ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, AND MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES AND NORWAY AND ICELAND

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Austria	Merck Sharp & Dohme GmbH Donau-City-Straße 6 A-1220 Wien Austria	Arcoxia	60mg	Film-coated tablet	Oral use
Austria	Merck Sharp & Dohme GmbH Donau-City-Straße 6 A-1220 Wien Austria	Arcoxia	90mg	Film-coated tablet	Oral use
Austria	Merck Sharp & Dohme GmbH Donau-City-Straße 6 A-1220 Wien Austria	Arcoxia	120mg	Film-coated tablet	Oral use
Austria	Merck Sharp & Dohme GmbH Donau-City-Straße 6 A-1220 Wien Austria	Auxib	60mg	Film-coated tablet	Oral use
Austria	Merck Sharp & Dohme GmbH Donau-City-Straße 6 A-1220 Wien Austria	Auxib	90mg	Film-coated tablet	Oral use
Austria	Merck Sharp & Dohme GmbH Donau-City-Straße 6 A-1220 Wien Austria	Auxib	120mg	Film-coated tablet	Oral use
Belgium	Merck Sharp & Dohme B.V. Chaussée de Waterloo 1135 B-1180 Brussels Belgium	Arcoxia	60 mg	Film-coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Belgium	Merck Sharp & Dohme B.V. Chaussée de Waterloo 1135 B-1180 Brussels Belgium	Arcoxia	90 mg	Film-coated tablet	Oral use
Belgium	Merck Sharp & Dohme B.V. Chaussée de Waterloo 1135 B-1180 Brussels Belgium	Arcoxia	120 mg	Film-coated tablet	Oral use
Belgium	Merck Sharp & Dohme B.V. Chaussée de Waterloo 1135 B-1180 Brussels Belgium	Ranacox	60 mg	Film-coated tablet	Oral use
Belgium	Merck Sharp & Dohme B.V. Chaussée de Waterloo 1135 B-1180 Brussels Belgium	Ranacox	90 mg	Film-coated tablet	Oral use
Belgium	Merck Sharp & Dohme B.V. Chaussée de Waterloo 1135 B-1180 Brussels Belgium	Ranacox	120 mg	Film-coated tablet	Oral use
Cyprus	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	60 mg	Film-coated tablet	Oral use
Cyprus	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	90 mg	Film-coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Cyprus	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	120 mg	Film-coated tablet	Oral use
Czech Republic	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	60 mg	Film-coated tablet	Oral use
Czech Republic	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	90 mg	Film-coated tablet	Oral use
Czech Republic	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	120 mg	Film-coated tablet	Oral use
Denmark	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	60 mg	Film-coated tablet	Oral use
Denmark	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	90 mg	Film-coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Denmark	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	120 mg	Film-coated tablet	Oral use
Estonia	Merck Sharp & Dohme OÜ Peterburi tee 46 11415 Tallinn Estonia	Arcoxia	60 mg	Film-coated tablet	Oral use
Estonia	Merck Sharp & Dohme OÜ Peterburi tee 46 11415 Tallinn Estonia	Arcoxia	90 mg	Film-coated tablet	Oral use
Estonia	Merck Sharp & Dohme OÜ Peterburi tee 46 11415 Tallinn Estonia	Arcoxia	120 mg	Film-coated tablet	Oral use
Finland	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	60mg	Film-coated tablet	Oral use
Finland	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	90mg	Film-coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Finland	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	120mg	Film-coated tablet	Oral use
Finland	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Turox	60mg	Film-coated tablet	Oral use
Finland	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Turox	90mg	Film-coated tablet	Oral use
Finland	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Turox	120mg	Film-coated tablet	Oral use
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 85540 Haar Germany	Etoricoxib MSD	120 mg	Film-coated tablet	Oral use
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 85540 Haar Germany	Etoricoxib MSD	90 mg	Film-coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 85540 Haar Germany	Etoricoxib MSD	60 mg	Film-coated tablet	Oral use
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 85540 Haar Germany	Auxib	120 mg	Film-coated tablet	Oral use
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 85540 Haar Germany	Auxib	90 mg	Film-coated tablet	Oral use
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 85540 Haar Germany	Auxib	60 mg	Film-coated tablet	Oral use
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 85540 Haar Germany	Arcoxia	120 mg	Film-coated tablet	Oral use
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 85540 Haar Germany	Arcoxia	90 mg	Film-coated tablet	Oral use
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 85540 Haar Germany	Arcoxia	60 mg	Film-coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Greece	Vianex S.A Tatoiou Street 18 Km Athens-Lamia National Road 14671 Nea Erythrea Athens Greece	Arcoxia	60mg	Film-coated tablet	Oral use
Greece	Vianex S.A Tatoiou Street 18 Km Athens-Lamia National Road 14671 Nea Erythrea Athens Greece	Arcoxia	90mg	Film-coated tablet	Oral use
Greece	Vianex S.A Tatoiou Street 18 Km Athens-Lamia National Road 14671 Nea Erythrea Athens Greece	Arcoxia	120mg	Film-coated tablet	Oral use
Greece	Vianex S.A Tatoiou Street 18 Km Athens-Lamia National Road 14671 Nea Erythrea Athens Greece	Turox	60mg	Film-coated tablet	Oral use
Greece	Vianex S.A Tatoiou Street 18 Km Athens-Lamia National Road 14671 Nea Erythrea Athens Greece	Turox	90mg	Film-coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Greece	Vianex S.A Tatoiou Street 18 Km Athens-Lamia National Road 14671 Nea Erythrea Athens Greece	Turox	120mg	Film-coated tablet	Oral use
Hungary	MSD Hungary Ltd. Alkotás utca 48-50 H-1123 Budapest Hungary	Arcoxia	60 mg	Film-coated tablet	Oral use
Hungary	MSD Hungary Ltd. Alkotás utca 48-50 H-1123 Budapest Hungary	Arcoxia	90 mg	Film-coated tablet	Oral use
Hungary	MSD Hungary Ltd. Alkotás utca 48-50 H-1123 Budapest Hungary	Arcoxia	120 mg	Film-coated tablet	Oral use
Iceland	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	60 mg	Film-coated tablet	Oral use
Iceland	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	90 mg	Film-coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Iceland	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	120 mg	Film-coated tablet	Oral use
Ireland	Merck Sharp & Dohme Limited Hertford Road Hoddesdon Hertfordshire EN11 9BU United Kingdom	Arcoxia	60 mg	Tablet	Oral use
Ireland	Merck Sharp & Dohme Limited Hertford Road Hoddesdon Hertfordshire EN11 9BU United Kingdom	Arcoxia	90 mg	Tablet	Oral use
Ireland	Merck Sharp & Dohme Limited Hertford Road Hoddesdon Hertfordshire EN11 9BU United Kingdom	Arcoxia	120 mg	Tablet	Oral use
Italy	Merck Sharp E Dohme Italia S.p.A Via G. Fabbroni, 6 I-00191 Roma Italy	Arcoxia	60mg	Film-coated tablet	Oral use
Italy	Merck Sharp E Dohme Italia S.p.A Via G. Fabbroni, 6 I-00191 Roma Italy	Arcoxia	90mg	Film-coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Italy	Merck Sharp E Dohme Italia S.p.A Via G. Fabbroni, 6 I-00191 Roma Italy	Arcoxia	120mg	Film-coated tablet	Oral use
Italy	Istituto Gentili S.p.A. Via Benedetto Croce, 37 I-56125 Pisa Italy	Algix	60mg	Film-coated tablet	Oral use
Italy	Istituto Gentili S.p.A. Via Benedetto Croce, 37 I-56125 Pisa Italy	Algix	90mg	Film-coated tablet	Oral use
Italy	Istituto Gentili S.p.A. Via Benedetto Croce, 37 I-56125 Pisa Italy	Algix	120mg	Film-coated tablet	Oral use
Italy	Neopharmed S.p.A. Via G. Fabbroni, 6 I-00191 Roma Italy	Recoxib	60mg	Film-coated tablet	Oral use
Italy	Neopharmed S.p.A. Via G. Fabbroni, 6 I-00191 Roma Italy	Recoxib	90mg	Film-coated tablet	Oral use
Italy	Neopharmed S.p.A. Via G. Fabbroni, 6 I-00191 Roma Italy	Recoxib	120mg	Film-coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Italy	Addenda Pharma S.r.l. Via dei Santi Pietro e Paolo, 30 00144 Roma Italy	Tauxib	60mg	Film-coated tablet	Oral use
Italy	Addenda Pharma S.r.l. Via dei Santi Pietro e Paolo, 30 00144 Roma Italy	Tauxib	90mg	Film-coated tablet	Oral use
Italy	Addenda Pharma S.r.l. Via dei Santi Pietro e Paolo, 30 00144 Roma Italy	Tauxib	120mg	Film-coated tablet	Oral use
Latvia	SIA ”Merck Sharp & Dohme Latvija” Skanstes iela 13 LV-1013 Riga Latvia	Arcoxia	60 mg	Film-coated tablet	Oral use
Latvia	SIA ”Merck Sharp & Dohme Latvija” Skanstes iela 13 LV-1013 Riga Latvia	Arcoxia	90 mg	Film-coated tablet	Oral use
Latvia	SIA ”Merck Sharp & Dohme Latvija” Skanstes iela 13 LV-1013 Riga Latvia	Arcoxia	120mg	Film-coated tablet	Oral use
Lithuania	Merck Sharp & Dohme UAB, Lithuania Gelezinio Vilko 18A 01112 Vilnius Lithuania	Arcoxia	60 mg	Film-coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Lithuania	Merck Sharp & Dohme UAB, Lithuania Gelezinio Vilko 18A 01112 Vilnius Lithuania	Arcoxia	90 mg	Film-coated tablet	Oral use
Lithuania	Merck Sharp & Dohme UAB, Lithuania Gelezinio Vilko 18A 01112 Vilnius Lithuania	Arcoxia	120 mg	Film-coated tablet	Oral use
Luxembourg	Merck Sharp&Dohme s.a. 1180, Chaussée de Waterloo B-1135 Bruxelles Belgium	Arcoxia	60 mg	Film-coated tablet	Oral use
Luxembourg	Merck Sharp&Dohme s.a. 1180, Chaussée de Waterloo B-1135 Bruxelles Belgium	Arcoxia	90 mg	Film-coated tablet	Oral use
Luxembourg	Merck Sharp&Dohme s.a. 1180, Chaussée de Waterloo B-1135 Bruxelles Belgium	Arcoxia	120 mg	Film-coated tablet	Oral use
Luxembourg	Merck Sharp&Dohme s.a. 1180, Chaussée de Waterloo B-1135 Bruxelles Belgium	Ranacox	60 mg	Film-coated tablet	Oral use
Luxembourg	Merck Sharp&Dohme s.a. 1180, Chaussée de Waterloo B-1135 Bruxelles Belgium	Ranacox	90 mg	Film-coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Luxembourg	Merck Sharp&Dohme s.a. 1180, Chaussée de Waterloo B-1135 Bruxelles Belgium	Ranacox	120mg	Film-coated tablet	Oral use
Malta	Merck Sharp & Dohme Limited Hertfordshire Road Hoddesdon Hertfordshire EN11 9BU United Kingdom	Arcoxia	60mg	Tablet	Oral use
Malta	Merck Sharp & Dohme Limited Hertfordshire Road Hoddesdon Hertfordshire EN11 9BU United Kingdom	Arcoxia	90mg	Tablet	Oral use
Malta	Merck Sharp & Dohme Limited Hertfordshire Road Hoddesdon Hertfordshire EN11 9BU United Kingdom	Arcoxia	120mg	Tablet	Oral use
The Netherlands	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	60 mg	Film-coated tablet	Oral use
The Netherlands	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	90 mg	Film-coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
The Netherlands	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	120 mg	Film-coated tablet	Oral use
The Netherlands	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Auxib	60 mg	Film-coated tablet	Oral use
The Netherlands	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Auxib	90 mg	Film-coated tablet	Oral use
The Netherlands	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Auxib	120 mg	Film-coated tablet	Oral use
Norway	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	60 mg	Film-coated tablet	Oral use
Norway	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	90 mg	Film-coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Norway	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	120 mg	Film-coated tablet	Oral use
Poland	MSD Polska Sp. z o.o. ul. Puławska 303 02-785 Warszawa Poland	Arcoxia	60 mg	Film-coated tablet	Oral use
Poland	MSD Polska Sp. z o.o. ul. Puławska 303 02-785 Warszawa Poland	Arcoxia	90 mg	Film-coated tablet	Oral use
Poland	MSD Polska Sp. z o.o. ul. Puławska 303 02-785 Warszawa Poland	Arcoxia	120 mg	Film-coated tablet	Oral use
Portugal	Merck Sharp & Dohme, Lda Quinta Da Fonte Edificio Vasco da Gama, nº19, Porto Salvo 2770-192 Paço d´Arcos Portugal	Arcoxia	60 mg	Film-coated tablet	Oral use
Portugal	Merck Sharp & Dohme, Lda Quinta Da Fonte Edificio Vasco da Gama, nº19, Porto Salvo 2770-192 Paço d´Arcos Portugal	Arcoxia	90 mg	Film-coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Portugal	Merck Sharp & Dohme, Lda Quinta Da Fonte Edificio Vasco da Gama, nº19, Porto Salvo 2770-192 Paço d´Arcos Portugal	Arcoxia	120 mg	Film-coated tablet	Oral use
Portugal	Bial-Portela & Ca., S.A. Av. Da Siderurgia Nacional 4745-457 S. Mamede do Coronado Portugal	Exxiv	60 mg	Film-coated tablet	Oral use
Portugal	Bial-Portela & Ca., S.A. Av. Da Siderurgia Nacional 4745-457 S. Mamede do Coronado Portugal	Exxiv	90 mg	Film-coated tablet	Oral use
Portugal	Bial-Portela & Ca., S.A. Av. Da Siderurgia Nacional 4745-457 S. Mamede do Coronado Portugal	Exxiv	120 mg	Film-coated tablet	Oral use
Portugal	Farmacox-Companhia Farmacêutica, Lda. Quinta Da Fonte Edificio Vasco da Gama, nº19, Porto Salvo 2770-192 Paço d´Arcos Portugal	Turox	60 mg	Film-coated tablet	Oral use
Portugal	Farmacox-Companhia Farmacêutica, Lda. Quinta Da Fonte Edificio Vasco da Gama, nº19, Porto Salvo 2770-192 Paço d´Arcos Portugal	Turox	90 mg	Film-coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Portugal	Farmacox-Companhia Farmacêutica, Lda. Quinta Da Fonte Edificio Vasco da Gama, nº19, Porto Salvo 2770-192 Paço d´Arcos Portugal	Turox	120 mg	Film-coated tablet	Oral use
Slovakia	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	60 mg	Film-coated tablet	Oral use
Slovakia	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	90 mg	Film-coated tablet	Oral use
Slovakia	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	120 mg	Film-coated tablet	Oral use
Slovenia	Merck sharp & Dohme Ltd. Šmartinska cesta 140 SI-1000 Ljubljana Slovenia	Arcoxia	60 mg	Film-coated tablet	Oral use
Slovenia	Merck sharp & Dohme Ltd. Šmartinska cesta 140 SI-1000 Ljubljana Slovenia	Arcoxia	90 mg	Film-coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Slovenia	Merck sharp & Dohme Ltd. Šmartinska cesta 140 SI-1000 Ljubljana Slovenia	Arcoxia	120 mg	Film-coated tablet	Oral use
Spain	Merck Sharp & Dohme de España S.A. Josefa Valcárcel 38 Madrid 28027 SPAIN	Arcoxia	60mg	Film-coated tablet	Oral use
Spain	Merck Sharp & Dohme de España S.A. Josefa Valcárcel 38 Madrid 28027 SPAIN	Arcoxia	90mg	Film-coated tablet	Oral use
Spain	Merck Sharp & Dohme de España S.A. Josefa Valcárcel 38 Madrid 28027 SPAIN	Arcoxia	120mg	Film-coated tablet	Oral use
Spain	Laboratorios Abelló S.A. Josefa Valcárcel 38 Madrid 28027 SPAIN	Exxiv	60mg	Film-coated tablet	Oral use
Spain	Laboratorios Abelló S.A. Josefa Valcárcel 38 Madrid 28027 SPAIN	Exxiv	90mg	Film-coated tablet	Oral use
Spain	Laboratorios Abelló S.A. Josefa Valcárcel 38 Madrid 28027 SPAIN	Exxiv	120mg	Film-coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Sweden	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	60 mg	Film-coated tablet	Oral use
Sweden	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	90 mg	Film-coated tablet	Oral use
Sweden	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Arcoxia	120 mg	Film-coated tablet	Oral use
Sweden	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Turox	60 mg	Film-coated tablet	Oral use
Sweden	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Turox	90 mg	Film-coated tablet	Oral use
Sweden	Merck Sharp & Dohme B.V Waarderweg 39 Post Bus 581 2003 PC Haarlem The Netherlands	Turox	120 mg	Film-coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
United Kingdom	Merck Sharp & Dohme Ltd Hertford Road Hoddesdon Hertfordshire EN11 9BU United Kingdom	Arcoxia	60 mg	Tablet	Oral use
United Kingdom	Merck Sharp & Dohme Ltd Hertford Road Hoddesdon Hertfordshire EN11 9BU United Kingdom	Arcoxia	90 mg	Tablet	Oral use
United Kingdom	Merck Sharp & Dohme Ltd Hertford Road Hoddesdon Hertfordshire EN11 9BU United Kingdom	Arcoxia	120 mg	Tablet	Oral use
United Kingdom	Merck Sharp & Dohme Ltd Hertford Road Hoddesdon Hertfordshire EN11 9BU United Kingdom	Auxib	60 mg	Tablet	Oral use
United Kingdom	Merck Sharp & Dohme Ltd Hertford Road Hoddesdon Hertfordshire EN11 9BU United Kingdom	Auxib	90 mg	Tablet	Oral use
United Kingdom	Merck Sharp & Dohme Ltd Hertford Road Hoddesdon Hertfordshire EN11 9BU United Kingdom	Auxib	120 mg	Tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
United Kingdom	Merck Sharp & Dohme Ltd Hertford Road Hoddesdon Hertfordshire EN11 9BU United Kingdom	Exxiv	60 mg	Tablet	Oral use
United Kingdom	Merck Sharp & Dohme Ltd Hertford Road Hoddesdon Hertfordshire EN11 9BU United Kingdom	Exxiv	90 mg	Tablet	Oral use
United Kingdom	Merck Sharp & Dohme Ltd Hertford Road Hoddesdon Hertfordshire EN11 9BU United Kingdom	Exxiv	120 mg	Tablet	Oral use
United Kingdom	Merck Sharp & Dohme Ltd Hertford Road Hoddesdon Hertfordshire EN11 9BU United Kingdom	Turox	60 mg	Tablet	Oral use
United Kingdom	Merck Sharp & Dohme Ltd Hertford Road Hoddesdon Hertfordshire EN11 9BU United Kingdom	Turox	90 mg	Tablet	Oral use
United Kingdom	Merck Sharp & Dohme Ltd Hertford Road Hoddesdon Hertfordshire EN11 9BU United Kingdom	Turox	120 mg	Tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration

ANNEX II

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

SCIENTIFIC CONCLUSIONS FOR THE AMENDMENT OF THE MARKETING AUTHORISATION

In September 2004, the Marketing Authorisation Holder (MAH) of rofecoxib (a selective Cox-2-inhibitor) informed the EMEA that new clinical trial (APPROVe) data for rofecoxib have revealed a risk of thrombotic cardiovascular (CV) events. These data resulted in the worldwide withdrawal of Vioxx (rofecoxib) from the market on 30 September 2004 by the MAH and raised questions regarding the cardiovascular safety of other Cox-2 inhibitors.

Further to discussions at the CHMP October 2004 plenary meeting, the European Commission recommended that this public health issue on all aspects of cardiovascular safety including thrombotic events and cardio-renal events is the subject of Community referrals under Article 31 of Directive 2001/83/EC, as amended regarding decentrally authorised products containing celecoxib, etoricoxib and lumiracoxib and subject to a review procedure under Article 18 of Council Regulation (EEC) No 2309/93, as amended regarding the centrally authorised products containing celecoxib (Onsenal), parecoxib (Dynastat/Rayzon) and valdecoxib (Bextra/Valdyn), which were started in November 2004.

During the CHMP meeting of February 2005, discussions on cardiovascular safety took place. The CHMP agreed that an Urgent Safety Restriction (USR) on cardiovascular safety was needed to introduce new contraindications and strengthen warnings and information on side effects in the SPC. This USR was initiated on 16 February 2005 and finalised on 17 February 2005.

On 7 April 2005, the FDA (Food and Drug Administration) and the EMEA requested that Pfizer voluntarily withdraw Bextra (valdecoxib) from the market and Pfizer agreed to suspend sale and marketing of Bextra worldwide pending further discussions on the unfavorable risk versus benefit due to data on serious skin reactions.
On 20 April 2005, Pfizer presented data on serious skin reactions for valdecoxib during a hearing.

Further to a request from the European Commission, the scope of the ongoing class was broadened review to include the assessment of serious skin reactions in addition to the cardiovascular safety aspects.

Between November 2004 and June 2005, the MAH made oral explanations to the CHMP on cardiovascular and skin safety aspects for etoricoxib on 18 January and 15 February 2005.

On 23 June 2005, the CHMP concluded that:

- Further to the assessment of:

  - the new data provided on rofecoxib by the APPROVe clinical study, which revealed a risk of thrombotic CV events,
  - the data on celecoxib presented in the APC study, which suggested a dose-related increased risk of serious CV events,
  - the data on valdecoxib and parecoxib presented in the CABG (Coronary Artery Bypass Graft) and in the CABG II studies, which showed a higher rate of serious CV thromboembolic events in the parecoxib/valdecoxib treatment arm compared to the group of patients receiving placebo,
  - the data on etoricoxib in the EDGE study and pooled analyses of other clinical trials, which suggested an association with a higher thrombotic risk than naproxen,
  - the data on lumiracoxib in the Target study, which suggested a small increase in thrombotic events (especially myocardial infarction) versus naproxen,

all available data show an increased risk of CV adverse reactions for Cox-2 inhibitors as a class and agreed that there is an association between duration and dose of intake and the probability of suffering a CV reaction.

- Further to the assessment of the data on serious skin reactions, etoricoxib is associated with a relatively low rate of serious skin reactions. However, current estimates are based on limited data and the extent of under-reporting is unquantifiable.

The CHMP confirmed changes to the Product Information already introduced through a type II variation adopted in May 2005 further to the February USR and requested further changes.

The changes of the Product Information related to the CV can be summarised as follows:

- Addition of a statement that decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks.
- Addition of a statement that prescribers should use the lowest effective dose, for the shortest possible duration, and that the need for pain relief should be re-evaluated frequently.
- Addition of the contraindications *Established ischaemic heart disease and/or cerebrovascular disease* and *Peripheral arterial disease*.
- Addition of a warning on clinical trials which suggest that selective Cox-2 inhibitors may be associated with a risk of thrombotic events (especially MI and stroke), relative to placebo and some NSAIDs.
- Addition of a warning for patients with risk factors for heart disease, such as hypertension, hyperlipidaemia (high cholesterol levels), diabetes and smoking.
- Addition of a warning for prescribers to consider discontinuation of therapy if during treatment, patients deteriorate in any of the organ system functions described.
- Addition of a warning for prescribers relating to hypertension and monitoring blood pressure during treatment with etoricoxib. If blood pressure rises significantly, alternative treatment should be considered.
- Addition of a warning for prescribers to exercise caution when prescribing NSAIDs, in combination with ACE inhibitors or angiotensin II receptor antagonists.

The changes of the Product Information related to the SCAR can be summarised as follows:

- Addition of a warning to report that the onset of skin reactions occur in the majority of cases within the first month of treatment.
- Addition of a warning for patients with a history of any drug allergy.
- Strengthening of a warning to highlight that fatal serious skin reactions have now occurred with Cox-2 inhibitors.
- Addition of a more detailed description of the first signs of skin reactions leading to discontinuation of the treatment.

GROUNDS FOR THE AMENDMENT OF THE MARKETING AUTHORISATION

Whereas, the CHMP

- is of the Opinion that the benefit/risk balance of medicinal products containing etoricoxib in the agreed indications remains favourable and the Marketing Authorisations should be maintained according to revised Summaries of Product Characteristics (attached in Annex III of the CHMP Opinion),
- concluded that the cardiovascular safety and serious skin reactions should be continuously and carefully monitored and assessed,

recommended follow up measures to further investigate the safety of etoricoxib.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS

Note: This SPC is the one that was Annexed to the Commission Decision on this Article 31 referral for etoricoxib containing medicinal products. The text was valid at that time.

After the Commission Decision, the Member State competent authorities will update the product information as required. Therefore, this SPC may not necessarily represent the current text.

1. NAME OF THE MEDICINAL PRODUCT

<INVENTED NAME (see Annex 1)> 60 mg Film-coated Tablets/Tablets
<INVENTED NAME (see Annex 1)> 90 mg Film-coated Tablets/Tablets
<INVENTED NAME (see Annex 1)> 120 mg Film-coated Tablets/Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

3. PHARMACEUTICAL FORM

Film-coated tablet/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 sections 4.3, 4.4).

4.2 Posology and method of administration

<INVENTED NAME> is administered orally and may be taken with or without food. The onset of drug effect may be faster when <INVENTED NAME> 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 60mg daily
The dose for RA should not exceed 90mg daily
The dose for acute gout should not exceed 120mg 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 sections 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 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 use: Etoricoxib is contra-indicated in children and adolescents under 16 years of age.

4.3 Contra-indications

History of 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 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 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 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, 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).

<INVENTED NAME> 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 mcg ethinyl estradiol (EE) and 0.5 to 1 mg norethindrone for 21 days increased the steady state $AUC_{0\text{-}24hr}$ of EE by 37%. Etoricoxib 120 mg given with the same oral contraceptive concomitantly or separated by 12 hours, increased the steady state $AUC_{0\text{-}24hr}$ of EE by 50 to 60%. This increase in EE concentration should be considered when selecting an oral contraceptive for use with etoricoxib. An increase in EE exposure

can increase the incidence of adverse events associated with oral contraceptives (e.g., venous thrombo-embolic events in women at risk).

Hormone Replacement Therapy: Administration of etoricoxib 120 mg with hormone replacement therapy consisting of conjugated estrogens (0.625 mg PREMARIN™ <or local TRADEMARK>) 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 (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 <or local TRADEMARK> were less than half of those observed when PREMARIN <or local TRADEMARK> 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 <or local TRADEMARK> 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 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 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 approximately 4800 individuals, including approximately 3400 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: gastroenteritis, 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.
Very rare: confusion, hallucinations.

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

Eye disorders:
Uncommon: blurred vision.

Ear and labyrinth disorders:
Uncommon: tinnitus.

Cardiac disorders:
Uncommon: congestive heart failure, non-specific ECG changes, myocardial infarction [*].

Vascular disorders:
Common: hypertension.
Uncommon: flushing, cerebrovascular accident [*].
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.

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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).

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

Hepatobiliary disorders:
Very rare: hepatitis.

Skin and subcutaneous tissue disorders:
Uncommon: ecchymosis, 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:
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.

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

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, <INVENTED NAME> 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.

Approximately 3100 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.

A study of approximately 7100 osteoarthritis patients compared the gastrointestinal tolerability of etoricoxib 90 mg (1.5 times the recommended OA dose) with diclofenac 150 mg. Patients were treated for a median duration of 11 months. Use of gastroprotective agents and low dose aspirin were permitted in the study. The gastrointestinal and cardiovascular safety data are summarized below.

Gastrointestinal tolerability and safety results: Etoricoxib was associated with a statistically significantly lower incidence of patient withdrawals due to a predefined composite endpoint of clinical gastrointestinal adverse events and laboratory adverse events related to elevated liver function tests compared to diclofenac. The incidence of clinical gastrointestinal events leading to withdrawal was statistically significantly lower for etoricoxib versus diclofenac (7.1% versus 9.1%, respectively). The rates for confirmed upper gastrointestinal perforations, ulcerations and bleeds were the same for etoricoxib and diclofenac (1.11 events per 100 patient years.)

The following additional safety results were observed in the study:

Cardiovascular data:
The event rates for serious thrombotic events were: Etoricoxib 1.25 events per 100 patient years versus 1.15 events per 100 patient years for diclofenac (relative risk 1.07;95% CI: 0.65%, 1.74%). The rates of myocardial infarction were 0.68 versus 0.42 events per 100 patient years on etoricoxib and diclofenac respectively. The rates of ischemic stroke were 0.14 versus 0.23 per 100 patient years on etoricoxib versus diclofenac respectively.

Cardiorenal events: Statistically significantly more patients treated with etoricoxib than diclofenac experienced adverse effects associated with hypertension (11.7% versus 5.9%) and oedema (7.5% versus

5.9%). A higher rate of discontinuation due to hypertension was seen (2.3% versus 0.7%) and this was statistically significant. The incidence of patient discontinuations due to oedema was 0.9% for etoricoxib versus 0.7% for diclofenac. The incidence of congestive heart failure was 0.4% for etoricoxib versus 0.2% for diclofenac.

Hepatic adverse events: Etoricoxib was associated with a statistically significantly lower rate of withdrawals than diclofenac (0.3% versus 5.2%), due largely to elevations in liver function tests. The majority of elevations in liver function tests on diclofenac that resulted in discontinuation were greater than 3 times the upper limit of normal.

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 4000 patients with OA, RA, or chronic low back pain assessed the incidence rate for the following endpoints: 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 endpoints 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.

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. 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 '*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, 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, 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 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), 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

To be filled in locally.

8. MARKETING AUTHORISATION NUMBER

To be filled in locally.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Month Day, Year

10. DATE OF REVISION OF THE TEXT

Month Day, Year

ANNEX IV

CONDITIONS OF THE MARKETING AUTHORISATION

Follow-up measures of the Marketing Authorisation Holder

As requested by the CHMP, the MAH agreed to submit the follow-up measures as listed below:

Area	Description
Clinical 1	The MAH commits to inform the CHMP of the outcome of the MEDAL and EDGE II studies on cardiovascular and GI safety upon completion and will provide necessary updates as applicable.
Clinical 2	To continue to monitor patient exposure to etoricoxib in GPRD and evaluate potential contribution of observational study(-ies). To submit a descriptive study protocol to CHMP.
Clinical 3	Further revisions to the SPC will be promptly communicated to HCPs and promptly incorporated into printed materials and product websites.
Clinical 4	To undertaking its risk management plan as communicated to the CHMP during May 2005 CHMP meeting and outlined in the assessment report response on 10 May 2005.