1.17 Summary Product Characteristics (SPC)

1. **Product Name:** ETOVAC 120 (ETORICOXIB TABLETS 120 MG)
2. **Qualitative / Quantitative composition of the substance (s) active (s) (in table form)** Each film coated contains:

Etoricoxib……..120 mg
Excipients……q.s
Colour: Quinoline Yellow

3. Pharmaceutical form

Film-coated tablet

A yellow coloured, round shaped biconvex tablet plain on both sides.

4. Clinical particulars

4.1 Therapeutic indications

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

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

The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks (see sections 4.3, 4.4).

4.2 Posology and method of administration

Posology

As the cardiovascular risks of etoricoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis (see sections 4.3, 4.4, 4.8 and 5.1).

Osteoarthritis

The recommended dose is 30 mg once daily. In some patients with insufficient relief from symptoms, an increased dose of 60 mg once daily may increase efficacy. In the absence of an increase in therapeutic benefit, other therapeutic options should be considered.

Rheumatoid arthritis

The recommended dose is 60 mg once daily. In some patients with insufficient relief from symptoms, an increased dose of 90 mg once daily may increase efficacy. Once the patient is clinically stabilised, down-titration to a 60 mg

once daily dose may be appropriate. In the absence of an increase in therapeutic benefit, other therapeutic options should be considered.

Ankylosing spondylitis

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

Acute pain conditions

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

Acute gouty arthritis

The recommended dose is 120 mg once daily. In clinical trials for acute gouty arthritis, etoricoxib was given for 8 days. *Postoperative dental surgery pain*

The recommended dose is 90 mg once daily, limited to a maximum of 3 days. Some patients may require other postoperative analgesia in addition to Etoricoxib during the three day treatment period.

Doses greater than those recommended for each indication have either not demonstrated additional efficacy or have not been studied. Therefore:

The dose for OA should not exceed 60 mg daily.

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

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

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

<u>Special populations</u>

Elderly patients

No dosage adjustment is necessary for elderly patients. As with other drugs, caution should be exercised in elderly patients (see section 4.4).

Patients with hepatic impairment

Regardless of indication, in patients with mild hepatic dysfunction (Child-Pugh score 5-6) a dose of 60 mg once daily should not be exceeded. In patients with moderate hepatic dysfunction (Child-Pugh score 7-9), regardless of indication, the dose of 30 mg once daily should not be exceeded.

Clinical experience is limited particularly in patients with moderate hepatic dysfunction and caution is advised. There is no clinical experience in patients

with severe hepatic dysfunction (Child-Pugh score ≥10); therefore, its use is contraindicated in these patients (see sections 4.3, 4.4 and 5.2).

Patients with renal impairment

No dosage adjustment is necessary for patients with creatinine clearance ≥30 ml/min (see section 5.2). The use of etoricoxib in patients with creatinine clearance <30 ml/min is contraindicated (see sections 4.3 and 4.4).

Paediatric population

Etoricoxib is contraindicated in children and adolescents under 16 years of age (see section 4.3).

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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any pf the excipients listed in section 6.1
- Active peptic ulceration or active gastrointestinal (GI) bleeding.
- Patients who, after taking acetylsalicylic or NSAIDs including COX-2 (cyclooxygenase-2) inhibitors, experience bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria, or allergictype reactions.
- Pregnancy and lactation (see sections 4.6 and 5.3).
- Severe hepatic dysfunction (serum albumin <25 g/1 or Child-Pugh score ≥10).
- Estimated renal creatinine clearance <30 ml/min.
- Children and adolescents under 16 years of age.
- Inflammatory bowel disease.
- Congestive heart failure (NYHA II-IV).
- Patients with hypertension whose blood pressure is persistently elevated above 140/90 mmHg and has not been adequately controlled.
- Established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease.

4.4 Special warnings and precautions for use *Gastrointestinal effects*

Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], some of them resulting in fatal outcome, have occurred in patients treated with etoricoxib.

Caution is advised with treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs; the elderly, patients using any other NSAID or acetylsalicylic acid concomitantly or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding.

There is a further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) when etoricoxib is taken concomitantly with acetylsalicylic acid (even at low doses). A significant difference in GI safety between selective COX-2 inhibitors + acetylsalicylic acid vs. NSAIDs + acetylsalicylic acid has not been demonstrated in longterm 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 reevaluated periodically, especially in patients with osteoarthritis (see sections 4.2, 4.3, 4.8 and 5.1).

Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with etoricoxib after careful consideration (see section 5.1).

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 (see sections above, 4.5 and 5.1.).

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 Antiinflammatory 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 preexisting 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 postmarketing 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 (see sections 4.6, 5.1, and 5.3).

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Oral anticoagulants: In subjects stabilised on chronic warfarin therapy, the administration of etoricoxib 120 mg daily was associated with an approximate 13% increase in prothrombin time International Normalised Ratio (INR). Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR, particularly in the first few days when therapy with etoricoxib is initiated or the dose of etoricoxib is changed (see section 4.4).

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

Acetylsalicylic Acid: In a study in healthy subjects, at steady state, etoricoxib 120 mg once daily had no effect on the anti-platelet activity of acetylsalicylic acid (81 mg once daily). Etoricoxib can be used concomitantly with acetylsalicylic acid at doses used for cardiovascular prophylaxis (low-dose acetylsalicylic acid). However, concomitant administration of low-dose acetylsalicylic acid with etoricoxib may result in an increased rate of GI ulceration or other complications compared to use of Etoricoxib alone.

Concomitant administration of etoricoxib with doses of acetylsalicylic acid above those for cardiovascular prophylaxis or with other NSAIDs is not recommended (see sections 5.1 and 4.4.).

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 methotrexaterelated 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 AUC024hr 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 thromboembolic events in women at risk).

Hormone Replacement Therapy (HRT): Administration of etoricoxib 120 mg with hormone replacement therapy consisting of conjugated estrogens (0.625 mg PREMARINTM) for 28 days, increased the mean steady state AUC0-24hr of unconjugated estrone (41%), equilin
(76%), and 17 β-estradiol (22%). 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 (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: Coadministration 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 coadministered 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.

4.6 Fertility, pregnancy and lactation

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 (see section 4.3). 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 (see sections 4.3 and 5.3).

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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 postmarketing experience (see 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, nonspecific 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	Uncommon
	perforation and bleeding, irritable bowel syndrome, pancreatitis‡	
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, flulike 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

In clinical studies, administration of single doses of etoricoxib up to 500 mg and multiple doses up to 150 mg/day for 21 days did not result in significant toxicity. There have been reports of acute overdosage with etoricoxib, although adverse experiences were not reported in the majority of cases. The most frequently observed adverse experiences were consistent with the safety profile for etoricoxib (e.g. gastrointestinal events, cardiorenal events).

In the event of overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the GI tract, employ clinical monitoring, and institute supportive therapy, if required.

Etoricoxib is not dialysable by haemodialysis; it is not known whether etoricoxib is dialysable by peritoneal dialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiinflammatory and antirheumatic products, nonsteroids, coxibs, ATC code: MO1 AH05

Mechanism of Action

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

Across clinical pharmacology studies, Etoricoxib produced dose-dependent inhibition of COX2 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.

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 stuidies 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 (0100 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 Longterm (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 gastroprotective 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. Cardiorenal 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 analyzed 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 nonstudy 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.

Cardiorenal 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 cardiorenal 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 patientyears 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 thromboembolic events. Selective COX2 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, placebocontrolled, parallelgroup 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 200mEq/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).

5.2 Pharmacokinetic properties

Absorption

Orally administered etoricoxib is well absorbed. The absolute bioavailability is approximately 100%. Following 120 mg oncedaily dosing to steady state, the peak plasma concentration (geometric mean Cmax = 3.6 µg/ml) was observed at approximately 1 hour (Tmax) after administration to fasted adults. The geometric mean area under the curve (AUC0-24hr) was 37.8 µg•hr/ml. The pharmacokinetics of etoricoxib are linear across the clinical dose range.

Dosing with food (a high-fat meal) had no effect on the extent of absorption of etoricoxib after administration of a 120-mg dose. The rate of absorption was affected, resulting in a 36% decrease in Cmax and an increase in Tmax by 2 hours. These data are not considered clinically significant. In clinical trials, etoricoxib was administered without regard to food intake.

Distribution

Etoricoxib is approximately 92% bound to human plasma protein over the range of concentrations of 0.05 to 5 µg/ml. The volume of distribution at steady state (Vdss) was approximately 1,20l in humans.

Etoricoxib crosses the placenta in rats and rabbits, and the blood-brain barrier in rats.

Biotransformation

Etoricoxib is extensively metabolised with <1% of a dose recovered in urine as the parent drug. The major route of metabolism to form the 6'-hydroxymethyl derivative is catalyzed by CYP enzymes. CYP3A4 appears to contribute to the metabolism of etoricoxib in vivo. In vitro studies indicate that CYP2D6, CYP2C9, CYP1A2 and CYP2C19 also can catalyse the main metabolic pathway, but their quantitative roles in vivo have not been studied. Five metabolites have been identified in man. The principal metabolite is the 6'carboxylic acid derivative of Etoricoxib formed by further oxidation of the 6'-hydroxymethyl derivative. These principal metabolites either demonstrate no measurable activity or are only weakly active as COX-2 inhibitors. None of these metabolites inhibit COX-1.

Elimination

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

Elimination of etoricoxib occurs almost exclusively through metabolism followed by renal excretion. Steady state concentrations of etoricoxib are reached within seven days of once daily administration of 120 mg, with an accumulation ratio of approximately 2, corresponding to a half-life of

approximately 22 hours. The plasma clearance after a 25-mg intravenous dose is estimated to be approximately 50 ml/min.

Characteristics in patients

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

Gender: The pharmacokinetics of etoricoxib are similar between men and women.

Hepatic impairment: Patients with mild hepatic dysfunction (Child-Pugh score 5-6) administered etoricoxib 60 mg once daily had an approximately 16% higher mean AUC as compared to healthy subjects given the same regimen. Patients with moderate hepatic dysfunction (Child-Pugh score 7-9) administered etoricoxib 60 mg every other day had similar mean AUC to the healthy subjects given etoricoxib 60 mg once daily; etoricoxib 30 mg once daily has not been studied in this population. There are no clinical or pharmacokinetic data in patients with severe hepatic dysfunction (Child-Pugh score ≥10). (See sections 4.2 and 4.3.)

Renal impairment: The pharmacokinetics of a single dose of etoricoxib 120 mg in patients with moderate to severe renal insufficiency and patients with end-stage renal disease on haemodialysis were not significantly different from those in healthy subjects. Haemodialysis contributed negligibly to elimination (dialysis clearance approximately 50 ml/min). (See sections 4.3 and 4.4.)

Paediatric patients: The pharmacokinetics of etoricoxib in paediatric patients (<12 years old) have not been studied.

In a pharmacokinetic study (n=16) conducted in adolescents (aged 12 to 17) the pharmacokinetics in adolescents weighing 40 to 60 kg given etoricoxib 60 mg once daily and adolescents >60 kg given etoricoxib 90 mg once daily were similar to the pharmacokinetics in adults given etoricoxib 90 mg once daily. Safety and effectiveness of etoricoxib in paediatric patients have not been established (see section 4.2).

5.3 Preclinical safety data

In preclinical studies, etoricoxib has been demonstrated not to be genotoxic. Etoricoxib was not carcinogenic in mice. Rats developed hepatocellular and thyroid follicular cell adenomas at >2times 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 106week 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 (see sections 4.3 and 4.6).

Etoricoxib is excreted in the milk of lactating rats at concentrations approximately two-fold those in plasma. There was a decrease in pup body weight following exposure of pups to milk from dams administered etoricoxib during lactation.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline Cellulose	USP
Corn Starch	USP
Methyl paraben Sodium	USP
Propyl Paraben Sodium	USP
Dibasic Calcium phosphate	USP
Povidone k-30	USP
Talc	USP
Magnesium stearate	USP
Sodium starch glycolate	USP
Colloidal Silicon Dioxide	USP
Purified water	USP
Coat SC- 1001 white for film Coat	IHS
Isopropyl Alcohol	USP
Methylene Chloride	USP
Talc	USP
Col. Quinoline yellow	USP
PEG-6000	USP

6.2
Incompatibilities
Not applicable.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container
10 tablets packed in ALU-ALU blister pack coded with batch number, manufacturing date and expiry date packed such 10 blisters packed in an inner carton with insert.

6.6 Special precautions for disposal and other handling No special requirements.