SUMMARY OF PRODUCT CHARACTERISTICS FOR MEDICAL USE OF DRUG

1. NAME OF THE MEDICINAL PRODUCT
ARCOXIA 60 mg film-coated tablets
ARCOXIA 90 mg film-coated tablets
ARCOXIA 120 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
2.1. Qualitative composition
Etoricoxib.

2.2 Quantitative composition
Each film-coated tablet contains
active substance: 60, 90 or 120 mg of etoricoxib.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablets.
60 mg tablets: Dark green, apple-shaped, biconvex tablets debossed 'ARCOXIA 60' on one side and '200' on the other side.
90 mg tablets: White, apple-shaped, biconvex tablets debossed 'ARCOXIA 90' on one side and '202' on the other side.
120 mg tablets: Pale-green, apple-shaped, biconvex tablets debossed 'ARCOXIA 120' on one side and '204' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
For the symptomatic relief of osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis, and the pain and signs of inflammation associated with acute gouty arthritis.
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.

4.2. Posology and method of administration

Posology
ARCOXIA is administered orally and may be taken with or without food. The onset of the effect of the medicinal product may be faster when ARCOXIA is administered before meals. This should be considered when rapid symptomatic relief is needed.
As the cardiovascular risks of etoricoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis.
Osteoarthritis
Etoricoxib under the trade name ARCOXIA is not marketed in the 30 mg strength. 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 or 90 mg once daily. The minimum effective daily dose is 60 mg once daily. In some patients, 90 mg once daily may provide increased therapeutic benefit.

Ankylosing spondylitis

The recommended dose is 60 mg or 90 mg once daily. The minimum effective daily dose is 60 mg once daily. In some patients, 90 mg once daily may provide increased therapeutic benefit.

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 additional postoperative 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 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.

Elderly

No dosage adjustment is necessary for elderly patients. As with other drugs, caution should be exercised in elderly patients.

Hepatic insufficiency

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 60 mg ***once every two days*** should not be exceeded; administration of 30 mg once daily can also be considered.

Clinical experience is limited particularly in patients with moderate hepatic dysfunction and caution is advised. There is no clinical experience in patients with severe hepatic dysfunction (Child-Pugh score ≥10); therefore, its use is contra-indicated in these patients.

Renal insufficiency

No dosage adjustment is necessary for patients with creatinine clearance ≥30 ml/min. The use of etoricoxib in patients with creatinine clearance <30 ml/min is contra-indicated.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Active peptic ulceration or active gastro-intestinal bleeding.
- Patients who have experienced bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria, or other allergic-type reactions after taking acetylsalicylic acid or NSAIDs including COX-2 (cyclo-oxygenase-2) inhibitors.
- Pregnancy and lactation.
- Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score ≥10).
- Estimated renal creatinine clearance <30 ml/min.
- Children and adolescents under 16 years of age.
- Inflammatory bowel disease.
- Congestive heart failure (NYHA II-IV).
- Patients with hypertension whose blood pressure is persistently elevated above 140/90 mmHg and has not been adequately controlled.
- Established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease.

4.4 Special warnings and precautions for use

Gastrointestinal effects

Upper gastrointestinal (GI) complications (perforations, ulcers or bleedings), 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 (patients using any other NSAID or acetylsalicylic acid concomitantly or patients with a prior history of gastrointestinal disease, such as ulceration and gastrointestinal bleeding).

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

Cardiovascular effects

Clinical trials suggest that the selective COX-2 inhibitor class of drugs may be associated with a risk of thrombotic events (especially myocardial infarction (MI) and stroke), relative to placebo and some NSAIDs. As the cardiovascular risks of etoricoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used.

The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis.

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

COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of antiplatelet effect. Therefore antiplatelet therapies should not be discontinued.

Renal effects

Renal prostaglandins may play a compensatory role in the maintenance of renal perfusion. Therefore, under conditions of compromised renal perfusion, administration of etoricoxib may cause a reduction in prostaglandin formation and, secondarily, in renal blood flow, and thereby impair renal function. Patients at greatest risk of this response are those with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis. Monitoring of renal function in such patients should be considered.

Fluid retention, oedema and hypertension

As with other medicinal products known to inhibit prostaglandin synthesis, fluid retention, oedema and hypertension have been observed in some patients taking etoricoxib. All NSAIDs, including etoricoxib, can be associated with new onset or recurrent congestive heart failure. Caution should be exercised in patients with a history of cardiac failure, left ventricular dysfunction, or hypertension and in patients with pre-existing oedema from any other reason. If there is clinical evidence of deterioration in the condition of these patients, appropriate measures including discontinuation of etoricoxib should be taken.

Etoricoxib may be associated with more frequent and severe hypertension than some other NSAIDs and selective COX-2 inhibitors, particularly at high doses. Therefore, hypertension should be controlled before treatment with etoricoxib and special attention should be paid to blood pressure monitoring during treatment with etoricoxib. Blood pressure should be monitored within two weeks after initiation of treatment and periodically thereafter. If blood pressure rises significantly, alternative treatment should be considered.

Hepatic effects

Elevations of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials treated for up to one year with etoricoxib 30, 60 and 90 mg daily.

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

abnormal liver function tests (three times the upper limit of normal) are detected, etoricoxib should be discontinued.

General

If during treatment, patients deteriorate in any of the organ system functions described above, appropriate measures should be taken and discontinuation of etoricoxib therapy should be considered. Medically appropriate supervision should be maintained when using etoricoxib in the elderly and in patients with renal, hepatic, or cardiac dysfunction.

Caution should be used when initiating treatment with etoricoxib in patients with dehydration. It is advisable to rehydrate patients prior to starting therapy with etoricoxib.

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

Etoricoxib may mask fever and other signs of inflammation.

Caution should be exercised when co-administering etoricoxib with warfarin or other oral anticoagulants.

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

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

4.5. Interactions with other medicinal products

Pharmacodynamic interactions.

Oral anticoagulants. In subjects stabilized on chronic warfarin therapy, the administration of etoricoxib 120 mg daily was associated with an approximate 13% increase in prothrombin time International Normalized 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, angeotensin converting enzyme (ACE) inhibitors and angiotensin II antagonists. NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking etoricoxib concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Acetylsalicylic acid. In a study in healthy subjects, at steady state, etoricoxib 120 mg once daily had no effect on the anti-platelet activity of acetylsalicylic acid (81 mg once daily). Etoricoxib can be used concomitantly with acetylsalicylic acid at doses used for cardiovascular prophylaxis (low-dose acetylsalicylic acid). However, concomitant administration of low-dose acetylsalicylic acid with etoricoxib may result in an increased rate of GI ulceration or other complications compared to use of etoricoxib alone. Concomitant administration of etoricoxib with doses of acetylsalicylic acid *above* those for cardiovascular prophylaxis or with other NSAIDs is not recommended.

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

Pharmacokinetic interactions.

The effect of etoricoxib on the pharmacokinetics of other drugs

Lithium. NSAIDs decrease lithium renal excretion and therefore increase lithium plasma levels. If necessary, monitor blood lithium closely and adjust the lithium dosage while the combination is being taken and when the NSAID is withdrawn.

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

Oral contraceptives. Etoricoxib 60 mg given concomitantly with an oral contraceptive containing 35 micrograms ethinyl estradiol (EE) and 0.5 to 1 mg norethindrone for 21 days increased the steady state $AUC_{0\text{-}24hr}$ of EE by 37%. Etoricoxib 120 mg given with the same oral contraceptive concomitantly or separated by 12 hours, increased the steady state $AUC_{0\text{-}24hr}$ of EE by 50 to 60%. This increase in EE concentration should be considered when selecting an oral contraceptive for use with etoricoxib. An increase in EE exposure can increase the incidence of adverse events associated with oral contraceptives (e.g., venous thrombo-embolic events in women at risk).

Hormone replacement therapy.: Administration of etoricoxib 120 mg with hormone replacement therapy consisting of conjugated estrogens (0.625 mg PREMARIN^{TM}) for 28 days, increased the mean steady state $AUC_{0\text{-}24hr}$ of unconjugated estrone (41%), equilin (76%), and 17-β-estradiol (22%). The effect of the recommended chronic doses of etoricoxib (30, 60, and 90 mg) has not been studied.

The effects of etoricoxib 120 mg on the exposure ($AUC_{0\text{-}24hr}$) to these estrogenic components of PREMARIN were less than half of those observed when PREMARIN was administered alone and the dose was increased from 0.625 to 1.25 mg. The clinical significance of these increases is unknown, and higher doses of PREMARIN were not studied in combination with etoricoxib. These increases in estrogenic concentration should be taken into consideration when selecting post-menopausal hormone therapy for use with etoricoxib because the increase in 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 metabolized 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 metabolized by human sulfotransferases (e.g., oral salbutamol and minoxidil).

Effect of etoricoxib on drugs metabolized 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 catalyze 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.
Antacids. Antacids do not affect the pharmacokinetics of etoricoxib to a clinically relevant extent.

4.6 Fertility, pregnancy and lactation
Pregnancy. The use of etoricoxib, as with any drug substance 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. The potential for human risk in pregnancy is unknown. Etoricoxib, as with other medicinal products inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus during the last trimester. Etoricoxib is contraindicated in pregnancy. If a woman becomes pregnant during treatment, etoricoxib must be discontinued.
Lactation. 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.

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 9295 individuals, including 5774 patients with OA, RA or chronic low back pain (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 8 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 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.
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.
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 for up to 12 weeks, or in the MEDAL Program studies, in short term studies for acute pain or in post-marketing experience:
The incidence is specified as follows: 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), Not Known (cannot be estimated from the available data).
*Infections and infestations**:** common:* alveolar osteitis***;*** uncommon - gastroenteritis, upper respiratory infection, urinary tract infection.
*Blood and lymphatic system disorders**:*** uncommon - anemia (primarily associated with gastrointestinal bleeding), leukopenia, thrombocytopenia.

Immune system disorders: very rare - hypersensitivity reactions, including angioedema, anaphylactic/anaphylactoid reactions including shock.
Metabolism and nutrition disorders: common - oedema/fluid retention; uncommon - appetite increase or decrease, weight gain.
Psychiatric disorders: uncommon - anxiety, depression, mental acuity decreased; very rare - confusion, hallucinations; not known - restlessness.
Nervous system disorders: common - dizziness, headache; uncommon - dysgeusia, insomnia, paresthaesia/hypaesthesia, somnolence.
Eye disorders: uncommon - blurred vision, conjunctivitis.
Ear and labyrinth disorders: uncommon - tinnitus, vertigo.
Cardiac disorders: common – palpitations; uncommon - atrial fibrillation, congestive heart failure, non-specific ECG changes, angina pectoris, myocardial infarction*; not known - tachycardia, arrhythmia.
Vascular disorders: common – hypertension; uncommon - flushing, cerebrovascular accident*, transient ischaemic attack; very rare - hypertensive crisis.
* 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).
Respiratory, thoracic and mediastinal disorders: uncommon - cough, dyspnoea, epistaxis; very rare - bronchospasm.
Gastrointestinal disorders: common - gastrointestinal disorders (e.g., abdominal pain, flatulence, heartburn), diarrhea, 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 - peptic ulcers including gastrointestinal perforation and bleeding (mainly in the elderly); not known - pancreatitis.
Hepatobiliary disorders: common - ALT increased, AST increased; very rare – hepatitis; not known – jaundice.
Skin and subcutaneous tissue disorders: common – ecchymosis; uncommon - facial oedema, pruritus, rash; rare – erythema; very rare - urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis; not known - fixed drug eruption.
Musculoskeletal, connective tissue and bone disorders: uncommon - muscular cramp/spasm, musculoskeletal pain/stiffness.
Renal and urinary disorders: uncommon - proteinuria, serum creatinine increased; very rare - renal insufficiency, including renal failure.
General disorders and administration site conditions: common - asthenia/fatigue, flu-like disease; uncommon - chest pain.
Investigations: uncommon - blood urea nitrogen increased, creatine phosphokinase increased, hyperkalemia, uric acid increased; rare - blood sodium decreased.
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.

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 gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required.
Etoricoxib is not dialyzable by haemodialysis; it is not known whether etoricoxib is dialyzable by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory , non-steroids, coxibs.
ATC code: M01 AH05.
Mechanism of action
Etoricoxib is an oral, selective cyclo-oxygenase-2 (COX-2) inhibitor within the clinical dose range.
Across clinical pharmacology studies, ARCOXIA produced dose-dependent inhibition of COX-2 without inhibition of COX-1 at doses up to 150 mg daily. Etoricoxib did not inhibit gastric prostaglandin synthesis and had no effect on platelet function.
Cyclooxygenase is responsible for generation of prostaglandins. Two isoforms, COX-1 and COX-2, have been identified. COX-2 is the isoform of the enzyme that has been shown to be induced by pro-inflammatory stimuli and has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. COX-2 is also involved in ovulation, implantation and closure of the ductus arteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in man but its relevance to ulcer healing has not been established.

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 Cmax= 3.6 µg/ml) was observed at approximately 1hour (T_{max}) after administration to fasted adults. The geometric mean area under the curve (AUC_{0-24hr}) was 37.8µg•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 120 l in humans. Etoricoxib crosses the placenta in rats and rabbits, and the blood-brain barrier in rats.
Biotransformation
Etoricoxib is extensively metabolised with <1% of a dose recovered in urine as the parent drug. The major route of metabolism to form the 6'-hydroxymethyl derivative is catalyzed by CYP enzymes. CYP3A4 appears to contribute to the metabolism of etoricoxib *in vivo*. *In vitro* studies indicate that CYP2D6, CYP2C9, CYP1A2 and CYP2C19 also can catalyse the main metabolic pathway, but their quantitative roles *in vivo* have not been studied.
Five metabolites have been identified in man. The principal metabolite is the 6'-carboxylic acid derivative of etoricoxib formed by further oxidation of the 6'-hydroxymethyl derivative. These principal metabolites either demonstrate no measurable activity or are only weakly active as COX-2 inhibitors. None of these metabolites inhibit COX-1.
Elimination
Following administration of a single 25-mg radiolabeled intravenous dose of etoricoxib to healthy subjects, 70% of radioactivity was recovered in urine and 20% in faeces, mostly as metabolites. Less than 2% was recovered as unchanged drug.
Elimination of etoricoxib occurs almost exclusively through metabolism followed by renal excretion.
Steady state concentrations of etoricoxib are reached within seven days of once daily administration of 120 mg, with an accumulation ratio of approximately 2, corresponding to a half-life of approximately

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

Characteristics in patients

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

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

Hepatic impairment: Patients with mild hepatic dysfunction (Child-Pugh score 5-6) administered etoricoxib 60 mg once daily had an approximately 16% higher mean AUC as compared to healthy subjects given the same regimen. Patients with moderate hepatic dysfunction (Child-Pugh score 7-9) administered etoricoxib 60 mg every other dayhad 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 hemodialysis were not significantly different from those in healthy subjects. Hemodialysis 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 andadolescents >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 >2-times the daily human dose [90 mg] based on systemic exposure when dosed daily for approximately two years.

Hepatocellular and thyroid follicular cell adenomas observed in rats are considered to be a consequence of rat-specific mechanism related to hepatic CYP enzyme induction. Etoricoxib has not been shown to cause hepatic CYP3A enzyme induction in humans.

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

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

Core:

Calcium hydrogen phosphate (anhydrous)

Croscarmellose sodium
Magnesium stearate
Microcrystalline cellulose
Tablet coating:
Carnauba wax
Lactose monohydrate
Hypromellose
Titanium dioxide (E171)
Triacetin
The 60-and 120-mg tablets also contain indigo carmine lake (E132) and yellow ferric oxide (E172).
Opadry II Green 39K11520 (for 60 mg tablets), Opadry II White 39K18305 (for 90 mg tablets), Opadry II Green 39K11529 (for 120 mg tablets).

6.2. Incompatibilities
Not applicable.

6.3. Shelf life.
3 years.
Do not use after expiry date indicated in the package.

6.4. Special precautions for storage
Keep away from children, at the temperature not above 30 °C.

6.5. Nature and contents of container
Film coated 60 mg, 90 mg and 120 mg tablets.
PVC/aluminum blisters in packs containing 7 tablets. 1 or 4 blisters with Prescribing Information in a cardboard box.

6.6. Special precautions for disposal and other handling
No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7. Category.
Prescription drug products.

7. MARKETING AUTHORISATION HOLDER
Organon Central East GmbH, Weystrasse 20, 6006 Luzern 6, Switzerland.

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first autorisation:
Date of last renewal:

10. DATE OF REVISION OF THE TEXT