Summary of Product Characteristics for Pharmaceutical Product

1. Name of the medicinal product:
ETHOS-8, Etoricoxib & Thiocolchicoside Tablets (60 mg & 8 mg)

2. Qualitative and quantitative composition
Each tablet contains**:**
Etoricoxib 60mg
Thiocholchicoside 8.0mg

Excipients with known effect: Lactose

3. Pharmaceutical form

Yellow coloured circular biconvex film coated tablets plain on both sides. An Alu Alu Blister pack of 10 tablets & 3 such Alu Alu Blister packs are packed in a carton along with package insert.

4. Clinical particulars
4.1 Therapeutic indications
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.

Special populations
Elderly patients

No dosage adjustment is necessary for elderly patients. As with other drugs, caution should be exercised in elderly patients.
Patients with hepatic impairment
Regardless of indication, in patients with mild hepatic dysfunction (Child-Pugh score 5-6) a dose of 60 mg once daily should not be exceeded. In patients with moderate hepatic dysfunction (Child-Pugh score 7-9), regardless of indication, the dose of 30 mg once daily should not be exceeded.
Clinical experience is limited particularly in patients with moderate hepatic dysfunction and caution is advised. There is no clinical experience in patients with severe hepatic dysfunction (Child-Pugh score ≥10); therefore, its use is contra-indicated in these patients.
Patients with renal impairment
No dosage adjustment is necessary for patients with creatinine clearance ≥30 ml/min. The use of etoricoxib in patients with creatinine clearance <30 ml/min is contra-indicated.
Paediatric population
Etoricoxib is contra-indicated in children and adolescents under 16 years of age.

Method of administration
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.

4.2 Posology and method of administration

Posology:
It can be taken with or without food. You should take it regularly as advised by your doctor. Do not take more or use it for a longer duration than recommended by your doctor.
Method of Admisitration
For Oral Use.

4.3 Contraindications

Etoricoxib

- Hypersensitivity to the active substance or to any of the excipients.
- Active peptic ulceration or active gastro-intestinal (GI) bleeding.
- Patients who, after taking acetylsalicylic acid or NSAIDs including COX-2 (cyclooxygenase-2) inhibitors, experience bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria, or allergic-type reactions. • Pregnancy and lactation

- Severe hepatic dysfunction (serum albumin
- Estimated renal creatinine clearance
- 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.

Thiocolchicoside IH:

- Hypersensitivity to the active substance or to any of the excipients being used.
- Contraindicated in muscle spasms.

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 when etoricoxib is taken concomitantly with acetylsalicylic acid.

A significant difference in GI safety between selective COX-2 inhibitors + acetylsalicylic acid vs. NSAIDs + acetylsalicylic acid has not been demonstrated in long-term clinical trials.

Cardiovascular effects: Clinical trials suggest that the selective COX-2 inhibitor class of drugs may be associated with a risk of thrombotic events, 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 should only be treated with etoricoxib after careful consideration.
COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular
Thrombo-embolic diseases because of their lack of antiplatelet effect. Therefore, antiplatelet therapies should not be discontinued

Renal effects: Renal prostaglandins may play a compensatory role in the maintenance of renal perfusion.
Therefore, under conditions of compromised renal perfusion, administration of etoricoxib may cause a reduction in prostaglandin formation and, secondarily, in renal blood flow, and thereby impair renal function.
Patients at greatest risk of this response are those with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis.
Monitoring of renal function in such patients should be considered.
Fluid retention, oedema and hypertension
As with other medicinal products known to inhibit prostaglandin synthesis, fluid retention, oedema and hypertension have been observed in patients taking etoricoxib. All Nonsteroidal Anti-inflammatory Drugs (NSAIDs), including etoricoxib, can be associated with new onset or recurrent congestive heart failure. For information regarding a dose related response for etoricoxib.
Caution should be exercised in patients with a history of cardiac failure, left ventricular dysfunction, or hypertension and in patients with pre-existing oedema from any other reason. If there is clinical evidence of deterioration in the condition of these patients, appropriate measures including discontinuation of etoricoxib should be taken.
Etoricoxib may be associated with more frequent and severe hypertension than some other NSAIDs and selective COX-2 inhibitors, particularly at high doses.
Therefore, hypertension should be controlled before treatment with etoricoxib and special attention should be paid to blood pressure monitoring during treatment with etoricoxib.
Blood pressure should be monitored within two weeks after initiation of treatment and periodically thereafter. If blood pressure rises significantly, alternative treatment should be considered. Hepatic effects Elevations of alanine aminotransferase (ALT) and/or aspartate

aminotransferase (AST) 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 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, StevensJohnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs and some selective COX-2 inhibitors during postmarketing surveillance. Patients appear to be at highest risk for these reactions early in the course of therapy with the onset of the reaction occurring in the majority of cases within the first month of treatment. Serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving etoricoxib. Some selective COX-2 inhibitors have been associated with an increased risk of skin reactions in patients with a history of any drug allergy.
Etoricoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.
Etoricoxib may mask fever and other signs of inflammation.

Caution should be exercised when co-administering etoricoxib with warfarin or other oral anticoagulants. The use of etoricoxib, as with any medicinal product known to inhibit cyclooxygenase / prostaglandin synthesis, is not recommended in women attempting to conceive.
This 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 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 induced aneuploidy at concentrations close to human exposure observed at doses 8 mg twice daily per OS.
Aneuploidy is considered as a risk factor for teratogenicity, embryo/foetotoxicity, 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 Interaction with other medicinal products and other forms of interaction

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.
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. 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. Etoricoxib can be used concomitantly with acetylsalicylic acid at doses used for cardiovascular prophylaxis.
However, concomitant administration of low-dose acetylsalicylic acid with etoricoxib may result in an increased rate of GI ulceration or other complications compared to use of etoricoxib alone. Concomitant administration of etoricoxib with doses of acetylsalicylic acid above those for cardiovascular prophylaxis or with other NSAIDs is not recommended.

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

Pharmacokinetic interactions
The effect of etoricoxib on the pharmacokinetics of other drugs Lithium:
NSAIDs decrease lithium renal excretion and therefore increase lithium plasma levels.
If necessary, monitor blood lithium closely and adjust the lithium dosage while the combination is being taken and when the NSAID is withdrawn.

Methotrexate:
Two studies investigated the effects of etoricoxib 60, 90 or 120 mg administered once daily for seven days in patients receiving once-weekly methotrexate doses of 7.5 to 20 mg for rheumatoid arthritis. Etoricoxib at 60 and 90 mg had no effect on methotrexate plasma concentrations or renal clearance.
In one study, etoricoxib 120 mg had no effect, but in the other study, etoricoxib 120 mg increased methotrexate plasma concentrations by 28% and reduced renal clearance of methotrexate by 13%. Adequate monitoring for methotrexate-related toxicity is recommended when etoricoxib and methotrexate are administered concomitantly.

Oral contraceptives:
Etoricoxib 60 mg given concomitantly with an oral contraceptive containing 35 micrograms ethinyl estradiol (EE) and 0.5 to 1 mg norethindrone for 21 days increased the steady state AUC0-24hr of EE by
37%. Etoricoxib 120 mg given with the same oral contraceptive concomitantly or separated by 12 hours, increased the steady state AUC0-24hr of EE by 50 to 60%.
This increase in EE concentration should be considered when selecting an

oral contraceptive for use with etoricoxib.
An increase in EE exposure can increase the incidence of adverse events associated with oral contraceptives.

Hormone Replacement Therapy (HRT):
Administration of etoricoxib 120 mg with hormone replacement therapy consisting of conjugated estrogens (0.625 mg PREMARINTM) for 28 days, increased the mean steady state AUC0-24hr of unconjugated estrone (41%), equilin (76%), and 17-β-estradiol (22%). 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 (AUC0-24hr) 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 AUC0-24hr or renal elimination of digoxin.
There was an increase in digoxin Cmax (approximately 33%). This increase is not generally important for most patients.
However, patients at high risk of digoxin toxicity should be monitored for this when etoricoxib and digoxin are administered concomitantly.
Effect of etoricoxib on drugs metabolised by sulfotransferases Etoricoxib is an inhibitor of human sulfotransferase activity, particularly SULT1E1, and has been shown to increase the serum concentrations of ethinyl estradiol. While knowledge about effects of multiple sulfotransferases is presently limited and the clinical consequences for many drugs are still being examined, it may be prudent to exercise care when administering etoricoxib concurrently with other drugs primarily metabolised by human sulfotransferases. 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.

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.

Thiocolchicoside
No studies on interactions were carried out

4.6 Pregnancy and lactation

Etoricoxib
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 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 fetus are unknown. Studies in animals have shown teratogenic effects.Etoricoxib is contraindicated during pregnancy and in women of childbearing potential not using contraceptionBreastfeeding: 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.
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‡ §	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 subcutaneoustissue disorders	ecchymosis	Common
	facial oedema, pruritus, rash, erythema[‡], urticaria[‡]	Uncommon
	Stevens-Johnson syndrome[‡], toxic epidermal necrolysis[‡], fixed drug eruption[‡]	Rare[†]
Musculoskeletal and connective tissue disorders	muscular cramp/spasm, musculoskeletal pain/stiffness	Uncommon
Renal and urinary disorders	proteinuria, serum creatinine increased, renal failure/renal insufficiency[‡]	Uncommon
General disorders and administration site conditions	asthenia/fatigue, flu-like disease	Common
	chest pain	Uncommon

Investigations	blood urea nitrogen increased, creatine phosphokinase increased, hyperkalaemia, uric acid increased	Uncommon
	blood sodium decreased	Rare

*Frequency Category: Defined for each Adverse Experience Term by the incidence reported in the clinical trials data base: Very Common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1000 to <1/100), Rare (≥1/10,000 to <1/1000), Very Rare (<1/10,000).
‡ This adverse reaction was identified through post-marketing surveillance. Its reported frequency has been estimated based upon the highest frequency observed across clinical trial data pooled by indication and approved dose. †The frequency category of "Rare" was defined per the Summary of Product Characteristics (SmPC) guidance (rev. 2, Sept 2009) on the basis of an estimated upper bound of the 95% confidence interval for 0 events given the number of subjects treated with Etoricoxib 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
Rare: agitation and clouding
Not noted: malaise associated or to a lesser extent vasovagal syncope in the minutes following intramuscular
Administration, Convulsions Gastrointestinal pathology Common: diarrhoea,
Stomach Pain
Uncommon: nausea, vomiting
Rare: heartburn after oral administration
Hepatobiliary pathology
Not noted: cytolytic hepatitis and cholestatic
Pathology of the skin and subcutaneous tissue

Uncommon: allergic skin reactions

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.

Thiocolchicoside IH:

No overdosage symptoms have been reported in patients treated with thiocolchicoside. Should overdosage occurs, medical supervision and symptomatic measures are recommended.

5. Pharmacological properties:

5.1 Pharmacodynamic Properties

Mechanism of Action

Etoricoxib: Etoricoxib is an oral, selective cyclo-oxygenase-2 (COX-2) inhibitor within the clinical dose range. Across clinical pharmacology studies of Etoricoxib produced dosedependent 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.

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 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 Cmax = 3.6 µg/ml) was observed at approximately 1 hour (Tmax) after administration to fasted adults.
The geometric mean area under the curve (AUC0-24hr) was 37.8 µg•hr/ml.
The pharmacokinetics of etoricoxib are linear across the clinical dose range.
Dosing with food had no effect on the extent of absorption of etoricoxib after administration of a 120-mg dose.
The rate of absorption was affected, resulting in a 36% decrease in Cmax and an increase in Tmax by 2 hours.
These data are not considered clinically significant. In clinical trials, etoricoxib was administered without regard to food intake.

Distribution: Etoricoxib is approximately 92% bound to human plasma protein over the range of concentrations of 0.05 to 5 µg/ml. The volume of distribution at steady state (Vdss) was approximately 1,20l in humans. Etoricoxib crosses the placenta in rats and rabbits, and the blood-brain barrier in rats.

Biotransformation: Etoricoxib is extensively metabolised with 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 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 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.

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.

Paediatric patients: The pharmacokinetics of etoricoxib in paediatric patients (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 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.
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. This step mainly occurs by intestinal metabolism explaining the lack of circulating unchanged thiocolchicoside by this route of administration 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.

5.3 Preclinical safety data

Summary of Product Characteristics for Pharmaceutical Product

Etoricoxib

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, 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 safety profile has been assessed in vitro, an in vivo following intramuscular and oral administration. Thicolchicoside 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 intra muscular route in the primate at repeated doses up to 0.5 mg/kg/day for 4 weeks.

At higher doses, thiocolchicoside induced diarrhea 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 i.m. route.

The compound did not induce adverse effect on fertility. By contrast, a teratogenic effect and perinatal toxicity was demonstrated. No evidence for

teratogenic effects of thiocolchicoside was described at doses up to 3 mg/kg/day. Thiocolchicoside was shown to be devoid of mutagenic potential when used at the therapeutic dose.

6. Pharmaceutical particulars

6.1 List of excipients

Following excipients are used in ETHOS-8 (Etoricoxib & Thiocolchicoside Tablets (60 mg & 8 mg.)

Sr. No.	Excipients	Specification
1	Dicalcium phosphate Anhydrous	BP
2	Lactose	BP
3	Microcrystalline Cellulose pH (101)	BP
4	Croscarmellose Sodium (Ac di Sol)	BP
5	Hypromellose (HPMC E-15)	BP
6	Purified Water	BP
7	Microcrystalline cellulose (Avicel pH 102)	BP
8	Magnesium Stearate	BP
9	Colour coat FC4WT 200109	IH
10	Ferric oxide (Yellow)	USP-NF
11	Isopropyl Alcohol	BP
12	Methylene Chloride	USP

6.2 Incompatibilities

None known

6.3 Shelf life

24 months

6.4 Special precautions for storage

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

6.5 Special precautions for disposal and other handling

Not applicable

6.6 Nature and contents of container

Solid oral dosage form, Film coated tablets.

An alu- alu blister pack of 10 tablets & 3 such Alu Alu Blister packs are packed in a carton along with package insert.

7. Marketing authorization holder and manufacturing site addresses

Marketing Authorisation Holder:

Acme Formulation Pvt. Ltd.

Ropar Road, Nalagarh, Distt. Solan, Himachal Pradesh -174101 India.
Telephone: 01795-228501-03

Manufacturing Site address:

Acme Formulation Pvt. Ltd
Ropar Road, Nalagarh, Distt. Solan,
Himachal Pradesh 174101.
INDIA

8. Marketing Authorisation number:

CTD6492

9. Date of first registration

27-02-2024

10. Date of revision of the text

Nov/2024