ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Austria	Merck Sharp & Dohme G.m.b.H. Donau-City Strasse 6 1220 - Wien, Austria	ZOCORD	5 mg	film coated tablets	oral use
Austria	Merck Sharp & Dohme G.m.b.H. Donau-City Strasse 6 1220 - Wien, Austria	ZOCORD	10 mg	film coated tablets	oral use
Austria	Merck Sharp & Dohme G.m.b.H. Donau-City Strasse 6 1220 - Wien, Austria	ZOCORD	20 mg	film coated tablets	oral use
Austria	Merck Sharp & Dohme G.m.b.H. Donau-City Strasse 6 1220 - Wien, Austria	ZOCORD	40 mg	film coated tablets	oral use
Austria	Merck Sharp & Dohme G.m.b.H. Donau-City Strasse 6 1220 - Wien, Austria	ZOCORD	80 mg	film coated tablets	oral use
Belgium	Merck Sharp & Dohme B.V. Succursale belge Chaussée de Waterloo 1135 1180 Bruxelles Belgique	ZOCOR	5 mg	tablets	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Belgium	Merck Sharp & Dohme B.V. Succursale belge Chaussée de Waterloo 1135 1180 Bruxelles Belgique	ZOCOR	10 mg	tablets	oral use
Belgium	Merck Sharp & Dohme B.V. Succursale belge Chaussée de Waterloo 1135 1180 Bruxelles Belgique	ZOCOR	20 mg	tablets	oral use
Belgium	Merck Sharp & Dohme B.V. Succursale belge Chaussée de Waterloo 1135 1180 Bruxelles Belgique	ZOCOR	20 mg	tablets	oral use
Belgium	Merck Sharp & Dohme B.V. Succursale belge Chaussée de Waterloo 1135 1180 Bruxelles Belgique	ZOCOR	40 mg	tablets	oral use
Belgium	Merck Sharp & Dohme B.V. Succursale belge Chaussée de Waterloo 1135 1180 Bruxelles Belgique	ZOCOR	40 mg	tablets	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Belgium	Merck Sharp & Dohme B.V. Succursale belge Chaussée de Waterloo 1135 1180 Bruxelles Belgique	ZOCOR	80 mg	tablets	oral use
Belgium	Merck Sharp & Dohme B.V. Succursale belge Chaussée de Waterloo 1135 1180 Bruxelles Belgique	ZOCOR	80 mg	tablets	oral use
Denmark	Merck Sharp & Dohme B.V. P.O. Box 581 2003PC Haarlem, The Netherlands	ZOCOR	5 mg	film coated tablets	oral use
Denmark	Merck Sharp & Dohme B.V. P.O. Box 581 2003PC Haarlem, The Netherlands	ZOCOR	10 mg	film coated tablets	oral use
Denmark	Merck Sharp & Dohme B.V. P.O. Box 581 2003PC Haarlem, The Netherlands	ZOCOR	20 mg	film coated tablets	oral use
Denmark	Merck Sharp & Dohme B.V. P.O. Box 581 2003PC Haarlem, The Netherlands	ZOCOR	40 mg	film coated tablets	oral use
Denmark	Merck Sharp & Dohme B.V. P.O. Box 581 2003PC Haarlem, The Netherlands	ZOCOR	80 mg	film coated tablets	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Finland	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCOR	10 mg	film coated tablets	oral use
Finland	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCOR	20 mg	film coated tablets	oral use
Finland	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCOR	40 mg	film coated tablets	oral use
Finland	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCOR	80 mg	film coated tablets	oral use
Finland	Oy Leiras Finland Ab Yliopistonkatu 34 A 20100 Turku, Finland	COROLIN	10 mg	film coated tablets	oral use
Finland	Oy Leiras Finland Ab Yliopistonkatu 34 A 20100 Turku, Finland	COROLIN	20 mg	film coated tablets	oral use
Finland	Oy Leiras Finland Ab Yliopistonkatu 34 A 20100 Turku, Finland	COROLIN	40 mg	film coated tablets	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
France	Laboratoires Merck Sharp & Dohme Chibret 3, Avenue Hoche 75008 Paris, France	ZOCOR	5 mg	tablets	oral use
France	Laboratoires Merck Sharp & Dohme Chibret 3, Avenue Hoche 75008 Paris, France	ZOCOR	5 mg	tablets	oral use
France	Laboratoires Merck Sharp & Dohme Chibret 3, Avenue Hoche 75008 Paris, France	ZOCOR	5 mg	tablets	oral use
France	Laboratoires Merck Sharp & Dohme Chibret 3, Avenue Hoche 75008 Paris, France	ZOCOR	10 mg	tablets	oral use
France	Laboratoires Merck Sharp & Dohme Chibret 3, Avenue Hoche 75008 Paris, France	ZOCOR	10 mg	tablets	oral use
France	Laboratoires Merck Sharp & Dohme Chibret 3, Avenue Hoche 75008 Paris, France	ZOCOR	20 mg	tablets	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
France	Laboratoires Merck Sharp & Dohme Chibret 3, Avenue Hoche 75008 Paris, France	ZOCOR	20 mg	tablets	oral use
France	Laboratoires Merck Sharp & Dohme Chibret 3, Avenue Hoche 75008 Paris, France	ZOCOR	40 mg	tablets	oral use
France	Laboratoires Merck Sharp & Dohme Chibret 3, Avenue Hoche 75008 Paris, France	ZOCOR	80 mg	tablets	oral use
France	Laboratoires SANOFI-SYNTHELABO FRANCE 174, Avenue de France 75013 Paris, France	LODALES	5 mg	tablets	oral use
France	Laboratoires SANOFI-SYNTHELABO FRANCE 174, Avenue de France 75013 Paris, France	LODALES	5 mg	tablets	oral use
France	Laboratoires SANOFI-SYNTHELABO FRANCE 174, Avenue de France 75013 Paris, France	LODALES	10 mg	tablets	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
France	Laboratoires SANOFI-SYNTHELABO FRANCE 174, Avenue de France 75013 Paris, France	LODALES	20 mg	tablets	oral use
France	Laboratoires SANOFI-SYNTHELABO FRANCE 174, Avenue de France 75013 Paris, France	LODALES	40 mg	tablets	oral use
France	Laboratoires SANOFI-SYNTHELABO FRANCE 174, Avenue de France 75013 Paris, France	LODALES	80 mg	tablets	oral use
Germany	Dieckmann Arzneimittel GmBH Lindenplatz 1 85540 Haar, Germany	ZOCOR	5 mg	film coated tablets	oral use
Germany	Dieckmann Arzneimittel GmBH Lindenplatz 1 85540 Haar, Germany	ZOCOR	10 mg	film coated tablets	oral use
Germany	Dieckmann Arzneimittel GmBH Lindenplatz 1 85540 Haar, Germany	ZOCOR	20 mg	film coated tablets	oral use
Germany	Dieckmann Arzneimittel GmBH Lindenplatz 1 85540 Haar, Germany	ZOCOR FORTE	40 mg	film coated tablets	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Germany	Dieckmann Arzneimittel GmBH Lindenplatz 1 85540 Haar, Germany	ZOCOR FORTE XL	80 mg	film coated tablets	oral use
	MSD Sharp & Dohme GmbH Lindenplatz 1 85540 Haar, Germany	LIPOCARD	5 mg	film coated tablets	oral use
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 85540 Haar, Germany	LIPOCARD	10 mg	film coated tablets	oral use
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 85540 Haar, Germany	LIPOCARD	20 mg	film coated tablets	oral use
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 85540 Haar, Germany	LIPOCARD	40 mg	film coated tablets	oral use
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 85540 Haar, Germany	ZEMOX	5 mg	film coated tablets	oral use
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 85540 Haar, Germany	ZEMOX	10 mg	film coated tablets	oral use
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 85540 Haar, Germany	ZEMOX	20 mg	film coated tablets	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 85540 Haar, Germany	ZEMOX	40 mg	film coated tablets	oral use
Germany	MSD Sharp & Dohme GmbH Lindenplatz 1 85540 Haar, Germany	ZEMOX	80 mg	film coated tablets	oral use
Germany	Boehringer Ingelheim Pharma KG Binger Strasse 173 55216 Ingelheim am Rhein, Germany	DENAN	5 mg	film coated tablets	oral use
Germany	Boehringer Ingelheim Pharma KG Binger Strasse 173 55216 Ingelheim am Rhein, Germany	DENAN	10 mg	film coated tablets	oral use
Germany	Boehringer Ingelheim Pharma KG Binger Strasse 173 55216 Ingelheim am Rhein, Germany	DENAN	20 mg	film coated tablets	oral use
Germany	Boehringer Ingelheim Pharma KG Binger Strasse 173 55216 Ingelheim am Rhein, Germany	DENAN	40 mg	film coated tablets	oral use
Germany	Boehringer Ingelheim Pharma KG Binger Strasse 173 55216 Ingelheim am Rhein, Germany	DENAN	80 mg	film coated tablets	oral use
Greece	Marketing Authorization Holder Merck & Co., INC Whitehouse Station, N.J. USA	ZOCOR	5 mg	tablets	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Greece	Marketing Authorization Holder Merck & Co., INC Whitehouse Station, N.J. USA	ZOCOR	10 mg	tablets	oral use
Greece	VIANEX S.A. Tatoioy Street P.O. Box 52894 146 10N. Erithrea, Greece	ZOCOR	20 mg	tablets	oral use
Greece	VIANEX S.A. Tatoioy Street P.O. Box 52894 146 10N. Erithrea, Greece	ZOCOR	40 mg	tablets	oral use
Greece	VIANEX S.A. Tatoioy Street P.O. Box 52894 146 10N. Erithrea, Greece	ZOCOR	80 mg	tablets	oral use
Iceland	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCOR	10 mg	tablets	oral use
Iceland	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCOR	20 mg	tablets	oral use
Iceland	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCOR	40 mg	tablets	oral use
Iceland	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCOR	80 mg	tablets	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Ireland	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Herts EN11 9BU United Kingdom	ZOCOR	5 mg	tablets	oral use
Ireland	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Herts EN11 9BU United Kingdom	ZOCOR	10 mg	tablets	oral use
Ireland	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Herts EN11 9BU United Kingdom	ZOCOR	20 mg	tablets	oral use
Ireland	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Herts EN11 9BU United Kingdom	ZOCOR	40 mg	tablets	oral use
Ireland	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Herts EN11 9BU United Kingdom	ZOCOR	80 mg	tablets	oral use
Italy	Merck Sharp & Dohme (Italia) SpA. Via G. Fabbroni 6 00191 Rome, Italy	SINVACOR	10 mg	film coated tablets	oral use
Italy	Merck Sharp & Dohme (Italia) SpA. Via G. Fabbroni 6 00191 Rome, Italy	SINVACOR	20 mg	film coated tablets	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Italy	Merck Sharp & Dohme (Italia) SpA. Via G. Fabbroni 6 00191 Rome, Italy	SINVACOR	40 mg	film coated tablets	oral use
Italy	Neopharmed SpA Via G. Fabbroni 6 00191 Rome, Italy	ZOCOR	10 mg	film coated tablets	oral use
Italy	Neopharmed SpA Via G. Fabbroni 6 00191 Rome, Italy	ZOCOR	20 mg	film coated tablets	oral use
Italy	Neopharmed SpA Via G. Fabbroni 6 00191 Rome, Italy	ZOCOR	40 mg	film coated tablets	oral use
Italy	Istituto Gentili SpA. Via Mazzini 112 56125 Pisa, Italy	LIPONORM	10 mg	film coated tablets	oral use
Italy	Istituto Gentili SpA. Via Mazzini 112 56125 Pisa, Italy	LIPONORM	20 mg	film coated tablets	oral use
Italy	Istituto Gentili SpA. Via Mazzini 112 56125 Pisa, Italy	LIPONORM	40 mg	film coated tablets	oral use
Italy	Sigma Tau SpA Via Pontina Km 30, 400 Pomezia (Rome) Italy	SIVASTIN	10 mg	film coated tablets	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Italy	Sigma Tau SpA Via Pontina Km 30, 400 Pomezia (Rome) Italy	SIVASTIN	20 mg	film coated tablets	oral use
Italy	Sigma Tau SpA Via Pontina Km 30, 400 Pomezia (Rome) Italy	SIVASTIN	40 mg	film coated tablets	oral use
Italy	Mediolanum SpA Via S.G. Cottolengo 15 20143 Milano, Italy	MEDIPO	10 mg	film coated tablets	oral use
Italy	Mediolanum SpA Via S.G. Cottolengo 15 20143 Milano, Italy	MEDIPO	20 mg	film coated tablets	oral use
Italy	Mediolanum SpA Via S.G. Cottolengo 15 20143 Milano, Italy	MEDIPO	40 mg	film coated tablets	oral use
Luxembourg	Merck Sharp & Dohme B.V. Succursale belge Chaussée de Waterloo 1135 1180 Bruxelles/Brussel, Belgique	ZOCOR	5 mg	tablets	oral use
Luxembourg	Merck Sharp & Dohme B.V. Succursale belge Chaussée de Waterloo 1135 1180 Bruxelles/Brussel, Belgique	ZOCOR	10 mg	tablets	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Luxembourg	Merck Sharp & Dohme B.V. Succursale belge Chaussée de Waterloo 1135 1180 Bruxelles/Brussel, Belgique	ZOCOR	20 mg	tablets	oral use
Luxembourg	Merck Sharp & Dohme B.V. Succursale belge Chaussée de Waterloo 1135 1180 Bruxelles/Brussel, Belgique	ZOCOR	20 mg	tablets	oral use
Luxembourg	Merck Sharp & Dohme B.V. Succursale belge Chaussée de Waterloo 1135 1180 Bruxelles/Brussel, Belgique	ZOCOR	40 mg	tablets	oral use
Luxembourg	Merck Sharp & Dohme B.V. Succursale belge Chaussée de Waterloo 1135 1180 Bruxelles/Brussel, Belgique	ZOCOR	40 mg	tablets	oral use
Luxembourg	Merck Sharp & Dohme B.V. Succursale belge Chaussée de Waterloo 1135 1180 Bruxelles/Brussel, Belgique	ZOCOR	80 mg	tablets	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Luxembourg	Merck Sharp & Dohme B.V. Succursale belge Chaussée de Waterloo 1135 1180 Bruxelles/Brussel, Belgique	ZOCOR	80 mg	tablets	oral use
Netherlands	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCOR	5 mg	tablets	oral use
Netherlands	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCOR	10 mg	tablets	oral use
Netherlands	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCOR	20 mg	tablets	oral use
Netherlands	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCOR	40 mg	tablets	oral use
Netherlands	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCOR	80 mg	tablets	oral use
Netherlands	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCOR	5 mg	tablets	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Netherlands	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	BOZARA	10 mg	tablets	oral use
Netherlands	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	BOZARA	20 mg	tablets	oral use
Netherlands	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	BOZARA	40 mg	tablets	oral use
Norway	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCOR	10 mg	tablets	oral use
Norway	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCOR	10 mg	tablets	oral use
Norway	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCOR	20 mg	tablets	oral use
Norway	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCOR	20 mg	tablets	oral use
Norway	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCOR	40 mg	tablets	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Norway	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCOR	40 mg	tablets	oral use
Norway	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCOR	80 mg	tablets	oral use
Norway	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCOR	80 mg	tablets	oral use
Portugal	Merck Sharp & Dohme, Lda, Quinta da Fonte Edifício Vasco da Gama, 19 P.O. Box 214 Porto Salvo 2780-730 Paço de Arcos, Portugal	ZOCOR	10 mg	film-coated tablets	oral use
Portugal	Merck Sharp & Dohme, Lda, Quinta da Fonte Edifício Vasco da Gama, 19 P.O. Box 214 Porto Salvo 2780-730 Paço de Arcos, Portugal	ZOCOR	20 mg	film-coated tablets	oral use
Portugal	Merck Sharp & Dohme, Lda, Quinta da Fonte Edifício Vasco da Gama, 19 P.O. Box 214 Porto Salvo 2780-730 Paço de Arcos, Portugal	ZOCOR	40 mg	film-coated tablets	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Portugal	Laboratórios Químico-Farmacêuticos Chibret, Lda. Quinta da Fonte Edifício Vasco da Gama, 19 P.O. Box 216 Porto Salvo P-2780-730 Paço de Arcos, Portugal	VACOLEST	10 mg	film-coated tablets	oral use
Portugal	Laboratórios Químico-Farmacêuticos Chibret, Lda. Quinta da Fonte Edifício Vasco da Gama, 19 P.O. Box 216 Porto Salvo P-2780-730 Paço de Arcos, Portugal	VACOLEST	20 mg	film-coated tablets	oral use
Spain	Merck Sharp & Dohme de España SA C/Josefa Valcárcel, 38 28027 Madrid, Spain	ZOCO	10 mg	film-coated tablets	oral use
Spain	Merck Sharp & Dohme de España SA C/Josefa Valcárcel, 38 28027 Madrid, Spain	ZOCOR	20 mg	film-coated tablets	oral use
Spain	Merck Sharp & Dohme de España SA C/Josefa Valcárcel, 38 28027 Madrid, Spain	ZOCOR	40 mg	film-coated tablets	oral use
Spain	LACER, SA Sardenya, 350 080254 Barcelona, Spain	PANTOK	10 mg	film-coated tablets	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Spain	LACER, SA Sardenya, 350 080254 Barcelona, Spain	PANTOK	20 mg	film-coated tablets	oral use
Spain	LACER, SA Sardenya, 350 080254 Barcelona, Spain	PANTOK	40 mg	film-coated tablets	oral use
Spain	J. Uriach & Cia SA Avda Camí Reial, 51-57 08184 Palau-solitá I Plegamans-Barcelona, Spain	COLEMIN	10 mg	film-coated tablets	oral use
Spain	J. Uriach & Cia SA Avda Camí Reial, 51-57 08184 Palau-solitá I Plegamans-Barcelona, Spain	COLEMIN	20 mg	film-coated tablets	oral use
Spain	J. Uriach & Cia SA Avda Camí Reial, 51-57 08184 Palau-solitá I Plegamans-Barcelona, Spain	COLEMIN	40 mg	film-coated tablets	oral use
Sweden	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCORD	10 mg	tablets	oral use
Sweden	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCORD	10 mg	tablets	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Sweden	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCORD	20 mg	tablets	oral use
Sweden	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCORD	20 mg	tablets	oral use
Sweden	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCORD	40 mg	tablets	oral use
Sweden	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCORD	40 mg	tablets	oral use
Sweden	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCORD	80 mg	tablets	oral use
Sweden	Merck Sharp & Dohme B.V. P.O. Box 581 2003 PC Haarlem, The Netherlands	ZOCORD	80 mg	tablets	oral use
United Kingdom	Merck Sharp & Dohme Limited Hertford Road Hoddesdon Herts EN11 9BU United Kingdom	ZOCOR	5 mg	tablets	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
United Kingdom	Merck Sharp & Dohme Limited Hertford Road Hoddesdon Herts EN11 9BU United Kingdom	ZOCOR	5 mg	tablets	oral use
United Kingdom	Merck Sharp & Dohme Limited Hertford Road Hoddesdon Herts EN11 9BU United Kingdom	ZOCOR	10 mg	tablets	oral use
United Kingdom	Merck Sharp & Dohme Limited Hertford Road Hoddesdon Herts EN11 9BU United Kingdom	ZOCOR	10 mg	tablets	oral use
United Kingdom	Merck Sharp & Dohme Limited Hertford Road Hoddesdon Herts EN11 9BU United Kingdom	ZOCOR	20 mg	tablets	oral use
United Kingdom	Merck Sharp & Dohme Limited Hertford Road Hoddesdon Herts EN11 9BU United Kingdom	ZOCOR	20 mg	tablets	oral use
United Kingdom	Merck Sharp & Dohme Limited Hertford Road Hoddesdon Herts EN11 9BU United Kingdom	ZOCOR	40 mg	tablets	oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
United Kingdom	Merck Sharp & Dohme Limited Hertford Road Hoddesdon Herts EN11 9BU United Kingdom	ZOCOR	40 mg	tablets	oral use
United Kingdom	Merck Sharp & Dohme Limited Hertford Road Hoddesdon Herts EN11 9BU United Kingdom	ZOCOR	80 mg	tablets	oral use

ANNEX II

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

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF ZOCORD AND ASSOCIATED NAMES (see Annex I)

- Quality issues

No significant issues relating to Quality were identified.

The pharmaceutical particulars of the SPC were harmonised, except the sections, which need to be introduced nationally by the Member States when implementing the harmonised SPC (section 6).

- Efficacy issues

The divergences that previously existed across the SPCs of EU Member States included:

Section 4.1 Therapeutic Indications

The MAH was requested to propose and scientifically justify a common EU wide approach as there were divergences between national approvals regarding the use of Zocord in:

Secondary prevention of cardiovascular events has been approved in all Member States, Iceland and Norway. However, the wording (and therefore the precise meaning) of the indication is very different from country to country.

Primary hypercholesterolemia (Fredrickson´s type's IIa and IIb) has been approved in all Member States, Iceland and Norway. However, the wording (and therefore the precise meaning) of the indication is very different in the nationally approved SPCs.

Dysbetalipoproteinemia (Fredrickson's type III) has only been granted in some Member States.

Hypertriglyceridemia (Fredrickson's type's IV) has only been granted in some Member States.

Homozygous familial hypercholesterolemia has been granted as "an adjunct to diet and other non-dietary measures when those measures have been inadequate" in some Member States and in others it has been granted as "an adjunct to diet and other non-dietary measures when diet and other non-pharmacological measures have been inadequate".

- **Treatment of primary hypercholesterolaemia or mixed dyslipidaemia, treatment of homozygous familial hypercholesterolaemia.**

Simvastatin has been shown to reduce both normal and elevated low-density lipoproteins (LDL) cholesterol concentrations. LDL are formed from very-low-density protein (VLDL) and are catabolised predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of simvastatin may involve both reduction of VLDL cholesterol concentration and induction of the LDL receptor, leading to reduced production and increased catabolism of LDL cholesterol. Apolipoprotein B also falls substantially during treatment with simvastatin. In addition, simvastatin moderately increases high density lipoprotein (HDL) cholesterol and reduces plasma triglycerides. As a result of these changes the ratios of total to HDL cholesterol and LDL to HDL cholesterol are reduced.

- **dysbetalipoproteinemia**

An indication for dysbetalipoproteinemia (Fredrickson's Type III hyperlipidaemia) has been approved in 6 Member States (Austria, France, Iceland, Ireland, the Netherlands, and Portugal). This indication for is mainly based in study 133, a randomised, double blind, placebo-controlled trial designed to

evaluate the efficacy of simvastatin in patients with combined hyperlipidaemia (elevated cholesterol and triglycerides). This condition includes a number of diseases such as familial combined hyperlipidemia, other poorly characterised polygenic syndromes, and dysbetalipoproteinemia.

The study included men and women 21 to 70 years with combined hyperlipidemia defined as LDL cholesterol greater than 130 mg/dl, and triglycerides between 300 and 700 mg/dl at Weeks -4 and -2. Patients with type 2 diabetes mellitus were eligible to participate provided hemoglobin A_{1C} at Week -4 was not ≤10%.

One hundred and thirty patients were randomised to 80 mg simvastatin, 40 mg simvastatin or placebo. The primary objective were to determine the LDL cholesterol lowering efficacy of simvastatin 80 mg/day plus diet, and simvastatin 40 mg/day plus diet relative to diet plus placebo in patients with combined hyperlipidaemia at the end of a 6-week treatment period.

The secondary objectives were: To evaluate in patients with combined hyperlipidaemia treated for 6 weeks: (1) the effects of S 80 mg/day + diet and simvastatin 40 mg/day + diet relative to diet + placebo on VLDL cholesterol, triglycerides, non HDL cholesterol, and HDL cholesterol; (2) the effects of simvastatin 80 mg/day plus diet and simvastatin 40 mg/day plus diet relative to diet plus placebo on LDL cholesterol, VLDL cholesterol, triglycerides, and non HDL cholesterol, in a subgroup of patients with combined hyperlipidaemia and non-insulin dependent diabetes mellitus (NIDDM; type 2 diabetes mellitus); and (3) the safety and tolerability of simvastatin 80 mg/day in patients with combined hyperlipidaemia.

Dose-dependent percent changes from baseline were observed across the placebo, simvastatin 40 mg and simvastatin 80 mg treatments for the primary end point (LDL cholesterol) and for the secondary end points (VLDL cholesterol, triglycerides, non HDL cholesterol, HDL cholesterol, apolipoprotein B, and apolipoprotein A-I). In patients with combined hyperlipidemia and type 2 diabetes mellitus (n=24 randomized), observed dose-dependent percent changes from baseline were not different from those observed in nondiabetic patients.

Eight patients were retrospectively found to have dysbetalipoproteinemia, based on elevated cholesterol and triglycerides, the presence of the apolipoprotein E2/2 genotype, and a VLDL/triglycerides ratio ≥0.25. The MAH presents data of 7 patients (randomised to three groups) and argues that a large and significant effect of simvastatin was found for all of the variables considered except HDL cholesterol (see table 1).

Table 1. Median percent (%) change (95% IC)

	Placebo	Simvastatin 40 mg	Simvastatin 80 mg
Total-c	-7.6 (-24.8;9.5)	-49.6 (-69.0;-30.3)	-51.6 (-57.9;-45.3)
LDL-c	-8.1 (-44.8;28.6)	-49.8(-63.1;-36.6)	-50.5 (-57.5;-43.4)
VLDL-c	-3.8 (-12.7;5.1)	-58.3 (-85.7;-30.9)	-59.5 (-72.9;-46.1)
HDL-c	-1.6 (-14.5;11.2)	6.7 (-10.6;23.9)	6.7 8-12.5;25.8)
triglycerides	3.5 (-15.3;22.4)	-40.5 (-64.1;-16.8)	38.2 (-50.2;-26.1)

A study conducted by Stuyt et al. was an open-label study including 12 patients with familial dysbetalipoproteinemia. After a three-week placebo period, they were treated with increasing doses (10 mg twice/day, 20 mg twice/day, and 40 mg twice/day) of simvastatin in six-week. With the 80 mg dose, the mean serum cholesterol level decreased from 12.30±4.96 to 5.29±1.24 mmol/l (mean reduction, 54%) and the mean serum triglycerides level decreased from 8.77 ± 7.16 to 3.61±1.33 mmol/l (-48%); this was due to a decrease in VLDL and LDL lipids. There was a decrease in the ratio of VLDL cholesterol to serum triglycerides and in the apolipoproteins B and E, suggesting a reduction in the amount of circulating atherogenic remnant particles.

Study conducted by Feussner et al. included 19 patients with dysbetalipoproteinemia who were treated with simvastatin (20 or 40 mg per day) alone or in combination with gemfibrozil (450 mg per day) during a 30-week outpatient study.

With the 20-mg dose (n=19) the mean plasma cholesterol level decreased by 39.3% ($p<0.05$), and the mean plasma triglycerides level decreased by 41.8% (ns); there was a decrease in VLDL cholesterol of 44.8% (ns), a decrease in LDL cholesterol of 36.5% ($p<0.01$), and an increase in HDL cholesterol of 18.1% (ns).

Thirteen (30) patients were treated with 40 mg simvastatin per day. Under this regimen there was a significant decrease in LDL cholesterol 22.3% ($p<0.01$). In six patients who remained with a hyperlipidaemia on monotherapy combination drug therapy with simvastatin (40 mg/day) and gemfibrozil (450 mg/day) was given. Compared to simvastatin alone the addition of gemfibrozil further lowered plasma concentrations of total cholesterol by 14.9%, VLDL cholesterol by 23.5%, and triglycerides by 17.1%, although this was not statistically significant.

Study conducted by Civeira et al. compared in a double-blind, randomised and placebo-controlled trial the effects of gemfibrozil (1200 mg/day) and simvastatin (20 mg/day) on lipids, apolipoprotein AI, apolipoprotein B, and apolipoprotein E and on lipids and apolipoprotein B content in VLDL, intermediate-density lipoprotein (IDL), LDL, and HDL in 10 patients with type III hyperlipoproteinemia.

Levels of total cholesterol, VLDL cholesterol, IDL cholesterol, and apolipoprotein B decreased with both drugs. Larger reductions in triglycerides (109±28.2 mg/dl, p=0.005), VLDL cholesterol (24.7±10.9 mg/dl, p=0.05), and VLDL triglycerides (86.3±20.2 mg/dl, p=0.003) were obtained with gemfibrozil compared with simvastatin. LDL cholesterol reduction was more effective with simvastatin than with gemfibrozil (44.3±17.1 mg/dl, p=0.03). HDL cholesterol after gemfibrozil was 5.71±2.37 mg/dl higher than after simvastatin.

- **hypertriglyceridemia**

An indication for hypertriglyceridemia (Fredrickson's Type IV hyperlipidaemia) was granted by 4 Member States (Austria, Germany, Iceland, and Portugal). This indication was mainly based on study

145, a randomised, double-blind, parallel-group, 4-arm, placebo-controlled, multicenter trial. Prior to randomisation, there was a 4-week diet/placebo run-in period. Eligible patients were randomised to 1 of 4 treatments (ratio 1:1:1:1); placebo, simvastatin 20, 40, or 80 mg.

The study included men and women 18 to 70 years old with average triglycerides values between 300 to 900 mg/dl at Weeks -4 and -1; the lower of the individual triglycerides values must be ≥70% of the higher value; the higher value must be ≤900 mg/dl.

A subgroup of 116 patients with isolated hypertriglyceridemia (Fredrickson's Type IV hyperlipidaemia) were identified by the following criteria: baseline LDL cholesterol <130 mg/dL, as all patients in this study had baseline triglycerides >200 mg/dl.

The primary objective was to evaluate the triglycerides lowering response across placebo, 20, 40, and 80 mg doses of simvastatin after a 6-week treatment period in patients with hypertriglyceridemia.

The secondary objective was to evaluate in patients with hypertriglyceridemia treated for 6 weeks with simvastatin: (1) the triglycerides-lowering efficacy of 20, 40, or 80mg/day doses; (2) the effect of baseline triglycerides levels on triglycerides-lowering efficacy; (3) the effects of simvastatin 20, 40, or 80 mg/day on LDL cholesterol, VLDL cholesterol, non-HDL cholesterol, HDL cholesterol, apolipoproteins (apos) B, A-I, E, C-III, and fibrinogen; (4) the effects of simvastatin 20, 40, or 80 mg/day on lipoprotein remnant metabolism; and (5) the tolerability of simvastatin at doses of 20, 40, or 80 mg/day.

Efficacy results: For the primary endpoint, triglycerides, the secondary endpoints, LDL cholesterol, apo B, HDL cholesterol, non-HDL cholesterol, and VLDL cholesterol, the trends tests were significant in the response across placebo, simvastatin 20, simvastatin 40, and simvastatin 80 mg.

In the subgroup of patients with isolated hypertriglyceridemia, median triglycerides percent changes of -13.3, -20.7, -20.6, and -33.0% were observed for the placebo, simvastatin 20, 40, and 80 mg treatment groups, respectively (see Table 3). The trend test was significant in the triglycerides response over the range of doses from placebo through simvastatin 80 mg (p=0.001). The treatment effect of the triglycerides-lowering response was significant between the placebo through simvastatin 40 mg (p=0.041). No significant difference between the placebo and 20-mg treatment was achieved (p>0.100). Total cholesterol, LDL cholesterol and apolipoprotein B were significantly reduced.

Table 2. Mean[1]/Median[2] percent change from baseline

	TG[2]	LDL-c[1]	Apo B[1]	HDL-c[1]	VLDL-c[2]
Placebo	-13.3(35.3)	3.4(16.1)	-1.6(8.7)	2.7(9.9)	-10.3(39.0)
S 20 mg	-20.7(38.6)	-22.6(15.5)	-22.2(15.8)	9.0(16.8)	-33.4(27.6)
S 40 mg	-20.6(26.1)	-25.2(18.2)	-23.5(10.1)	9.1(11.3)	-34.9(29.5)
S 80 mg	-33.0(19.6)	-34.5(14.5)	-31.2(11.7)	10.8(9.5)	-43.8(22.1)

No patient experienced any elevation of ALT and/or AST >3 X ULN. One patient in the simvastatin 40-mg group had an elevation of CK >5 X ULN during the study, but was not considered an AE by the investigator. No evidence of an increasing trend in the incidence of CK >5 X ULN was observed with increasing doses from the placebo to the simvastatin 80-mg dose. No myopathy or elevation of CK >10 X ULN was observed during the study.

According to the NCEP Expert Panel III, when LDL cholesterol levels are not significantly elevated, the goal for non-HDL cholesterol with a triglycerides-lowering drug usually is within reach. Among these, nicotinic acid is usually the most effective as it reduces triglycerides by 30-50 percent usually without causing a reciprocal increase in LDL cholesterol and at the same time, nicotinic acid raises HDL cholesterol concentrations by 20-30 percent. In persons with contraindications to nicotinic acid or in whom this drug is poorly tolerated, fibric acid derivatives reduce triglycerides by 40–60%, and cause a 15–25 percent increase in HDL-cholesterol concentrations. Nevertheless, fibrates often raise

LDL cholesterol levels by 5–30 percent. This reciprocal increase in LDL cholesterol usually means that fibrates alone do not lower non-HDL cholesterol level.

Study 145 shows that simvastatin achieves triglycerides reductions but they are lower (-20.6 and -33 for simvastatin 40 mg and 80mg respectively) than those seen for nicotinic acid or fibric acid derivatives. As simvastatin is not a powerful triglyceride-lowering drug it should be considered second-line drug therapy. Additionally, study 145 have some methodological deficiencies, e.g., the lack of a controlled group treated with nicotinic acid and the small number of patients included with isolated hypercholesterolemia.

- **homozygous familial hypercholesterolaemia**

An indication for Zocord in homozygous familial hypercholesterolaemia (FH) was granted by 11 Member States (Austria, Belgium, Luxembourg, France, Greece, UK, Ireland, the Netherlands, Portugal, Spain, and Iceland.). This indication is based on Study 114, a single-centre, double blind, parallel, 2-period, dose escalation study to evaluate the efficacy and safety of high-dose simvastatin (80 and 160 mg) in patients with Homozygous Familial Hypercholesterolemia.

In this study 12 patients with homozygous familial hypercholesterolemia were randomized to simvastatin 40 mg administered as a single dose or 80 mg/day (in 3 doses), following a 4-week diet/placebo run-in phase. Eight patients randomised to simvastatin 80 mg/day and 4 patients to 40 mg/day. After 9 weeks of treatment, patients initially receiving simvastatin 80 mg/day had their dose increased to 160 mg/day (given in 3 divided doses) for an additional 9 weeks while those on simvastatin 40 mg in the evening received 40 mg given in 3 divided doses.

The primary objective was to evaluate the LDL cholesterol lowering efficacy of simvastatin at doses of 80 and 160 mg/day in patients with homozygous familial hypercholesterolemia and the secondary objective was to determine the short-term safety profile of simvastatin at doses of 80 and 160 mg/day in this patient population.

Homozygous familiar hypercholesterolemia was defined by an LDL cholesterol level ≥500 mg/dl and the presence of at least 2 of the following: tendinous xanthoma, both parents with a diagnosis of familial hypercholesterolemia or an LDL-receptor genotype indicating the presence of a mutation in both LDL receptor genes. Twelve patients aged between 13 to 40 years were recruited.

Regarding efficacy, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, Lp(a), apolipoproteins B and E were assessed. Evaluation of clinical and laboratory adverse experiences (AEs), vital signs, and routine laboratory safety tests were made. Predefined limits of change analyses were performed for the following laboratory tests: alkaline phosphatase, total bilirubin, hematocrit, hemoglobin, neutrophils, platelet count, serum creatinine, serum glucose, serum uric acid, and WBC count.

A mean change from baseline of –24.6 and –30.6% at the 80 mg and 160 mg doses for LDL cholesterol, respectively, a mean change of -23.0% and -28.8% in total cholesterol and respectively, and a mean change of +7.4% and +4.7% 24.5% at the 80 mg and 160 mg, respectively, were found (see Table 3).

Table 3. Mean change (%) from baseline (SD)

	LDL-c (mg/dl)	Total-c (mg/dl)	HDL-c(mg/dl)	TG (mg/dl)
40 mg/day (1 dose)	-13.7 (7.5)	-12.3 (6.6	9.3 (11.1)	-3.5 (28.7)
40 mg/day (3 doses)	-13.2 (10.3)	-11.4 (9.4)	20.5 (15.6)	-6.5 (19.7)
80 mg/day (3 dose)	-24.6 (18.9)	-23.0 (16.7)	7.4 (18.2)	- 18.5 (22.5)
160 mg/day (3 doses)	30.6 (20.0)	-28.8 (17.7)	4.7 (16.3)	-24.5 (13.9)

There was no case of myopathy and no consistent effect observed on mean CK levels in the study cohort. With regard to liver, no patients developed ALT or AST increases more than 3-fold the ULN.

In spite of the small number of patients included in this study, the Rapporteur considers that this indication could be acceptable since homozygous familial hypercholesterolemia is a very rare condition and it is a hard-to-treat disease because patients express little or no LDL receptor activity and therefore are resistant to the effects of therapeutic diets and most cholesterol-lowering medications. Current accepted therapy consists of modified forms of plasmapheresis that selectively remove VLDL and LDL from the plasma.

- **Primary and secondary prevention of cardiovascular events**

The indication of secondary prevention was initially based on study 4S that was designed to evaluate the effect of cholesterol lowering with simvastatin on mortality and morbidity in patients with coronary heart disease (CHD). 4,444 patients with angina pectoris or previous myocardial infarction and hypercholesterolemia on a lipid-lowering diet were randomised to double-blind treatment with simvastatin or placebo and followed up for a median of 5.4 years. The study investigated a) the effect of simvastatin on mortality, b) the effect of simvastatin on major coronary events, and c) the effect of simvastatin on any coronary event.

This is a large study, well conducted over many years and provides sufficient data to support the benefit of simvastatin in the reduction of clinical events in the secondary prevention in hypercholesterolemic population.

Another and more recent trial, the Heart Protection Study (HPS) supports the indication for primary prevention. The aim of this clinical trial, with over 20,000 participants aged 40–80 years, was to establish whether statin therapy is of benefit to people who are at high risk of cardiovascular disease (CVD) but have average to low levels of total cholesterol and LDL cholesterol.

High-risk patients (defined as those having previous coronary heart disease, diabetes, stroke, or peripheral vascular disease) were treated with simvastatin (40 mg daily), antioxidant vitamins (20 mg beta-carotene, 250 mg vitamin C and 600 mg vitamin E daily) or placebo in a 2 × 2 factorial design.

The primary outcomes were deaths from all causes, deaths from coronary heart disease, and death from other causes. Secondary end-points included the effect on specific non-coronary causes of death major coronary events and major vascular events, fatal and non-fatal strokes. Other secondary analyses included the effects on major coronary events (MCE) and on major vascular events (MVE) in different subcategories of prior disease and in other major subcategories determined at study entry.
20,536 patients were randomised in this study. Approximately two-thirds of the patient population had CHD with or without noncoronary occlusive vascular disease, diabetes or hypertension. Almost 4,000 patients had diabetes without CHD. A quarter of the patients was woman and the average age of the whole study population at baseline was 64, with 5,806 patients aged 70 or older.

The vitamins had no detectable effect on clinical outcomes nor did they affect the risk reductions, which were similar in presence and in absence of the vitamins. Therefore, the analyses were performed in the whole population.

Primary end-point: Over 5 years of follow up 12.9% of patients allocated simvastatin and 14.7% allocated placebo died (p=0.0003). This equates to an absolute risk reduction of 1.8%. This reduction can mainly be attributed to reductions in coronary death rate (absolute risk reduction of 1.2%) and deaths from other vascular causes (absolute risk reduction of 0.3%).

Secondary end-points: The analysis of secondary end-points indicates that simvastatin was associated with reductions in the incidence of non-fatal myocardial infarction absolute risk reduction of 2.1%, stroke (absolute risk reduction of 1.4%), and revascularisation (absolute risk reduction of 2.56%).

The risk reductions observed with simvastatin were significant for the secondary comparison endpoints MVE and MCE within all the major predefined subgroups including patients with diabetes, peripheral vascular disease or cerebrovascular disease. Within all three of these prior disease subgroups, the effect of simvastatin on MVE and MCE were significant with or without the inclusion of patients who also had known CHD.

In the HPS study, the safety profiles of simvastatin and placebo were similar. There was a low incidence of myopathy (defined as serum creatine kinase levels exceeding 10 times the upper limit of normal), that occurred in only 11 simvastatin-treated patients and six placebo-treated patients. There were no apparent safety concerns in patients with low baseline LDL cholesterol levels (< 3 mmol/l), in whom average LDL cholesterol levels during the trial were 1.8 mmol/l in the simvastatin-treated group and 2.7 mmol/l in the group receiving placebo. The association between low levels of total cholesterol and increased cerebral haemorrhage found in a study (Iso et al. 1989) was not confirmed by the HPS.

All the indications discussed above are covered by the new harmonised indication adopted by the CPMP.

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Zocord, the following was considered to be the most suitable harmonised Section 4.1 indications text:

4.1 Therapeutic indications

Hypercholesterolaemia
Treatment of primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.

Treatment of homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

Cardiovascular prevention
Reduction of cardiovascular mortality and morbidity in patients with manifest atherosclerotic cardiovascular disease or diabetes mellitus, with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors and other cardioprotective therapy (see section 5.1).

Section 4.2. Posology and method of administration

Member States have approved different starting dose and daily dose. Maximum daily dose was not specified in some of the approved SPCs.

The MAH was requested to substantiate scientifically the divergent information across member states and justify a proposed common wording, especially with regard to therapeutic daily dose range.

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Zocord the following was considered to be the most suitable harmonised Section 4.2 Posology text:

4.2 Posology and method of administration

The dosage range is 5-80 mg/day given orally as a single dose in the evening. Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks, to a maximum of 80 mg/day given as a single dose in the evening. The 80 mg dose is only recommended in patients with severe hypercholesterolaemia and high risk for cardiovascular complications.

Hypercholesterolaemia

The patient should be placed on a standard cholesterol-lowering diet, and should continue on this diet during treatment with < Zocord >. The usual starting dose is 10-20 mg/day given as a single dose in the evening. Patients who require a large reduction in LDL-C (more than 45 %) may be started at 20-40 mg/day given as a single dose in the evening. Adjustments of dosage, if required, should be made as specified above.

Homozygous familial hypercholesterolaemia

Based on the results of a controlled clinical study, the recommended dosage is < Zocord > 40 mg/day in the evening or 80 mg/day in 3 divided doses of 20 mg, 20 mg, and an evening dose of 40 mg. < Zocord > should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

Cardiovascular prevention

The usual dose of < Zocord > is 20 to 40 mg/day given as a single dose in the evening in patients at high risk of coronary heart disease (CHD, with or without hyperlipidaemia). Drug therapy can be initiated simultaneously with diet and exercise. Adjustments of dosage, if required, should be made as specified above.

Concomitant therapy

< Zocord > is effective alone or in combination with bile acid sequestrants. Dosing should occur either > 2 hours before or > 4 hours after administration of a bile acid sequestrant.

In patients taking cyclosporine, gemfibrozil, other fibrates (except fenofibrate) or lipid-lowering doses (≥ 1 g/day) of niacin concomitantly with < Zocord >, the dose of < Zocord > should not exceed 10 mg/day. In patients taking amiodarone or verapamil concomitantly with < Zocord >, the dose of < Zocord > should not exceed 20 mg/day. (See sections 4.4 and 4.5.)

Dosage in renal insufficiency

No modification of dosage should be necessary in patients with moderate renal insufficiency.
In patients with severe renal insufficiency (creatinine clearance < 30 mL/min), dosages above 10 mg/day should be carefully considered and, if deemed necessary, implemented cautiously.

Use in the elderly

No dosage adjustment is necessary.

Use in children and adolescents

Efficacy and safety of use in children has not been established. Therefore < Zocord > is not recommended for paediatric use.

- Safety issues

Section 4.3 Contraindications

The MAH was requested to propose and scientifically justify a common EU wide approach as the contraindications text was considered to differ to a large extent between Member States especially relating to the use in patients with:

- porphyria,
- myopathy,
- concomitant use of other medicinal products interacting with simvastatin,
- biliary cirrhosis,
- secondary hypercholesterolemia (hypothyroidism, nephrotic syndrome).

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Zocord, the following was considered to be the most suitable harmonised Section 4.3 Contraindications, the text in the harmonised SPC is not so dissimilar to the currently approved SPCs that it will significantly change clinical practices:

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Zocord, the following was considered to be the most suitable harmonised Section 4.3 Contraindications, the text in the harmonised SPC is not so dissimilar to the currently approved SPCs that it will significantly change clinical practices:

4.3 Contraindications

- Hypersensitivity to simvastatin or to any of the excipients
- Active liver disease or unexplained persistent elevations of serum transaminases
- Pregnancy and lactation (see section 4.6)
- Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone) (see section 4.5).

Section 4.4. Special warnings and precautions for use

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Zocord, the most suitable harmonised Section 4.4 Special Warnings and Precautions for Use text was approved (See Annex III). The text in the harmonised SPC is not so dissimilar to the currently approved SPCs that it will significantly change clinical practices.

All other sections of the SPC were harmonised as a result of the referral procedure (except See Below; Administrative Issues).

Finally, the CPMP considered that all presentations may be useful to treat the patients in the approved indications.

GROUNDS FOR AMENDMENT OF THE SUMMARY(IES) OF PRODUCT CHARACTERISTICS

Whereas,

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics,
- the Summary of Products Characteristic proposed by the Marketing Authorisation Holders has been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CPMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics is set out in Annex III of the Opinion for Zocord and associated names (see Annex I). The divergences identified at the start of the referral have been resolved.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTS

NOTE:
THIS SPC IS THE ONE THAT WAS ANNEXED TO THE COMMISSION DECISION CONCERNING THIS REFERRAL FOR ARBITRATION; THE TEXT WAS VALID AT THAT TIME.

IT IS NOT SUBSEQUENTLY MAINTAINED OR UPDATED BY THE EMEA, AND THEREFORE MAY NOT NECESSARILY REPRESENT THE CURRETN TEXT.

1. NAME OF THE MEDICINAL PRODUCT

Zocord 5 mg, film-coated tablets.
Zocord 10 mg, film-coated tablets.
Zocord 20 mg, film-coated tablets.
Zocord 40 mg, film-coated tablets.
Zocord 80 mg, film-coated tablets.

[To be implemented nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of simvastatin.
Each tablet contains 10 mg of simvastatin.
Each tablet contains 20 mg of simvastatin.
Each tablet contains 40 mg of simvastatin.
Each tablet contains 80 mg of simvastatin.

For excipients, see section 6.1.

[To be implemented nationally]

3. PHARMACEUTICAL FORM

Film-coated tablet.
["<*Colour*>-coloured, <*shape*>-shaped film-coated tablet marked "<*description of tablet image on both sides*>" containing <*strength*> mg simvastatin."]

[To be implemented nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia
Treatment of primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.

Treatment of homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

Cardiovascular prevention
Reduction of cardiovascular mortality and morbidity in patients with manifest atherosclerotic cardiovascular disease or diabetes mellitus, with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors and other cardioprotective therapy (see section 5.1).

4.2 Posology and method of administration

The dosage range is 5-80 mg/day given orally as a single dose in the evening. Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks, to a maximum of 80 mg/day given as a single dose in the evening. The 80-mg dose is only recommended in patients with severe hypercholesterolaemia and high risk for cardiovascular complications.

Hypercholesterolaemia

The patient should be placed on a standard cholesterol-lowering diet, and should continue on this diet during treatment with < Zocord >. The usual starting dose is 10-20 mg/day given as a single dose in the evening. Patients who require a large reduction in LDL-C (more than 45 %) may be started at 20-40 mg/day given as a single dose in the evening. Adjustments of dosage, if required, should be made as specified above.

Homozygous familial hypercholesterolaemia

Based on the results of a controlled clinical study, the recommended dosage is < Zocord > 40 mg/day in the evening or 80 mg/day in 3 divided doses of 20 mg, 20 mg, and an evening dose of 40 mg. < Zocord > should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

Cardiovascular prevention

The usual dose of < Zocord > is 20 to 40 mg/day given as a single dose in the evening in patients at high risk of coronary heart disease (CHD, with or without hyperlipidaemia). Drug therapy can be initiated simultaneously with diet and exercise. Adjustments of dosage, if required, should be made as specified above.

Concomitant therapy

< Zocord > is effective alone or in combination with bile acid sequestrants. Dosing should occur either > 2 hours before or > 4 hours after administration of a bile acid sequestrant.

In patients taking cyclosporine, gemfibrozil, other fibrates (except fenofibrate) or lipid-lowering doses (≥ 1 g/day) of niacin concomitantly with < Zocord >, the dose of < Zocord > should not exceed 10 mg/day. In patients taking amiodarone or verapamil concomitantly with < Zocord >, the dose of < Zocord > should not exceed 20 mg/day. (See sections 4.4 and 4.5.)

Dosage in renal insufficiency

No modification of dosage should be necessary in patients with moderate renal insufficiency. In patients with severe renal insufficiency (creatinine clearance < 30 ml/min), dosages above 10 mg/day should be carefully considered and, if deemed necessary, implemented cautiously.

Use in the elderly

No dosage adjustment is necessary.

Use in children and adolescents

Efficacy and safety of use in children have not been established. Therefore < Zocord > is not recommended for paediatric use.

4.3 Contraindications

- Hypersensitivity to simvastatin or to any of the excipients
- Active liver disease or unexplained persistent elevations of serum transaminases
- Pregnancy and lactation (see section 4.6)
- Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone) (see section 4.5).

4.4 Special warnings and special precautions for use

Myopathy/Rhabdomyolysis
Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above ten times the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and very rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

The risk of myopathy/rhabdomyolysis is dose related. The incidence in clinical trials, in which patients were carefully monitored and some interacting medicinal products were excluded, has been approximately 0.03 % at 20 mg, 0.08 % at 40 mg and 0.4 % at 80 mg.

Creatine Kinase measurement
Creatine Kinase (CK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes value interpretation difficult. If CK levels are significantly elevated at baseline (> 5 x ULN), levels should be re-measured within 5 to 7 days later to confirm the results.

Before the treatment
All patients starting therapy with simvastatin, or whose dose of simvastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness.

Caution should be exercised in patients with pre-disposing factors for rhabdomyolysis. In order to establish a reference baseline value, a CK level should be measured before starting a treatment in the following situations:

- Elderly (age > 70 years)
- Renal impairment
- Uncontrolled hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Alcohol abuse.

In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended. If a patient has previously experienced a muscle disorder on a fibrate or a statin, treatment with a different member of the class should only be initiated with caution. If CK levels are significantly elevated at baseline (> 5 x ULN), treatment should not be started.

Whilst on treatment
If muscle pain, weakness or cramps occur whilst a patient is receiving treatment with a statin, their CK levels should be measured. If these levels are found, in the absence of strenuous exercise, to be significantly elevated (> 5 x ULN), treatment should be stopped. If muscular symptoms are severe and cause daily discomfort, even if CK levels are < 5 x ULN, treatment discontinuation may be considered. If myopathy is suspected for any other reason, treatment should be discontinued.

If symptoms resolve and CK levels return to normal, then re-introduction of the statin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.

Therapy with simvastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

Measures to reduce the risk of myopathy caused by medicinal product interactions (see also section 4.5)

The risk of myopathy and rhabdomyolysis is significantly increased by concomitant use of simvastatin with potent inhibitors of CYP3A4 (such as itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone), as well as gemfibrozil and cyclosporine (see section 4.2)

The risk of myopathy and rhabdomyolysis is also increased by concomitant use of other fibrates, lipid-lowering doses (≥ 1 g/day) of niacin or by concomitant use of amiodarone or verapamil with higher doses of simvastatin (see sections 4.2 and 4.5). There is also a slight increase in risk when diltiazem is used with simvastatin 80 mg.

Consequently, regarding CYP3A4 inhibitors, the use of simvastatin concomitantly with itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone is contraindicated (see sections 4.3 and 4.5). If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with simvastatin must be suspended during the course of treatment. Moreover, caution should be exercised when combining simvastatin with certain other less potent CYP3A4 inhibitors: cyclosporine, verapamil, diltiazem (see sections 4.2 and 4.5). Concomitant intake of grapefruit juice and simvastatin should be avoided.

The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with cyclosporine, gemfibrozil, or lipid-lowering doses (≥ 1 g/day) of niacin. The combined use of simvastatin with gemfibrozil should be avoided, unless the benefits are likely to outweigh the increased risks of this drug combination. The benefits of the combined use of simvastatin 10 mg daily with other fibrates (except fenofibrate), niacin or cyclosporine should be carefully weighed against the potential risks of these combinations. (See sections 4.2 and 4.5.)

Caution should be used when prescribing fenofibrate with simvastatin, as either agent can cause myopathy when given alone.

The combined use of simvastatin at doses higher than 20 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy (see sections 4.2 and 4.5).

Hepatic effects

In clinical studies, persistent increases (to > 3 x ULN) in serum transaminases have occurred in a few adult patients who received simvastatin. When simvastatin was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pre-treatment levels.

It is recommended that liver function tests be performed before treatment begins and thereafter when clinically indicated. Patients titrated to the 80-mg dose should receive an additional test prior to titration, 3 months after titration to the 80-mg dose, and periodically thereafter (e.g., semi-annually) for the first year of treatment. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 x ULN and are persistent, simvastatin should be discontinued.

The product should be used with caution in patients who consume substantial quantities of alcohol.

As with other lipid-lowering agents, moderate (< 3 x ULN) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Interactions with lipid-lowering medicinal products that can cause myopathy when given alone
The risk of myopathy, including rhabdomyolysis, is increased during concomitant administration with fibrates and niacin (nicotinic acid) (≥ 1 g/day). Additionally, there is a pharmacokinetic interaction with gemfibrozil resulting in increased simvastatin plasma levels (see below *Pharmacokinetic interactions* and sections 4.2 and 4.4). When simvastatin and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent. Adequate pharmacovigilance and pharmacokinetic data are not available for other fibrates.

Pharmacokinetic interactions

Effects of other medicinal products on simvastatin

Interactions involving CYP3A4
Simvastatin is a substrate of cytochrome P450 3A4. Potent inhibitors of cytochrome P450 3A4 increase the risk of myopathy and rhabdomyolysis by increasing the concentration of HMG-CoA reductase inhibitory activity in plasma during simvastatin therapy. Such inhibitors include itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, and nefazodone. Concomitant administration of itraconazole resulted in a more than 10-fold increase in exposure to simvastatin acid (the active beta-hydroxyacid metabolite). Telithromycin caused an 11-fold increase in exposure to simvastatin acid.

Therefore, combination with itraconazole, ketoconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone is contraindicated. If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with simvastatin must be suspended during the course of treatment. Caution should be exercised when combining simvastatin with certain other less potent CYP3A4 inhibitors: cyclosporine, verapamil, diltiazem (see sections 4.2 and 4.4).

Cyclosporine
The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine particularly with higher doses of simvastatin (see sections 4.2 and 4.4). Therefore, the dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with cyclosporine. Although the mechanism is not fully understood, cyclosporine increases the AUC of simvastatin acid presumably due, in part, to inhibition of CYP3A4.

Gemfibrozil
Gemfibrozil increases the AUC of simvastatin acid by 1.9-fold, possibly due to inhibition of the glucuronidation pathway (see sections 4.2 and 4.4).

Amiodarone and verapamil
The risk of myopathy and rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil with higher doses of simvastatin (see section 4.4). In an ongoing clinical trial, myopathy has been reported in 6 % of patients receiving simvastatin 80 mg and amiodarone.

An analysis of the available clinical trials showed an approximately 1 % incidence of myopathy in patients receiving simvastatin 40 mg or 80 mg and verapamil. In a pharmacokinetic study, concomitant administration with verapamil resulted in a 2.3-fold increase in exposure of simvastatin acid, presumably due, in part, to inhibition of CYP3A4. Therefore, the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone or verapamil, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

Diltiazem
An analysis of the available clinical trials showed a 1 % incidence of myopathy in patients receiving simvastatin 80 mg and diltiazem. The risk of myopathy in patients taking simvastatin 40 mg was not increased by concomitant diltiazem (see section 4.4). In a pharmacokinetic study, concomitant administration of diltiazem caused a 2.7-fold increase in exposure of simvastatin acid, presumably due to inhibition of CYP3A4. Therefore, the dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with diltiazem, unless the clinical benefit is likely to outweigh the increased risk of myopathy and rhabdomyolysis.

Grapefruit juice
Grapefruit juice inhibits cytochrome P450 3A4. Concomitant intake of large quantities (over 1 litre daily) of grapefruit juice and simvastatin resulted in a 7-fold increase in exposure to simvastatin acid. Intake of 240 ml of grapefruit juice in the morning and simvastatin in the evening also resulted in a 1.9-fold increase. Intake of grapefruit juice during treatment with simvastatin should therefore be avoided.

Oral anticoagulants
In two clinical studies, one in normal volunteers and the other in hypercholesterolaemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. Very rare cases of elevated INR have been reported. In patients taking coumarin anticoagulants, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Effects of simvastatin on the pharmacokinetics of other medicinal products
Simvastatin does not have an inhibitory effect on cytochrome P450 3A4. Therefore, simvastatin is not expected to affect plasma concentrations of substances metabolised via cytochrome P450 3A4.

4.6 Pregnancy and lactation

Pregnancy

< Zocord > is contraindicated during pregnancy (see section 4.3).

Safety in pregnant women has not been established. No controlled clinical trials with simvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. However, in an analysis of approximately 200 prospectively followed pregnancies exposed during the first trimester to < Zocord > or another closely related HMG-CoA reductase inhibitor, the incidence of congenital anomalies was comparable to that seen in the general population. This number of pregnancies was statistically sufficient to exclude a 2.5-fold or greater increase in congenital anomalies over the background incidence.

Although there is no evidence that the incidence of congenital anomalies in offspring of patients taking < Zocord > or another closely related HMG-CoA reductase inhibitor differs from that observed in the general population, maternal treatment with < Zocord > may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia. For these reasons, < Zocord > should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with < Zocord > should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant. (See section 4.3.)

Lactation

It is not known whether simvastatin or its metabolites are excreted in human milk. Because many medicinal products are excreted in human milk and because of the potential for serious adverse reactions, women taking < Zocord > should not breast-feed their infants (see section 4.3).

4.7 Effects on ability to drive and use machines

< Zocord > has no or negligible influence on the ability to drive and use machines. However, when driving vehicles or operating machines, it should be taken into account that dizziness has been reported rarely in post-marketing experiences.

4.8 Undesirable effects

The frequencies of the following adverse events, which have been reported during clinical studies and/or post-marketing use, are categorized based on an assessment of their incidence rates in large, long-term, placebo-controlled, clinical trials including HPS and 4S with 20,536 and 4,444 patients, respectively (see section 5.1). For HPS, only serious adverse events were recorded as well as myalgia, increases in serum transaminases and CK. For 4S, all the adverse events listed below were recorded. If the incidence rates on simvastatin were less than or similar to that of placebo in these trials, and there were similar reasonably causally related spontaneous report events, these adverse events are categorized as “rare”.

In HPS (see section 5.1) involving 20,536 patients treated with 40 mg/day of < Zocord > (n = 10,269) or placebo (n = 10,267), the safety profiles were comparable between patients treated with < Zocord > 40 mg and patients treated with placebo over the mean 5 years of the study. Discontinuation rates due to side effects were comparable (4.8 % in patients treated with < Zocord > 40 mg compared with 5.1 % in patients treated with placebo). The incidence of myopathy was < 0.1 % in patients treated with < Zocord > 40 mg. Elevated transaminases (> 3 x ULN confirmed by repeat test) occurred in 0.21 % (n = 21) of patients treated with < Zocord > 40 mg compared with 0.09 % (n = 9) of patients treated with placebo.

The frequencies of adverse events are ranked according to the following: 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 reports.

<u>Blood and lymphatic system disorders:</u>
Rare: anaemia

<u>Nervous system disorders:</u>
Rare: headache, paresthesia, dizziness, peripheral neuropathy

<u>Gastrointestinal disorders:</u>
Rare: constipation, abdominal pain, flatulence, dyspepsia, diarrhoea, nausea, vomiting, pancreatitis

<u>Hepato-biliary disorders:</u>

Rare: hepatitis/jaundice

Skin and subcutaneous tissue disorders:
Rare: rash, pruritus, alopecia

Musculoskeletal, connective tissue and bone disorders:
Rare: myopathy, rhabdomyolysis (see section 4.4), myalgia, muscle cramps

General disorders and administration site conditions:
Rare: asthenia

An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features: angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, ESR increased, arthritis and arthralgia, urticaria, photosensitivity, fever, flushing, dyspnoea and malaise.

Investigations:
Rare: increases in serum transaminases (alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transpeptidase) (see section 4.4 *Hepatic effects*), elevated alkaline phosphatase; increase in serum CK levels (see section 4.4).

4.9 Overdose

To date, a few cases of overdosage have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae. There is no specific treatment in the event of overdose. In this case, symptomatic and supportive measures should be adopted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitor
ATC-Code: C10A A01

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed in the liver to the corresponding active beta-hydroxyacid form which has a potent activity in inhibiting HMG-CoA reductase (3 hydroxy – 3 methylglutaryl CoA reductase). This enzyme catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.

< Zocord > has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very-low-density protein (VLDL) and is catabolised predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of < Zocord > may involve both reduction of VLDL-cholesterol (VLDL-C) concentration and induction of the LDL receptor, leading to reduced production and increased catabolism of LDL-C. Apolipoprotein B also falls substantially during treatment with < Zocord >. In addition, < Zocord > moderately increases HDL-C and reduces plasma TG. As a result of these changes the ratios of total- to HDL-C and LDL- to HDL-C are reduced.

High Risk of Coronary Heart Disease (CHD) or Existing Coronary Heart Disease
In the Heart Protection Study (HPS), the effects of therapy with < Zocord > were assessed in 20,536 patients (age 40-80 years), with or without hyperlipidaemia, and with coronary heart disease, other occlusive arterial disease or diabetes mellitus. In this study, 10,269 patients were treated with < Zocord > 40 mg/day and 10,267 patients were treated with placebo for a mean duration of 5 years. At baseline, 6,793 patients (33 %) had LDL-C levels below 116 mg/dL; 5,063 patients (25 %) had levels between 116 mg/dL and 135 mg/dL; and 8,680 patients (42 %) had levels greater than 135 mg/dL.

Treatment with < Zocord > 40 mg/day compared with placebo significantly reduced the risk of all cause mortality (1328 [12.9 %] for simvastatin-treated patients versus 1507 [14.7 %] for patients given placebo; p = 0.0003), due to an 18 % reduction in coronary death rate (587 [5.7 %] versus 707 [6.9 %]; p = 0.0005; absolute risk reduction of 1.2 %). The reduction in non-vascular deaths did not reach statistical significance. < Zocord > also decreased the risk of major coronary events (a composite endpoint comprised of non-fatal MI or CHD death) by 27 % (p < 0.0001). < Zocord > reduced the need for undergoing coronary revascularization procedures (including coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) and peripheral and other non-coronary revascularization procedures by 30 % (p < 0.0001) and 16 % (p = 0.006), respectively. < Zocord > reduced the risk of stroke by 25 % (p < 0.0001), attributable to a 30 % reduction in ischemic stroke (p < 0.0001). In addition, within the subgroup of patients with diabetes, < Zocord > reduced the risk of developing macrovascular complications, including peripheral revascularization procedures (surgery or angioplasty), lower limb amputations, or leg ulcers by 21 % (p = 0.0293). The proportional reduction in event rate was similar in each subgroup of patients studied, including those without coronary disease but who had cerebrovascular or peripheral artery disease, men and women, those aged either under or over 70 years at entry into the study, presence or absence of hypertension, and notably those with LDL cholesterol below 3.0 mmol/l at inclusion.

In the Scandinavian Simvastatin Survival Study (4S), the effect of therapy with < Zocord > on total mortality was assessed in 4,444 patients with CHD and baseline total cholesterol 212-309 mg/dL (5.5-8.0 mmol/L). In this multicenter, randomised, double-blind, placebo-controlled study, patients with angina or a previous myocardial infarction (MI) were treated with diet, standard care, and either < Zocord > 20-40 mg/day (n = 2,221) or placebo (n = 2,223) for a median duration of 5.4 years. < Zocord > reduced the risk of death by 30 % (absolute risk reduction of 3.3 %). The risk of CHD death was reduced by 42 % (absolute risk reduction of 3.5 %). < Zocord > also decreased the risk of having major coronary events (CHD death plus hospital-verified and silent nonfatal MI) by 34 %. Furthermore, < Zocord > significantly reduced the risk of fatal plus nonfatal cerebrovascular events (stroke and transient ischemic attacks) by 28 %. There was no statistically significant difference between groups in non-cardiovascular mortality.

Primary Hypercholesterolaemia and Combined Hyperlipidaemia
In studies comparing the efficacy and safety of simvastatin 10, 20, 40 and 80 mg daily in patients with hypercholesterolemia, the mean reductions of LDL-C were 30, 38, 41 and 47 %, respectively. In studies of patients with combined (mixed) hyperlipidaemia on simvastatin 40 mg and 80 mg, the median reductions in triglycerides were 28 and 33 % (placebo: 2 %), respectively, and mean increases in HDL-C were 13 and 16 % (placebo: 3 %), respectively.

5.2 Pharmacokinetic properties

Simvastatin is an inactive lactone which is readily hydrolyzed *in vivo* to the corresponding beta-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Hydrolysis takes place mainly in the liver; the rate of hydrolysis in human plasma is very slow.

Absorption
In man simvastatin is well absorbed and undergoes extensive hepatic first-pass extraction. The extraction in the liver is dependent on the hepatic blood flow. The liver is the primary site of action of the active form. The availability of the beta-hydroxyacid to the systemic circulation following an oral dose of simvastatin was found to be less than 5 % of the dose. Maximum plasma concentration of active inhibitors is reached approximately 1-2 hours after administration of simvastatin. Concomitant food intake does not affect the absorption.

The pharmacokinetics of single and multiple doses of simvastatin showed that no accumulation of medicinal product occurred after multiple dosing.

Distribution
The protein binding of simvastatin and its active metabolite is > 95 %.

Elimination
Simvastatin is a substrate of CYP3A4 (see sections 4.3 and 4.5). The major metabolites of simvastatin present in human plasma are the beta-hydroxyacid and four additional active metabolites. Following an oral dose of radioactive simvastatin to man, 13 % of the radioactivity was excreted in the urine and 60 % in the faeces within 96 hours. The amount recovered in the faeces represents absorbed medicinal product equivalents excreted in bile as well as unabsorbed medicinal product. Following an intravenous injection of the beta-hydroxyacid metabolite, its half-life averaged 1.9 hours. An average of only 0.3 % of the IV dose was excreted in urine as inhibitors.

5.3 Preclinical safety data

Based on conventional animal studies regarding pharmacodynamics, repeated dose toxicity, genotoxicity and carcinogenicity, there are no other risks for the patient than may be expected on account of the pharmacological mechanism. At maximally tolerated doses in both the rat and the rabbit, simvastatin produced no foetal malformations, and had no effects on fertility, reproductive function or neonatal development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be implemented nationally]

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

[To be implemented nationally]

6.4 Special precautions for storage

[To be implemented nationally]

6.5 Nature and contents of container

[To be implemented nationally]

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be implemented nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be implemented nationally]

9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF AUTHORIZATION

10. DATE OF (PARTIAL) REVISION OF THE TEXT