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MERCK SHARP & DOHME

New prescribing advice for ARCOXIA® [etoricoxib] following review of cardiovascular safety

23 February 2005

Dear Healthcare Professional,

The Committee for Medicinal Products for Human Use (CHMP), of the European Medicines Agency (EMEA), in conjunction with national regulatory authorities including the Irish Medicines Board (IMB), has issued new advice regarding the cardiovascular safety of all licensed COX-2 inhibitor medicines, following review of the cardiovascular safety data for these products.

The available evidence suggests that the selective COX-2 inhibitor class of drugs may be associated with a risk of thrombotic events (especially myocardial infarction and stroke), relative to placebo and some NSAIDs. This new advice is designed to restrict use in patients at highest risk of such disorders.

Summary of the prescribing information and new advice for ARCOXIA® [etoricoxib]:

- ARCOXIA® [etoricoxib] is indicated for the symptomatic relief of osteoarthritis (OA), rheumatoid arthritis (RA) and the pain and signs of inflammation associated with acute gouty arthritis.
- In osteoarthritis, the recommended daily dose is 60 mg once daily and should not be exceeded.
- In rheumatoid arthritis the recommended dose is 90 mg once daily and should not be exceeded.
- In acute gouty arthritis, the recommended dose is 120 mg once daily and should not be exceeded. ARCOXIA® [etoricoxib] 120 mg should be used only for the acute symptomatic period, limited to a maximum of 8 days of treatment.
- The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis. The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks.

- Established ischaemic heart disease (IHD), cerebrovascular disease and congestive heart failure (NYHA II-IV)* are now contraindications for use of all selective COX-2 inhibitors, including ARCOXIA® [etoricoxib]. Patients with these conditions who are currently taking etoricoxib should be switched to alternative treatments.

- As the cardiovascular risk may increase with duration of exposure and with high doses, the lowest effective dose should be used for the shortest duration necessary.

- For patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) or those with peripheral arterial disease, the balance of risks should be considered before prescribing a selective COX-2 inhibitor.

- Similarly, careful consideration should be given to the balance of these risks for patients who are taking low dose aspirin for (primary) prevention of cardiovascular events, as a clear gastrointestinal safety advantage has not been established when COX-2 inhibitors are combined with aspirin.

- ARCOXIA® [etoricoxib] may be associated with more frequent and severe effects on blood pressure than some other COX-2 inhibitors and NSAIDs, particularly at high doses. Therefore careful monitoring of blood pressure is advised for all patients taking ARCOXIA® [etoricoxib].

- ARCOXIA® [etoricoxib] treatment should not be initiated in patients whose hypertension is not under control.

**** Patients with congestive heart failure (NYHA III-IV) were previously contraindicated****

Merck Sharp & Dohme (MSD) is updating product information to reflect the new advice. Please refer to the attached ARCOXIA® SmPC for full prescribing advice.

Any suspected adverse drug reactions should be notified to the company and the Irish Medicines Board in the usual way.

Please contact us on 01 – 299 8700 if you have any questions about this letter.

Yours sincerely,

Dr. Neil Boyle FFPM RCP (UK)
Medical Director.

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

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: Green, apple-shaped, biconvex tablets debossed '447' on one side and 'MSD' on the other side.

90 mg Tablets: White, apple-shaped, biconvex tablets debossed '454' on one side and 'MSD' on the other side.

120 mg Tablets: Pale-green, apple-shaped, biconvex tablets debossed '541' on one side and 'MSD' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

ARCOXIA is administered orally and may be taken with or without food. The onset of drug effect may be faster when ARCOXIA is administered without food. This should be considered when rapid symptomatic relief is needed.

Osteoarthritis
The recommended dose is 60 mg once daily.

Rheumatoid arthritis
The recommended dose is 90 mg once daily.

Acute gouty arthritis
The recommended dose is 120 mg once daily. Etoricoxib 120 mg should be used only for the acute symptomatic period. In clinical trials for acute gouty arthritis, etoricoxib was given for 8 days.

Doses greater than those recommended for each indication have either not demonstrated additional efficacy or have not been studied. Therefore, the dose for each indication is the maximum recommended dose.

The dose for OA should not exceed 60 mg daily.
The dose for RA 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.

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 4.3, 4.4, 4.8 and 5.1).

Elderly: No dosage adjustment is necessary for elderly patients.

Hepatic insufficiency: 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) the recommended dose of 60 mg ***every other day*** 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 4.3, 4.4 and 5.2).

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

Paediatric use: Etoricoxib is contraindicated in children and adolescents under 16 years of age.

4.3 Contraindications

History of hypersensitivity to the active substance or to any of the excipients (see 6.1).

Active peptic ulceration or active gastro-intestinal (GI) bleeding.

Patients who have experienced bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria, or allergic-type reactions after taking acetylsalicylic acid or NSAIDs including COX-2 (cyclo-oxygenase-2) inhibitors.

Pregnancy and lactation (see 4.6 and 5.3).

Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score ≥10).

Estimated renal creatinine clearance <30 ml/min.

Children and adolescents under 16 years of age.

Inflammatory bowel disease.

Congestive heart failure (NYHA II-IV).

Patients with hypertension whose blood pressure has not been adequately controlled.

Established ischaemic heart disease and/or cerebrovascular disease.

4.4 Special warnings and precautions for use

Gastro-intestinal effects
Upper gastro-intestinal 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 gastro-intestinal complication with NSAIDs: the elderly, patients using any other NSAID or acetylsalicylic acid concomitantly, or patients with a prior history of gastro-intestinal disease, such as ulceration and GI bleeding.

There is a further increase in the risk of gastro-intestinal adverse effects (gastro-intestinal ulceration or other gastro-intestinal complications) when etoricoxib is taken concomitantly with acetylsalicylic acid (even at low doses). A significant difference in GI safety between selective COX-2 inhibitors + acetylsalicylic acid *vs.* NSAIDs + acetylsalicylic acid has not been demonstrated in long-term clinical trials (see 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 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 (see 4.2, 4.3, 4.8 and 5.1).

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

COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thromboembolic diseases because of their lack of antiplatelet effect. Therefore antiplatelet therapies should not be discontinued (see 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 drugs known to inhibit prostaglandin synthesis, fluid retention, oedema and hypertension have been observed in patients taking etoricoxib. Caution should be exercised in patients with a history of cardiac failure, left ventricular dysfunction, or hypertension and in patients with pre-existing oedema from any other reason. If there is clinical evidence of deterioration in the condition of these patients, appropriate measures including discontinuation of etoricoxib should be taken.

Etoricoxib may be associated with more frequent and severe hypertension than some other NSAIDs and selective COX-2 inhibitors, particularly at high doses. Therefore, special attention should be paid to blood pressure monitoring during treatment with etoricoxib. 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 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, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported in association with the use of NSAIDs including other COX-2 (cyclo-oxygenase-2) inhibitors and cannot be ruled out for etoricoxib (see 4.8). Hypersensitivity reactions (anaphylaxis, angioedema) have been reported in patients receiving etoricoxib (see 4.8). Etoricoxib should be discontinued at the first 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 4.5).

The use of etoricoxib, as with any medicinal product known to inhibit cyclo-oxygenase/prostaglandin synthesis, is not recommended in women attempting to conceive (see 4.6, 5.1 and 5.3).

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 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 4.4).

Diuretics and ACE inhibitors: 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 and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, which is usually reversible. These interactions should be given consideration in patients taking etoricoxib concomitantly with ACE inhibitors.

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 5.1 and 4.4.)

Ciclosporin and tacrolimus: Although this interaction has not been studied with etoricoxib, co-administration of ciclosporin or tacrolimus with any NSAID may increase the nephrotoxic effect of ciclosporin 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: Administration of etoricoxib 120 mg with an oral contraceptive containing 35 µg ethinyl estradiol (EE) and 0.5 to 1 mg norethindrone for 21 days, either concomitantly or separated by 12 hours, increased the steady state $AUC_{0\text{-}24hr}$ of EE by 50 to 60%; however, norethindrone concentrations generally did not increase to a clinically relevant degree. 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).

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).

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 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 (see 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 4.3). If a woman becomes pregnant during treatment, etoricoxib should 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 should not breast feed. (See 4.3 and 5.3.)

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 approximately 4,800 individuals, including approximately 3,400 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 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.

The following undesirable effects were reported at an incidence greater than placebo in clinical trials in patients with OA, RA or chronic low back pain treated with etoricoxib 60 mg or 90 mg for up to 12 weeks or in post-marketing experience:

[Very Common (>1/10) Common (>1/100, <1/10) Uncommon (>1/1000, <1/100) Rare (>1/10,000, <1/1,000) Very rare (<1/10,000) including isolated cases]

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

Immune system disorder:
Very rare: hypersensitivity reactions, including angioedema, anaphylactic/anaphylactoid reactions.

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: 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.
Very rare: peptic ulcers including gastro-intestinal perforation and bleeding (mainly in the elderly).

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

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

Renal and urinary disorders:
Uncommon: proteinuria.
Very rare: renal insufficiency, including renal failure, usually reversible upon discontinuation of treatment (see 4.4).

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.

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 jaundice; cutaneo-mucosal adverse effects and severe skin reactions (see 4.4).

4.9 Overdose

No overdoses of etoricoxib were reported during clinical trials.

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.

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 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.

Cyclo-oxygenase 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.

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

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.

In patients with rheumatoid arthritis (RA), etoricoxib 90 mg once daily provided significant improvements in pain, inflammation, and mobility. These beneficial effects were maintained over the 12-week treatment periods.

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.

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.

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 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 naproxen 500 mg twice daily or diclofenac 50 mg three times daily. There were no statistically significant differences between etoricoxib and placebo.

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 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. There are no clinical or pharmacokinetic data in patients with severe hepatic dysfunction (Child-Pugh score ≥10). (See 4.2 and 4.3.)

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 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 4.2 *'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. A non-dose-related low incidence of cardiovascular malformations was observed in etoricoxib-treated rabbits. The relationship to treatment is not established. 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 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), glycerol triacetate. The 60- and 120-mg tablets also contain indigo carmine lake (E132) and yellow ferric oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

2 years.

6.4 Special precautions for storage

Bottles: Keep the container tightly closed.
Blisters: Store in the original package.

6.5 Nature and contents of container

Aluminum/aluminium blisters in packs containing 2, 5, 7, 10, 14, 20, 28, 30, 50, 84, 98 or 100 tablets.

Aluminum/aluminium blisters (unit doses) in packs of 50 or 100 tablets.

White, round, HDPE bottles with a white, polypropylene closure containing 30 or 90 tablets.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK

8. MARKETING AUTHORISATION NUMBER

60 mg Tablets	PA 35/94/1
90 mg Tablets	PA 35/94/2
120 mg Tablets	PA 35/94/3

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

60 mg Tablets	11 October 2002
90 mg Tablets	11 October 2002
120 mg Tablets	11 October 2002

10. DATE OF REVISION OF THE TEXT

February 2005

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