Dexcel® pharma

ETORIDEX™ 60, 90, 120 mg Film-coated Tablets

1. NAME OF THE MEDICINAL PRODUCT

ETORIDEX™ 60 mg Film-coated Tablets
ETORIDEX™ 90 mg Film-coated Tablets
ETORIDEX™ 120 mg Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 60, 90 or 120 mg of etoricoxib. For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

60 mg Tablets: Round dark green colored tablets.

90 mg Tablets: Round white colored tablets.

120 mg Tablets: Round pale green colored tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ETORIDEX™ tablets are indicated for:
- Symptomatic relief of osteoarthritis (OA),
- Rheumatoid arthritis (RA),
- Symptomatic relief of ankylosing spondylitis (AS),
- Pain and signs of inflammation associated with acute gouty arthritis,
- Treatment of acute pain, including that related to primary dysmenorrhea and minor dental procedures.

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

4.2 Posology and method of administration

ETORIDEX™ is administered orally and may be taken with or without food. The onset of drug effect may be faster when ETORIDEX™ is administered without food. This should be considered when rapid symptomatic relief is needed. ETORIDEX™ should be administered for the shortest duration possible and the lowest effective daily dose should be used.

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 Gouty Arthritis
The recommended dose is 120 mg once daily. Etoricoxib 120 mg should be used only for the acute symptomatic period, limited to a maximum of 8 days treatment. In clinical trials for acute gouty arthritis, etoricoxib was given for 8 days.

Acute Pain
For acute pain conditions, the recommended dose is 90 mg or 120 mg once daily. ETORIDEX™ should be used only for the acute symptomatic period, limited to a maximum of 8 days treatment.

Primary Dysmenorrhea
The recommended dose is 120 mg once daily.

Post-Procedure Dental Pain
The recommended dose is 90 mg once daily, limited to a maximum of 3 days. Some patients may require additional post-operative analgesia.

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 should not exceed 90 mg daily.
The dose for ankylosing spondylitis should not exceed 90 mg daily.
The dose for acute gout should not exceed 120 mg daily.
The dose for acute pain and primary dysmenorrhea should not exceed 120 mg daily.
The dose for post-procedure dental surgery pain should not exceed 90 mg daily.

As the cardiovascular risks of selective COX-2 inhibitors 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 (see 4.4 ' Special warnings and precautions for use').

Renal insufficiency: No dosage adjustment is necessary for patients with creatinine clearance ≥ 30 ml/min (see 5.2 ' Pharmacokinetic properties'). The use of etoricoxib in patients with creatinine clearance <30 ml/min is contra-indicated (see 4.3 ' Contra-indications' and 4.4 ' Special warnings and precautions for use').

Hepatic insufficiency: In patients with mild hepatic insufficiency (Child-Pugh score 5-6) a dose of 60 mg once daily should not be exceeded. In patients with moderate hepatic insufficiency (Child-Pugh score 7-9) the recommended dose of 60 mg every other day should not be exceeded; administration of 30 mg once daily can also be considered.
Clinical experience is limited, particularly in patients with moderate hepatic insufficiency and caution is advised. There is no clinical experience in patients with severe hepatic insufficiency (Child-Pugh score >9); therefore, its use is contra-indicated in these patients (see 4.3 Contra-indications, 4.4 ' Special warnings and precautions for use' and 5.2 ' Pharmacokinetic properties').

Paediatric use: Etoricoxib is contra-indicated in children and adolescents under 16 years of age (see 4.3 ' Contra-indications').

4.3 Contra-indications

Etoricoxib is contra-indicated in:
- patients with known hypersensitivity to etoricoxib or to any of the excipients of this medicinal product
- patients with congestive heart failure (NYHA II-IV)
- patients with established ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease (including patients who have recently undergone coronary artery bypass graft surgery or angioplasty)
- patients with hypertension whose blood pressure has not been adequately controlled
- patients with active peptic ulceration or gastro-intestinal (GI) bleeding
- patients with severe hepatic dysfunction (Child-Pugh score >9)
- patients with estimated creatinine clearance <30 ml/min
- patients who have developed signs of asthma, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria following the administration of acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs)
- pregnancy and lactation (see 4.6 ' Pregnancy and lactation' and 5.3 ' Preclinical safety data')
- children and adolescents under 16 years of age
- patients with inflammatory bowel disease

4.4 Special warnings and precautions for use

Cardiovascular effects
Clinical trials suggest that the selective COX-2 inhibitor class of drugs may be associated with an increased risk of thrombotic events (especially MI and stroke), relative to placebo and some NSAIDs (naproxen). As the cardiovascular risks of selective COX-2 inhibitors 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.

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

Selective COX-2 inhibitors are not a substitute for aspirin for cardiovascular prophylaxis because of their lack of effect on platelets. Because etoricoxib, a member of this class, does not inhibit platelet aggregation, antiplatelet therapies should not be discontinued.

There is a further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) for etoricoxib, other selective COX-2 inhibitors and NSAIDs, when taken concomitantly with acetylsalicylic acid (even at low doses). The relative difference in gastrointestinal safety between selective COX-2 inhibitors + acetylsalicylic acid vs. NSAIDs + acetylsalicylic acid has not been adequately evaluated in long-term clinical trials.

Renal effects
Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. 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 drugs known to inhibit prostaglandin synthesis, fluid retention, oedema and hypertension have been observed in patients taking etoricoxib. All Nonsteroidal Anti-inflammatory Drugs (NSAIDs), including etoricoxib, can be associated with new onset or recurrent congestive heart failure. For information regarding a dose related response for etoricoxib see section 5.1 ' Pharmacodynamic properties' . Caution should be exercised in patients with a history of cardiac failure, left ventricular dysfunction, or hypertension and in patients with pre-existing oedema from any other reason. If there is clinical evidence of deterioration in the condition of these patients, appropriate measures including discontinuation of etoricoxib should be taken. Etoricoxib may be associated with more frequent and severe hypertension than some other NSAIDs and selective COX-2 inhibitors, particularly at high doses. Therefore, hypertension should be controlled before treatment with etoricoxib (see section 4.3 ' Contraindications') 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.

Gastro-intestinal effects
In clinical studies, some patients treated with etoricoxib developed perforations, ulcers or bleeds (PUBs). Independent of treatment, patients with a history of gastro-intestinal (GI) perforation, ulcers and bleeding (PUB) and patients greater than 65 years of age are known to be at a higher risk for a PUB.

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
Medically appropriate supervision should be maintained when using etoricoxib in the elderly and in patients with renal, hepatic, or cardiac dysfunction. If these patients deteriorate during treatment, appropriate measures should be taken, including discontinuation of therapy.
Caution should be used when initiating treatment with etoricoxib in patients with dehydration. It is advisable to rehydrate patients prior to starting therapy with etoricoxib.

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs and some selective COX-2 inhibitors during post-marketing surveillance (see 4.8). These serious events may occur without warning.
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 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 or infection.

The use of etoricoxib, as with any drug known to inhibit cyclooxygenase/ prostaglandin synthesis, is not recommended in women attempting to conceive (see 4.6 ' Pregnancy and lactation' , 5.1 ' Pharmacodynamic properties' , and 5.3 ' Preclinical safety data').

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.

Diuretics, Angiotensin II Antagonists and ACE inhibitors: Reports suggest that NSAIDs, including selective COX-2 inhibitors may reduce the antihypertensive effect of diuretics, ACE inhibitors and Angiotensin II Antagonists. This interaction should be given consideration in patients taking etoricoxib concomitantly with these products.

In some patients with compromised renal function (e.g. elderly patients with compromised renal function or dehydrated patients, including those on diuretic therapy) the co-administration of an ACE inhibitor or Angiotension II Antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Therefore, the combination should be administered with caution, especially in the elderly.

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 results 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 5.1 ' Pharmacodynamic properties' and 4.4 ' Special warnings and precautions for use' .)

Cyclosporin and tacrolimus: Although this interaction has not been studied with etoricoxib, co-administration 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 mcg ethinyl estradiol (EE) and 0.5 to 1 mg norethindrone for 21 days increased the steady state $AUC_{0\text{-}24hr}$ of EE by 37%. etoricoxib 120 mg given with the same oral contraceptive either concomitantly or separated by 12 hours, increased the steady state $AUC_{0\text{-}24hr}$ of EE by 50 to 60%. This increase in EE concentration should be considered when selecting an oral contraceptive for use with etoricoxib. An increase in EE exposure can increase the incidence of adverse events associated with oral contraceptives (e.g. venous thrombo-embolic events in women at risk).

Hormone Replacement Therapy: Administration of etoricoxib 120 mg with hormone replacement therapy consisting of conjugated estrogens (0.625 mg PREMARIN™) for 28 days, increased the mean steady state $AUC_{0\text{-}24hr}$ of unconjugated estrone (41%), equilin (76%), and 17-β –estradiol (22%). The effect of the recommended chronic doses of etoricoxib (30,60 and 90 mg) has not been studied. The effects etoricoxib 120 mg on the exposure ($AUC_{0\text{-}24hr}$) to these estrogenic components of PREMARIN were less than half of those observed when PREMARIN was administered alone and the dose was increased from 0.625 to 1.25 mg. The clinical significance of these increases is unknown, and higher doses of PREMARIN were not studied in combination with etoricoxib. These increases in estrogenic concentration should be taken into consideration when selecting post-menopausal hormone therapy for use with etoricoxib because the increase in estrogen exposure might increase the risk of adverse events associated with hormone replacement therapy.

Prednisone/prednisolone: In drug-interaction studies, etoricoxib did not have clinically important effects on the pharmacokinetics of prednisone/prednisolone.

Digoxin: Etoricoxib 120 mg administered once daily for 10 days to healthy volunteers did not alter the steady-state plasma $AUC_{0\text{-}24hr}$ or renal elimination of digoxin. There was an increase in digoxin C_{max} (approximately 33%). This increase is not generally important for most patients. However, patients at high risk of digoxin toxicity should be monitored for this when etoricoxib and digoxin are administered concomitantly.

Effect of etoricoxib on drugs metabolised by sulfotransferases

Etoricoxib is an inhibitor of human sulfotransferase activity, particularly SULT1E1 and has been shown to increase the serum concentrations of ethinyl estradiol. While knowledge about effects of multiple sulfotransferases is presently limited and the clinical consequences for many drugs are still being examined, it may be prudent to exercise care when administering etoricoxib concurrently with other drugs primarily metabolised by human sulfotransferases (e.g. oral salbutamol and minoxidil).

Effect of etoricoxib on drugs metabolised by CYP isoenzymes

Based on in vitro studies, etoricoxib is not expected to inhibit cytochromes P450 (CYP) 1A2, 2C9, 2C19, 2D6, 2E1 or 3A4. In a study in healthy subjects, daily administration of etoricoxib 120 mg did not alter hepatic CYP3A4 activity as assessed by the erythromycin breath test.

Effects of other drugs on the pharmacokinetics of etoricoxib

The main pathway of etoricoxib metabolism is dependent on CYP enzymes. CYP3A4 appears to contribute to the metabolism of etoricoxib *in vivo.* In vitro studies indicate that CYP2D6, CYP2C9, CYP1A2 and CYP2C19 also can catalyse the main metabolic pathway, but their quantitative roles have not been studied *in vivo.*

Ketoconazole: Ketoconazole, a potent inhibitor of CYP3A4, dosed at 400 mg once a day for 11 days to healthy volunteers, did not have any clinically important effect on the single-dose pharmacokinetics of 60 mg etoricoxib (43% increase in AUC).

Rifampicin: Co-administration of etoricoxib with rifampicin, a potent inducer of CYP enzymes, produced a 65% decrease in etoricoxib plasma concentrations. This interaction may result in recurrence of symptoms when etoricoxib is co-administered with rifampicin. While this information may suggest an increase in dose, doses of etoricoxib greater than those listed for each indication have not been studied in combination with rifampicin and are therefore not recommended (see 4.2 ' Posology and method of administration').

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

4.6 Pregnancy and lactation

Pregnancy

The use of etoricoxib, as with any drug known to inhibit COX-2, is not recommended in women attempting to conceive.

No clinical data on exposed pregnancies are available for etoricoxib. Studies in animals have shown reproductive toxicity (see 5.3 ' Preclinical safety data'). The potential for human risk in pregnancy is unknown. Etoricoxib, as with other drugs inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus during the last trimester. Etoricoxib is contra-indicated in all trimesters of pregnancy (see 4.3 ' Contra-indications'). If a woman becomes pregnant during treatment, etoricoxib should be discontinued.

Breast-feeding mothers

It is not known whether etoricoxib is excreted in human milk. Etoricoxib is excreted in the milk of lactating rats. Women who use etoricoxib should not breast feed. (See 4.3 ' Contra-indications' and 5.3 ' Preclinical safety data' .)

4.7 Effects on ability to drive and use machines

No studies on the effect of etoricoxib on the ability to drive or use machines have been performed. However, patients who experience dizziness, vertigo or somnolence while taking etoricoxib should refrain from driving or operating machinery.

4.8 Undesirable effects

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 a cardiovascular safety outcomes program 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 program are presented in section 5.1.

In clinical studies the following undesirable effects were reported at an incidence greater than placebo in patients with OA, RA, chronic low back pain or ankylosing spondylitis treated with etoricoxib 30 mg, 60 mg or 90 mg for up to 12 weeks or in the MEDAL Program studies.

[Common (≥ 1/100, <1/10) Uncommon (≥ 1/1000, <1/100) Rare (≥1/10,000, <1/1,000) Very rare (<1/10,000), not known (cannot be estimated from the available data)]

Infections and infestations:
Uncommon: gastro-enteritis, upper respiratory infection, urinary tract infection.

Immune system disorder:
Very rare: drug hypersensitivity.

Metabolism and nutrition disorders:
Common: oedema/fluid retention
Uncommon: appetite increase or decrease, weight gain.

Psychiatric disorders:
Uncommon: anxiety, depression, mental acuity decreased.

Nervous system disorder:
Common: dizziness, headache.
Uncommon: dysgeusia, insomnia, paraesthesia/hypaesthesia, somnolence.

Eye disorders:
Uncommon: blurred vision.

Ear and labyrinth disorders:
Uncommon: tinnitus.

Cardiac disorders:
Uncommon: atrial fibrillation, congestive heart failure, non-specific ECG changes.
Very rare: myocardial infarction.

Vascular disorders:
Common: hypertension
Uncommon: flushing.
Very rare: cerebrovascular accident.

Respiratory, thoracic and mediastinal disorders:
Uncommon: cough, dyspnoea, epistaxis.

Gastro-intestinal disorders:
Common: gastro-intestinal disorders (e.g. abdominal pain, flatulence, heartburn), diarrhoea, dyspepsia, epigastric discomfort, nausea.
Uncommon: abdominal distention, acid reflux, bowel movement pattern change, constipation, dry mouth, gastroduodenal ulcer, irritable bowel syndrome, oesophagitis, oral ulcer, vomiting, gastritis.
Very Rare: gastro-intestinal perforation and bleeding.

Skin and subcutaneous tissue disorders:
Uncommon: ecchymosis, facial oedema, pruritus, rash.

Musculoskeletal, connective tissue and bone disorders:
Uncommon: muscular cramp/spasm, musculoskeletal pain/stiffness.

Renal and urinary disorders:
Uncommon: proteinuria.

General disorders and administration site conditions:
Common: asthenia/fatigue, flu-like disease.
Uncommon: chest pain.

Investigations:
Common: ALT increased, AST increased.
Uncommon: blood urea nitrogen increased, creatine phosphokinase increased, haematocrit decreased, haemoglobin decreased, hyperkalaemia, leukocytes decreased, platelets decreased, serum creatinine increased, uric acid increased. 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 combined analysis of phase IIb to V clinical studies of 4 weeks duration or longer (excluding the MEDAL Program Studies), there was no discernible difference in the rate of confirmed thrombotic cardiovascular serious adverse events between patients receiving etoricoxib ≥30 mg or non-naproxen NSAIDs. The rate of these events was higher in patients receiving etoricoxib compared with those receiving naproxen 500 mg twice daily.

In a clinical study for ankylosing spondylitis, patients were treated with Etoricoxib 90 mg once daily for up to 1 year (N=126). In another clinical study for ankylosing spondylitis (N-857), patients were treated with Etoricoxib 60 mg or 90 mg once daily for up to 26 weeks. The adverse experience profile in these studies was generally similar to that reported in chronic studies in OA, RA and chronic low back pain.

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 initial clinical studies for acute analgesia, patients were treated with Etoricoxib 120 mg once daily for one to seven days. The adverse experience profile in these studies was generally similar to that reported in the combined OA, RA, and chronic low back pain studies.

In additional clinical studies for acute post-operative pain including 1222 patients treated

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with Etoricoxib (90 mg or 120 mg), the adverse experience profile was generally similar to that reported in the combined OA, RA, and chronic low back pain studies.
In the combined studies for acute post-operative dental pain, the incidence of post-dental extraction alveolitis (dry socket) reported in patients treated with Etoricoxib was similar to that of patients treated with active comparators.

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; hepatotoxicity including hepatic failure and pancreatitis.

Post-marketing experience

The following adverse reactions have been reported in post-marketing experience:
Blood and lymphatic system disorders: thrombocytopenia.
Immune system disorders: hypersensitivity reactions, anaphylactic/anaphylactoid reactions, including shock.
Metabolism and nutrition disorders: hyperkalemia
Psychiatric disorders: anxiety, insomnia, confusion, hallucinations, depression, restlessness.
Nervous *system disorders:* dysgeusia, somnolence.
Cardiac disorders: congestive heart failure, palpitations, angina, arrhythmia
Vascular disorders: hypertensive crisis.
Respiratory, thoracic and mediastinal disorders: bronchospasm.
Gastrointestinal disorders: abdominal pain, oral ulcers, peptic ulcers including perforation and bleeding (mainly in elderly patients), vomiting, diarrhea.
Hepatobiliary disorders: hepatitis, jaundice, hepatic failure.
Skin and subcutaneous tissue disorders: angioedema, pruritus, erythema, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, fixed drug eruption.
Renal and urinary disorders: renal insufficiency, including renal failure (see Special warnings and precautions for use).

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, renovascular 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: Anti-inflammatory and antirheumatic products, non-steroids, coxibs

ATC Code: MO1 AH05
Etoricoxib, a non-steroidal anti-inflammatory drug (NSAID), is an orally active, highly selective cyclo-oxygenase-2 (COX-2) inhibitor within the clinical dose range. Selective inhibition of COX-2 by etoricoxib provides anti-inflammatory and analgesic effects.
Across clinical pharmacology studies, Etoricoxib produced dose-dependent inhibition of COX-2 without inhibition of COX-1 at doses up to 150 mg daily. The influence on gastroprotective COX-1 activity was also assessed in a clinical study where prostaglandin synthesis was measured in gastric biopsy samples from subjects administered either Etoricoxib 120 mg daily, naproxen 500 mg twice daily, or placebo.
Etoricoxib did not inhibit gastric prostaglandin synthesis as compared to placebo. In contrast, naproxen inhibited gastric prostaglandin synthesis by approximately 80% compared with placebo. These data further support the COX-2 selectivity of Etoricoxib.
In patients with osteoarthritis (OA), etoricoxib 60 mg once daily provided significant improvements in pain and patient assessments of disease status. These beneficial effects were observed as early as the second day of therapy and maintained for up to 52 weeks. Studies with etoricoxib 30 mg once daily demonstrated efficacy superior to placebo over a 12 week treatment period (using similar assessments as the above studies). In a dose ranging study, etoricoxib 60 mg demonstrated significantly greater improvement than 30 mg for all 3 primary endpoints over 6 weeks of treatment. The 30 mg dose has not been studied in osteoarthritis of hands.
In patients with rheumatoid arthritis (RA), etoricoxib 60 mg and 90 mg once daily both provided significant improvements in pain, inflammation, and mobility. In studies evaluating the 60 mg and 90 mg dose, these beneficial effects were maintained over the 12-week treatment periods. In a study evaluating the 60 mg dose compared to the 90 mg dose, etoricoxib 60 mg once daily and 90 mg once daily were both more effective than placebo. The 90 mg dose was superior to the 60 mg dose for Patient Global Assessment of Pain (0-100mm visual analogue scale), with an average improvement of -2.71 mm (95% CI: -4.98 mm, -0.45 mm).

Ankylosing Spondylitis (AS)
Etoricoxib has demonstrated significant improvements in spine pain, inflammation, stiffness, function and mobility. Etoricoxib was evaluated for the treatment of AS in a 52- week, two-part, double-blind, parallel group clinical trial that enrolled approximately 400 patients. In the 6-week placebo-controlled portion of the study, Etoricoxib 90 mg once daily was superior to placebo on all primary endpoints (patient assessment of spine pain, patient assessment of disease activity and Bath AS Functional Index assessment). Additionally, Etoricoxib 90 mg demonstrated statistically greater treatment effects than naproxen 500 mg twice daily in patient assessment of spine pain and patient assessment of disease activity in the 6-week placebo-controlled portion of the study. The beneficial effects of Etoricoxib 90 mg were maintained throughout the 52-week double-blind, active-comparator treatment period. Etoricoxib demonstrated statistically greater treatment effects than naproxen for assessments of spine pain, inflammation, stiffness and function for 1 year. The clinical benefit of etoricoxib was observed as early as 4 hours after initiation of treatment. A 120 mg once daily dose of Etoricoxib was also studied; however, no additional efficacy was seen compared to the 90 mg dose.

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 1000 mg daily. Among inadequate responders to 60 mg daily for 6 weeks, dose escalation to 90 mg daily improved spinal pain intensity score (0-100mm 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).

Acute Pain
Acute Gouty Arthritis

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 studies specifically designed to measure the onset of action of etoricoxib, the onset of action occurred as early as 24 minutes after dosing.

Acute Pain including Primary Dysmenorrhea and Post-Operative Surgical Pain
In single-dose clinical studies which treated approximately 1200 patients, Etoricoxib relieved moderate-to-severe pain in acute analgesic models of post-operative dental pain and primary dysmenorrhea. The analgesic effect of a 120 mg dose of Etoricoxib was similar to a maximum analgesic dose of naproxen sodium (550 mg) or ibuprofen (400 mg) and greater than acetaminophen (600 mg) with codeine (60 mg). The onset of analgesia with Etoricoxib occurred as early as 24 minutes after dosing and persisted for as long as 24 hours.

In a multiple-dose post-dental surgery study, Etoricoxib 90 mg administered once daily for up to three days provided a significantly greater analgesic effect compared to placebo. Etoricoxib 90 mg provided a shorter time to onset and longer duration of pain relief, greater peak pain relief, in addition to a lower use of rescue analgesic medication following the initial first day dose compared to placebo. Etoricoxib 90 mg was non-inferior to ibuprofen 600 mg Q6h, and superior to acetaminophen/codeine 600 mg/60 mg Q6h in total pain relief.

Chronic Low Back Pain
Etoricoxib relieved pain in studies of patients with chronic low back pain (approximately 650 patients). The analgesic effect of Etoricoxib was shown by measures of pain-related responses (e.g., pain symptoms, mobility, patient and investigator assessments of therapy). Etoricoxib 60 mg once daily demonstrated significant efficacy within one week of treatment (the first determination). A reduction of chronic low back pain was maintained in patients treated with Etoricoxib over the 12-week, placebo-controlled treatment period.

Safety

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

The MEDAL Program was a prospectively designed Cardiovascular (CV) Safety Outcomes Program 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 7111 OA patients treated with a dose of etoricoxib 90 mg daily (1.5 to 3 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 4086 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 Program, 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 Program 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 1: Rates of Confirmed Thrombotic CV Events (Pooled MEDAL Program)

	Etoricoxib (N=16819) 25836 Patient-Years	Diclofenac (N=16483) 24766 Patient-Years	Between Treatment Comparison
	Rate† (95% CI)	Rate† (95% CI)	Relative Risk (95% CI)
Confirmed Thrombotic Cardiovascular Serious Adverse Events			
Per-protocol	1.24 (1.11, 1.38)	1.30 (1.17, 1.45)	0.95 (0.81, 1.11)
Intent-to-treat	1.25 (1.14, 1.36)	1.19 (1.08, 1.30)	1.05 (0.93, 1.19)
Confirmed Cardiac Events			
Per-protocol	0.71 (0.61, 0.82)	0.78 (0.68, 0.90)	0.90 (0.74, 1.10)
Intent-to-treat	0.69 (0.61, 0.78)	0.70 (0.62, 0.79)	0.99 (0.84, 1.17)
Confirmed Cerebrovascular Events			
Per-protocol	0.34 (0.28, 0.42)	0.32 (0.25, 0.40)	1.08 (0.80, 1.46)
Intent-to-treat	0.33 (0.28, 0.39)	0.29 (0.24, 0.35)	1.12 (0.87, 1.44)
Confirmed Peripheral Vascular Events			
Per-protocol	0.20 (0.15, 0.27)	0.22 (0.17, 0.29)	0.92 (0.63, 1.35)
Intent-to-treat	0.24 (0.20, 0.30)	0.23 (0.18, 0.28)	1.08 (0.81, 1.44)

† Events per 100 Patient-Years; CI=confidence interval
N=total number of patients included in Per-protocol population

Per-protocol: all events on study therapy or within 14 days of discontinuation (excluded: patients who took < 75% of their study medication or took non-study NSAIDs >10% of the time).

Intent-to-treat: all confirmed events up to the end of the trial (included patients potentially exposed to non-study interventions following discontinuation of study medication). Total number of patients randomised, n= 17412 on etoricoxib and 17289 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 edema-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 Program 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 edema, and up to 1.1% for congestive heart failure, with higher rates of discontinuation observed with etoricoxib 90 mg than etoricoxib 60 mg.

MEDAL Program 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 Program. The rates of discontinuations due to adverse clinical GI events per hundred patient-years over the entire period of study were as follows: 3.23 for etoricoxib and 4.96 for diclofenac in the MEDAL Study; 9.12 with etoricoxib and 12.28 with diclofenac in the EDGE study; and 3.71 with etoricoxib and 4.81 with diclofenac in the EDGE II study.

MEDAL Program 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 hemorrhage 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 hemorrhage, (POBs)) were not significantly different between etoricoxib and diclofenac.

MEDAL Program 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 Program, 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 Program were non-serious.

Gastrointestinal Safety Studies
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.

Gastrointestinal Clinical Tolerability Combined Analysis
A prespecified, combined analysis of eight clinical trials of approximately 4,000 patients with OA, RA, or chronic low back pain assessed the incidence rate for the following end-points: 1) discontinuation for upper GI symptoms; 2) discontinuation for any GI adverse experiences; 3) new use of gastroprotective medications (including H2 receptor antagonists, misoprostol, and proton pump inhibitors); and 4) new use of any GI medications. There was an approximate 50% risk reduction for these end-points in patients treated with etoricoxib (60, 90 or 120 mg daily) as compared to patients treated with nonselective NSAIDs (naproxen 500 mg twice daily or diclofenac 50 mg three times daily). There were no statistically significant differences between etoricoxib and placebo.

Additional Thrombotic Cardiovascular Safety Data
In a combined analysis of all phase IIb to V clinical studies of 4 weeks duration or longer (excluding the MEDAL Program Studies), there was no discernible difference in the rate of confirmed thrombotic cardiovascular serious adverse events between patients receiving etoricoxib ≥ 30 mg (n=2147 patients; mean duration of exposure approximately 309 days) or non-naproxen NSAIDs (ibuprofen 2400 mg daily or diclofenac 150 mg daily, n=1470 patients; mean duration of exposure approximately 161 days). The rate of these events was higher in patients receiving etoricoxib (n=1960 patients; mean duration of exposure approximately 462 days) compared with those receiving naproxen 500 mg twice daily (n=1497 patients; mean duration of exposure approximately 421 days). The difference in antiplatelet activity between some COX-1 inhibiting NSAIDs and selective COX-2 inhibitors may be of clinical significance in patients at risk of thrombo-embolic events. Selective COX-2 inhibitors reduce the formation of systemic (and therefore possibly endothelial) prostacyclin without affecting platelet thromboxane.

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

5.2 Pharmacokinetic properties

Absorption
Orally administered etoricoxib is well absorbed. The absolute bioavailability is approximately 100%. Following 120 mg once-daily dosing to steady state, the peak plasma concentration (geometric mean C_{max} = 3.6 µg/ml) was observed at approximately 1 hour (T_{max}) after administration to fasted adults. The geometric mean area under the curve (AUC_{0-24hr}) was 37.8 µg• hr/ml. The pharmacokinetics of etoricoxib are linear across the clinical dose range.

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

Distribution
Etoricoxib is approximately 92% bound to human plasma protein over the range of concentrations of 0.05 to 5 µg/ml. The volume of distribution at steady state (V_{dss}) was approximately 120 L in humans.

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

Metabolism
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 catalysed 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: 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 insufficiency: Patients with mild hepatic insufficiency (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 insufficiency (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 insufficiency (Child-Pugh score >9). (See 4.2 ' Posology and method of administration' and 4.3 ' Contra-indications' .)

Renal insufficiency: 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 4.3 ' Contra-indications' and 4.4 ' Special warnings and precautions for use' .)

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 4.2 ' Posology and method of administration, Paediatric use' .)

5.3 Preclinical safety data

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

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

Etoricoxib was not teratogenic in reproductive toxicity studies conducted in rats at 15 mg/kg/day (this represents approximately 1.5 times the daily human dose [90 mg] based on systemic exposure). In rabbits, no treatment-related external or skeletal foetal malformations were seen. At doses approximately 2 times the adult human exposure (90 mg) based on systemic exposure, a low incidence of cardiovascular malformations and increases in post implantation loss were observed in etoricoxib-treated rabbits. No developmental effects were seen at systemic exposure of approximately equal to or less than the daily human dosage (90mg). In rats and rabbits, no embryo/foetal effects were seen at systemic exposures equal to or less than those at the daily human dose [90 mg]. However, there was a decrease in embryo/foetal survival at exposures greater than or equal to 1.5 times the human exposure. (See 4.3 ' Contra-indications' and 4.6 ' Pregnancy and lactation'.)

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

In addition to the active ingredient, the medicine also contains:
Lactose monohydrate, Microcrystalline cellulose, Povidone, Croscarmellose sodium, Hyperomellose (E464), Magnesium stearate, Titanium dioxide (E171), Triacetin (E1518), Carnauba wax.

ETORIDEX™ 60 and 120 mg tablets contain:
Lake brilliant blue (E133), Lake quinolone yellow (E104) and Iron oxide yellow (E172).

6.2 Incompatibilities
Not applicable.

6.3 Shelf-life
Refer to outer carton.

6.4 Special precautions for storage
Refer to outer carton.

6.5 Nature and contents of container

ETORIDEX™ Tablets 60-, 90- and 120-mg are packed in 10 tablets/blister x 10' .

6.6 Name of Batch Releaser
Dexcel Ltd., 1 Dexcel St., Or-Akiva 3060000, Israel.

6.7 Name of Product Owner
AmediusTec Ltd., 9 Raffles Place, Republic Plaza, #27-00, Singapore 048619

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