take too many ETOXIB MR Tablets, you should seek medical attention immediately.

If you forget to take ETOXIB MR

It is important to take ETOXIB MR as your doctor has prescribed. If you miss a dose, just resume your usual schedule the following day. Do not take a double dose to make up for the forgotten tablet if you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. If you develop any of these signs you should stop ETOXIB MR and talk to your doctor immediately (see what you need to know before you take ETOXIB MR section

- Shortness of breath, chest pains, or ankle swelling appear or if they get worse
- yellowing of the skin and eyes (jaundice) – these are signs of liver problems
- Severe or continual stomach pain or your stools become black
- an allergic reaction- which can include skin problems such as ulcers or blistering, or swelling of the face, lips, tongue, or throat which may cause difficulty in breathing

The frequency of possible side effects listed below is defined using the following convention:

Very common (affects more than 1 user in 10)

Common (affects 1 to 10 users in 100)

Uncommon (affects 1 to 10 users in 1,000)

Rare (affects 1 to 10 users in 10,000)

Very rare (affects less than 1 user in 10,000).

The following side effects can occur during treatment with ETOXIB MR:

Very Common:

- Stomach pain

Common:

- Dry socket (inflammation and pain after a tooth extraction)
- swelling of the legs and/or feet due to fluid retention (oedema)
- Dizziness, headache
- Palpitations (fast or irregular heartbeat), irregular heart rhythm (arrhythmia)
- increased blood pressure
- Wheezing or shortness of breath (bronchospasms)
- Constipation, wind (excessive gas), gastritis (inflammation of the lining of the stomach), Heartburn, diarrhoea, indigestion (dyspepsia)/stomach discomfort, nausea, being sick (vomiting), Inflammation of the oesophagus, mouth ulcers
- Changes in blood tests related to your liver
- Bruising
- Weakness and fatigue, flu-like illness

Uncommon:

- Gastroenteritis (inflammation of the gastrointestinal tract that involves both the stomach and small intestine/stomach flu), upper respiratory infection, urinary tract infection
- changes in laboratory values (decreased number of red blood cells, decreased number of white blood cells, platelets decreased)
- Hypersensitivity (an allergic reaction including hives which may be serious enough to require immediate medical attention)
- Appetite increases or decreases, weight gain
- Anxiety, depression, decreases in mental sharpness; seeing, feeling or hearing things that are not there (hallucinations)
- Taste alteration, inability to sleep, numbness or tingling, sleepiness
- Blurred vision, eye irritation and redness
- ringing in the ears, vertigo (sensation of spinning while remaining still)
- abnormal heart rhythm (atrial fibrillation), fast heart rate, heart failure, feeling of tightness, pressure or heaviness in the chest (angina pectoris), heart attack
- flushing, stroke, mini-stroke (transient ischaemic attack), severe increase in blood pressure, inflammation of the blood vessels
- cough, breathlessness, nose bleed
- stomach or bowel bloating, changes in your bowel habits, dry mouth, stomach ulcer, inflammation of the stomach lining that can become serious and may lead to bleeding, irritable bowel syndrome, inflammation of the pancreas
- swelling of the face, skin rash or itchy skin, redness of the skin
- Muscle cramp/spasm, muscle pain/stiffness
- High levels of potassium in your blood, changes in blood or urine tests relating to your kidney, serious kidney problems
- Chest pain

Rare:

- Angioedema (an allergic reaction with swelling of the face, lips, tongue and/or throat which may

Cause difficulty in breathing or swallowing, which may be serious enough to require immediate medical attention)/anaphylactic/anaphylactoid reactions including shock (a serious allergic reaction that requires immediate medical attention)

- Confusion, restlessness
- Liver problems (hepatitis)
- Low blood levels of sodium
- Liver failure, yellowing of the skin and/or eyes (jaundice)
- Severe skin reactions

Disturbances in immunity system
Anaphylactic reactions:

Uncommon: pruritis,
Rare: urticarial
Very rare: hypotension
Not noted: angioeodema and anaphylactic shock after intramuscular administration.
Pathology of the nervous system
Common: drowsiness (see paragraph 4.7)
Rare: agitation and clouding
Not noted: malaise associated or to a lesser extent vasovagal syncope in the minutes following intramuscular administration, convulsions (see paragraph 4.4).
Gastrointestinal pathology
Common: diarrhoea (see paragraph 4.4), stomach pain
Uncommon: nausea, vomiting
Rare: heartburn after oral administration
Hepatobiliary pathology
Not noted: cytolytic hepatitis and cholestatic (see paragraph 4.4).
Pathology of the skin and subcutaneous tissue
Uncommon: allergic skin reactions

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting. By reporting side effects, you can help provide more information on the safety of this medicine

9.5 How to store ETOXIB MR

Store below 30°C. Protect from light & moisture.

Keep all medicine out of reach of children.

9.6 Contents of the pack and other information

What ETOXIB MR contains

The active substance is etoricoxib 60 mg And Thiocolchicoside I.P 4 mg
The excipients used are Lactose, Microcrystalline Cellulose, Croscarmellose Sodium, Maize Starch, PVPK-30, Purified Talc, Magnesium Stearate, Colloidal Silicon Dioxide, Instacoat ICS 6046 White, Isopropyl Alcohol and Methylene Chloride.
Colours: Tartrazine Lake & Titanium Dioxide I.P.

10. Details of manufacturer

Manufactured in India by:

Ravenbhel Healthcare Pvt Ltd.

16-17, EPIP, SIDCO, Kartholi, Bari Brahmana, Jammu – 181133.

11. Details of permission or licence number with date

Mfg Lic No. JK/01/56 issued on 09.02.2013

12. Date of revision

Not applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ ETOXIB MR 60 and 4 mg/MAY-20/01/PI