ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, 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	Ceoxx 25 mg tabletten	25 mg	Tablet	Oral use
Austria	Merck Sharp & Dohme GmbH. Donau-City-Straße 6 A-1220 Wien Austria	Ceoxx 50 mg tabletten	50 mg	Tablet	Oral use
Austria	Merck Sharp & Dohme GmbH. Donau-City-Straße 6 A-1220 Wien Austria	Coxxil 12, 5 mg/5 ml orale suspension	12, 5 mg/5 ml	Oral suspension	Oral use
Austria	Merck Sharp & Dohme GmbH. Donau-City-Straße 6 A-1220 Wien Austria	Coxxil 25 mg/5 ml orale suspension	25 mg/5 ml	Oral suspension	Oral use
Austria	Merck Sharp & Dohme GmbH. Donau-City-Straße 6 A-1220 Wien Austria	Coxxil 12, 5 mg tabletten	12, 5 mg	Tablet	Oral use
Austria	Merck Sharp & Dohme GmbH. Donau-City-Straße 6 A-1220 Wien Austria	Coxxil 25 mg tabletten	25 mg	Tablet	Oral use
Austria	Merck Sharp & Dohme GmbH.	Vioxx 12,5 mg tabletten	12,5 mg	Tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	Donau-City-Straße 6 A-1220 Wien Austria				
Austria	Merck Sharp & Dohme GmbH. Donau-City-Straße 6 A-1220 Wien Austria	Vioxx 25 mg tabletten	25 mg	Tablet	Oral use
Austria	Merck Sharp & Dohme GmbH. Donau-City-Straße 6 A-1220 Wien Austria	Vioxx 12, 5 mg/5 ml orale suspension	12, 5 mg/5 ml	Oral suspension	Oral use
Austria	Merck Sharp & Dohme GmbH. Donau-City-Straße 6 A-1220 Wien Austria	Vioxx 25 mg/5 ml orale suspension	25 mg/5 ml	Oral suspension	Oral use
Austria	Merck Sharp & Dohme GmbH. Donau-City-Straße 6 A-1220 Wien Austria	Vioxx Dolor 25 mg tabletten	25 mg	Tablet	Oral use
Austria	Merck Sharp & Dohme GmbH. Donau-City-Straße 6 A-1220 Wien Austria	Vioxx Dolor 50 mg tabletten	50 mg	Tablet	Oral use
Belgium	Merck Sharp & Dohme, B.V. Chaussée de Waterloo Waterloosesteenweg, 1135	Vioxx	12, 5 mg	Tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	B-1180 Bruxelles Belgium				
Belgium	Merck Sharp & Dohme B.V. Chaussée de Waterloo Waterloosesteenweg, 1135 B-1180 Bruxelles Belgium	Vioxx	12, 5 mg/5 ml	Oral suspension	Oral use
Belgium	Merck Sharp & Dohme B.V. Chaussée de Waterloo Waterloosesteenweg, 1135 B-1180 Bruxelles Belgium	Vioxx	25 mg/ 5 ml	Oral suspension	Oral use
Belgium	Merck Sharp & Dohme B.V. Chaussée de Waterloo Waterloosesteenweg, 1135 B-1180 Bruxelles Belgium	Vioxx	25 mg	Tablet	Oral use
Belgium	Merck Sharp & Dohme B.V. Chaussée de Waterloo Waterloosesteenweg, 1135 B-1180 Bruxelles Belgium	Flogoxxa	25 mg	Tablet	Oral use
Belgium	Merck Sharp & Dohme B.V. Chaussée de Waterloo Waterloosesteenweg, 1135 B-1180 Bruxelles Belgium	Flogoxxa	50 mg	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 Waterloosesteenweg, 1135 B-1180 Bruxelles Belgium	Foldoxx	12, 5 mg	Tablet	Oral use
Belgium	Merck Sharp & Dohme B.V. Chaussée de Waterloo Waterloosesteenweg, 1135 B-1180 Bruxelles Belgium	Foldoxx	25 mg	Tablet	Oral use
Belgium	Merck Sharp & Dohme B.V. Chaussée de Waterloo Waterloosesteenweg, 1135 B-1180 Bruxelles Belgium	Foldoxx	12, 5 mg/5 ml	Oral suspension	Oral use
Belgium	Merck Sharp & Dohme B.V. Chaussée de Waterloo Waterloosesteenweg, 1135 B-1180 Bruxelles Belgium	Foldoxx	25 mg/5 ml	Oral suspension	Oral use
Belgium	Merck Sharp & Dohme B.V. Chaussée de Waterloo Waterloosesteenweg, 1135 B-1180 Bruxelles Belgium	Vioxxdolor	25 mg	Tablet	Oral use
Belgium	Merck Sharp & Dohme B.V.	Vioxxdolor	50 mg	Tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	Chaussée de Waterloo Waterloosesteenweg, 1135 B-1180 Bruxelles Belgium				
Denmark	Merck Sharp & Dohme B.V. Waarderweg 39, Post Bus 581 2003 PC Haarleem The Netherlands	Vioxx	12, 5 mg	Tablet	Oral use
Denmark	Merck Sharp & Dohme B.V. Waarderweg 39, Post Bus 581 2003 PC Haarleem The Netherlands	Vioxx	25 mg	Tablet	Oral use
Denmark	Merck Sharp & Dohme B.V. Waarderweg 39, Post Bus 581 2003 PC Haarleem The Netherlands	Vioxx	12, 5 mg/5 ml	Oral suspension	Oral use
Denmark	Merck Sharp & Dohme B.V. Waarderweg 39, Post Bus 581 2003 PC Haarleem The Netherlands	Vioxx	25 mg/5 ml	Oral suspension	Oral use
Denmark	Merck Sharp & Dohme B.V. Waarderweg 39, Post Bus 581 2003 PC Haarleem The Netherlands	Meroxx	12, 5 mg	Tablet	Oral use
Denmark	Merck Sharp & Dohme B.V. Waarderweg 39, Post Bus 581	Meroxx	25 mg	Tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	2003 PC Haarleem The Netherlands				
Denmark	Merck Sharp & Dohme B.V. Waarderweg 39, Post Bus 581 2003 PC Haarleem The Netherlands	Meroxx	12, 5 ml/5 ml	Oral suspension	Oral use
Denmark	Merck Sharp & Dohme B.V. Waarderweg 39, Post Bus 581 2003 PC Haarleem The Netherlands	Meroxx	25 ml/5 ml	Oral suspension	Oral use
Denmark	Merck Sharp & Dohme B.V. Waarderweg 39, Post Bus 581 2003 PC Haarleem The Netherlands	Vioxxalt	25 mg	Tablet	Oral use
Denmark	Merck Sharp & Dohme B.V. Waarderweg 39, Post Bus 581 2003 PC Haarleem The Netherlands	Vioxxalt	50 mg	Tablet	Oral use
Denmark	Merck Sharp & Dohme B.V. Waarderweg 39, Post Bus 581 2003 PC Haarleem The Netherlands	Rofecoxib, MSD	25 mg	Tablet	Oral use
Denmark	Merck Sharp & Dohme B.V. Waarderweg 39, Post Bus 581 2003 PC Haarleem The Netherlands	Rofecoxib, MSD	50 mg	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 Haarleem The Netherlands	Ceoxxa	25 mg	Tablet	Oral use
Finland	Merck Sharp & Dohme B.V. Waarderweg 39, Post Bus 581 2003 PC Haarleem The Netherlands	Ceoxxa	50 mg	Tablet	Oral use
Finland	Merck Sharp & Dohme B.V. Waarderweg 39, Post Bus 581 2003 PC Haarleem The Netherlands	Vioxx	12, 5 mg	Tablet	Oral use
Finland	Merck Sharp & Dohme B.V. Waarderweg 39, Post Bus 581 2003 PC Haarleem The Netherlands	Vioxx	25 mg	Tablet	Oral use
Finland	Merck Sharp & Dohme B.V. Waarderweg 39, Post Bus 581 2003 PC Haarleem The Netherlands	Vioxx	12, 5 mg/5 ml	Oral suspension	Oral use
Finland	Merck Sharp & Dohme B.V. Waarderweg 39, Post Bus 581 2003 PC Haarleem The Netherlands	Vioxx	25 mg/5 ml	Oral suspension	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 Haarleem The Netherlands	Vioxxakut	25 mg	Tablet	Oral use
Finland	Merck Sharp & Dohme B.V. Waarderweg 39, Post Bus 581 2003 PC Haarleem The Netherlands	Vioxxakut	50 mg	Tablet	Oral use
France	Laboratoires Merck Sharp & Dohme – Chibret 3, avenue Hoche 75114 Paris cedex 08 France	Vioxx	12, 5 mg	Tablet	Oral use
France	Laboratoires Merck Sharp & Dohme – Chibret 3, avenue Hoche 75114 Paris cedex 08 France	Vioxx	12, 5 mg/5 ml	Oral suspension	Oral use
France	Laboratoires Merck Sharp & Dohme – Chibret 3, avenue Hoche 75114 Paris cedex 08 France	Vioxx	25 mg	Tablet	Oral use
France	Laboratoires Merck Sharp & Dohme – Chibret 3, avenue Hoche 75114 Paris cedex 08	Vioxx	25 mg/5 ml	Oral suspension	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	France				
France	Laboratoires Merck Sharp & Dohme – Chibret 3, avenue Hoche 75114 Paris cedex 08 France	Meoroxx	12, 5 mg	Tablet	Oral use
France	Laboratoires Merck Sharp & Dohme – Chibret 3, avenue Hoche 75114 Paris cedex 08 France	Meoroxx	12, 5 mg/5 ml	Oral suspension	Oral use
France	Laboratoires Merck Sharp & Dohme – Chibret 3, avenue Hoche 75114 Paris cedex 08 France	Meoroxx	25 mg	Tablet	Oral use
France	Laboratoires Merck Sharp & Dohme – Chibret 3, avenue Hoche 75114 Paris cedex 08 France	Meoroxx	25 mg/5 ml	Oral suspension	Oral use
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 D-85540 Haar Germany	Vioxx Dolor 25 mg Tabletten	25 mg	Tablet	Oral use
Germany	MSD Sharp & Dohme GmbH	Vioxx Dolor 50 mg Tabletten	50 mg	Tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	Lindenplatz 1 D-85540 Haar Germany				
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 D-85540 Haar Germany	Ceoxx 25 mg Tabletten	25 mg	Tablet	Oral use
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 D-85540 Haar Germany	Ceoxx 50 mg Tabletten	50 mg	Tablet	Oral use
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 D-85540 Haar Germany	Rofecoxib MSD 12,5 mg/5 ml Suspension zum Einnehmen	12,5 mg/5 ml	Oral suspension	Oral use
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 D-85540 Haar Germany	Rofecoxib MSD 25 mg/5 ml Suspension zum Einnehmen	25 mg/5 ml	Oral suspension	Oral use
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 D-85540 Haar Germany	Rofecoxib MSD 12, 5 mg Tabletten	12, 5 mg	Tablet	Oral use
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 D-85540 Haar	Rofecoxib MSD 25 mg Tabletten	25 mg	Tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	Germany				
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 D-85540 Haar Germany	Vioxx 12,5 mg/5 ml Suspension zum Einnehmen	12,5 mg/5 ml	Oral suspension	Oral use
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 D-85540 Haar Germany	Vioxx 25 mg/5 ml Suspension zum Einnehmen	25 mg/5 ml	Oral suspension	Oral use
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 D-85540 Haar Germany	Vioxx 12, 5 mg Tabletten	12, 5 mg	Tablet	Oral use
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 D-85540 Haar Germany	Vioxx 25 mg Tabletten	25 mg	Tablet	Oral use
Greece	Vianex S.A. Pharmaceuticals & Cosmetic Industry Licensee/Distributor of Merck Sharp & Dohme Tatoiou Street. 18th Km Athens-Lamia National Road 14671 Nea Erythrea, Athens Greece	Vioxx	12, 5 mg	Tablet	Oral use
Greece	Vianex S.A.	Vioxx	25 mg	Tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	Pharmaceuticals & Cosmetic Industry Licensee/Distributor of Merck Sharp & Dohme Tatoiou Street. 18th Km Athens-Lamia National Road 14671 Nea Erythrea, Athens Greece				
Greece	Vianex S.A. Pharmaceuticals & Cosmetic Industry Licensee/Distributor of Merck Sharp & Dohme Tatoiou Street. 18th Km Athens-Lamia National Road 14671 Nea Erythrea, Athens Greece	Vioxx	12, 5 mg/5 ml	Oral suspension	Oral use
Greece	Vianex S.A. Pharmaceuticals & Cosmetic Industry Licensee/Distributor of Merck Sharp & Dohme Tatoiou Street. 18th Km Athens-Lamia National Road 14671 Nea Erythrea, Athens Greece	Vioxx	25 mg/5 ml	Oral suspension	Oral use
Greece	Vianex S.A. Pharmaceuticals & Cosmetic Industry Licensee/Distributor of Merck Sharp & Dohme Tatoiou Street. 18th Km Athens-Lamia National Road	Peroxx	12, 5 mg	Tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	14671 Nea Erythrea, Athens Greece				
Greece	Vianex S.A. Pharmaceuticals & Cosmetic Industry Licensee/Distributor of Merck Sharp & Dohme Tatoiou Street. 18th Km Athens-Lamia National Road 14671 Nea Erythrea, Athens Greece	Peroxx	25 mg	Tablet	Oral use
Greece	Vianex S.A. Pharmaceuticals & Cosmetic Industry Licensee/Distributor of Merck Sharp & Dohme Tatoiou Street. 18th Km Athens-Lamia National Road 14671 Nea Erythrea, Athens Greece	Peroxx	12, 5 mg/5 ml	Oral suspension	Oral use
Greece	Vianex S.A. Pharmaceuticals & Cosmetic Industry Licensee/Distributor of Merck Sharp & Dohme Tatoiou Street. 18th Km Athens-Lamia National Road 14671 Nea Erythrea, Athens Greece	Peroxx	25 mg/5 ml	Oral suspension	Oral use
Iceland	Merck Sharp & Dohme B.V., Waarderweg 39, Post Bus 581,	Vioxx	12, 5 mg/5 ml	Oral suspension	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	2003 P.C., Haarlem, The Netherlands				
Iceland	Merck Sharp & Dohme B.V., Waarderweg 39, Post Bus 581, 2003 P.C., Haarlem, The Netherlands	Vioxx	25 mg/5 ml	Oral suspension	Oral use
Iceland	Merck Sharp & Dohme B.V., Waarderweg 39, Post Bus 581, 2003 P.C., Haarlem, The Netherlands	Vioxx	12, 5 mg	Tablet	Oral use
Iceland	Merck Sharp & Dohme B.V., Waarderweg 39, Post Bus 581, 2003 P.C., Haarlem, The Netherlands	Vioxx	25 mg	Tablet	Oral use
Iceland	Merck Sharp & Dohme B.V., Waarderweg 39, Post Bus 581, 2003 P.C., Haarlem, The Netherlands	Vioxxakut	25 mg	Tablet	Oral use
Iceland	Merck Sharp & Dohme B.V., Waarderweg 39, Post Bus 581, 2003 P.C., Haarlem, The Netherlands	Vioxxakut	50 mg	Tablet	Oral use
Iceland	Merck Sharp & Dohme B.V., Waarderweg 39, Post Bus 581, 2003 P.C., Haarlem, The Netherlands	Ceoxx	25 mg	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 P.C., Haarlem, The Netherlands	Ceoxx	50 mg	Tablet	Oral use
Ireland	Merck Sharp & Dohme Limited; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU United Kingdom	Ceoxx	25 mg	Tablet	Oral use
Ireland	Merck Sharp & Dohme Limited; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU United Kingdom	Ceoxx	50 mg	Tablet	Oral use
Ireland	Merck Sharp & Dohme Limited; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU United Kingdom	Vioxx	12, 5 mg/5 ml	Oral suspension	Oral use
Ireland	Merck Sharp & Dohme Limited; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU United Kingdom	Vioxx	25 mg/5 ml	Oral suspension	Oral use
Ireland	Merck Sharp & Dohme Limited; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU United Kingdom	Vioxx	12, 5 mg	Tablet	Oral use
Ireland	Merck Sharp & Dohme Limited;	Vioxx	25 mg	Tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	Hertford Road, Hoddesdon, Hertfordshire EN11 9BU United Kingdom				
Italy	Merck Sharp E Dohme (Italia) S.p.A. Via G. Fabbroni, 6 00191 Rome Italy	Vioxx	12, 5 mg	Tablet	Oral use
Italy	Merck Sharp E Dohme (Italia) S.p.A. Via G. Fabbroni, 6 00191 Rome Italy	Vioxx	25 mg	Tablet	Oral use
Italy	Merck Sharp E Dohme (Italia) S.p.A. Via G. Fabbroni, 6 00191 Rome Italy	Vioxx	12, 5 mg/5 ml	Oral suspension	Oral use
Italy	Merck Sharp E Dohme (Italia) S.p.A. Via G. Fabbroni, 6 00191 Rome Italy	Vioxx	25 mg/5 ml	Oral suspension	Oral use
Italy	Neopharmed S.p.A. Via G. Fabbroni, 6 00191 Rome Italy	Arofexx	12, 5 mg	Tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Italy	Neopharmed S.p.A. Via G. Fabbroni, 6 00191 Rome Italy	Arofexx	25 mg	Tablet	Oral use
Italy	Neopharmed S.p.A. Via G. Fabbroni, 6 00191 Rome Italy	Arofexx	12, 5 mg/5 ml	Oral suspension	Oral use
Italy	Neopharmed S.p.A. Via G. Fabbroni, 6 00191 Rome Italy	Arofexx	25 mg/5 ml	Oral suspension	Oral use
Italy	Istituto Gentili S.p.A. Via Mazzini, 112 56125 Pisa Italy	Coxxil	12, 5 mg	Tablet	Oral use
Italy	Istituto Gentili S.p.A. Via Mazzini, 112 56125 Pisa Italy	Coxxil	25 mg	Tablet	Oral use
Italy	Istituto Gentili S.p.A. Via Mazzini, 112 56125 Pisa Italy	Coxxil	12, 5 mg/5 ml	Oral suspension	Oral use
Italy	Istituto Gentili S.p.A.	Coxxil	25 mg/5 ml	Oral suspension	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	Via Mazzini, 112 56125 Pisa Italy				
Italy	Merck Sharp E Dohme (Italia) S.p.A. Via G. Fabbroni, 6 00191 Rome Italy	Dolcoxx	25 mg	Tablet	Oral use
Italy	Merck Sharp E Dohme (Italia) S.p.A. Via G. Fabbroni, 6 00191 Rome Italy	Dolcoxx	50 mg	Tablet	Oral use
Italy	Neopharmed S.p.A. Via G. Fabbroni, 6 00191 Rome Italy	Miraxx	25 mg	Tablet	Oral use
Italy	Neopharmed S.p.A. Via G. Fabbroni, 6 I-00191 Rome Italy	Miraxx	50 mg	Tablet	Oral use
Italy	Istituto Gentili S.p.A. Via Mazzini, 112 I-56100 Pisa Italy	Dolostop	25 mg	Tablet	Oral use
Italy	Istituto Gentili S.p.A.	Dolostop	50 mg	Tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	Via Mazzini, 112 I-56100 Pisa Italy				
Luxembourg	Merck Sharp & Dohme B.V. Chaussée de Waterloo Waterloosesteenweg 1135 B-1180 Brussels Belgium	Vioxx	12, 5 mg	Tablet	Oral use
Luxembourg	Merck Sharp & Dohme B.V. Chaussée de Waterloo Waterloosesteenweg 1135 B-1180 Brussels Belgium	Vioxx	25 mg	Tablet	Oral use
Luxembourg	Merck Sharp & Dohme B.V. Chaussée de Waterloo Waterloosesteenweg 1135 B-1180 Bruxelles Belgium	Vioxx	12, 5 mg/5 ml	Oral suspension	Oral use
Luxembourg	Merck Sharp & Dohme B.V. Chaussée de Waterloo 1135 1180 Brussels Belgium	Vioxx	25 mg/5 ml	Oral suspension	Oral use
Luxembourg	Merck Sharp & Dohme B.V. Chaussée de Waterloo Waterloosesteenweg 1135 1180 Brussels Belgium	Foldoxx	12, 5 mg	Tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Luxembourg	Merck Sharp & Dohme B.V. Chaussée de Waterloo Waterloosesteenweg 1135 1180 Brussels Belgium	Foldoxx	25 mg	Tablet	Oral use
Luxembourg	Merck Sharp & Dohme B.V. Chaussée de Waterloo Waterloosesteenweg 1135 1180 Brussels Belgium	Foldoxx	12, 5 mg/5 ml	Oral suspension	Oral use
Luxembourg	Merck Sharp & Dohme B.V. Chaussée de Waterloo Waterloosesteenweg 1135 1180 Brussels Belgium	Foldoxx	25 mg/5 ml	Oral suspension	Oral use
Luxembourg	Merck Sharp & Dohme B.V. Chaussée de Waterloo Waterloosesteenweg 1135 1180 Brussels Belgium	Flogoxxa	25 mg	Tablet	Oral use
Luxembourg	Merck Sharp & Dohme B.V. Chaussée de Waterloo Waterloosesteenweg 1135 1180 Brussels Belgium	Flogoxxa	50 mg	Tablet	Oral use
Luxembourg	Merck Sharp & Dohme B.V.	Vioxxdolor	25 mg	Tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	Chaussée de Waterloo Waterloosesteenweg 1135 1180 Brussels Belgium				
Luxembourg	Merck Sharp & Dohme B.V. Chaussée de Waterloo Waterloosesteenweg 1135 1180 Brussels Belgium	Vioxxdolor	50 mg	Tablet	Oral use
The Netherlands	Merck Sharp & Dohme BV, Waarderweg 39, Post Bus 581 2003 P.C. Haarlem The Netherlands	Vioxx 12, 5 mg tabletten	12, 5 mg	Tablet	Oral use
The Netherlands	Merck Sharp & Dohme BV, Waarderweg 39, Post Bus 581 2003 P.C. Haarlem The Netherlands	Vioxx 25 mg tabletten	25 mg	Tablet	Oral use
The Netherlands	Merck Sharp & Dohme BV, Waarderweg 39, Post Bus 581 2003 P.C. Haarlem The Netherlands	Vioxx 12, 5 mg/5 ml suspensie	12, 5 mg/5 ml	Oral suspension	Oral use
The Netherlands	Merck Sharp & Dohme BV, Waarderweg 39, Post Bus 581 2003 P.C. Haarlem The Netherlands	Vioxx 25 mg/5 ml suspensie	25 mg/5 ml	Oral suspension	Oral use
The Netherlands	Merck Sharp & Dohme BV,	Balasys 12, 5 mg tabletten	12, 5 mg	Tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	Waarderweg 39, Post Bus 581 2003 P.C. Haarlem The Netherlands				
The Netherlands	Merck Sharp & Dohme BV, Waarderweg 39, Post Bus 581 2003 P.C. Haarlem The Netherlands	Balasys 25 mg tabletten	25 mg	Tablet	Oral use
The Netherlands	Merck Sharp & Dohme BV, Waarderweg 39, Post Bus 581 2003 P.C. Haarlem The Netherlands	Balasys 12, 5 mg/5 ml suspensie	12, 5 mg/5 ml	Oral suspension	Oral use
The Netherlands	Merck Sharp & Dohme BV, Waarderweg 39, Post Bus 581 2003 P.C. Haarlem The Netherlands	Balasys 25 mg/5 ml suspensie	25 mg/5 ml	Oral suspension	Oral use
The Netherlands	Merck Sharp & Dohme BV, Waarderweg 39, Post Bus 581 2003 P.C. Haarlem The Netherlands	Ceoxx 25 mg tabletten	25 mg	Tablet	Oral use
The Netherlands	Merck Sharp & Dohme BV, Waarderweg 39, Post Bus 581 2003 P.C. Haarlem The Netherlands	Ceoxx 50 mg tabletten	50 mg	Tablet	Oral use
The Netherlands	Merck Sharp & Dohme BV, Waarderweg 39, Post Bus 581 2003 P.C. Haarlem	Vioxx acute pijn 25 mg tabletten	25 mg	Tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	The Netherlands				
The Netherlands	Merck Sharp & Dohme BV, Waarderweg 39, Post Bus 581 2003 P.C. Haarlem The Netherlands	Vioxx acute pijn 50 mg tabletten	50 mg	Tablet	Oral use
Norway	Merck Sharp & Dohme BV, Waarderweg 39, Post Bus 581 2003 P.C. Haarlem The Netherlands	Vioxx	12, 5 mg/ml	Oral suspension	Oral use
Norway	Merck Sharp & Dohme BV, Waarderweg 39, Post Bus 581 2003 P.C. Haarlem The Netherlands	Vioxx	25 mg/ml	Oral suspension	Oral use
Norway	Merck Sharp & Dohme BV, Waarderweg 39, Post Bus 581 2003 P.C. Haarlem The Netherlands	Vioxx	12,5 mg	Tablet	Oral use
Norway	Merck Sharp & Dohme BV, Waarderweg 39, Post Bus 581 2003 P.C. Haarlem The Netherlands	Vioxx	12,5 mg	Tablet	Oral use
Norway	Merck Sharp & Dohme BV, Waarderweg 39, Post Bus 581 2003 P.C. Haarlem The Netherlands	Vioxx	25 mg	Tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Norway	Merck Sharp & Dohme BV, Waarderweg 39, Post Bus 581 2003 P.C. Haarlem The Netherlands	Ceoxx	25 mg	Tablet	Oral use
Norway	Merck Sharp & Dohme BV, Waarderweg 39, Post Bus 581 2003 P.C. Haarlem The Netherlands	Ceoxx	50 mg	Tablet	Oral use
Norway	Merck Sharp & Dohme BV, Waarderweg 39, Post Bus 581 2003 P.C. Haarlem The Netherlands	Vioxx AC	25 mg	Tablet	Oral use
Norway	Merck Sharp & Dohme BV, Waarderweg 39, Post Bus 581 2003 P.C. Haarlem The Netherlands	Vioxx AC	50 mg	Tablet	Oral use
Portugal	Laboratórios Químico-Farmacêuticos Chibret, Lda. Quinta da Fonte Edifício Vasco da Gama 19 P.O Box 214 Porto Salvo 2770-192 Paço d'Arcos Portugal	Acoxxin	12, 5 mg	Tablet	Oral use
Portugal	Laboratórios Químico-Farmacêuticos Chibret, Lda. Quinta da Fonte	Acoxxin	25 mg	Tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	Edifício Vasco da Gama 19 P.O Box 214 Porto Salvo 2770-192 Paço d'Arcos Portugal				
Portugal	Laboratórios Químico-Farmacêuticos Chibret, Lda. Quinta da Fonte Edifício Vasco da Gama 19 P.O Box 214 Porto Salvo 2770-192 Paço d'Arcos Portugal	Acoxxin	12, 5 mg/ml	Oral suspension	Oral use
Portugal	Laboratórios Químico-Farmacêuticos Chibret, Lda. Quinta da Fonte Edifício Vasco da Gama 19 P.O Box 214 Porto Salvo 2770-192 Paço d'Arcos Portugal	Acoxxin	25 mg/ml	Oral suspension	Oral use
Portugal	Merck Sharp & Dohme, Lda. Quinta da Fonte, Edifício Vasco da Gama 19 P.O Box 214 Porto Salvo 2770-192 Paço d' Arcos - Portugal	Ceoxx	25 mg	Tablet	Oral use
Portugal	Merck Sharp & Dohme, Lda.	Ceoxx	50 mg	Tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	Quinta da Fonte, Edifício Vasco da Gama 19 P.O Box 214 Porto Salvo 2780-730 Paço d' Arcos Portugal				
Portugal	Ferraz Lynce, S.A. Rua Consiglieri Pedroso, 123 Queluz de Baixo P.O Box 1001 2745-557 Barcarena Portugal	Coxxil	12, 5 mg	Tablet	Oral use
Portugal	Ferraz Lynce, S.A. Rua Consiglieri Pedroso, 123 Queluz de Baixo P.O Box 1001 2745-557 Barcarena Portugal	Coxxil	25 mg	Tablet	Oral use
Portugal	Laboratórios Químico-Farmacêuticos Chibret, Lda. Quinta da Fonte Edifício Vasco da Gama 19 P.O Box 214 Porto Salvo 2770-192 Paço d'Arcos - Portugal	Coxxil	12, 5 mg/ml	Oral suspension	Oral use
Portugal	Laboratórios Químico-Farmacêuticos Chibret, Lda. Quinta da Fonte Edifício Vasco	Coxxil	25 mg/ml	Oral suspension	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	da Gama 19 P.O Box 214 Porto Salvo 2770-192 Paço d'Arcos - Portugal				
Portugal	Laboratórios Químico-Farmacêuticos Chibret, Lda. Quinta da Fonte Edifício Vasco da Gama 19- P.O. Box 214 Porto Salvo 2770-192 Paço D'Arcos - Portugal	Dolocoxx	25 mg	Tablet	Oral use
Portugal	Laboratórios Químico-Farmacêuticos Chibret, Lda. Quinta da Fonte Edifício Vasco da Gama 19 - P.O. Box 214 Porto Salvo 2770-192 Paço D'Arcos - Portugal	Dolocoxx	50 mg	Tablet	Oral use
Portugal	Farmacox - Companhia Farmacêutica, Lda Quinta da Fonte, Edifício Vasco da Gama, 19 - P.O. Box 214 Porto Salvo 2770-192 Paço d'Arcos - Portugal	Trioxx	25 mg	Tablet	Oral use
Portugal	Farmacox - Companhia Farmacêutica, Lda Quinta da Fonte, Edifício Vasco da Gama, 19 P.O. Box 214	Trioxx	50 mg	Tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	Porto Salvo 2770-192 Paço d'Arcos - Portugal				
Portugal	Merck Sharp & Dohme, Lda. Quinta da Fonte, Edifício Vasco da Gama 19, P.O. Box 214 Porto Salvo 2770-192 Paço d' Arcos – Portugal	Vioxx	12, 5 mg/ml	Oral suspension	Oral use
Portugal	Merck Sharp & Dohme, Lda. Quinta da Fonte, Edifício Vasco da Gama 19, P.O. Box 214 Porto Salvo 2770-192 Paço d' Arcos – Portugal	Vioxx	25 mg/ml	Oral suspension	Oral use
Portugal	Merck Sharp & Dohme, Lda. Quinta da Fonte, Edifício Vasco da Gama 19, P.O. Box 214 Porto Salvo 2770-192 Paço d' Arcos – Portugal	Vioxx	12, 5 mg	Tablet	Oral use
Portugal	Merck Sharp & Dohme, Lda. Quinta da Fonte, Edifício Vasco da Gama 19, P.O. Box 214 Porto Salvo 2770-192 Paço d' Arcos – Portugal	Vioxx	12, 5 mg	Tablet	Oral use
Spain	Laboratorios Abello S.A	Movtor 25 mg	25 mg	Tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	Josefa Valcarcel, 38 28027 Madrid Spain				
Spain	Laboratorios Abello S.A C/Josefa Valcarcel, 38 28027 Madrid Spain	Movtor 50 mg	50 mg	Tablet	Oral use
Spain	Laboratorios Abello S.A C/Josefa Valcarcel, 38 28027 Madrid Spain	Ceoxx 25 mg	25 mg	Tablet	Oral use
Spain	Laboratorios Abello S.A C/Josefa Valcarcel, 38 28027 Madrid Spain	Ceoxx 50 mg	50 mg	Tablet	Oral use
Spain	Laboratorios Abello S.A C/Josefa Valcarcel, 38 28027 Madrid Spain	Vioxx 12, 5 mg/5 ml	12, 5 mg/5 ml	Oral suspension	Oral use
Spain	Laboratorios Abello S.A C/Josefa Valcarcel, 38 28027 Madrid Spain	Vioxx 25 mg/5 ml	25 mg/5 ml	Oral suspension	Oral use
Spain	Laboratorios Abello S.A C/Josefa Valcarcel, 38 28027 Madrid	Vioxx	12, 5 mg	Tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	Spain				
Spain	Laboratorios Abello S.A C/Josefa Valcarcel, 38 28027 Madrid Spain	Vioxx	25 mg	Tablet	Oral use
Spain	Laboratorios Abello S.A C/Josefa Valcarcel, 38 28027 Madrid Spain	Recox 12, 5 mg	12, 5 mg	Tablet	Oral use
Spain	Laboratorios Abello S.A C/Josefa Valcarcel, 38 28027 Madrid Spain	Recox 25 mg	25 mg	Tablet	Oral use
Spain	Laboratorios Abello S.A C/Josefa Valcarcel, 38 28027 Madrid Spain	Recox 12, 5 mg/5ml	12, 5 mg/5 ml	Oral suspension	Oral use
Spain	Laboratorios Abello S.A C/Josefa Valcarcel, 38 28027 Madrid Spain	Recox 25 mg/5ml	25 mg/5 ml	Oral suspension	Oral use
Sweden	Merck Sharp & Dohme B.V. Waarderweg 39, Post Bus 581 2003 P.C. Haarlem The Netherlands	Vioxx	12, 5 mg	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 P.C. Haarlem The Netherlands	Vioxx	25 mg	Tablet	Oral use
Sweden	Merck Sharp & Dohme BV Warderweg 39, Post Bus 581 2003 P.C. Haarlem The Netherlands	Vioxx	12,5 mg/ml	Oral suspension	Oral use
Sweden	Merck Sharp & Dohme B.V. Waarderweg 39, Post Bus 581 2003 P.C. Haarlem The Netherlands	Vioxx	25 mg/ml	Oral suspension	Oral use
Sweden	Merck Sharp & Dohme BV Warderweg 39, Post Bus 581 2003 P.C. Haarlem The Netherlands	Ceoxx	25 mg	Tablet	Oral use
Sweden	Merck Sharp & Dohme B.V. Waarderweg 39, Post Bus 581 2003 P.C. Haarlem The Netherlands	Ceoxx	50 mg	Tablet	Oral use
Sweden	Merck Sharp & Dohme B.V. Waarderweg 39, Post Bus 581 2003 P.C. Haarlem The Netherlands	Vioxxakut	25 mg	Tablet	Oral use
Sweden	Merck Sharp & Dohme B.V. Waarderweg 39, Post Bus 581	Vioxxakut	50mg	Tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	2003 P.C. Haarlem The Netherlands				
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire, EN11 9BU United Kingdom	Axxelor	12,5 mg	Tablet	Oral use
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire, EN11 9BU United Kingdom	Axxelor	25 mg	Tablet	Oral use
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire, EN11 9BU United Kingdom	Axxelor	12,5 mg/5 ml	Oral suspension	Oral use
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire, EN11 9BU United Kingdom	Axxelor	25 mg/5 ml	Oral suspension	Oral use
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire, EN11 9BU United Kingdom	Coxxid	12, 5 mg	Tablet	Oral use
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire, EN11 9BU United Kingdom	Coxxid	25 mg	Tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire EN11 9BU United Kingdom	Coxxid	12,5 mg/5 ml	Oral suspension	Oral use
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire, EN11 9BU United Kingdom	Coxxid	25 mg/5 ml	Oral suspension	Oral use
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire, EN11 9BU United Kingdom	Ceoxx	25 mg	Tablet	Oral use
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire, EN11 9BU United Kingdom	Ceoxx	50 mg	Tablet	Oral use
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire, EN11 9BU United Kingdom	Movtor	25 mg	Tablet	Oral use
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire, EN11 9BU United Kingdom	Movtor	50 mg	Tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire, EN11 9BU United Kingdom	Vioxx	12,5 mg/5 ml	Oral suspension	Oral use
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire, EN11 9BU United Kingdom	Vioxx	25 mg/5 ml	Oral suspension	Oral use
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire, EN11 9BU United Kingdom	Vioxx	12, 5 mg	Tablet	Oral use
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire, EN11 9BU United Kingdom	Vioxx	25 mg	Tablet	Oral use
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire, EN11 9BU United Kingdom	Vioxxacute	25 mg	Tablet	Oral use
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire, EN11 9BU United Kingdom	Vioxxacute	50 mg	Tablet	Oral use

ANNEX II

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

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF MEDICINAL PRODUCTS CONTAINING CELECOXIB, ETORICOXIB, PARECOXIB, ROFECOXIB AND VALDECOXIB <(see Annex I for medicinal products containing rofecoxib)>

- INTRODUCTION

The COX-2 inhibitors celecoxib, etoricoxib, rofecoxib, parecoxib and valdecoxib, comprise a relatively new group of substances whose common pharmacological action is the selective inhibition of cyclooxygenase-2. COX-2 inhibitors have been introduced in medical practice for treatment of patients with chronic inflammatory degenerative diseases such as rheumatoid arthritis and osteoarthritis.
Rofecoxib and celecoxib have been first authorised in the EU for these indications, and subsequently rofecoxib for treatment of acute pain and pain due to primary dysmenorrhoea. Etoricoxib received later authorisation for rheumatic diseases, including gouty athritis, in some EU-member states. Valdecoxib is authorised for the rheumatic indications and primary dysmenorrhoea and was authorised after start of the referral procedure. Parecoxib, a prodrug of valdecoxib, is authorised for short-term treatment of post-surgical pain, when used intravenously or intramuscularly. Celecoxib received an authorisation in October 2003 in an orphan drug indication (familial adenomatous polyposis).

COX-2 inhibitors have been investigated in large clinical studies, and a large body of data - toxicological, pharmacological, clinical, and epidemiological - is available today. When first authorised there were insufficient data showing a benefit in long-term treatment of rheumatoid arthritis and osteoarthritis patients compared to usual NSAIDs. Moreover, knowledge of tolerability under normal use of COX-2 inhibitors, ie. outside clinical studies, was limited as with nearly all new chemical entities introduced in broad medical practice. Large clinical trials (VIGOR: rofecoxib versus naproxen, CLASS: celecoxib versus diclofenac or ibuprofen) using high doses have been conducted and published in this respect, especially looking at gastrointestinal (GI) tolerability.

In July 2002, France requested the CPMP to give its opinion under Article 31 of Directive 2001/83 EC as amended, on whether the marketing authorisations for medicinal products containing celecoxib, etoricoxib, rofecoxib, valdecoxib and parecoxib should be maintained, changed, suspended or withdrawn by reassessing the benefit-risk profile of the class of products.

The CPMP, during its meeting held from 23 to 25 July 2002 decided to start a referral procedure under Article 31 of Directive 2001/83/EC as amended, for medicinal products containing COX-2 inhibitors (celecoxib, etoricoxib, parecoxib, rofecoxib and valdecoxib). The questions identified related to gastrointestinal and cardiovascular safety. In October 2002, the CPMP asked additional questions relating to serious hypersensitivity reactions (anaphylaxis and angioedema) and serious skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and exfoliative dermatitis in patients treated with COX-2 inhibitors.

- EFFICACY ISSUES

Efficacy has been demonstrated for rofecoxib in the treatment of rheumatoid arthritis or osteoarthritis, acute pain and pain due to primary dysmenorrhoea. Efficacy was superior to placebo and similar to non-selective NSAIDs (diclofenac, naproxen, ibuprofen) in comparative clinical settings, equipotent dosage, and duration of treatment.

- **SAFETY ISSUES**

Gastrointestinal toxicity

Available data indicated that significant and consistent gastrointestinal benefit of COX-2 inhibitors compared with conventional NSAIDs has not been demonstrated. The clinical data provided specifically for rofecoxib were consistent with a GI benefit compared with naproxen. However, GI benefit was less when compared to diclofenac.
The CPMP decided to add a general statement in section 4.4 "Special warnings and special precautions for use" and 5.1 "Pharmacodynamic properties" of the SPC for all COX-2 inhibitors relating to patients at risk of developing gastrointestinal complications with NSAIDs.

It is unknown whether the gastrointestinal toxicity profile of COX-2 inhibitors in association with acetylsalicylic acid is inferior to conventional NSAIDs given with acetylsalicylic acid but there is no evidence to suggest it would be superior. Based on the current data on rofecoxib the product information should be updated to include the potential for increase in gastrointestinal toxicity compared with COX-2 inhibitors or acetylsalicylic acid alone.
Further to discussions and considering the assessment of the data presented for the other COX-2 inhibitors, the CPMP decided to update section 4.4 "Special warnings and special precautions for use" of the Summary of Products Characteristics (SPC) regarding concomitant use of all COX-2 inhibitors with acetylsalicylic acid.

Cardiovascular toxicity

The available pre-clinical data raised concern about cardiovascular (CV) safety, in particular myocardial infarction (MI), however, conflicting results have often been obtained. 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 reactions.
It can be considered that there is a distinct trend towards a higher overall CV risk, in particular MI risk, associated with the use of rofecoxib compared to naproxen. In contrast to COX-1 inhibiting NSAIDs, COX-2 inhibitors, including rofecoxib, have no anti-platelet effects in therapeutic doses. With respect to CV risk, it can be considered that there may be a small safety disadvantage of COX-2 inhibitors compared to conventional NSAIDs. Therefore, the SPC should be updated for all COX-2 inhibitors, including rofecoxib, in its section 4.4 "Special warnings and special precautions for use" by adding a warning statement for patients with a medical history of cardiovascular disease or those using low dose of ASA-treatment for prophylaxis of cardiovascular thrombo-embolic diseases.

Hypersensitivity and serious skin reactions

For rofecoxib small numbers of skin reactions or hypersensitivity reactions have been observed in clinical studies. Also spontaneous reports were not very frequent for rofecoxib.

Furthermore, single cases of serious cutaneous adverse reactions, i.e., Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported for rofecoxib. The absolute numbers and estimates for frequency suggest that these adverse reactions occur very rarely and frequency seems not to be different from conventional NSAIDs.

In order to assure the attention to this potentially life threatening adverse reactions in clinical practice, the CPMP decided that a general statement relating to hypersensitivity and serious skin reactions will be included in section 4.4 "Special warnings and special precautions for use" of all COX-2 inhibitors SPCs.

HARMONISED WORDING FOR ALL COX-2 INHIBITORS SUMMARIES OF PRODUCT CHARACTERISTICS

Further to the assessment of data provided for celecoxib, etoricoxib, rofecoxib, valdecoxib and parecoxib, the CPMP has adopted a harmonised wording, which should be included in the SPC of all COX-2 inhibitors involved in this referral or concerned by the scientific assessment. The wording for rofecoxib is the following:

Section 4.4 "Special warnings and special precautions for use"

Because of the possibility for increased adverse reactions at higher doses of rofecoxib, other COX-2 inhibitors and NSAIDs, patients treated with rofecoxib should be reviewed following dose increase and, in the absence of increase in efficacy, other therapeutic options should be considered (see 4.2).

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

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 an increased risk of gastrointestinal adverse effects for rofecoxib, other COX-2 inhibitors and NSAIDs when taken concomitantly with acetylsalicylic acid (even at low doses).

COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thromboembolic diseases because of their lack of effect on platelet function. Because rofecoxib, does not inhibit platelet aggregation, antiplatelet therapies (eg acetylsalicylic acid) should not be discontinued and if indicated should be considered in patients at risk for or with a history of cardiovascular or other thrombotic events (prior history of MI, angina, ischemic heart disease, atherosclerotic heart disease, CVA, cerebral ischemia, coronary bypass graft surgery or peripheral vascular surgery). However, it should be noted that concomitant use of rofecoxib 25 mg plus low-dose acetylsalicylic acid (81 mg) results in an increased rate of endoscopic ulceration compared to the use of low-dose acetylsalicylic acid alone. (See 4.5 and 5.1.)

Caution should be exercised in patients with a medical history of ischemic heart disease because of the pharmacodynamic profile of COX-2 selective inhibitors noted above. Appropriate measures should be taken and discontinuation of rofecoxib therapy should be considered if there is clinical evidence of deterioration in the condition of specific clinical symptoms in these patients.

Serious skin reactions, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported in association with the use of NSAIDS including rofecoxib during postmarketing surveillance (see 4.8). Hypersensitivity reactions (anaphylaxis and angioedema) have been reported in patients receiving rofecoxib (see 4.8). Rofecoxib should be discontinued at the first sign of hypersensitivity.

Section 5.1 "Pharmacodynamic properties"

Rofecoxib is an oral, selective, cyclo-oxygenase-2 (COX-2) inhibitor within the clinical dose range.

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.

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 reactions. COX-2 selective 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.

GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS

Whereas

- The Committee considered the referral made under article 31 of Directive 2001/83/EC, as amended, for medicinal products containing celecoxib, etoricoxib, parecoxib, rofecoxib and valdecoxib;
- The Committee considered that no new contra-indications should be added in any of the concerned Summaries of Products Characteristics;
- The Committee concluded that a warning should be added concerning the gastrointestinal safety of medicinal products containing celecoxib, etoricoxib, parecoxib, rofecoxib and valdecoxib, mainly concerning the association with acetylsalicylic acid;
- The Committee concluded that a warning should be added concerning the cardiovascular safety of medicinal products containing celecoxib, etoricoxib, parecoxib, rofecoxib and valdecoxib, mainly concerning the risk of myocardial infarction;
- The Committee concluded that a warning should be added concerning observed or potential serious skin effects and hypersensitivity reactions of medicinal products containing celecoxib, etoricoxib, parecoxib, rofecoxib and valdecoxib;
- The Committee, as a consequence considered that the benefit/risk balance of medicinal products containing celecoxib, etoricoxib, parecoxib, rofecoxib and valdecoxib remains favourable.

As a consequence, the CPMP recommended the granting or the maintenance of the Applications/Marketing Authorisations for medicinal products containing rofecoxib referred in Annex I in the symptomatic relief of osteoarthritis (OA), rheumatoid arthritis (RA), acute pain and pain due to primary dysmenorrhoea as amended in accordance with the revised SPC as set out in Annex III.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<INVENTED NAME (see Annex 1)> 25 mg Tablets
<INVENTED NAME (see Annex 1)> 50 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg or 50 mg of rofecoxib.

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Tablet.

50 mg: Orange, round tablets <marked 'MSD 744' on one side>.

25 mg: Yellow, round tablets <marked 'MSD 741' on one side>.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Relief of acute pain.

Relief of pain due to primary dysmenorrhea.

4.2 Posology and method of administration

<INVENTED NAME> is administered orally.

<INVENTED NAME> may be taken with or without food.

<INVENTED NAME> should not be used concomitantly with other products containing the same active substance, rofecoxib.

<INVENTED NAME> is indicated for the acute symptomatic period only (usually not more than 5 days). Chronic use of <INVENTED NAME> 50 mg daily is not recommended.

Acute pain
The recommended initial dose is 50 mg once daily. Subsequent doses should be 25 or 50 mg once daily. The maximum recommended daily dose is 50 mg.

Primary dysmenorrhea
The recommended dose is 25 or 50 mg once daily. The maximum recommended daily dose is 50 mg.

<INVENTED NAME> may be most effective in patients with mild to moderately severe acute pain. In patients with severe acute pain, <INVENTED NAME> has been shown to decrease narcotic usage although it is not a substitute for narcotics. (See 5.1.)

Elderly: In the elderly (>65 years old) the lower dose (25 mg per day) should be used initially. Care should be exercised when increasing the daily dose from 25 mg to 50 mg in the elderly.

Hepatic insufficiency: (see 4.3).

Renal insufficiency: no dosage adjustment is necessary for patients with creatinine clearance 30-80 ml/min (see 4.4and 5.2). <INVENTED NAME> is contra-indicated in patients with creatinine clearance <30 ml/min (see 4.3).

Paediatric use: <INVENTED NAME> is not indicated for use in children.

4.3 Contra-indications

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

Active peptic ulceration or 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.

Third trimester of pregnancy and lactation (see 4.6 and 5.3)

Hepatic dysfunction

Estimated renal creatinine clearance <30 ml/min

Inflammatory bowel disease

Severe congestive heart failure (NYHA III-IV).

4.4 Special warnings and special precautions for use

Because of the possibility for increased adverse reactions at higher doses of rofecoxib, other COX-2 inhibitors and NSAIDs, patients treated with rofecoxib should be reviewed following dose increase and, in the absence of increase in efficacy, other therapeutic options should be considered (see 4.2).

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

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 an increased risk of gastrointestinal adverse effects for rofecoxib, other COX-2 inhibitors and NSAIDs when taken concomitantly with acetylsalicylic acid (even at low doses).

COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thromboembolic diseases because of their lack of effect on platelet function. Because rofecoxib, does not inhibit platelet aggregation, antiplatelet therapies (eg acetylsalicylic acid) should not be discontinued and if indicated should be considered in patients at risk for or with a history of cardiovascular or other thrombotic events (prior history of MI, angina, ischemic heart disease, atherosclerotic heart disease, CVA, cerebral ischemia, coronary bypass graft surgery or peripheral vascular surgery). However, it should be noted that concomitant use of rofecoxib 25 mg plus low-dose acetylsalicylic acid (81 mg) results in an increased rate of endoscopic ulceration compared to the use of low-dose acetylsalicylic acid alone. (See 4.5 and 5.1.)

Caution should be exercised in patients with a medical history of ischemic heart disease because of the pharmacodynamic profile of COX-2 selective inhibitors noted above. Appropriate measures should be

taken and discontinuation of rofecoxib therapy should be considered if there is clinical evidence of deterioration in the condition of specific clinical symptoms in these patients.

Renal prostaglandins may play a compensatory role in the maintenance of renal perfusion. Therefore, under conditions of compromised renal perfusion, administration of rofecoxib 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.

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

Fluid retention, oedema and hypertension have been observed in patients taking rofecoxib. These effects appear to be dose-related and are seen with an increased frequency with chronic use of rofecoxib and at higher therapeutic doses. The reporting rates for hypertension with rofecoxib have been similar to or, on occasion, slightly greater than some other NSAIDs, at comparable doses. Because treatment with rofecoxib may result in fluid retention, caution should be exercised in patients with history of cardiac failure, left ventricular dysfunction, or hypertension and in patients with pre-existing oedema from any other reason. Rofecoxib should be introduced at the lowest recommended dose in those patients. (See 4.5.)

Medically appropriate supervision should be maintained when using rofecoxib in the elderly and in patients with renal, hepatic, or cardiac dysfunction (see 4.2 and 4.3).

Serious skin reactions, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported in association with the use of NSAIDS including rofecoxib during postmarketing surveillance (see 4.8). Hypersensitivity reactions (anaphylaxis and angioedema) have been reported in patients receiving rofecoxib (see 4.8). Rofecoxib should be discontinued at the first sign of hypersensitivity.

Rofecoxib may mask fever and other signs of inflammation.

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

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

Elevations of ALT and/or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in osteoarthritis clinical trials with rofecoxib. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for abnormal liver function tests. If persistently abnormal liver function tests (three times the upper limit of normal) are detected, rofecoxib should be discontinued.

Paediatric patients: Rofecoxib has not been studied in children and should only be used in adult patients.

<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

In subjects stabilised on chronic warfarin therapy, the administration of rofecoxib 25 mg daily was associated with an approximate 8% increase in prothrombin time International Normalised Ratio (INR). There have been reports of increases in INR, which led to interruption of warfarin treatment and in some cases prompted reversal of anticoagulation, in patients taking rofecoxib at clinical doses concurrently with warfarin. There have also been isolated reports of increases in INR in patients taking rofecoxib and the anticoagulant fluindione. Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR, particularly in the first few days when therapy with rofecoxib is initiated or the dose of rofecoxib is changed (see 4.4).

In patients with mild-to-moderate hypertension, administration of 25 mg daily of rofecoxib with an ACE inhibitor (benazepril, 10 mg to 40 mg daily) for four weeks was associated with a small attenuation of the antihypertensive effect (average increase in Mean Arterial Pressure of 2.8 mm Hg) compared to the ACE inhibitor alone. As for other agents, which inhibit cyclo-oxygenase, in some patients with compromised renal function the co-administration of an ACE inhibitor and rofecoxib may result in further deterioration of renal function, which is usually reversible. These interactions should be given consideration in patients taking rofecoxib concomitantly with ACE inhibitors.

Concomitant use of NSAIDs may also reduce the antihypertensive efficacy of beta-blockers and diuretics and the other effects of diuretics. There are no data on the possible interaction between rofecoxib and either beta-blockers or diuretics.

At steady state, rofecoxib 50 mg once daily had no effect on the anti-platelet activity of low-dose acetylsalicylic acid. Concomitant administration of rofecoxib with higher doses of acetylsalicylic acid or other NSAIDs should be avoided.

Concomitant use of rofecoxib 25 mg plus low-dose acetylsalicylic acid (81 mg) results in an increased rate of endoscopic ulceration, compared to the use of low-dose acetylsalicylic acid alone. (See 5.1).

Coadministration of cyclosporin or tacrolimus and NSAIDs may increase the nephrotoxic effect of cyclosporin or tacrolimus. Renal function should be monitored when rofecoxib and either of these drugs is used in combination.

Pharmacokinetic interactions

The effect of rofecoxib on the pharmacokinetics of other drugs

The plasma concentration of lithium could be increased by NSAIDs. In post-marketing experience with rofecoxib, there have been reports of increases in plasma lithium levels.

Rofecoxib 12.5, 25, and 50 mg, each dose administered once daily for 7 days, had no significant effect on the plasma concentration of methotrexate as measured by $AUC_{0\text{-}24h}$ in patients receiving single weekly methotrexate doses of 7.5 to 20 mg for rheumatoid arthritis. Rofecoxib 75 mg (three to six times higher than the recommended doses for osteoarthritis) administered once daily for 10 days increased plasma methotrexate concentrations ($AUC_{(0\text{-}24hr)}$) by 23% in patients with RA receiving methotrexate 7.5 mg to 15 mg/week. Adequate monitoring for methotrexate-related toxicity should be considered when rofecoxib and methotrexate are administered concomitantly.

No interaction with digoxin has been observed in pharmacokinetic studies. However, patients at high risk of digoxin toxicity should be monitored when rofecoxib and digoxin are administered concomitantly.

In vivo data concerning rofecoxib/warfarin and rofecoxib/theophylline interactions suggest that rofecoxib may produce a modest inhibition of CYP1A2. Care should be exercised when administering rofecoxib concurrently with other drugs primarily metabolised by CYP1A2 (e.g., tacrine, zileuton, olanzapine and clozapine). Rofecoxib 12.5, 25 and 50 mg administered once daily for 7 days increased plasma theophylline concentrations ($AUC_{(0\text{-}\infty)}$) by 38 to 60% in healthy subjects administered a single 300-mg dose of theophylline. Adequate monitoring of theophylline plasma

concentrations should be considered when therapy with rofecoxib is initiated or changed in patients receiving theophylline.

The potential for rofecoxib to inhibit or induce CYP3A4 activity was investigated in human studies using the oral midazolam test and the intravenous erythromycin breath test. Rofecoxib (25 mg daily for 12 days) produced a modest induction of CYP3A4 catalysed metabolism of midazolam, reducing the AUC of midazolam by 30%. This reduction is most likely due to increased first pass metabolism through induction of intestinal CYP3A4 activity by rofecoxib. Compared to placebo, rofecoxib (75 mg daily for 14 days) did not produce any significant effect in erythromycin demethylation, indicating no induction of hepatic CYP3A4 activity.

Although rofecoxib produces a modest induction of intestinal CYP3A4 activity, the pharmacokinetics of drugs that are primarily metabolised by CYP3A4 are not expected to be affected to a clinically significant extent. However, care should be exercised when co-prescribing substrates of CYP3A4.

In drug-interaction studies, rofecoxib did not have clinically important effects on the pharmacokinetics of prednisone/prednisolone or oral contraceptives (ethinyl oestradiol/norethindrone 35/1).

Based on *in vitro* studies, rofecoxib is not expected to inhibit cytochromes P450 2C9, 2C19, 2D6, or 2E1, although *in vivo* data are not available.

Effects of other drugs on the pharmacokinetics of rofecoxib

The main pathway of rofecoxib metabolism is reduction to produce *cis*- and *trans*-dihydro rofecoxib (as hydroxy acids). In the absence of potent cytochrome P450 (CYP) inducers, CYP-catalysed metabolism is not the dominant pathway for rofecoxib metabolism.

However, co-administration of rofecoxib with rifampicin, a potent inducer of CYP enzymes, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, the use of the highest recommended dose of rofecoxib for each indication should be considered when rofecoxib is co-administered with potent inducers of hepatic metabolism.

Administration of ketoconazole (a potent inhibitor of CYP3A4) did not affect rofecoxib plasma pharmacokinetics. Cimetidine or antacids do not affect the pharmacokinetics of rofecoxib to a clinically relevant extent.

4.6 Pregnancy and lactation

Pregnancy
The use of rofecoxib, as with any drug substance known to inhibit COX-2 is not recommended in women attempting to conceive (see 5.1).

The use of rofecoxib is contraindicated in the last trimester of pregnancy because, as with other drug substances known to inhibit prostaglandin synthesis, it may cause uterine inertia and premature closure of the ductus arteriosus (see 4.3).

The use of rofecoxib in pregnant women has not been studied in adequate and well-controlled clinical trials and therefore it should not be used during the first two trimesters of pregnancy unless the potential benefit to the patient justifies the potential risk to the foetus (see 5.3).

Breast-feeding mothers
It is not known whether rofecoxib is excreted in human milk. Rofecoxib is excreted in the milk of lactating rats. Women who use rofecoxib should not breast feed. (See 4.3 and 5.3.)

4.7 Effects on ability to drive and use machines

Patients who experience dizziness, vertigo or somnolence while taking rofecoxib should refrain from driving or operating machinery.

4.8 Undesirable effects

In clinical trials, rofecoxib was evaluated for safety in approximately 11,800 individuals.

Approximately 1200 patients were treated with rofecoxib in analgesia clinical studies. The following undesirable effects were reported at an incidence greater than 1% and greater than placebo in analgesia clinical studies in patients treated with rofecoxib 50 mg or 25 mg for 1 to 5 days: dizziness, diarrhea, diaphoresis, dyspepsia.

Approximately 9,800 patients were treated with rofecoxib in osteoarthritis and rheumatoid arthritis clinical studies. The following undesirable effects were reported at an incidence greater than placebo in these clinical studies in patients treated with rofecoxib 12.5 mg or 25 mg for up to six months or in post-marketing experience.

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

***Blood and the lymphatic system disorders*:**
Common: haematocrit decreased.
Uncommon: haemoglobin decreased, erythrocytes decreased, leukocytes decreased.
Very rare: aplastic anemia, pancytopenia, thrombocytopenia.

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

***Metabolism and nutrition disorders*:**
Uncommon: weight gain.

***Psychiatric disorders*:**
Uncommon: depression, mental acuity decreased.
Very rare: anxiety, confusion, hallucinations.

***Nervous system disorders*:**
Common: dizziness, headache.
Uncommon: insomnia, somnolence, vertigo.
Very rare: epilepsy aggravated, paraesthesia, aseptic meningitis.

***Eye disorders*:**
Very rare: blurred vision.

***Ear and labyrinth disorders*:**
Uncommon: tinnitus.

***Cardiac disorders*:**
Rare: congestive heart failure.
Very rare: palpitations, myocardial infarction, pulmonary oedema.

***Vascular disorders*:**
Common: hypertension.
Very rare: cerebrovascular accident, hypertensive crisis, vasculitis.

***Respiratory, thoracic and mediastinal disorders*:**
Uncommon: dyspnoea.

Very rare: bronchospasm.

***Gastrointestinal disorders*:**
Common: abdominal pain, heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia.
Uncommon: abdominal distension, constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux.
Rare: peptic ulcers, gastrointestinal perforation and bleeding (mainly in elderly patients), gastritis.
Very rare: aggravation of inflammatory bowel disease, colitis, pancreatitis.

***Hepato-biliary disorders*:**
Common: alanine aminotransferase increased, aspartate aminotransferase increased.
Uncommon: alkaline phosphatase increased.
Very rare: hepatotoxicity including hepatitis with or without jaundice, hepatic failure.(See 4.4).

***Skin and subcutaneous tissue disorders*:**
Common: pruritus, rash.
Uncommon: atopic dermatitis.
Very rare: alopecia, photosensitivity reactions, urticaria, cutaneo-mucosal adverse effects and severe skin reactions including Stevens-Johnson Syndrome, toxic epidermal necrolysis.

***Musculoskeletal, connective tissue and bone disorders*:**
Uncommon: muscular cramp.

***Renal and urinary disorders*:**
Uncommon: BUN increased, serum creatinine increased, proteinuria.
Very rare: hyperkalaemia, renal insufficiency, including renal failure, usually reversible upon discontinuation of therapy (see 4.4), interstitial nephritis.

***Reproductive system and breast disorders*:**
Very rare: menstrual disturbances.

***General disorders and administration site conditions*:**
Common: oedema/fluid retention.
Uncommon: asthenia/fatigue, chest pain.

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

Nephrotic syndrome has been reported in association with the use of other NSAIDs and cannot be ruled out for rofecoxib.

4.9 Overdose

In clinical studies, administration of single doses of rofecoxib up to 1,000 mg and multiple doses up to 250 mg/day for 14 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.

Rofecoxib is not dialysable by haemodialysis; it is not known whether rofecoxib 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 AH02

Rofecoxib is an oral, selective, cyclo-oxygenase-2 (COX-2) inhibitor within the clinical dose range.

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.

Statistically significant inhibition of COX-1 has not been documented in humans with any dose of rofecoxib. Based on *in vitro* data, inhibition of COX-1 might occur during chronic administration of rofecoxib at >250 mg per day.

The anti-inflammatory effects of rofecoxib were demonstrated in standard animal models used to evaluate NSAIDs.

Across clinical pharmacology studies, as compared to placebo, rofecoxib produced dose-dependent inhibition of COX-2 with daily doses of 12.5 mg and 25 mg inhibiting COX-2 by ~70%, while rofecoxib at daily doses of 375 mg and a single 1000 mg dose inhibited COX-2 by ~95%. There was no dose-dependent inhibition of COX-1 compared with placebo. Rofecoxib did not inhibit gastric prostaglandin synthesis and had no effect on platelet function.

A large clinical trial (approximately 8000 patients) in rheumatoid arthritis patients has compared the long-term safety of rofecoxib 50 mg once daily (twice the maximum dose recommended for chronic use) and naproxen 500 mg twice daily. The rate of serious cardiovascular thrombo-embolic adverse events was significantly lower in patients receiving naproxen than in the rofecoxib treated patients: 0.70 events per 100 patient-years compared with 1.67 events per 100 patient-years. 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 reactions. COX-2 selective inhibitors reduce the formation of systemic (and therefore possibly endothelial) prostacyclin without affecting platelet thromboxane. The clinical relevance of these observations has not been established.

In clinical studies, rofecoxib relieved pain in acute analgesic models of post-operative dental pain, post-orthopedic surgical pain, and primary dysmenorrhea. The onset of analgesia with the single 50-mg dose of rofecoxib occurred within 45 minutes and persisted for as long as 24 hours after dosing. In multiple-dose clinical studies, lasting up to 5 days, of post-orthopedic surgical pain and pain from primary dysmenorrhea, after an initial 50-mg dose, 25 to 50 mg once daily of rofecoxib was effective in relieving pain. In the post-orthopedic surgical pain study, which evaluated moderate to severe pain after major orthopedic surgery (e.g., total knee replacement or hip replacement) and enrolled a total of 218 patients, of whom 20% experienced severe pain prior to dosing, use of rofecoxib significantly reduced narcotic usage compared to placebo. Rofecoxib has not been studied in a model of pure visceral pain or in major abdominal or thoracic surgery.

In a predefined, combined analysis of two 24-week endoscopy studies in OA patients, the percentages of patients with endoscopically detected gastroduodenal ulceration were similar between placebo, and rofecoxib 25 mg and 50 mg daily at 12 weeks. In each of these studies, the cumulative incidence of gastroduodenal ulcers was significantly less over 12 and 24 weeks in patients treated with rofecoxib than in patients treated with ibuprofen 2,400 mg daily. In an additional 12-week endoscopy study in OA patients, the cumulative incidence of endoscopically detected gastroduodenal ulcers was

significantly higher in patients treated with low-dose acetylsalicylic acid 81 mg plus rofecoxib 25 mg daily than in patients treated with low-dose acetylsalicylic acid 81 mg daily alone, and similar to patients treated with ibuprofen 2400 mg daily alone. In patients aged 65 years and over, the low-dose acetylsalicylic acid plus rofecoxib group showed a 2-fold increase in the frequency of endoscopic ulcers compared with younger patients. Patients taking low-dose acetylsalicylic acid plus ibuprofen have not been studied.

In a predefined, combined analysis of eight clinical trials, the cumulative incidence of confirmed upper GI PUBs in patients treated with rofecoxib was significantly lower than the combined cumulative incidence observed in patients treated with NSAID comparators (diclofenac 50 mg three times daily, ibuprofen 800 mg three times daily and nabumetone 1500 mg daily. These results were primarily influenced by the experience with ibuprofen 800 mg three times daily. At a dosage of 50 mg the incidence of PUBs was numerically greater compared to 25 mg, however it remained lower than the risk with combined data on NSAIDs used in these studies. Discontinuations for GI adverse experiences over 12 months were less with rofecoxib. Incidences of a predefined set of drug-related GI adverse experiences were lower with rofecoxib over 12 months; this effect was greater over the first 6 months.

A similar reduction in the incidence of PUBs was seen in the large clinical trial (approximately 8000 patients) conducted in rheumatoid arthritis patients. Patients requiring acetylsalicylic acid for cardiovascular prophylaxis were excluded from the study. The use of rofecoxib 50 mg once daily (two times the maximum recommended dose for chronic use) compared to naproxen 500 mg twice daily was associated with significant reductions in gastrointestinal event rates: PUBs (2.08 events per 100 patient-years versus 4.49 events per 100 patient-years), complicated PUBs (0.59 per 100 patient-years versus 1.37 per 100 patient-years) and upper or lower GI bleeds (1.15 per 100 patient-years versus 3.04 per 100 patient-years).

5.2 Pharmacokinetic properties

Absorption

Orally administered rofecoxib is well absorbed at the recommended doses of 25 mg and 50 mg. The mean oral bioavailability is approximately 93%. Following 25-mg once-daily dosing to steady-state, the peak plasma concentration (geometric mean C_{max} = 0.305 mcg/ml) was observed at approximately two to four hours (T_{max}) after administration to fasted adults. The geometric mean area under the curve (AUC_{24hr}) was 3.87 mcg•hr/ml.

Concomitant food intake does not affect the pharmacokinetics of rofecoxib.

Distribution

Rofecoxib is approximately 85% bound to human plasma protein at concentrations of 0.05 mcg/ml to 25 mcg/ml. The volume of distribution (V_{dss}) is approximately 100 litres (approximately 1.55 L/kg) in humans.

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

Metabolism

Rofecoxib is extensively metabolised with ~1% of a dose recovered in urine as the parent drug. The main metabolic pathway is hepatic reduction to produce *cis*- and *trans*-dihydro rofecoxib (as hydroxy acids), and not oxidation by cytochrome P450 (CYP) enzymes.

Six metabolites have been identified in man. The principal metabolites were *cis*- and *trans*-dihydro rofecoxib (as hydroxy acids), which accounted for approximately 56% of recovered radioactivity in the urine, and the 5-hydroxy glucuronide metabolite, which accounted for an additional 9%. These

principal metabolites either demonstrated no measurable activity as cyclo-oxygenase inhibitors or were only weakly active as COX-2 inhibitors.

Elimination

Following administration of a 125-mg radiolabelled oral dose of rofecoxib to healthy subjects, 72% of radioactivity was recovered in urine and 14% in faeces.

Elimination of rofecoxib occurs almost exclusively through metabolism followed by renal excretion. Steady-state concentrations of rofecoxib are reached within four days of once-daily administration of 25 mg, with an accumulation ratio of approximately 1.7, corresponding to an accumulation half-life of ~17 hours. The plasma clearance is estimated to be approximately 120 ml/min for a 25-mg dose.

Characteristics in patients

Elderly: pharmacokinetics in the elderly (65 years of age and older) are similar to those in the young. The systemic exposure is ~30% greater in the elderly than in the young.

Gender: the pharmacokinetics of rofecoxib are comparable in men and women.

Hepatic insufficiency: Cirrhotic patients with mild hepatic insufficiency (Child-Pugh score 5-6) administered a single 25-mg dose of rofecoxib had a mean AUC similar to healthy subjects given the same dose. Patients with moderate hepatic insufficiency (Child-Pugh score 7-9) had an approximately 69% higher mean AUC than healthy subjects given the same dose. There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9). (See 4.3.)

Renal insufficiency: the pharmacokinetics of a single 50-mg dose of rofecoxib in patients with end-stage renal disease on haemodialysis were not significantly different from those of healthy subjects. Haemodialysis contributed negligibly to elimination (dialysis clearance ~40 ml/min). (See 4.3 and 4.4.)

Paediatric patients: the pharmacokinetics of rofecoxib in paediatric patients have not been studied.

5.3 Preclinical safety data

In preclinical studies, rofecoxib has been demonstrated to be neither genotoxic, mutagenic, nor carcinogenic.

In a chronic toxicity study in rats, rofecoxib caused intestinal ulcers at doses comparable to and slightly above the human chronic therapeutic dose for osteoarthritis, based on systemic exposure. At exposures several times above the human therapeutic level, renal tubular basophilia, and at higher exposures renal papillary necrosis, were induced in the rat. At high exposures renal and gastro-intestinal abnormalities were seen in the dog as well.

Reproductive toxicity studies showed that rofecoxib (at doses <1 times the recommended daily human dose based on systemic exposure) decreased fertility and embryo/foetal survival in the rat. A treatment-related decrease in the diameter of the ductus arteriosus was also observed, a finding known to be associated with NSAIDs. Reproductive toxicity studies conducted in rats and rabbits have demonstrated no evidence of developmental abnormalities at doses up to 50 mg/kg/day (in rats this represents ~10 times the recommended daily human dose based on systemic exposure). (See 4.3 and 4.6.) In rabbits, however, the metabolite profile was not determined, thus making the clinical relevance of the rabbit model difficult to assess.

Data from a cross-fostering study indicated pup toxicity, probably due to exposure via milk from treated dams. (See 4.6.)

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, magnesium stearate, yellow ferric oxide (E172), and red ferric oxide (E172) (only in the 50 mg strength).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Opaque PVC/aluminium blisters in packs containing 2 (only in the 50 mg strength), 5, 6, 7, 10, 14, 15, 20, or 30 tablets.

Opaque PVC/aluminium blisters (unit doses) in packs of 50 or 500 tablets.

White, round, HDPE bottles with a white, polypropylene, non-child resistant closure containing 100 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

July 20, 2001

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

<INVENTED NAME (see Annex 1)> 12,5 mg Tablets
<INVENTED NAME (see Annex 1)> 25 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 12.5mg or 25mg of rofecoxib.

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Tablet.

12.5 mg: Cream/off white, round, shallow cup tablet <marked 'MSD 74' on one side and <INVENTED NAME> on the other>.
25 mg: Yellow, round tablets marked <'MSD 110' on one side and <INVENTED NAME> on the other>.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic relief in the treatment of osteoarthritis or rheumatoid arthritis in adults.

4.2 Posology and method of administration

<INVENTED NAME> is administered orally.

<INVENTED NAME> may be taken with or without food.

<INVENTED NAME> should not be used concomitantly with other products containing the same active substance, rofecoxib.

Osteoarthritis
The recommended adult starting dose is 12.5 mg once daily. In some patients, with insufficient relief from symptoms, an increase of dose up to 25 mg daily may increase efficacy. A daily dose of 25 mg should not be exceeded.

For dosing at 12.5 mg once daily, a 12.5-mg tablet is also available.

Rheumatoid Arthritis
The recommended dose is 25 mg once daily. In rheumatoid arthritis (RA) patients, no significant additional efficacy was seen with the 50-mg once daily dose compared to the 25-mg once daily dose. The maximum recommended daily dose is 25 mg.

For dosing at 25 mg once daily, a 25-mg tablet is also available.

Elderly: In the elderly (>65 years old), the lower dose (12.5 mg per day) should be used initially. Care should be exercised when increasing the daily dose from 12.5 mg to 25 mg in the elderly.

Hepatic insufficiency: no dosage adjustment is necessary for patients with mild hepatic insufficiency (Child-Pugh score 5-6). In patients with moderate hepatic insufficiency (Child-Pugh score 7-9 or serum albumin 25-35 g/L) the lowest recommended dose of 12.5 mg once daily should not be exceeded. Clinical experience is limited particularly in patients with moderate hepatic insufficiency and caution is advised (see 4.4 and 5.2).

Renal insufficiency: no dosage adjustment is necessary for osteoarthritis (OA) patients with renal creatinine clearance 30-80 ml/min (see 4.4 and 5.2). At present, there are only limited data in RA patients with renal creatinine clearance 30-80 ml/min.

Paediatric use: <INVENTED NAME> is not indicated for use in children.

4.3 Contra-indications

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

Active peptic ulceration or 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.

Third trimester of pregnancy and lactation (see 4.6 and 5.3)

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

Estimated renal creatinine clearance <30 ml/min

Inflammatory bowel disease

Severe congestive heart failure (NYHA III-IV).

4.4 Special warnings and special precautions for use

Because of the possibility for increased adverse reactions at higher doses of rofecoxib, other COX-2 inhibitors and NSAIDs, patients should be reviewed following dose increase and, in the absence of increase in efficacy, other therapeutic options should be considered (see 4.2).

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

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 an increased risk of gastrointestinal adverse effects for rofecoxib, other COX-2 inhibitors and NSAIDs when taken concomitantly with acetylsalicylic acid (even at low doses).

COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thromboembolic diseases because of their lack of effect on platelet function. Because rofecoxib, does not inhibit platelet aggregation, antiplatelet therapies (eg acetylsalicylic acid) should not be discontinued and if indicated should be considered in patients at risk for or with a history of cardiovascular or other thrombotic events (prior history of MI, angina, ischemic heart disease, atherosclerotic heart disease, CVA, cerebral ischemia, coronary bypass graft surgery or peripheral vascular surgery). However, it should be noted that concomitant use of rofecoxib 25 mg plus low-

dose acetylsalicylic acid (81 mg) results in an increased rate of endoscopic ulceration compared to the use of low-dose acetylsalicylic acid alone. (See 4.5 and 5.1.)

Caution should be exercised in patients with a medical history of ischemic heart disease because of the pharmacodynamic profile of COX-2 selective inhibitors noted above. Appropriate measures should be taken and discontinuation of rofecoxib therapy should be considered if there is clinical evidence of deterioration in the condition of specific clinical symptoms in these patients.

Renal prostaglandins may play a compensatory role in the maintenance of renal perfusion. Therefore, under conditions of compromised renal perfusion, administration of rofecoxib 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.

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

Fluid retention, oedema and hypertension have been observed in patients taking rofecoxib. These effects appear to be dose-related and are seen with an increased frequency with chronic use of rofecoxib and at higher therapeutic doses. The reporting rates for hypertension with rofecoxib have been similar to or, on occasion, slightly greater than some other NSAIDs, at comparable doses. Because treatment with rofecoxib may result in fluid retention, caution should be exercised in patients with history of cardiac failure, left ventricular dysfunction, or hypertension and in patients with pre-existing oedema from any other reason. Rofecoxib should be introduced at the lowest recommended dose in those patients. (See 4.5)

Medically appropriate supervision should be maintained when using rofecoxib in the elderly and in patients with renal, hepatic, or cardiac dysfunction.

Serious skin reactions, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported in association with the use of NSAIDS including rofecoxib during postmarketing surveillance (see 4.8). Hypersensitivity reactions (anaphylaxis and angioedema) have been reported in patients receiving rofecoxib (see 4.8). Rofecoxib should be discontinued at the first sign of hypersensitivity.

Rofecoxib may mask fever and other signs of inflammation.

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

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

Elevations of ALT and/or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with rofecoxib.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for persistently abnormal liver function tests. If persistently abnormal liver function tests (three times the upper limit of normal) are detected, rofecoxib should be discontinued.

Paediatric patients: Rofecoxib has not been studied in children and should only be used in adult patients.

<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

In subjects stabilised on chronic warfarin therapy, the administration of rofecoxib 25 mg daily was associated with an approximate 8% increase in prothrombin time International Normalised Ratio (INR). There have been reports of increases in INR, which led to interruption of warfarin treatment and in some cases prompted reversal of anticoagulation, in patients taking rofecoxib at clinical doses concurrently with warfarin. There have also been isolated reports of increases in INR in patients taking rofecoxib and the anticoagulant fluindione. Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR, particularly in the first few days when therapy with rofecoxib is initiated or the dose of rofecoxib is changed (see 4.4).

In patients with mild-to-moderate hypertension, administration of 25 mg daily of rofecoxib with an ACE inhibitor (benazepril, 10 mg to 40 mg daily) for four weeks was associated with a small attenuation of the antihypertensive effect (average increase in Mean Arterial Pressure of 2.8 mm Hg) compared to the ACE inhibitor alone. As for other agents which inhibit cyclo-oxygenase, in some patients with compromised renal function the co-administration of an ACE inhibitor and rofecoxib may result in further deterioration of renal function, which is usually reversible. These interactions should be given consideration in patients taking rofecoxib concomitantly with ACE inhibitors.

Concomitant use of NSAIDs may also reduce the antihypertensive efficacy of beta-blockers and diuretics and the other effects of diuretics. There are no data on the possible interaction between rofecoxib and either beta-blockers or diuretics.

At steady state, rofecoxib 50 mg once daily had no effect on the anti-platelet activity of low-dose acetylsalicylic acid. Concomitant administration of rofecoxib with higher doses of acetylsalicylic acid or other NSAIDs should be avoided.

Concomitant use of rofecoxib 25 mg plus low-dose acetylsalicylic acid (81 mg) results in an increased rate of endoscopic ulceration, compared to the use of low-dose acetylsalicylic acid alone. (See 5.1 .)

Coadministration of cyclosporin or tacrolimus and NSAIDs may increase the nephrotoxic effect of cyclosporin or tacrolimus. Renal function should be monitored when rofecoxib and either of these drugs is used in combination.

Pharmacokinetic interactions

The effect of rofecoxib on the pharmacokinetics of other drugs

The plasma concentration of lithium could be increased by NSAIDs. In post-marketing experience with rofecoxib, there have been reports of increases in plasma lithium levels.

<INVENTED NAME> 12.5, 25, and 50 mg, each dose administered once daily for 7 days, had no significant effect on the plasma concentration of methotrexate as measured by $AUC_{0\text{-}24h}$ in patients receiving single weekly methotrexate doses of 7.5 to 20 mg for rheumatoid arthritis. Rofecoxib 75 mg (three to six times higher than the recommended doses for osteoarthritis) administered once-daily for 10 days increased plasma methotrexate concentrations ($AUC_{(0\text{-}24hr)}$) by 23% in patients with RA receiving methotrexate 7.5 mg to 15 mg/week. Adequate monitoring for methotrexate-related toxicity should be considered when rofecoxib and methotrexate are administered concomitantly.

No interaction with digoxin has been observed in pharmacokinetic studies. However, patients at high risk of digoxin toxicity should be monitored when rofecoxib and digoxin are administered concomitantly.

In vivo data concerning rofecoxib/warfarin and rofecoxib/theophylline interactions suggest that rofecoxib may produce a modest inhibition of CYP1A2. Care should be exercised when administering rofecoxib concurrently with other drugs primarily metabolised by CYP1A2 (e.g., tacrine, zileuton, olanzapine and clozapine). Rofecoxib 12.5, 25 and 50 mg administered once daily for 7 days increased plasma theophylline concentrations ($AUC_{(0-\infty)}$) by 38 to 60% in healthy subjects administered a single 300-mg dose of theophylline. Adequate monitoring of theophylline plasma concentrations should be considered when therapy with rofecoxib is initiated or changed in patients receiving theophylline.

The potential for rofecoxib to inhibit or induce CYP3A4 activity was investigated in human studies using the oral midazolam test and the intravenous erythromycin breath test. Rofecoxib (25 mg daily for 12 days) produced a modest induction of CYP3A4 catalysed metabolism of midazolam, reducing the AUC of midazolam by 30%. This reduction is most likely due to increased first pass metabolism through induction of intestinal CYP3A4 activity by rofecoxib. Compared to placebo, rofecoxib (75 mg daily for 14 days) did not produce any significant effect in erythromycin demethylation, indicating no induction of hepatic CYP3A4 activity.

Although rofecoxib produces a modest induction of intestinal CYP3A4 activity, the pharmacokinetics of drugs that are primarily metabolised by CYP3A4 are not expected to be affected to a clinically significant extent. However, care should be exercised when co-prescribing substrates of CYP3A4.

In drug-interaction studies, rofecoxib did not have clinically important effects on the pharmacokinetics of prednisone/prednisolone or oral contraceptives (ethinyl oestradiol/norethindrone 35/1).

Based on *in vitro* studies, rofecoxib is not expected to inhibit cytochromes P450 2C9, 2C19, 2D6, or 2E1, although *in vivo* data are not available.

Effects of other drugs on the pharmacokinetics of rofecoxib

The main pathway of rofecoxib metabolism is reduction to produce *cis*- and *trans*-dihydro rofecoxib (as hydroxy acids). In the absence of potent cytochrome P450 (CYP) inducers, CYP-catalysed metabolism is not the dominant pathway for rofecoxib metabolism.

However, co-administration of rofecoxib with rifampicin, a potent inducer of CYP enzymes, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, the use of the 25-mg dose of rofecoxib should be considered when rofecoxib is co-administered with potent inducers of hepatic metabolism.

Administration of ketoconazole (a potent inhibitor of CYP3A4) did not affect rofecoxib plasma pharmacokinetics. Cimetidine or antacids do not affect the pharmacokinetics of rofecoxib to a clinically relevant extent.

4.6 Pregnancy and lactation

Pregnancy

The use of rofecoxib, as with any drug substance known to inhibit COX-2 is not recommended in women attempting to conceive (see 5.1).

The use of rofecoxib is contraindicated in the last trimester of pregnancy because, as with other drug substances known to inhibit prostaglandin synthesis, it may cause uterine inertia and premature closure of the ductus arteriosus (see 4.3.).

The use of rofecoxib in pregnant women has not been studied in adequate and well-controlled clinical trials and therefore it should not be used during the first two trimesters of pregnancy unless the potential benefit to the patient justifies the potential risk to the foetus (see 5.3).

Breast-feeding mothers

It is not known whether rofecoxib is excreted in human milk. Rofecoxib is excreted in the milk of lactating rats. Women who use rofecoxib should not breast feed. (See 4.3 and 5.3)

4.7 Effects on ability to drive and use machines

Patients who experience dizziness, vertigo or somnolence while taking rofecoxib should refrain from driving or operating machinery.

4.8 Undesirable effects

In clinical trials, rofecoxib was evaluated for safety in approximately 11,600 individuals, including approximately 1,000 patients treated for one year or longer.

The following undesirable effects were reported at an incidence greater than placebo in osteoarthritis and rheumatoid arthritis clinical studies in patients treated with rofecoxib 12.5 mg or 25 mg for up to six months or in post-marketing experience:

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

***Blood and the lymphatic system disorders*:**
Common: haematocrit decreased.
Uncommon: haemoglobin decreased, erythrocytes decreased, leukocytes decreased.
Very rare: aplastic anaemia, pancytopenia, thrombocytopenia.

***Immune system disorders*:**
Very rare: hypersensitivity reactions, including angioedema, anaphylactic/anaphylactoid reactions

***Metabolism and nutrition disorders*:**
Uncommon: weight gain.

***Psychiatric disorders*:**
Uncommon: depression, mental acuity decreased.
Very rare: anxiety, confusion, hallucinations.

***Nervous system disorders*:**
Common: dizziness, headache.
Uncommon: insomnia, somnolence, vertigo.
Very rare: epilepsy aggravated, paraesthesia, aseptic meningitis.

***Eye disorders*:**
Very rare: blurred vision.

***Ear and labyrinth disorders*:**
Uncommon: tinnitus.

***Cardiac disorders*:**
Rare: congestive heart failure,.
Very rare: palpitations, myocardial infarction, pulmonary oedema.

***Vascular disorders*:**
Common: hypertension.
Very rare: cerebrovascular accident, hypertensive crisis, vasculitis.

***Respiratory, thoracic and mediastinal disorders*:**
Uncommon: dyspnoea.
Very rare: bronchospasm.

***Gastrointestinal disorders*:**
Common: abdominal pain, heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia.
Uncommon: abdominal distension, constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux.
Rare: peptic ulcers, gastrointestinal perforation and bleeding (mainly in elderly patients), gastritis.
Very rare: aggravation of inflammatory bowel disease, colitis, pancreatitis.

***Hepato-biliary disorders*:**
Common: alanine aminotransferase increased, aspartate aminotransferase increased.
Uncommon: alkaline phosphatase increased.
Very rare: hepatotoxicity including hepatitis with or without jaundice, hepatic failure.
(See 4.4.)

***Skin and subcutaneous tissue disorders*:**
Common: pruritus, rash.
Uncommon: atopic dermatitis.
Very rare: alopecia, photosensitivity reactions, urticaria, cutaneo-mucosal adverse effects and severe skin reactions including Stevens-Johnson Syndrome, toxic epidermal necrolysis.

***Musculoskeletal, connective tissue and bone disorders*:**
Uncommon: muscular cramp.

***Renal and urinary disorders*:**
Uncommon: BUN increased, serum creatinine increased, proteinuria.
Very rare: hyperkalaemia, renal insufficiency, including renal failure, usually reversible upon discontinuation of therapy (see 4.4), interstitial nephritis.

***Reproductive system and breast disorders*:**
Very rare: menstrual disturbances.

***General disorders and administration site conditions*:**
Common: oedema/fluid retention.
Uncommon: asthenia/fatigue, chest pain.

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

Nephrotic syndrome has been reported in association with the use of other NSAIDs and cannot be ruled out for rofecoxib.

4.9 Overdose

In clinical studies, administration of single doses of rofecoxib up to 1,000 mg and multiple doses up to 250 mg/day for 14 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.

Rofecoxib is not dialysable by haemodialysis; it is not known whether rofecoxib 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 AH02

Rofecoxib is an oral, selective, cyclo-oxygenase-2 (COX-2) inhibitor within the clinical dose range.

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.

Statistically significant inhibition of COX-1 has not been documented in humans with any dose of rofecoxib. Based on *in vitro* data, inhibition of COX-1 might occur during chronic administration of rofecoxib at >250 mg per day.

The anti-inflammatory effects of rofecoxib were demonstrated in standard animal models used to evaluate NSAIDs.

Across clinical pharmacology studies, as compared to placebo, rofecoxib produced dose-dependent inhibition of COX-2 with daily doses of 12.5 mg and 25 mg inhibiting COX-2 by ~70%, while rofecoxib at daily doses of 375 mg and a single 1000 mg dose inhibited COX-2 by ~95%. There was no dose-dependent inhibition of COX-1 compared with placebo. Rofecoxib did not inhibit gastric prostaglandin synthesis and had no effect on platelet function.

A large clinical trial (approximately 8000 patients) in rheumatoid arthritis patients has compared the long-term safety of rofecoxib 50 mg once daily (twice the maximum dose recommended) and naproxen 500 mg twice daily. The rate of serious cardiovascular thrombo-embolic adverse events was significantly lower in patients receiving naproxen than in the rofecoxib treated patients: 0.70 events per 100 patient-years compared with 1.67 events per 100 patient-years. 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. (See 4.4.) COX-2 selective 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.

Rofecoxib was studied for the symptomatic treatment of osteoarthritis (OA). The primary assessments for efficacy were made only on either the hip or knee joints; however, the study population included 33% of patients with concomitant OA of the inter-phalangeal joints, 21% with OA of the thumb and 35% with OA of the spine. After one week of therapy (the first efficacy determination timepoint), rofecoxib provided significant reduction in pain in OA patients. Timepoints earlier than one week were not evaluated. Therefore, consideration should be given to the T_{max} of rofecoxib (two to four hours) when immediate onset of action is desired.

Rofecoxib 25 mg once daily was studied for the symptomatic treatment of RA. In RA patients, rofecoxib 25 mg once daily provided significant improvements in disease-related measures of response, including assessments of pain and function. The beneficial effects were maintained over the 12-week placebo-controlled periods. No significant additional efficacy was seen with the 50-mg once daily dose compared to the 25-mg once daily dose.

In a predefined, combined analysis of two 24-week endoscopy studies in OA patients, the percentages of patients with endoscopically detected gastroduodenal ulceration were similar between placebo, and rofecoxib 25 mg and 50 mg daily at 12 weeks. In each of these studies, the cumulative incidence of gastroduodenal ulcers was significantly less over 12 and 24 weeks in patients treated with rofecoxib than in patients treated with ibuprofen 2,400 mg daily. In an additional 12-week endoscopy study in OA patients, the cumulative incidence of endoscopically detected gastroduodenal ulcers was significantly higher in patients treated with low-dose acetylsalicylic acid 81 mg plus rofecoxib 25 mg daily than in patients treated with low-dose acetylsalicylic acid 81 mg daily alone, and similar to patients treated with ibuprofen 2400 mg daily alone. In patients aged 65 years and over, the low-dose acetylsalicylic acid plus rofecoxib group showed a 2-fold increase in the frequency of endoscopic ulcers compared with younger patients. Patients taking low-dose acetylsalicylic acid plus ibuprofen have not been studied. In a 12-week, double-blind, placebo- and active-controlled endoscopy study in RA patients, the cumulative incidence of gastroduodenal ulcers was significantly less over 12 weeks in patients treated with rofecoxib 50 mg once daily (twice the maximum dose recommended) than in patients treated with naproxen 500 mg twice daily.

In a predefined, combined analysis of eight clinical trials, the cumulative incidence of confirmed upper GI PUBs in patients treated with rofecoxib was significantly lower than the combined cumulative incidence observed in patients treated with NSAID comparators (diclofenac 50 mg three times daily, ibuprofen 800 mg three times daily and nabumetone 1500 mg daily. These results were primarily influenced by the experience with ibuprofen 800 mg three times daily. At a dosage of 50 mg the incidence of PUBs was numerically greater compared to 25 mg, however it remained lower than the risk with combined data on NSAIDs used in these studies. Discontinuations for GI adverse experiences over 12 months were less with rofecoxib. Incidences of a predefined set of drug-related GI adverse experiences were lower with rofecoxib over 12 months; this effect was greater over the first 6 months.

A similar reduction in the incidence of PUBs was seen in the large clinical trial (approximately 8000 patients) conducted in rheumatoid arthritis patients. Patients requiring acetylsalicylic acid for cardiovascular prophylaxis were excluded from the study. The use of rofecoxib 50 mg once daily (two times the maximum recommended dose) compared to naproxen 500 mg twice daily was associated with significant reductions in gastrointestinal event rates: PUBs (2.08 events per 100 patient-years versus 4.49 events per 100 patient-years), complicated PUBs (0.59 per 100 patient-years versus 1.37 per 100 patient-years) and upper or lower GI bleeds (1.15 per 100 patient-years versus 3.04 per 100 patient-years).

5.2 Pharmacokinetic properties

Absorption
Orally administered rofecoxib is well absorbed at the recommended doses of 12.5 mg and 25 mg. The mean oral bioavailability is approximately 93%. Following 25-mg once-daily dosing to steady state, the peak plasma concentration (geometric mean C_{max} = 0.305 mcg/ml) was observed at approximately two to four hours (T_{max}) after administration to fasted adults. The geometric mean area under the curve (AUC_{24hr}) was 3.87 mcg•hr/ml. <INVENTED NAME> Tablets and <INVENTED NAME> Oral Suspension are bioequivalent.

Concomitant food intake does not affect the pharmacokinetics of rofecoxib.

Distribution

Rofecoxib is approximately 85% bound to human plasma protein at concentrations of 0.05 mcg/ml to 25 mcg/ml. The volume of distribution (V_{dss}) is approximately 100 litres (approximately 1.55 L/kg) in humans.

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

Metabolism
Rofecoxib is extensively metabolised with ~1% of a dose recovered in urine as the parent drug. The main metabolic pathway is hepatic reduction to produce *cis*- and *trans*-dihydro rofecoxib (as hydroxy acids), and not oxidation by cytochrome P450 (CYP) enzymes.

Six metabolites have been identified in man. The principal metabolites were *cis*- and *trans*-dihydro rofecoxib (as hydroxy acids), which accounted for approximately 56% of recovered radioactivity in the urine, and the 5-hydroxy glucuronide metabolite, which accounted for an additional 9%. These principal metabolites either demonstrated no measurable activity as cyclo-oxygenase inhibitors or were only weakly active as COX-2 inhibitors.

Elimination
Following administration of a 125-mg radiolabelled oral dose of rofecoxib to healthy subjects, 72% of radioactivity was recovered in urine and 14% in faeces.

Elimination of rofecoxib occurs almost exclusively through metabolism followed by renal excretion. Steady-state concentrations of rofecoxib are reached within four days of once-daily administration of 25 mg, with an accumulation ratio of approximately 1.7, corresponding to an accumulation half-life of ~17 hours. The plasma clearance is estimated to be approximately 120 ml/min for a 25-mg dose.

Characteristics in patients

Elderly: pharmacokinetics in the elderly (65 years of age and older) are similar to those in the young. The systemic exposure is ~30% greater in the elderly than in the young (see 4.2).

Gender: the pharmacokinetics of rofecoxib are comparable in men and women.

Hepatic insufficiency: Cirrhotic patients with mild hepatic insufficiency (Child-Pugh score 5-6) administered a single 25-mg dose of rofecoxib had a mean AUC similar to healthy subjects given the same dose. Patients with moderate hepatic insufficiency (Child-Pugh score 7-9) administered 12.5 mg daily for ten days had an approximately 55% higher mean steady-state AUC than healthy subjects given the same dose. For patients with moderate hepatic insufficiency (Child-Pugh score 7-9 or serum albumin 25-35 g/L), the maximum daily dose of rofecoxib should be 12.5 mg. There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9 or serum albumin <25 g/L). (See 4.2 and 4.3.)

Renal insufficiency: the pharmacokinetics of a single 50-mg dose of rofecoxib in patients with end-stage renal disease on haemodialysis were not significantly different from those of healthy subjects. Haemodialysis contributed negligibly to elimination (dialysis clearance ~40 ml/min). (See 4.3 ‘and 4.4.)

Paediatric patients: the pharmacokinetics of rofecoxib in paediatric patients have not been studied.

5.3 Preclinical safety data

In preclinical studies, rofecoxib has been demonstrated to be neither genotoxic, mutagenic, nor carcinogenic.

In a chronic toxicity study in rats, rofecoxib caused intestinal ulcers at doses comparable to and slightly above the human therapeutic dose, based on systemic exposure. At exposures several times above the human therapeutic level, renal tubular basophilia, and at higher exposures renal papillary

necrosis, were induced in the rat. At high exposures renal and gastro-intestinal abnormalities were seen in the dog as well.

Reproductive toxicity studies showed that rofecoxib (at doses ≥2 times the recommended daily human dose based on systemic exposure) decreased fertility and embryo/foetal survival in the rat. A treatment-related decrease in the diameter of the ductus arteriosus was also observed, a finding known to be associated with NSAIDs. Reproductive toxicity studies conducted in rats and rabbits have demonstrated no evidence of developmental abnormalities at doses up to 50 mg/kg/day (in rats this represents ~29 times the recommended daily human dose based on systemic exposure). (See 4.3 'and 4.6). In rabbits, however, the metabolite profile was not determined, thus making the clinical relevance of the rabbit model difficult to assess.

Data from a cross-fostering study indicated pup toxicity, probably due to exposure via milk from treated dams. (See 4.6.)

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, magnesium stearate, and yellow ferric oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Opaque PVC/aluminium blisters in packs containing 2, 5, 7, 10, 14, 15, 20, 28, 30, 50, 56, 60, 84, 90 or 98 tablets.

Opaque PVC/aluminium blisters (unit doses) in packs of 50 or 500 tablets.

White, round, HDPE bottles with a white, polypropylene, non-child resistant closure containing 30 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

Not applicable.

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

June 4, 1999

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

<INVENTED NAME (see Annex 1)> 12.5 mg/5ml Oral Suspension
<INVENTED NAME (see Annex 1)> 25 mg/5ml Oral Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

12.5 mg/5ml Oral Suspension
Each 5 ml of oral suspension contains 12.5 mg of rofecoxib.
25 mg/5ml Oral Suspension
Each 5 ml of oral suspension contains 25 mg of rofecoxib.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Oral Suspension.

<INVENTED NAME> is available as an opaque, white to faint yellow suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic relief in the treatment of osteoarthritis or rheumatoid arthritis in adults.

4.2 Posology and method of administration

<INVENTED NAME> is administered orally.

<INVENTED NAME> may be taken with or without food.

<INVENTED NAME> should not be used concomitantly with other products containing the same active substance, rofecoxib.

Osteoarthritis
The recommended adult starting dose is 12.5 mg once daily. In some patients, with insufficient relief from symptoms, an increase of dose up to 25 mg daily may increase efficacy. A daily dose of 25 mg should not be exceeded.

For dosing at 12.5 mg once daily, a 12.5 mg/5 mL oral suspension is also available.

Rheumatoid Arthritis
The recommended dose is 25 mg once daily. In rheumatoid arthritis (RA) patients, no significant additional efficacy was seen with the 50-mg once daily dose compared to the 25-mg once daily dose. The maximum recommended daily dose is 25 mg.

For dosing at 25 mg once daily, a 25 mg/5 mL oral suspension is also available.

Elderly: In the elderly (>65 years old), the lower dose (12.5 mg per day) should be used initially. Care should be exercised when increasing the daily dose from 12.5 mg to 25 mg in the elderly.

Hepatic insufficiency: no dosage adjustment is necessary for patients with mild hepatic insufficiency (Child-Pugh score 5-6). In patients with moderate hepatic insufficiency (Child-Pugh score 7-9 or serum albumin 25-35 g/L) the lowest recommended dose of 12.5 mg once daily should not be exceeded. Clinical experience is limited particularly in patients with moderate hepatic insufficiency and caution is advised (see 4.4 and 5.2).

Renal insufficiency: no dosage adjustment is necessary for osteoarthritis (OA) patients with renal creatinine clearance 30-80 ml/min (see 4.4 and 5.2). At present, there are only limited data in RA patients with renal creatinine clearance 30-80 ml/min.

Paediatric use: <INVENTED NAME> is not indicated for use in children.

4.3 Contra-indications

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

Active peptic ulceration or 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.

Third trimester of pregnancy and lactation (see 4.6 and 5.3)

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

Estimated renal creatinine clearance <30 ml/min

Inflammatory bowel disease

Severe congestive heart failure (NYHA III-IV).

4.4 Special warnings and special precautions for use

Because of the possibility for increased adverse reactions at higher doses of rofecoxib, other COX-2 inhibitors and NSAIDs, patients should be reviewed following dose increase and, in the absence of increase in efficacy, other therapeutic options should be considered (see 4.2).

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

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 an increased risk of gastrointestinal adverse effects for rofecoxib, other COX-2 inhibitors and NSAIDs when taken concomitantly with acetylsalicylic acid (even at low doses).

COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thromboembolic diseases because of their lack of effect on platelet function. Because rofecoxib, does not inhibit platelet aggregation, antiplatelet therapies (eg acetylsalicylic acid) should not be discontinued and if indicated should be considered in patients at risk for or with a history of cardiovascular or other thrombotic events (prior history of MI, angina, ischemic heart disease, atherosclerotic heart disease, CVA, cerebral ischemia, coronary bypass graft surgery or peripheral vascular surgery). However, it should be noted that concomitant use of rofecoxib 25 mg plus low-

dose acetylsalicylic acid (81 mg) results in an increased rate of endoscopic ulceration compared to the use of low-dose acetylsalicylic acid alone. (See 4.5 and 5.1.)

Caution should be exercised in patients with a medical history of ischemic heart disease because of the pharmacodynamic profile of COX-2 selective inhibitors noted above. Appropriate measures should be taken and discontinuation of rofecoxib therapy should be considered if there is clinical evidence of deterioration in the condition of specific clinical symptoms in these patients.

Renal prostaglandins may play a compensatory role in the maintenance of renal perfusion. Therefore, under conditions of compromised renal perfusion, administration of rofecoxib 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.

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

Fluid retention, oedema and hypertension have been observed in patients taking rofecoxib. These effects appear to be dose-related and are seen with an increased frequency with chronic use of rofecoxib and at higher therapeutic doses. The reporting rates for hypertension with rofecoxib have been similar to or, on occasion, slightly greater than some other NSAIDs, at comparable doses. Because treatment with rofecoxib may result in fluid retention, caution should be exercised in patients with history of cardiac failure, left ventricular dysfunction, or hypertension and in patients with pre-existing oedema from any other reason. Rofecoxib should be introduced at the lowest recommended dose in those patients. (See 4.5)

Medically appropriate supervision should be maintained when using rofecoxib in the elderly and in patients with renal, hepatic, or cardiac dysfunction.

Serious skin reactions, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported in association with the use of NSAIDS including rofecoxib during postmarketing surveillance (see 4.8). Hypersensitivity reactions (anaphylaxis and angioedema) have been reported in patients receiving rofecoxib (see 4.8). Rofecoxib should be discontinued at the first sign of hypersensitivity.

Rofecoxib may mask fever and other signs of inflammation.

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

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

Elevations of ALT and/or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with rofecoxib.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for persistently abnormal liver function tests. If persistently abnormal liver function tests (three times the upper limit of normal) are detected, rofecoxib should be discontinued.

Paediatric patients: Rofecoxib has not been studied in children and should only be used in adult patients.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

In subjects stabilised on chronic warfarin therapy, the administration of rofecoxib 25 mg daily was associated with an approximate 8% increase in prothrombin time International Normalised Ratio (INR). There have been reports of increases in INR, which led to interruption of warfarin treatment and in some cases prompted reversal of anticoagulation, in patients taking rofecoxib at clinical doses concurrently with warfarin. There have also been isolated reports of increases in INR in patients taking rofecoxib and the anticoagulant fluindione. Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR, particularly in the first few days when therapy with rofecoxib is initiated or the dose of rofecoxib is changed (see 4.4).

In patients with mild-to-moderate hypertension, administration of 25 mg daily of rofecoxib with an ACE inhibitor (benazepril, 10 mg to 40 mg daily) for four weeks was associated with a small attenuation of the antihypertensive effect (average increase in Mean Arterial Pressure of 2.8 mm Hg) compared to the ACE inhibitor alone. As for other agents, which inhibit cyclo-oxygenase, in some patients with compromised renal function the co-administration of an ACE inhibitor and rofecoxib may result in further deterioration of renal function, which is usually reversible. These interactions should be given consideration in patients taking rofecoxib concomitantly with ACE inhibitors.

Concomitant use of NSAIDs may also reduce the antihypertensive efficacy of beta-blockers and diuretics and the other effects of diuretics. There are no data on the possible interaction between rofecoxib and either beta-blockers or diuretics.

At steady state, rofecoxib 50 mg once daily had no effect on the anti-platelet activity of low-dose acetylsalicylic acid. Concomitant administration of rofecoxib with higher doses of acetylsalicylic acid or other NSAIDs should be avoided.

Concomitant use of rofecoxib 25 mg plus low-dose acetylsalicylic acid (81 mg) results in an increased rate of endoscopic ulceration, compared to the use of low-dose acetylsalicylic acid alone. (See 5.1).

Coadministration of cyclosporin or tacrolimus and NSAIDs may increase the nephrotoxic effect of cyclosporin or tacrolimus. Renal function should be monitored when rofecoxib and either of these drugs is used in combination.

Pharmacokinetic interactions

The effect of rofecoxib on the pharmacokinetics of other drugs

The plasma concentration of lithium could be increased by NSAIDs. In post-marketing experience with rofecoxib, there have been reports of increases in plasma lithium levels.

<INVENTED NAME> 12.5, 25, and 50 mg, each dose administered once daily for 7 days, had no significant effect on the plasma concentration of methotrexate as measured by $AUC_{0\text{-}24h}$ in patients receiving single weekly methotrexate doses of 7.5 to 20 mg for rheumatoid arthritis. Rofecoxib 75 mg (three to six times higher than the recommended doses for osteoarthritis) administered once-daily for 10 days increased plasma methotrexate concentrations ($AUC_{(0\text{-}24hr)}$) by 23% in patients with RA receiving methotrexate 7.5 mg to 15 mg/week. Adequate monitoring for methotrexate-related toxicity should be considered when rofecoxib and methotrexate are administered concomitantly.

No interaction with digoxin has been observed in pharmacokinetic studies. However, patients at high risk of digoxin toxicity should be monitored when rofecoxib and digoxin are administered concomitantly.

In vivo data concerning rofecoxib/warfarin and rofecoxib/theophylline interactions suggest that rofecoxib may produce a modest inhibition of CYP1A2. Care should be exercised when administering rofecoxib concurrently with other drugs primarily metabolised by CYP1A2 (e.g., tacrine zileuton, olanzapine and clozapine). Rofecoxib 12.5, 25 and 50 mg administered once daily for 7 days

increased plasma theophylline concentrations ($AUC_{(0-\infty)}$) by 38 to 60% in healthy subjects administered a single 300-mg dose of theophylline. Adequate monitoring of theophylline plasma concentrations should be considered when therapy with rofecoxib is initiated or changed in patients receiving theophylline.

The potential for rofecoxib to inhibit or induce CYP3A4 activity was investigated in human studies using the oral midazolam test and the intravenous erythromycin breath test. Rofecoxib (25 mg daily for 12 days) produced a modest induction of CYP3A4 catalysed metabolism of midazolam, reducing the AUC of midazolam by 30%. This reduction is most likely due to increased first pass metabolism through induction of intestinal CYP3A4 activity by rofecoxib. Compared to placebo, rofecoxib (75 mg daily for 14 days) did not produce any significant effect in erythromycin demethylation, indicating no induction of hepatic CYP3A4 activity.

Although rofecoxib produces a modest induction of intestinal CYP3A4 activity, the pharmacokinetics of drugs that are primarily metabolised by CYP3A4 are not expected to be affected to a clinically significant extent. However, care should be exercised when co-prescribing substrates of CYP3A4.

In drug-interaction studies, rofecoxib did not have clinically important effects on the pharmacokinetics of prednisone/prednisolone or oral contraceptives (ethinyl oestradiol/norethindrone 35/1).

Based on *in vitro* studies, rofecoxib is not expected to inhibit cytochromes P450 2C9, 2C19, 2D6, or 2E1, although *in vivo* data are not available.

Effects of other drugs on the pharmacokinetics of rofecoxib

The main pathway of rofecoxib metabolism is reduction to produce *cis*- and *trans*-dihydro rofecoxib (as hydroxy acids). In the absence of potent cytochrome P450 (CYP) inducers, CYP-catalysed metabolism is not the dominant pathway for rofecoxib metabolism.

However, co-administration of rofecoxib with rifampicin, a potent inducer of CYP enzymes, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, the use of the 25-mg dose of rofecoxib should be considered when rofecoxib is co-administered with potent inducers of hepatic metabolism.

Administration of ketoconazole (a potent inhibitor of CYP3A4) did not affect rofecoxib plasma pharmacokinetics. Cimetidine or antacids do not affect the pharmacokinetics of rofecoxib to a clinically relevant extent.

4.6 Pregnancy and lactation

Pregnancy

The use of rofecoxib, as with any drug substance known to inhibit COX-2 is not recommended in women attempting to conceive (see 5.1).

The use of rofecoxib is contraindicated in the last trimester of pregnancy because, as with other drug substances known to inhibit prostaglandin synthesis, it may cause uterine inertia and premature closure of the ductus arteriosus (see 4.3.).

The use of rofecoxib in pregnant women has not been studied in adequate and well-controlled clinical trials and therefore it should not be used during the first two trimesters of pregnancy unless the potential benefit to the patient justifies the potential risk to the foetus (see 5.3).

Breast-feeding mothers

It is not known whether rofecoxib is excreted in human milk. Rofecoxib is excreted in the milk of lactating rats. Women who use rofecoxib should not breast feed. (See 4.3 and 5.3)

4.7 Effects on ability to drive and use machines

Patients who experience dizziness, vertigo or somnolence while taking rofecoxib should refrain from driving or operating machinery.

4.8 Undesirable effects

In clinical trials, rofecoxib was evaluated for safety in approximately 11,600 individuals, including approximately 1,000 patients treated for one year or longer.

The following undesirable effects were reported at an incidence greater than placebo in osteoarthritis and rheumatoid arthritis clinical studies in patients treated with rofecoxib 12.5 mg or 25 mg for up to six months or in post-marketing experience:

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

***Blood and the lymphatic system disorders*:**
Common: haematocrit decreased.
Uncommon: haemoglobin decreased, erythrocytes decreased, leukocytes decreased.
Very rare: aplastic anemia, pancytopenia, thrombocytopenia.

***Immune system disorders*:**
Very rare: hypersensitivity reactions, including angioedema, anaphylactic/anaphylactoid reactions

***Metabolism and nutrition disorders*:**
Uncommon: weight gain.

***Psychiatric disorders*:**
Uncommon: depression, mental acuity decreased.
Very rare: anxiety, confusion, hallucinations.

***Nervous system disorders*:**
Common: dizziness, headache.
Uncommon: insomnia, somnolence, vertigo.
Very rare: epilepsy aggravated, paraesthesia, aseptic meningitis.

***Eye disorders*:**
Very rare: blurred vision.

***Ear and labyrinth disorders*:**
Uncommon: tinnitus.

***Cardiac disorders*:**
Rare: congestive heart failure.
Very rare: palpitations, myocardial infarction, pulmonary oedema.

***Vascular disorders*:**
Common: hypertension.
Very rare: cerebrovascular accident, hypertensive crisis, vasculitis.

***Respiratory, thoracic and mediastinal disorders*:**
Uncommon: dyspnoea.
Very rare: bronchospasm.

***Gastrointestinal disorders*:**

Common: abdominal pain, heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia.
Uncommon: abdominal distension, constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux.
Rare: peptic ulcers, gastrointestinal perforation and bleeding (mainly in elderly patients), gastritis.
Very rare: aggravation of inflammatory bowel disease, colitis, pancreatitis.

***Hepato-biliary disorders*:**
Common: alanine aminotransferase increased, aspartate aminotransferase increased.
Uncommon: alkaline phosphatase increased.
Very rare: hepatotoxicity including hepatitis with or without jaundice, hepatic failure.
(See 4.4.)

***Skin and subcutaneous tissue disorders*:**
Common: pruritus, rash.
Uncommon: atopic dermatitis.
Very rare: alopecia, photosensitivity reactions, urticaria, cutaneo-mucosal adverse effects and severe skin reactions including Stevens-Johnson Syndrome, toxic epidermal necrolysis.

***Musculoskeletal, connective tissue and bone disorders*:**
Uncommon: muscular cramp.

***Renal and urinary disorders*:**
Uncommon: BUN increased, serum creatinine increased, proteinuria.
Very rare: hyperkalaemia, renal insufficiency, including renal failure, usually reversible upon discontinuation of therapy (see 4.4), interstitial nephritis.

***Reproductive system and breast disorders*:**
Very rare: menstrual disturbances.

***General disorders and administration site conditions*:**
Common: oedema/fluid retention.
Uncommon: asthenia/fatigue, chest pain.

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

Nephrotic syndrome has been reported in association with the use of other NSAIDs and cannot be ruled out for rofecoxib.

4.9 Overdose

In clinical studies, administration of single doses of rofecoxib up to 1,000 mg and multiple doses up to 250 mg/day for 14 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.

Rofecoxib is not dialysable by haemodialysis; it is not known whether rofecoxib 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 AH02

Rofecoxib is an oral, selective, cyclo-oxygenase-2 (COX-2) inhibitor within the clinical dose range.

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.

Statistically significant inhibition of COX-1 has not been documented in humans with any dose of rofecoxib. Based on *in vitro* data, inhibition of COX-1 might occur during chronic administration of rofecoxib at >250 mg per day.

The anti-inflammatory effects of rofecoxib were demonstrated in standard animal models used to evaluate NSAIDs.

Across clinical pharmacology studies, as compared to placebo, rofecoxib produced dose-dependent inhibition of COX-2 with daily doses of 12.5 mg and 25 mg inhibiting COX-2 by ~70%, while rofecoxib at daily doses of 375 mg and a single 1000 mg dose inhibited COX-2 by ~95%. There was no dose-dependent inhibition of COX-1 compared with placebo. Rofecoxib did not inhibit gastric prostaglandin synthesis and had no effect on platelet function.

A large clinical trial (approximately 8000 patients) in rheumatoid arthritis patients has compared the long-term safety of rofecoxib 50 mg once daily (twice the maximum dose recommended) and naproxen 500 mg twice daily. The rate of serious cardiovascular thrombo-embolic adverse events was significantly lower in patients receiving naproxen than in the rofecoxib treated patients: 0.70 events per 100 patient-years compared with 1.67 events per 100 patient-years. 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. (See 4.4.) COX-2 selective 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.

Rofecoxib was studied for the symptomatic treatment of osteoarthritis (OA). The primary assessments for efficacy were made only on either the hip or knee joints; however, the study population included 33% of patients with concomitant OA of the inter-phalangeal joints, 21% with OA of the thumb and 35% with OA of the spine. After one week of therapy (the first efficacy determination timepoint), rofecoxib provided significant reduction in pain in OA patients. Timepoints earlier than one week were not evaluated. Therefore, consideration should be given to the T_{max} of rofecoxib (two to four hours) when immediate onset of action is desired.

Rofecoxib 25 mg once daily was studied for the symptomatic treatment of RA. In RA patients, rofecoxib 25 mg once daily provided significant improvements in disease-related measures of response, including assessments of pain and function. The beneficial effects were maintained over the 12-week placebo-controlled periods. No significant additional efficacy was seen with the 50-mg once daily dose compared to the 25-mg once daily dose.

In a predefined, combined analysis of two 24-week endoscopy studies in OA patients, the percentages of patients with endoscopically detected gastroduodenal ulceration were similar between placebo, and rofecoxib 25 mg and 50 mg daily at 12 weeks. In each of these studies, the cumulative incidence of gastroduodenal ulcers was significantly less over 12 and 24 weeks in patients treated with rofecoxib

than in patients treated with ibuprofen 2,400 mg daily. In an additional 12-week endoscopy study in OA patients, the cumulative incidence of endoscopically detected gastroduodenal ulcers was significantly higher in patients treated with low-dose acetylsalicylic acid 81 mg plus rofecoxib 25 mg daily than in patients treated with low-dose acetylsalicylic acid 81 mg daily alone, and similar to patients treated with ibuprofen 2400 mg daily alone. In patients aged 65 years and over, the low-dose acetylsalicylic acid plus rofecoxib group showed a 2-fold increase in the frequency of endoscopic ulcers compared with younger patients. Patients taking low-dose acetylsalicylic acid plus ibuprofen have not been studied.

In a 12-week, double-blind, placebo- and active-controlled endoscopy study in RA patients, the cumulative incidence of gastroduodenal ulcers was significantly less over 12 weeks in patients treated with rofecoxib 50 mg once daily (twice the maximum dose recommended) than in patients treated with naproxen 500 mg twice daily.

In a predefined, combined analysis of eight clinical trials, the cumulative incidence of confirmed upper GI PUBs in patients treated with rofecoxib was significantly lower than the combined cumulative incidence observed in patients treated with NSAID comparators (diclofenac 50 mg three times daily, ibuprofen 800 mg three times daily and nabumetone 1500 mg daily. These results were primarily influenced by the experience with ibuprofen 800 mg three times daily. At a dosage of 50 mg the incidence of PUBs was numerically greater compared to 25 mg, however it remained lower than the risk with combined data on NSAIDs used in these studies. Discontinuations for GI adverse experiences over 12 months were less with rofecoxib. Incidences of a predefined set of drug-related GI adverse experiences were lower with rofecoxib over 12 months; this effect was greater over the first 6 months.

A similar reduction in the incidence of PUBs was seen in the large clinical trial (approximately 8000 patients) conducted in rheumatoid arthritis patients. Patients requiring acetylsalicylic acid for cardiovascular prophylaxis were excluded from the study. The use of rofecoxib 50 mg once daily (two times the maximum recommended dose) compared to naproxen 500 mg twice daily was associated with significant reductions in gastrointestinal event rates: PUBs (2.08 events per 100 patient-years versus 4.49 events per 100 patient-years), complicated PUBs (0.59 per 100 patient-years versus 1.37 per 100 patient-years) and upper or lower GI bleeds (1.15 per 100 patient-years versus 3.04 per 100 patient-years).

5.2 Pharmacokinetic properties

Absorption
Orally administered rofecoxib is well absorbed at the recommended doses of 12.5 mg and 25 mg. The mean oral bioavailability is approximately 93%. Following 25-mg once-daily dosing to steady-state, the peak plasma concentration (geometric mean C_{max} = 0.305 mcg/ml) was observed at approximately two to four hours (T_{max}) after administration to fasted adults. The geometric mean area under the curve (AUC_{24hr}) was 3.87 mcg•hr/ml. <INVENTED NAME> Tablets and <INVENTED NAME> Oral Suspension are bioequivalent.

Concomitant food intake does not affect the pharmacokinetics of rofecoxib.

Distribution
Rofecoxib is approximately 85% bound to human plasma protein at concentrations of 0.05 mcg/ml to 25 mcg/ml. The volume of distribution (V_{dss}) is approximately 100 litres (approximately 1.55 L/kg) in humans.

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

Metabolism
Rofecoxib is extensively metabolised with ~1% of a dose recovered in urine as the parent drug. The main metabolic pathway is hepatic reduction to produce *cis*- and *trans*-dihydro rofecoxib (as hydroxy acids), and not oxidation by cytochrome P450 (CYP) enzymes.

Six metabolites have been identified in man. The principal metabolites were *cis*- and *trans*-dihydro rofecoxib (as hydroxy acids), which accounted for approximately 56% of recovered radioactivity in the urine, and the 5-hydroxy glucuronide metabolite, which accounted for an additional 9%. These principal metabolites either demonstrated no measurable activity as cyclo-oxygenase inhibitors or were only weakly active as COX-2 inhibitors.

Elimination
Following administration of a 125-mg radiolabelled oral dose of rofecoxib to healthy subjects, 72% of radioactivity was recovered in urine and 14% in faeces.

Elimination of rofecoxib occurs almost exclusively through metabolism followed by renal excretion. Steady-state concentrations of rofecoxib are reached within four days of once-daily administration of 25 mg, with an accumulation ratio of approximately 1.7, corresponding to an accumulation half-life of ~17 hours. The plasma clearance is estimated to be approximately 120 ml/min for a 25-mg dose.

Characteristics in patients

Elderly: pharmacokinetics in the elderly (65 years of age and older) are similar to those in the young. The systemic exposure is ~30% greater in the elderly than in the young (see 4.2).

Gender: the pharmacokinetics of rofecoxib are comparable in men and women.

Hepatic insufficiency: Cirrhotic patients with mild hepatic insufficiency (Child-Pugh score 5-6) administered a single 25-mg dose of rofecoxib had a mean AUC similar to healthy subjects given the same dose. Patients with moderate hepatic insufficiency (Child-Pugh score 7-9) administered 12.5 mg daily for ten days had an approximately 55% higher mean steady-state AUC than healthy subjects given the same dose. For patients with moderate hepatic insufficiency (Child-Pugh score 7-9 or serum albumin 25-35 g/L), the maximum daily dose of rofecoxib should be 12.5 mg. There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9 or serum albumin <25 g/L). (See 4.2 and 4.3.)

Renal insufficiency: the pharmacokinetics of a single 50-mg dose of rofecoxib in patients with end-stage renal disease on haemodialysis were not significantly different from those of healthy subjects. Haemodialysis contributed negligibly to elimination (dialysis clearance ~40 ml/min). (See 4.3 ‘and 4.4.)

Paediatric patients: the pharmacokinetics of rofecoxib in paediatric patients have not been studied.

5.3 Preclinical safety data

In preclinical studies, rofecoxib has been demonstrated to be neither genotoxic, mutagenic, nor carcinogenic.

In a chronic toxicity study in rats, rofecoxib caused intestinal ulcers at doses comparable to and slightly above the human therapeutic dose, based on systemic exposure. At exposures several times above the human therapeutic level, renal tubular basophilia, and at higher exposures renal papillary necrosis, were induced in the rat. At high exposures renal and gastro-intestinal abnormalities were seen in the dog as well.

Reproductive toxicity studies showed that rofecoxib (at doses ≥2 times the recommended daily human dose based on systemic exposure) decreased fertility and embryo/foetal survival in the rat. A treatment-related decrease in the diameter of the ductus arteriosus was also observed, a finding known to be associated with NSAIDs. Reproductive toxicity studies conducted in rats and rabbits have demonstrated no evidence of developmental abnormalities at doses up to 50 mg/kg/day (in rats this represents ~29 times the recommended daily human dose based on systemic exposure). (See 4.3 ‘and

4.6). In rabbits, however, the metabolite profile was not determined, thus making the clinical relevance of the rabbit model difficult to assess.

Data from a cross-fostering study indicated pup toxicity, probably due to exposure via milk from treated dams. (See 4.6.)

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

xanthan gum, sorbitol solution, sodium citrate, citric acid monohydrate, strawberry flavour (Givaudan Roure) and purified water. Added as preservatives are sodium methylparaben and sodium propylparaben.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

2 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Amber glass bottle with child-resistant closure containing 150 ml oral suspension. A 5 ml polystyrene measuring spoon is provided in each pack.

Each pack contains either 1 or 2 bottles.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

Shake well before use.

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

June 4, 1999

10. DATE OF REVISION OF THE TEXT