ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTH OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, APPLICANTS / MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of adminitration
Austria	Merck Sharp & Dohme GmbH Donau - City - Straße 6 A-1220 Wien Austria	Arcoxia	90 mg	film-coated tablets	oral use
Belgium	Merck Sharp and Dohme Chasussée de Waterloo 1135 B-1180 Brussels Belgium	Arcoxia	90 mg	film-coated tablets	oral use
Czech Republic	Merck Sharp & Dohme B.V. Waanderweg 39 NL-2031 BN Haarlem The Netherlands	Arcoxia	90 mg	film-coated tablets	oral use
Cyprus	Merck Sharp & Dohme BV. Waarderweg 39 NL-2031 BN Haarlem The Netherlands	Arcoxia	90 mg	film-coated tablets	oral use
Denmark	Merck Sharp & Dohme B.V. Waarderweg 39 Postbox 581 NL 2031 BN Haarlem The Netherlands	Arcoxia	90 mg	film-coated tablets	oral use
Estonia	Merck Sharp & Dohme OÜ Peterburi tee 46 11415 Tallinn Estonia	Arcoxia	90 mg	film-coated tablets	oral use
Finland	Merck Sharp & Dohme B.V. Waarderweg 39, P.O Box 581 NL-2031 BN Haarlem The Netherlands	Arcoxia	90 mg	film-coated tablets	oral use

France	Merck Sharp Dohme Chibret 3 avenue Hoche 75114 Paris Cedex 8 France	Arcoxia	90 mg	film-coated tablets	oral use
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 D-85540 Haar Germany	Arcoxia	90 mg	film-coated tablets	oral use
Greece	VIANEX S.A. Tatoiou Street Nea Erythrea 14671 Greece	Arcoxia	90 mg	film-coated tablets	oral use
Hungary	Merck Sharp & Dohme Magyarország Kft. Alkotás utca 50 1123 Budapest Hungary	Arcoxia	90 mg	film-coated tablets	oral use
Iceland	Merck Sharp & Dohme - Regulatory Affairs Iceland Smedeland 8 DK-2600 Glostrup Danmark	Arcoxia	90 mg	film-coated tablets	oral use
Ireland	Merck Sharp and Dohme Ltd Hertford Road Hoddesdon Hertfordshire EN11 9B4 England	Arcoxia	90 mg	film-coated tablets	oral use
Italy	Merck Sharp & Dohme S.p.A. Via G. Fabbroni, 6 00191 Roma Italy	Arcoxia	90 mg	film-coated tablets	oral use

Latvia	SIA Merck Sharp & Dohme Latvija Skanstes 13 Riga, LV-1013 Latvia	Arcoxia	90 mg	film-coated tablets	oral use
Lithuania	UAB„Merck Sharp & Dohme“ Lenktoji str. 27/ Kestucio str. 59 LT-08124 Vilnius Lithuania	Arcoxia	90 mg	film-coated tablets	oral use
Luxemburg	Merck Sharp & Dohme Chaussee de Waterloo 1135 B – 1180 Bruxelles Belgium	Arcoxia	90 mg	film-coated tablets	oral use
Malta	Merck, Sharp & Dohme Ltd. Hertfordshire Road Hoddesdon Hertsfordshire EN11 9BU United Kindgdom	Arcoxia	90 mg	film-coated tablets	oral use
Netherlands	Merck Sharp & Dohme B.V. Waanderweg 39 NL-2031 BN Haarlem The Netherlands	Arcoxia	90 mg	film-coated tablets	oral use
Norway	Merck Sharp & Dohme B.V. Waarderweg 39 NL-2031 BN Haarlem The Netherlands	Arcoxia	90 mg	film-coated tablets	oral use
Poland	MSD Polska Sp. z o.o. ul. Chłodna 51 00-867 Warsaw Poland	Arcoxia	90 mg	film-coated tablets	oral use
Portugal	Merck Sharp & Dohme, Lda. PRT Quinta da Fonte – Edifício Vasco da Gama, 19 - Porto Salvo Paço d' Arcos	Arcoxia	90 mg	film-coated tablets	oral use

	Portugal				
Slovakia	Merck Sharp & Dohme B.V. Waarderweg 39 P.O. Box 581 NL-2031 BN Haarlem The Netherlands	Arcoxia	90 mg	film-coated tablets	oral use
Slovenia	Merck Sharp & Dohme inovativna zdravila d.o.o. Šmartinska 140 1000 Ljubljana Slovenia	Arcoxia	90 mg	film-coated tablets	oral use
Spain	Merck Sharp & Dohme de España, S.A. Josefa Valcárcel, 38 28027 Madrid Spain	Arcoxia	90 mg	film-coated tablets	oral use
Sweden	Merck Sharp & Dohme BV PO Box 581 NL-2003 PC Haarlem The Netherlands	Arcoxia	90 mg	film-coated tablets	oral use
United Kingdom	Merck Sharpe & Dohme Limited Hertford Road Hoddesdon Hertfordshire EN11 9BU United Kingdom	Arcoxia	90 mg	film-coated tablets	oral use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLET PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

Introduction

Etoricoxib is a selective inhibitor of COX-2 (cyclooxygenase 2) indicated in the symptomatic relief of osteoarthritis (OA, 30-60mg once daily (od)), rheumatoid arthritis (RA, 90mg od) and the pain and signs of inflammation associated with acute gouty arthritis (120mg od).

Etoricoxib was included in previous CHMP referrals on the safety of COX-2 selective inhibitors in which concluded in 2004 and 2005. Both referral procedures pertained to the safety of the COX-2 inhibitor products, including etoricoxib, with a particular focus on gastrointestinal (GI) and cardiovascular (CV) safety. These led to updates of the product information to include class warnings on the risk of CV thrombotic, GI and severe skin reactions with COX-2 selective inhibitors. In addition to class warnings and contraindications, introduced for all COX-2 selective inhibitors, a contraindication in patients with hypertension whose blood pressure is not adequately controlled was included specifically for etoricoxib because of evidence of higher rates of cardiorenal events than other COX-2 inhibitor products.

In March 2006, the marketing authorisation holders (MAH) for Arcoxia (etoricoxib) submitted an application to extend the licensed indication to include treatment of ankylosing spondylitis (AS), at a recommended daily dose of 90mg. During the assessment of the procedure, concerns were raised over the long-term safety of etoricoxib 90mg in patients with AS. Following concerns of a possible increased cardiovascular (CV) risk related to the use of the 90mg dose of etoricoxib, France considered that a review of the benefit/risk profile of Arcoxia was needed. Therefore, France sent a notification that was received by the EMEA on 19 September 2007 and a referral under Article 6 (12) of Commission Regulation EC No 1084/2003 was started on 20 September 2007.

The CHMP reviewed the data submitted by the marketing authorisation holders from clinical trials, drug utilisation studies and spontaneous reporting of adverse drug reactions. The CHMP assessed efficacy data submitted for AS and safety data collected regarding AS, and also in the rheumatoid arthritis population for which the same dose is approved for treatment.

The CHMP concluded on 26 June 2008 that the data confirm the known relatively adverse renovascular safety profile of etoricoxib (hypertension, oedema and congestive heart failure), but similar CV thrombotic risk as diclofenac and some degree of upper GI safety advantage over naproxen and diclofenac (though no particular lower GI safety advantage). There is little direct comparative safety data for individual NSAIDs other than diclofenac and naproxen and it is therefore difficult to determine risks for etoricoxib compared with ibuprofen, ketoprofen or other less-commonly used NSAIDs.
Drug utilisation data showed that some patients with high blood pressure are being initiated on etoricoxib. The CHMP therefore recommends the strengthening of the contraindication in hypertensive patients and alerts prescribers that blood pressure needs to be monitored, especially within 2 weeks of treatment initiation. Healthcare professionals were to be reminded of these measures through a communication letter (DHCP).

Data from clinical studies showed clinically meaningful treatment effect for the 90mg etoricoxib once daily dose for AS indications; however, some data are available to indicate that lower doses might also show effect. The CHMP therefore recommends that dose finding studies are explored to conclude if treatment with 60mg once daily would also be adequate for some patients.

Based on the review of the available data, the CHMP considers that the benefits of etoricoxib outweigh the risks in the treatment of ankylosing spondylitis.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLET

- The Committee considered the referral made under Article 6(12) of Commission Regulation EC No 1084/2003, for Arcoxia and associated names.

Whereas

- In view of the available data, the CHMP considered that the benefit/risk balance for Arcoxia (etoricoxib) 90mg dose in AS indication is positive; however, revisions to the contraindications and warnings sections have been added to the summary of product characteristics and package leaflet in relation to cardiorenal safety.

The CHMP recommended the granting of the variation of the Marketing Authorisations for which the summaries of product characteristics, labelling and package leaflets are set out in Annex III and under the conditions set out in Annex IV.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<ARCOXIA (see Annex 1)> 30 mg film-coated tablets
<ARCOXIA (see Annex 1)> 60 mg film-coated tablets
<ARCOXIA (see Annex 1)> 90 mg film-coated tablets
<ARCOXIA (see Annex 1)> 120 mg film-coated tablets
[See Annex 1- To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 30, 60, 90 or 120 mg of etoricoxib.

Excipient:
30 mg: lactose 1.4 mg
60 mg: lactose 2.8 mg
90 mg: lactose 4.2 mg
120 mg: lactose 5.6 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

30 mg Tablets: Blue-green, apple-shaped biconvex tablets <debossed '101' on one side and 'ACX 30' on the other side>.

60 mg Tablets: Dark green, apple-shaped, biconvex tablets <debossed '200' on one side and 'ARCOXIA 60' on the other side>.

90 mg Tablets: White, apple-shaped, biconvex tablets <debossed '202' on one side and 'ARCOXIA 90' on the other side>.

120 mg Tablets: Pale-green, apple-shaped, biconvex tablets <debossed '204' on one side and 'ARCOXIA 120' 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.

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

4.2 Posology and method of administration

<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 without food. 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 (see sections 4.3, 4.4, 4.8 and 5.1).

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

Rheumatoid arthritis
The recommended dose is 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.

Ankylosing spondylitis
The recommended dose is 90 mg once daily.

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.

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

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 ***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 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 (see sections 4.3, 4.4 and 5.2).

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

Paediatric patients
Etoricoxib is contra-indicated in children and adolescents under 16 years of age (see section 4.3).

4.3 Contra-indications

Hypersensitivity to the active substance or to any of the excipients (see section 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 (cyclooxygenase-2) inhibitors.

Pregnancy and lactation (see sections 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 is persistently elevated above 140/90mmHg and has not been adequately controlled.

Established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease.

4.4 Special warnings and precautions for use

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

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

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

Cardiovascular effects
Clinical trials suggest that the selective COX-2 inhibitor class of drugs may be associated with a risk of thrombotic events (especially myocardial infarction (MI) and stroke), relative to placebo and some NSAIDs. As the cardiovascular risks of etoricoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis (see sections 4.2, 4.3, 4.8 and 5.1).

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

COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of antiplatelet effect. Therefore antiplatelet therapies should not be discontinued (see sections above, 4.5 and 5.1.).

Renal effects
Renal prostaglandins may play a compensatory role in the maintenance of renal perfusion. Therefore, under conditions of compromised renal perfusion, administration of etoricoxib may cause a reduction in prostaglandin formation and, secondarily, in renal blood flow, and thereby impair renal function. Patients at greatest risk of this response are those with pre-existing significantly impaired renal function,

uncompensated heart failure, or cirrhosis. Monitoring of renal function in such patients should be considered.

Fluid retention, oedema and hypertension
As with other medicinal products known to inhibit prostaglandin synthesis, fluid retention, oedema and hypertension have been observed in patients taking etoricoxib. All Nonsteroidal Antiinflammatory Drugs (NSAIDs), including etoricoxib, can be associated with new onset or recurrent congestive heart failure. For information regarding a dose related response for etoricoxib see section 5.1. Caution should be exercised in patients with a history of cardiac failure, left ventricular dysfunction, or hypertension and in patients with 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) 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 (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy with the onset of the reaction occurring in the majority of cases within the first month of treatment. Serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving etoricoxib (see section 4.8). Some selective COX-2 inhibitors have been associated with an increased risk of skin reactions in patients with a history of any drug allergy. Etoricoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Etoricoxib may mask fever and other signs of inflammation.

Caution should be exercised when co-administering etoricoxib with warfarin or other oral anticoagulants (see section 4.5).

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

<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 section 4.4).

Diuretics, ACE inhibitors and Angiotensin II Antagonists: NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the 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 (see sections 5.1 and 4.4.).

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

Pharmacokinetic interactions

The effect of etoricoxib on the pharmacokinetics of other drugs

Lithium: NSAIDs decrease lithium renal excretion and therefore increase lithium plasma levels. If necessary, monitor blood lithium closely and adjust the lithium dosage while the combination is being taken and when the NSAID is withdrawn.
Methotrexate: Two studies investigated the effects of etoricoxib 60, 90 or 120 mg administered once daily for seven days in patients receiving once-weekly methotrexate doses of 7.5 to 20 mg for rheumatoid arthritis. Etoricoxib at 60 and 90 mg had no effect on methotrexate plasma concentrations or renal clearance. In one study, etoricoxib 120 mg had no effect, but in the other study, etoricoxib 120 mg increased methotrexate plasma concentrations by 28% and reduced renal clearance of methotrexate by 13%. Adequate monitoring for 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 (HRT): 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 oestrogen exposure might increase the risk of adverse events associated with HRT.

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

Digoxin: Etoricoxib 120 mg administered once daily for 10 days to healthy volunteers did not alter the steady-state plasma $AUC_{0\text{-}24hr}$ 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 section 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 section 5.3). The potential for human risk in pregnancy is unknown. Etoricoxib, as with other medicinal products inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus during the last trimester. Etoricoxib is contraindicated in pregnancy (see section 4.3). If a woman becomes pregnant during treatment, etoricoxib must be discontinued.

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 (see sections 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 7152 individuals, including 4614 patients with OA, RA, chronic low back pain or ankylosing spondylitis (approximately 600 patients with OA or RA were treated for one year or longer).

In clinical studies, the undesirable effects profile was similar in patients with OA or RA treated with etoricoxib for one year or longer.

In a clinical study for acute gouty arthritis, patients were treated with etoricoxib 120 mg once daily for eight days. The adverse experience profile in this study was generally similar to that reported in the combined OA, RA, and chronic low back pain studies.

In a cardiovascular safety outcomes 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.

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, or in post-marketing experience:

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

Infections and infestations:
Uncommon: gastroenteritis, upper respiratory infection, urinary tract infection.

Immune system disorder:
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.

Nervous system disorder:
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, myocardial infarction*.

Vascular disorders:
Common: hypertension.
Uncommon: flushing, cerebrovascular accident*, transient ischaemic attack.
Very rare: hypertensive crisis.

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).

Hepatobiliary disorders:
Very rare: hepatitis.

Skin and subcutaneous tissue disorders:
Common: ecchymosis.
Uncommon: facial oedema, pruritus, rash.
Very rare: urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis.

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

Renal and urinary disorders:

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* 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).

Uncommon: proteinuria.
Very rare: renal insufficiency, including renal failure, usually reversible upon discontinuation of treatment (see section 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.
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, jaundice and pancreatitis.

4.9 Overdose

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

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, 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.

Efficacy

In patients with osteoarthritis (OA), etoricoxib 60 mg once daily provided significant improvements in pain and patient assessments of disease status. These beneficial effects were observed as early as the second day of therapy and maintained for up to 52 weeks. Studies with etoricoxib 30 mg once daily demonstrated efficacy superior to placebo over a 12 week treatment period (using similar assessments as the above studies). In a dose ranging study, etoricoxib 60 mg demonstrated significantly greater improvement than 30 mg for all 3 primary endpoints over 6 weeks of treatment. The 30 mg dose has not been studied in osteoarthritis of hands.

In patients with rheumatoid arthritis (RA), etoricoxib 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 patients with ankylosing spondylitis, etoricoxib 90 mg once daily provided significant improvements in spine pain, inflammation, stiffness and function. The clinical benefit of etoricoxib was observed as early as the second day of therapy after initiation of treatment and was maintained throughout the 52-week treatment period.

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

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 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.

Additional Thrombotic Cardiovascular Safety Data
In clinical studies excluding the MEDAL Program Studies, approximately 3100 patients were treated with etoricoxib ≥60 mg daily for 12 weeks or longer. There was no discernible difference in the rate of confirmed serious thrombotic cardiovascular events between patients receiving etoricoxib ≥60 mg, placebo, or non-

naproxen NSAIDs. However, the rate of these events was higher in patients receiving etoricoxib compared with those receiving naproxen 500 mg twice daily. The difference in antiplatelet activity between some COX-1 inhibiting NSAIDs and selective COX-2 inhibitors may be of clinical significance in patients at risk of thrombo-embolic events. Selective 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.

Additional Gastrointestinal Safety Data
In two 12-week double-blind endoscopy studies, the cumulative incidence of gastroduodenal ulceration was significantly lower in patients treated with etoricoxib 120 mg once daily than in patients treated with either naproxen 500 mg twice daily or ibuprofen 800 mg three times daily. Etoricoxib had a higher incidence of ulceration as compared to placebo.

Renal Function Study in the Elderly
A randomized, double-blind, 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 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: 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; 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 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 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 and adolescents >60 kg given etoricoxib 90 mg once daily were similar to the pharmacokinetics in adults given etoricoxib 90 mg once daily. Safety and effectiveness of etoricoxib in paediatric patients have not been established (see section 4.2).

5.3 Preclinical safety data

In preclinical studies, etoricoxib has been demonstrated not to be genotoxic. Etoricoxib was not carcinogenic in mice. Rats developed hepatocellular and thyroid follicular cell adenomas at >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 30-, 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

3 years.

6.4 Special precautions for storage

Bottles: Keep the container tightly closed in order to protect from moisture.

Blisters: Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

30 mg
Aluminum/aluminium blisters in packs containing 7 and 28 tablets.

60, 90 and 120 mg
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 tablets and two1-gram desiccant containers or 90 tablets and one1-gram desiccant container.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex 1- *To be completed nationally.*]
{Name and address}
{tel}
{fax}
{e-mail}

8. MARKETING AUTHORISATION NUMBER

[*To be completed nationally.*]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

[*To be completed nationally.*]

10. DATE OF REVISION OF THE TEXT

[*To be completed nationally.*]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

<ARCOXIA (see Annex 1)> 30 mg film-coated tablets
<ARCOXIA (see Annex 1)> 60 mg film-coated tablets
<ARCOXIA (see Annex 1)> 90 mg film-coated tablets
<ARCOXIA (see Annex 1)> 120 mg film-coated tablets
[See Annex I - To be completed nationally]

Etoricoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film coated tablet contains 30 mg etoricoxib.
Each film coated tablet contains 60 mg etoricoxib.
Each film coated tablet contains 90 mg etoricoxib.
Each film coated tablet contains 120 mg etoricoxib.

3. LIST OF EXCIPIENTS

Lactose (see leaflet for more information).

4. PHARMACEUTICAL FORM AND CONTENTS

30mg
7 Film-coated tablets
28 Film-coated tablets

60 mg – 90 mg -120mg
2 Film coated tablets
5 Film-coated tablets
7 Film-coated tablets
10 Film-coated tablets
14 Film-coated tablets
20 Film-coated tablets
28 Film-coated tablets
30 Film-coated tablets
50 Film-coated tablets
84 Film-coated tablets
98 Film-coated tablets
100 Film-coated tablets
50 Film-coated tablets (unit dose)
100 Film-coated tablets (unit dose)
30 Film-coated tablets (HDPE bottles)
90 Film-coated tablets (HDPE bottles)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Bottles
Keep the container tightly closed in order to protect from moisture.

Blisters
Store in original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

<ARCOXIA (see Annex 1)> 30 mg film-coated tablets
<ARCOXIA (see Annex 1)> 60 mg film-coated tablets
<ARCOXIA (see Annex 1)> 90 mg film-coated tablets
<ARCOXIA (see Annex 1)> 120 mg film-coated tablets
[See Annex I - To be completed nationally]

Etoricoxib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

MSD

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

HDPE BOTTLE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

<ARCOXIA (see Annex 1)> 60 mg film-coated tablets
<ARCOXIA (see Annex 1)> 90 mg film-coated tablets
<ARCOXIA (see Annex 1)> 120 mg film-coated tablets
[See Annex I - To be completed nationally]

Etoricoxib

2. METHOD OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30 Film coated tablets (HDPE bottles)
90 Film coated tablets (HDPE bottles)

6. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

<ARCOXIA> 30 mg film-coated tablets
<ARCOXIA> 60 mg film-coated tablets
< ARCOXIA > 90 mg film-coated tablets
< ARCOXIA > 120 mg film-coated tablets

[See Annex I – To be completed nationally]

Etoricoxib

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT <ARCOXIA> IS AND WHAT IT IS USED FOR

- <ARCOXIA> is one of a group of medicines called selective COX-2 inhibitors. These belong to a family
of medicines called non-steroidal anti-inflammatory drugs (NSAIDs).
- <ARCOXIA> helps to reduce the pain and swelling (inflammation) in the joints and muscles of people with osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and gout.

What is osteoarthritis?
Osteoarthritis is a disease of the joints. It results from the gradual breakdown of cartilage that cushions the ends of the bones. This causes swelling (inflammation), pain, tenderness, stiffness and disability.

What is rheumatoid arthritis?
Rheumatoid arthritis is a long term inflammatory disease of the joints. It causes pain, stiffness, swelling, and increasing loss of movement in the joints it affects. It may also cause inflammation in other areas of the body.

What is gout?
Gout is a disease of sudden, recurring attacks of very painful inflammation and redness in the joints. It is caused by deposits of mineral crystals in the joint.

What is ankylosing spondylitis?
Ankylosing spondylitis is an inflammatory disease of the spine and large joints.

2. BEFORE YOU TAKE <ARCOXIA>

Do not take <ARCOXIA>**:**

- if you are allergic (hypersensitive) to etoricoxib or any of the other ingredients of <ARCOXIA> (see Further information, section 6)
- if you are allergic to non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin and COX-2 inhibitors (see Possible Side Effects, section 4)
- if you have a current stomach ulcer or bleeding in your stomach or intestines
- if you have serious liver disease
- if you have serious kidney disease
- if you are or could be pregnant or are breast-feeding (see 'Pregnancy and breast feeding')
- if you are under 16 years of age
- if you have inflammatory bowel disease, such as Crohn's Disease, Ulcerative Colitis, or Colitis
- if your doctor has diagnosed heart problems including heart failure (moderate or severe types), angina (chest pain) or if you have had a heart attack, bypass surgery, peripheral arterial disease (poor circulation in legs or feet due to narrow or blocked arteries), or any kind of stroke (including mini-stroke, transient ischaemic attack or TIA). Etoricoxib may slightly increase your risk of heart attack and stroke and this is why it should not be used in those who have already had heart problems or stroke
- if you have high blood pressure that has not been controlled by treatment (check with your doctor or nurse if you are not sure whether your blood pressure is adequately controlled)

If you think any of these are relevant to you, do not take the tablets until you have consulted your doctor.

Take special care with <ARCOXIA>
<ARCOXIA> may not be suitable for you, or you may need to be monitored regularly while taking it if any of the following apply to you:

- You have a history of stomach bleeding or ulcers.
- You are dehydrated, for example by a prolonged bout of vomiting or diarrhoea.
- You have swelling due to fluid retention.
- You have a history of heart failure, heart attack or any other form of heart disease.
- You have a history of stroke or mini stroke.
- You have a history of high blood pressure. <ARCOXIA> can increase blood pressure in some people, especially in high doses, and your doctor will want to check your blood pressure from time to time.
- You have any history of liver or kidney disease.
- You are being treated for an infection. <ARCOXIA> can mask or hide a fever, which is a sign of infection.
- You are a woman trying to become pregnant.
- You are elderly (i.e., over 65 years of age).
- You have diabetes, high cholesterol, or are a smoker. These can increase your risk of heart disease.

If you are not sure if any of the above apply to you, **talk to your doctor before taking <ARCOXIA>** to see if this medicine is suitable for you.

<ARCOXIA> works equally well in older and younger adult patients. If you are elderly (i.e., over 65 years of age), your doctor will want to appropriately keep a check on you. No dosage adjustment is necessary for elderly patients.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

In particular if you are taking any of the following medicines, your doctor may want to monitor you to check that your medicines are working properly, once you start taking <ARCOXIA>:

- medicines that thin your blood (anticoagulants), such as warfarin
- rifampicin (an antibiotic)
- methotrexate (a drug used for suppressing the immune system, and often used in rheumatoid arthritis)
- medicines used to help control high blood pressure and heart failure called ACE inhibitors and angiotensin receptor blockers, examples include enalapril and ramipril, and losartan and valsartan
- lithium (a medicine used to treat some types of depression)
- diuretics (water tablets)
- ciclosporin or tacrolimus (drugs used for suppressing the immune system)
- digoxin (a medicine for heart failure and irregular heart rhythm)
- minoxidil (a drug used to treat high blood pressure)
- salbutamol tablets or oral solution (a medicine for asthma)
- birth control pills
- hormone replacement therapy
- aspirin, the risk of stomach ulcers is greater if you take <ARCOXIA> with aspirin.
  -<ARCOXIA> can be taken with low-dose aspirin. If you are currently taking low-dose aspirin to prevent heart attacks or stroke, you should not stop taking aspirin until you talk to your doctor
  -do not take high dose aspirin or other anti-inflammatory medicines while taking <ARCOXIA>

Pregnancy and breast-feeding
<ARCOXIA> tablets must not be taken during pregnancy. If you are pregnant or think you could be pregnant, or if you are planning to become pregnant, do not take the tablets. If you become pregnant, stop taking the tablets and consult your doctor. Consult your doctor if you are unsure or need more advice.

It is not known if <ARCOXIA> is excreted in human milk. If you are breast-feeding, or planning to breast-feed, consult your doctor before taking <ARCOXIA>. If you are using <ARCOXIA>, you must not breast-feed.

Driving and using machines
Dizziness and sleepiness have been reported in some patients taking <ARCOXIA>.
Do not drive if you experience dizziness or sleepiness.
Do not use any tools or machines if you experience dizziness or sleepiness.

Important information about some of the ingredients of <ARCOXIA>
<ARCOXIA> contains lactose. If you have been told by your doctor that you are unable to tolerate some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE <ARCOXIA>

Always take <ARCOXIA> exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

<ARCOXIA> Tablets should not be taken by children or adolescents under 16 years of age.

Take <ARCOXIA> Tablets by mouth once a day. <ARCOXIA> can be taken with or without food.

Do not take more than the recommended dose for your condition. Your doctor will want to discuss your treatment from time to time. It is important that you use the lowest dose that controls your pain and you should not take <ARCOXIA> for longer than necessary. This is because the risk of heart attacks and strokes might increase after prolonged treatment, especially with high doses.

Osteoarthritis
The recommended dose is 30 mg once a day, increase to a maximum of 60 mg once a day if needed.

Rheumatoid arthritis
The recommended dose is 90 mg once a day.

Gout
The recommended dose is 120 mg once a day which should only be used for the acute painful period, limited to a maximum of 8 days treatment.

Ankylosing spondylitis
The recommended dose is 90 mg once a day.

People with liver problems
- If you have mild liver disease, you should not take more than 60 mg a day.
- If you have **moderate** liver disease, you should not take more than 60 mg **every other day** or 30 mg a day.

If you take more <ARCOXIA> than you should
You should never take more tablets than the doctor recommends. If you do take too many <ARCOXIA> tablets, you should seek medical attention immediately.

If you forget to take <ARCOXIA>
It is important to take <ARCOXIA> as your doctor has prescribed. If you miss a dose, just resume your usual schedule the following day. Do not take a double dose to make up for the forgotten tablet.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, <ARCOXIA> can cause side effects, although not everybody gets them.

If you develop any of these signs you should stop <ARCOXIA> and talk to your doctor immediately:
- shortness of breath, chest pains, or ankle swelling appear or if they get worse
- yellowing of the skin and eyes (jaundice) – these are signs of liver problems
- severe or continual stomach pain or your stools become black
- an allergic reaction- which can include skin problems such as ulcers or blistering, or swelling of the face, lips, tongue, or throat which may cause difficulty in breathing

The following side effects can occur during treatment with <ARCOXIA>:

Common **(occurring in greater than 1 out of 100 and less than 1 out of 10 people)**
Weakness and fatigue, dizziness, headache, flu-like illness, diarrhoea, wind, nausea, indigestion (dyspepsia), stomach pain or discomfort, heartburn, changes in blood tests related to your liver, swelling of the legs and/or feet due to fluid retention (oedema), increased blood pressure, palpitations, bruising.

Uncommon **(occurring in greater than 1 out of 1000 and less than 1 out of 100 people)**
Stomach or bowel bloating, chest pain, heart failure, heart attack, stroke, mini-stroke (transient ischaemic attack), abnormal heart rhythm (atrial fibrillation), upper respiratory infection, high levels of potassium in your blood, changes in blood or urine tests relating to your kidney, changes in your bowel habits including constipation, dry mouth, mouth ulcers, taste alteration, gastroenteritis, gastritis, stomach ulcer, being sick (vomiting), irritable bowel syndrome, inflammation of the esophagus, blurred vision, eye irritation and redness, nose bleed, ringing in the ears, vertigo, appetite increases or decreases, weight gain, muscle cramp/spasm, muscle pain/stiffness, inability to sleep, sleepiness, numbness or tingling, anxiety, depression,

decreases in mental sharpness, breathlessness, cough, swelling of the face, flushing, skin rash or itchy skin, urinary tract infection.

Rare **(occurring in greater than 1 out of 10,000 and less than 1 out of 1000 people)**
Low blood levels of sodium.

Very Rare **(occurring in less than 1 out of 10,000 people)**
Allergic reactions (which may be serious enough to require immediate medical attention) including hives, swelling of the face, lips, tongue, and/or throat which may cause difficulty in breathing or swallowing, bronchospasm (wheezing or shortness of breath), severe skin reactions, inflammation of the stomach lining or stomach ulcers that can become serious and may lead to bleeding, liver problems, serious kidney problems, severe increase in blood pressure, confusion, seeing, feeling or hearing things that are not there (hallucinations).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE <ARCOXIA>

Keep out of the reach and sight of children.

Do not use <ARCOXIA> after the expiry date which is stated on the pack. The expiry date refers to the last day of the month.

Bottles: Keep the container tightly closed in order to protect from moisture.

Blisters: Store in the original package in order to protect from moisture.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What <ARCOXIA> contains

- The active substance is etoricoxib. Each film coated tablet contains 30, 60, 90 or 120 mg of etoricoxib.

- The other ingredients are:
  Core: calcium hydrogen phosphate (anhydrous), croscarmellose sodium, magnesium stearate, microcrystalline cellulose.
  Tablet coating: carnauba wax, lactose monohydrate, hypromellose, titanium dioxide (E171), triacetin. The 30-, 60- and 120-mg tablets also contain yellow ferric oxide (E172, colouring agent) and indigo carmine lake (E132, colouring agent).

What <ARCOXIA> looks like and contents of the pack

<ARCOXIA> Tablets are available in four strengths:

30 mg blue-green, apple-shaped, biconvex film coated tablets marked ‘ACX 30’ on one side and ‘101’ on the other.

60 mg dark green, apple-shaped, biconvex film coated tablets marked ‘ARCOXIA 60’ on one side and ‘200’ on the other.

90 mg white, apple-shaped, biconvex film coated tablets marked ‘ARCOXIA 90’ on one side and ‘202’ on the other.

120 mg pale-green, apple-shaped, biconvex film coated tablets marked ‘ARCOXIA 120’ on one side and ‘204’ on the other.

Pack sizes:
30 mg:
Pack sizes of 7 and 28 tablets in blisters.

60, 90, 120 mg:
Pack sizes of 2, 5, 7, 10, 14, 20, 28, 30, 50, 84, 98 or 100 tablets in blisters; or 30 and 90 tablets in bottles.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
[See Annex 1-*To be filled in nationally*]
{Name and address}
{tel}
{fax}
{e-mail}

This medicinal product is authorized in the Member States of the EEA under the following names:

Austria	Arcoxia 30 mg, 60 mg, 90 mg, 120 mg-Filmtabletten
Belgium	Arcoxia 30 mg, 60 mg, 90 mg, 120 mg, comprimés pelliculés
Bulgaria	ARCOXIA
Czech Rep.	ARCOXIA 30 mg, 60 mg, 90 mg, 120 mg
Cyprus	Arcoxia 30, 60, 90, 120 mg
Denmark	Arcoxia
Estonia	Arcoxia
Finland	Arcoxia 30, 60, 90 ja 120 mg tabletti, kalvopäällysteinen
France	Arcoxia 30 mg, comprimé pelliculé
Germany	ARCOXIA 30/60/90/120 mg Filmtabletten
Greece	ARCOXIA 30mg, 60mg, 90mg,120mg film-coated tablets
Hungary	Arcoxia 30 mg, 60 mg, 90 mg, 120 mg filmtabletta
Iceland	Arcoxia
Ireland	Arcoxia 30, 60, 90 or 120 mg film-coated tablets
Italy	Arcoxia 30, 60, 90, 120 mg compresse rivestite con film
Latvia	Arcoxia 30 mg, 60 mg, 90 mg un 120 mg apvalkotās tablets
Lithuania	Arcoxia 30, 60, 90, 120 mg plėvele dengtos tabletės
Luxembourg	Arcoxia 30 mg, 60 mg, 90 mg, 120 mg, comprimés pelliculés
Malta	ARCOXIA 30, 60, 90 or 120 mg film-coated tablets
Netherlands	Arcoxia 30 mg, 60 mg, 90 mg, 120 mg
Norway	Arcoxia
Poland	ARCOXIA 30 mg, 60 mg, 90 mg, 120 mg tabletki powlekane
Portugal	ARCOXIA 30 mg, 60 mg, 90 mg, 120 mg comprimidos revestidos por película
Romania	ARCOXIA 60 mg, 90 mg, 120 mg, comprimate filmate
Slovakia	ARCOXIA 30 mg, 60 mg, 90 mg, 120 mg
Slovenia	Arcoxia 30/60/90/120 mg filmsko obložene tablete
Spain	Arcoxia 30, 60, 90 y 120 mg comprimidos recubiertos con película

Sweden	Arcoxia 30 mg, 60 mg, 90 mg och 120 mg filmdragerade tabletter
United Kingdom	ARCOXIA 30, 60, 90 or 120 mg film-coated tablets

This leaflet was last approved in (MM/YYYY).

ANNEX IV

CONDITIONS OF THE MARKETING AUTHORISATION

CONDITIONS OF THE MARKETING AUTHORISATION

National competent authorities (NCA) shall ensure that the following conditions are fulfilled by the marketing authorisation holders:

- A direct healthcare professional communication (DHPC) must be sent to all healthcare professionals who prescribe etoricoxib according to national practice. This information should inform healthcare professionals on the cardiorenal risks associated with Arcoxia and should be in line with the DHPC endorsed by the CHMP.