ANNEX I

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

ANNEX I

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package-size
Austria	Bayer Austria Gesellschaft G.m.b.H. Lerchenfelder Guertel 9-11 A-1164 Wien	Lipobay	0.1 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
Austria	Bayer Austria Gesellschaft G.m.b.H. Lerchenfelder Guertel 9-11 A-1164 Wien	Lipobay	0.2 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
Austria	Bayer Austria Gesellschaft G.m.b.H. Lerchenfelder Guertel 9-11 A-1164 Wien	Lipobay	0.3 mg	Film-coated tablet	Oral use	Blister	30 tablets
Austria	Bayer Austria Gesellschaft G.m.b.H. Lerchenfelder Guertel 9-11 A-1164 Wien	Lipobay	0.4 mg	Film-coated tablet	Oral use	Blister	30 tablets
Austria	Bayer Austria Gesellschaft G.m.b.H. Lerchenfelder Guertel 9-11 A-1164 Wien	Liposterol	0.4 mg	Film-coated tablet	Oral use	Blister	30 tablets

Belgium	Bayer NV Louizalaan 143 B-1050 Brussel Belgium	Lipobay	0.1 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
Belgium	Bayer NV Louizalaan 143 B-1050 Brussel Belgium	Lipobay	0.2 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
Belgium	Bayer NV Louizalaan 143 B-1050 Brussel Belgium	Lipobay	0.3 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
Belgium	Bayer NV Louizalaan 143 B-1050 Brussel Belgium	Lipobay	0.4 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
Belgium	Fournier Pharma S.A. Rue des Trois Arbres, 16b B-1180 Bruxelles Belgium	Cholstat	0.4 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
Denmark	Bayer AG Monheim D-51368 Leverkusen Germany	Lipobay	0.1 mg	Film-coated tablet	Oral use	Blister	28 tablets

Denmark	Bayer AG Monheim D-51368 Leverkusen Germany	Lipobay	0.2 mg	Film-coated tablet	Oral use	Blister	28 and 98 tablets
Denmark	Bayer AG Monheim D-51368 Leverkusen Germany	Lipobay	0.3 mg	Film-coated tablet	Oral use	Blister	28 and 98 tablets
Denmark	Bayer AG Monheim D-51368 Leverkusen Germany	Lipobay	0.4 mg	Film-coated tablet	Oral use	Blister	28 and 98 tablets
Finland	Bayer AG Monheim D-51369 Leverkusen Germany	Lipobay	0.1 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
Finland	Bayer AG Monheim D-51369 Leverkusen Germany	Lipobay	0.2 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
Finland	Bayer AG Monheim D-51369 Leverkusen Germany	Lipobay	0.3 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets

Finland	Bayer AG Monheim D-51369 Leverkusen Germany	Lipobay	0.4 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
France	Fournier 9, rue Petitot F-21000 Dijon	Cholstat	0.1 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 tablets 160 tablets (hospital)
France	Fournier 9, rue Petitot F-21000 Dijon	Cholstat	0.2 mg	Film-coated tablet	Oral use	Blister	14, 20, 28 and 30 tablets 50, 98, 100 and 160 tablets (hospital)
France	Fournier 9, rue Petitot F-21000 Dijon	Cholstat	0.3 mg	Film-coated tablet	Oral use	Blister	14, 20, 28 and 30 tablets 50, 98, 100 and 160 tablets (hospital)
France	Fournier 9, rue Petitot F-21000 Dijon	Cholstat	0.4 mg	Film-coated tablet	Oral use	Blister	14, 20, 28 and 30 tablets 50, 98, 100 and 160 tablets (hospital)

France	Bayer Pharma 13, rue Jean Jaurès F-92807 Puteaux Cedex	Staltor	0.1 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 tablets 160 tablets (hospital)
France	Bayer Pharma 13, rue Jean Jaurès F-92807 Puteaux Cedex	Staltor	0.2 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 tablets 160 tablets (hospital)
France	Bayer Pharma 13, rue Jean Jaurès F-92807 Puteaux Cedex	Staltor	0.3 mg	Film-coated tablet	Oral use	Blister	14, 20, 28 and 30 tablets 50, 98, 100 and 160 tablets (hospital)
France	Bayer Pharma 13, rue Jean Jaurès F-92807 Puteaux Cedex	Staltor	0.4 mg	Film-coated tablet	Oral use	Blister	14, 20, 28 and 30 tablets 50, 98, 100 and 160 tablets (hospital)
Germany	Bayer Vital GmbH & Co. KG Geb. D162 D-51368 Leverkusen	Lipobay	0.1 mg	Film-coated tablet	Oral use	Blister	30, 50, 100 (OP) 10x16 (AP)

Germany	Bayer Vital GmbH & Co. KG Geb. D162 D-51368 Leverkusen	Lipobay	0.2 mg	Film-coated tablet	Oral use	Blister	30, 50, 100 (OP) 10x16 (AP)
Germany	Bayer Vital GmbH & Co. KG Geb. D162 D-51368 Leverkusen	Lipobay	0.3 mg	Film-coated tablet	Oral use	Blister	30, 50, 100 (OP) 10x16 (AP)
Germany	Bayer Vital GmbH & Co. KG Geb. D162 D-51368 Leverkusen	Lipobay	0.4 mg	Film-coated tablet	Oral use	Blister	20, 30, 50, 100 (OP) 160 (AP) 20 (UM)
Germany	Bayer AG Pharma Deutschland D-51368 Leverkusen	Vazqol	0.1 mg	Film-coated tablet	Oral use	Blister	30, 50, 100 (OP) 10x16 (AP)
Germany	Bayer AG Pharma Deutschland D-51368 Leverkusen	Vazqol	0.2 mg	Film-coated tablet	Oral use	Blister	30, 50, 100 (OP) 10x16 (AP)
Germany	Bayer AG Pharma Deutschland D-51368 Leverkusen	Vazqol	0.3 mg	Film-coated tablet	Oral use	Blister	30, 50, 100 (OP) 10x16 (AP)
Germany	Bayer AG Pharma Deutschland D-51368 Leverkusen	Vazqol	0.4 mg	Film-coated tablet	Oral use	Blister	20, 30, 50, 100 (OP) 160 (AP) 20 (UM)

Germany	Fournier Pharma GmbH Justus-von-Liebig-Str. 16 D-66280 Sulzbach	Zenas	0.1 mg	Film-coated tablet	Oral use	Blister	30, 50, 100 (OP) 10x16 (AP)
Germany	Fournier Pharma GmbH Justus-von-Liebig-Str. 16 D-66280 Sulzbach	Zenas	0.2 mg	Film-coated tablet	Oral use	Blister	30, 50, 100 (OP) 10x16 (AP)
Germany	Fournier Pharma GmbH Justus-von-Liebig-Str. 16 D-66280 Sulzbach	Zenas	0.3 mg	Film-coated tablet	Oral use	Blister	30, 50, 100 (OP) 10x16 (AP)
Germany	Fournier Pharma GmbH Justus-von-Liebig-Str. 16 D-66280 Sulzbach	Zenas	0.4 mg	Film-coated tablet	Oral use	Blister	20, 30, 50, 100 (OP) 20 (UM)
Greece	Bayer Hellas ABEE Ακακίων 54[A] GR-15125 Μαρούσι Αθήνα	Lipoban	0.1 mg	Film-coated tablet	Oral use	Blister	14, 28, 30, 50, 98 and 100 tablets
Greece	Bayer Hellas ABEE Ακακίων 54[A] GR-15125 Μαρούσι Αθήνα	Lipoban	0.2 mg	Film-coated tablet	Oral use	Blister	14, 28, 30, 50, 98 and 100 tablets
Greece	Bayer Hellas ABEE Ακακίων 54[A] GR-15125 Μαρούσι Αθήνα	Lipoban	0.3 mg	Film-coated tablet	Oral use	Blister	14, 28, 30, 50, 98 and 100 tablets
Greece	Bayer Hellas ABEE Ακακίων 54[A] GR-15125 Μαρούσι Αθήνα	Lipoban	0.4 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets

Greece	Elpen AE 21^{o} χλμ Λεωφ. Μαραθώνα GR- 19009 Πικέρμι Αττική	Eltina	0.1 mg	Film-coated tablet	Oral use	Blister	14, 28, 30, 50, 98 and 100 tablets
Greece	Elpen AE 21^{o} χλμ Λεωφ. Μαραθώνα GR- 19009 Πικέρμι Αττική	Eltina	0.2 mg	Film-coated tablet	Oral use	Blister	14, 28, 30, 50, 98 and 100 tablets
Greece	Elpen AE 21^{o} χλμ Λεωφ. Μαραθώνα GR- 19009 Πικέρμι Αττική	Eltina	0.3 mg	Film-coated tablet	Oral use	Blister	14, 28, 30, 50, 98 and 100 tablets
Greece	Elpen AE 21^{o} χλμ Λεωφ. Μαραθώνα GR- 19009 Πικέρμι Αττική	Eltina	0.4 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
Iceland	Bayer AG Bayerwerk D-51368 Leverkusen Germany	Lipobay	0.1 mg	Film-coated tablet	Oral use	Blister	28 and 98 tablets
Iceland	Bayer AG Bayerwerk D-51368 Leverkusen Germany	Lipobay	0.2 mg	Film-coated tablet	Oral use	Blister	28 tablets
Iceland	Bayer AG Bayerwerk D-51368 Leverkusen Germany	Lipobay	0.3 mg	Film-coated tablet	Oral use	Blister	98 tablets

Iceland	Bayer AG Bayerwerk D-51368 Leverkusen Germany	Lipobay	0.4 mg	Film-coated tablet	Oral use	Blister	28 and 98 tablets
Ireland	Bayer PLC Bayer House Strawberry Hill Newbury Berkshire RG14 1JA – UK, United Kingdom	Lipobay	0.1 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
Ireland	Bayer PLC Bayer House Strawberry Hill Newbury Berkshire RG14 1JA – UK, United Kingdom	Lipobay	0.2 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
Ireland	Bayer PLC Bayer House Strawberry Hill Newbury Berkshire RG14 1JA – UK, United Kingdom	Lipobay	0.3 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
Ireland	Bayer PLC Bayer House Strawberry Hill Newbury Berkshire RG14 1JA – UK, United Kingdom	Lipobay	0.4 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets

Italy	Bayer S.p.A. Viale Certosa, 130 I-20156 Milano	Lipobay	0.1 mg	Film-coated tablet	Oral use	Blister	14, 28 and 98 tablets
Italy	Bayer S.p.A. Viale Certosa, 130 I-20156 Milano	Lipobay	0.2 mg	Film-coated tablet	Oral use	Blister	14, 28 and 98 tablets
Italy	Bayer S.p.A. Viale Certosa, 130 I-20156 Milano	Lipobay	0.3 mg	Film-coated tablet	Oral use	Blister	14, 28 and 98 tablets
Italy	Bayer S.p.A. Viale Certosa, 130 I-20156 Milano	Lipobay	0.4 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
Italy	Fournier Pharma S.p.A. Via Cassanese, 224 I-2090 Segrate Milano	Cervasta	0.1 mg	Film-coated tablet	Oral use	Blister	14, 28 and 98 tablets
Italy	Fournier Pharma S.p.A. Via Cassanese, 224 I-2090 Segrate Milano	Cervasta	0.2 mg	Film-coated tablet	Oral use	Blister	14, 28 and 98 tablets
Italy	Fournier Pharma S.p.A. Via Cassanese, 224 I-2090 Segrate Milano	Cervasta	0.3 mg	Film-coated tablet	Oral use	Blister	14, 28 and 98 tablets
Italy	Fournier Pharma S.p.A. Via Cassanese, 224 I-2090 Segrate Milano	Cervasta	0.4 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets

Italy	Chiesi Farmaceutici S.p.A. Via Palermo, 26/A I-43100 Parma	Stativa	0.1 mg	Film-coated tablet	Oral use	Blister	14, 28 and 98 tablets
Italy	Chiesi Farmaceutici S.p.A. Via Palermo, 26/A I-43100 Parma	Stativa	0.2 mg	Film-coated tablet	Oral use	Blister	14, 28 and 98 tablets
Italy	Chiesi Farmaceutici S.p.A. Via Palermo, 26/A I-43100 Parma	Stativa	0.3 mg	Film-coated tablet	Oral use	Blister	14, 28 and 98 tablets
Italy	Chiesi Farmaceutici S.p.A. Via Palermo, 26/A I-43100 Parma	Stativa	0.4 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
Luxembourg	Bayer Belgium 143 Avenue Louise B-1050 Bruxelles Belgium	Lipobay	0.1 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
Luxembourg	Bayer Belgium 143 Avenue Louise B-1050 Bruxelles Belgium	Lipobay	0.2 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
Luxembourg	Bayer Belgium 143 Avenue Louise B-1050 Bruxelles Belgium	Lipobay	0.3 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets

Luxembourg	Bayer Belgium 143 Avenue Louise B-1050 Bruxelles Belgium	Lipobay	0.4 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
Luxembourg	Fournier Pharma 16b rue des Trois Arbres B-1180 Bruxelles Belgium	Cholstat	0.1 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
Luxembourg	Fournier Pharma 16b rue des Trois Arbres B-1180 Bruxelles Belgium	Cholstat	0.2 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
Luxembourg	Fournier Pharma 16b rue des Trois Arbres B-1180 Bruxelles Belgium	Cholstat	0.3 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
Luxembourg	Fournier Pharma 16b rue des Trois Arbres B-1180 Bruxelles Belgium	Cholstat	0.4 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, and 100 tablets
The Netherlands	Bayer B.V. Nijverheidsweg 26 NL-3641 RR Mijdrecht	Lipobay	0.1 mg	Film-coated tablets	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
The Netherlands	Bayer B.V. Nijverheidsweg 26 NL-3641 RR Mijdrecht	Lipobay	0.2 mg	Film-coated tablets	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets

The Netherlands	Bayer B.V. Nijverheidsweg 26 NL-3641 RR Mijdrecht	Lipobay	0.3 mg	Film-coated tablets	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
The Netherlands	Bayer B.V. Nijverheidsweg 26 NL-3641 RR Mijdrecht	Lipobay	0.4 mg	Film-coated tablets	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
Portugal	Fournier Farmacêutica Portugal Lda. PRT Avenida Eng. Duarte Pacheco Amoreiras P-1070 Lisboa	Cholstat	0.4 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
Portugal	Bayer Portugal, S.A. PRT Rua da Quinta do Pinheiro, 5 P-2795 Carnaxide - Lisboa	Lipobay	0.1 mg	Film-coated tablet	Oral use	Blister	14 and 28 tablets
Portugal	Bayer Portugal, S.A. PRT Rua da Quinta do Pinheiro, 5 P-2795 Carnaxide - Lisboa	Lipobay	0.2 mg	Film-coated tablet	Oral use	Blister	14, 28, and 56 tablets
Portugal	Bayer Portugal, S.A. PRT Rua da Quinta do Pinheiro, 5 P-2795 Carnaxide - Lisboa	Lipobay	0.3 mg	Film-coated tablet	Oral use	Blister	14, 28, and 56 tablets
Portugal	Bayer Portugal, S.A. PRT Rua da Quinta do Pinheiro, 5 P-2795 Carnaxide - Lisboa	Lipobay	0.4 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets

Spain	Quimica Farmaceutica Bayer S.A. c/Calabria 268 E-08029 Barcelona	Lipobay	0.1 mg	Film-coated tablet	Oral use	Blister	28 tablets
Spain	Quimica Farmaceutica Bayer S.A. c/Calabria 268 E-08029 Barcelona	Lipobay	0.2 mg	Film-coated tablet	Oral use	Blister	28 tablets
Spain	Quimica Farmaceutica Bayer S.A. c/Calabria 268 E-08029 Barcelona	Lipobay	0.3 mg	Film-coated tablet	Oral use	Blister	28 tablets
Spain	Quimica Farmaceutica Bayer S.A. c/Calabria 268 E-08029 Barcelona	Lipobay	0.4 mg	Film-coated tablet	Oral use	Blister	28 tablets
Spain	Laboratorios Fournier SA Ronda de Poniente 16 E-28760 Tres Cantos	Zenas micro	0.1 mg	Film-coated tablet	Oral use	Blister	28 tablets
Spain	Laboratorios Fournier SA Ronda de Poniente 16 E-28760 Tres Cantos	Zenas micro	0.2 mg	Film-coated tablet	Oral use	Blister	28 tablets
Spain	Laboratorios Fournier SA Ronda de Poniente 16 E-28760 Tres Cantos	Zenas micro	0.3 mg	Film-coated tablet	Oral use	Blister	28 tablets

Spain	Laboratorios Fournier SA Ronda de Poniente 16 E-28760 Tres Cantos	Zenas micro	0.4 mg	Film-coated tablet	Oral use	Blister	28 tablets
Sweden	Bayer AG, Monheim D-51368 Leverkusen Germany	Lipobay	0.1 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
Sweden	Bayer AG, Monheim D-51368 Leverkusen Germany	Lipobay	0.2 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
Sweden	Bayer AG, Monheim D-51368 Leverkusen Germany	Lipobay	0.3 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
Sweden	Bayer AG, Monheim D-51368 Leverkusen Germany	Lipobay	0.4 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
United Kingdom	Bayer plc Bayer House Strawberry Hill Newbury Berkshire RG14 1JA – UK	Lipobay	0.1 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets

United Kingdom	Bayer plc Bayer House Strawberry Hill Newbury Berkshire RG14 1JA – UK	Lipobay	0.2 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
United Kingdom	Bayer plc Bayer House Strawberry Hill Newbury Berkshire RG14 1JA – UK	Lipobay	0.3 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
United Kingdom	Bayer plc Bayer House Strawberry Hill Newbury Berkshire RG14 1JA – UK	Lipobay	0.4 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
United Kingdom	Bayer plc Bayer House Strawberry Hill Newbury Berkshire RG14 1JA – UK	Vaslip	0.1 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
United Kingdom	Bayer plc Bayer House Strawberry Hill Newbury Berkshire RG14 1JA – UK	Vaslip	0.2 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets

United Kingdom	Bayer plc Bayer House Strawberry Hill Newbury Berkshire RG14 1JA – UK	Vaslip	0.3 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
United Kingdom	Bayer plc Bayer House Strawberry Hill Newbury Berkshire RG14 1JA – UK	Vaslip	0.4 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
United Kingdom	Bayer plc Bayer House Strawberry Hill Newbury Berkshire RG14 1JA – UK	Liposterol	0.1 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
United Kingdom	Bayer plc Bayer House Strawberry Hill Newbury Berkshire RG14 1JA – UK	Liposterol	0.2 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
United Kingdom	Bayer plc Bayer House Strawberry Hill Newbury Berkshire RG14 1JA – UK	Liposterol	0.3 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets

United Kingdom	Bayer plc Bayer House Strawberry Hill Newbury Berkshire RG14 1JA – UK	Liposterol	0.4 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
United Kingdom	Bayer plc Bayer House Strawberry Hill Newbury Berkshire RG14 1JA – UK	Zenas	0.1 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
United Kingdom	Bayer plc Bayer House Strawberry Hill Newbury Berkshire RG14 1JA – UK	Zenas	0.2 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
United Kingdom	Bayer plc Bayer House Strawberry Hill Newbury Berkshire RG14 1JA – UK	Zenas	0.3 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets
United Kingdom	Bayer plc Bayer House Strawberry Hill Newbury Berkshire RG14 1JA – UK	Zenas	0.4 mg	Film-coated tablet	Oral use	Blister	14, 20, 28, 30, 50, 98, 100 and 160 tablets

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR WITHDRAWAL OF THE MARKETING AUTHORISATIONS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF CERIVASTATIN CONTAINING MEDICINAL PRODUCTS AUTHORISED UNDER THE MUTUAL RECOGNITION PROCEDURE.

Cerivastatin (Lipobay) is an HMG CoA reductase inhibitor authorised in Europe through the Mutual Recognition system at doses of 0.1- 0.4mg for the treatment of hyperlipidaemia. Warnings about the risk of myopathy, including rhabdomyolysis, as well as warnings about the interaction with gemfibrozil have been included in product information since Lipobay was first licensed in the EU. In the US a specific contra-indication against co-prescription with gemfibrozil was added to product information in 1999.

The Europe-wide update of Lipobay product information (Type II variation), was under discussion when the Spanish authorities raised concerns about a number of reports in Spain of fatal cases of rhabdomyolysis in association with Lipobay. There were concerns about a possibly increased risk of rhabdomyolysis associated with the use of cerivastatin – particularly in combination with gemfibrozil. Following discussions between the UK, as Reference Member State for Lipobay, Spain and the marketing authorisation holder (MAH), Bayer, an Urgent Safety Restriction took place on 25/26 June. The changes to the Summary of Product Characteristics (SPC) included the following: the introduction of a contraindication to the concomitant use of cerivastatin and gemfibrozil, restriction of the maximum dose to 0.4mg and reinforcement of the importance of dose titration.

On 8 August 2001 Bayer announced that it was voluntarily suspending its marketing and distribution of cerivastatin from both the European and US markets pending further evaluation of the risk of rhabdomyolysis associated with its use.

On 19 September 2001, Portugal notified the EMEA of a referral under Article 15a of Directive 75/319/EEC (now Article 36 of Directive 2001/83/EC) regarding all cerivastatin containing medicinal products approved under a Mutual Recognition procedure. Portugal requested that a full assessment of the risk-benefit of cerivastatin be carried out because of concerns regarding a possible increased risk of rhabdomyolysis.

OVERVIEW OF EFFICACY

A discussion on the efficacy of cerivastatin containing medicinal products took place at CPMP based on the assessment reports of the Rapporteur and co-Rapporteur and the data presented by the MAH. The main points are summarised below.

Pooled analysis of efficacy from clinical trials

The analysis included 19 randomised, double-blind, placebo and/or active controlled studies that were conducted between Summer 1992 and Summer 2000. The studies were performed in 7568 patients, the majority with primary hypercholesterolaemia, though some enrolled patients with mixed hyperlipidaemia and hypertriglyceridaemia.

Table 1 shows the changes in lipid parameters at 8 weeks. The reduction in LDL-C across all cerivastatin dosages is significantly different from placebo ($p<0.0001$), ranging from -22.7% (0.1mg) to -41.9% (0.8mg) after 8 weeks of treatment. The difference between all cerivastatin dosages is also significant ($p<0.01$). The effects on LDL-C though maintained are slightly lower after 52 weeks.

Table 1: Changes in lipid parameters after 8 weeks - ITT population, LS means adjusted

Treatment Group	LDL-C	TC	TG	HDL-C	Apo B
Placebo	-0.2%	+0.6%	+2.9%	+1.1%	+2.2%
Cerivastatin 0.1mg	-22.7%	-15.8%	-7.2%	+4.7%	-16.4%
Cerivastatin 0.2mg	-28.1%	-19.9%	-10.6%	+5.4%	-19.8%
Cerivastatin 0.3mg	-32.2%	-23.1%	-14.7%	+6.8%	-24.4%
Cerivastatin 0.4mg	-35.1%	-25.0%	-15.0%	+7.4%	-26.0%
Cerivastatin 0.8mg	-41.9%	-29.8%	-18.7%	+8.4%	-31.0%

Comparative efficacy of the statins

Published data on the comparative efficacy of the statins demonstrates a pattern of equipotent LDL cholesterol lowering doses as shown in Table 2 below. A lowering of LDL-cholesterol of 27% was found with doses of 10mg simvastatin or 20mg lovastatin or 20mg pravastatin or 40mg fluvastatin or 0.2mg cerivastatin. This is consistent with the MAH's examination of published clinical trial data.

Table 2: Comparative efficacy of the six currently available statins on lipids and lipoproteins in patients without hypertriglyceridaemia (adapted from Maron et al. Circulation 2000; 101:207-213)

Equipotent dose of statin (mg)						Change in Lipid and lipoprotein levels			
Atorva	Simva	Lova	Prava	Fluva	Ceriva	TC	LDL-C	HDL-C	Trigs
----	10	20	20	40	0.2	-22%	-27%	4-8%	-10-15%
10	20	40	40	80	0.4	-27%	-34%	4-8%	-10-15%
20	40	80	----	----	0.8	-32%	-41%	4-8%	-15-25%
40	80	----	----	----	----	-37%	-48%	4-8%	-20-30%
80	----	----	----	----	----	-42%	-55%	4-8%	-25-35%

The review of the original data provided by the MAH elicited several issues for which the CPMP required further information. The additional data suggest that cerivastatin 0.4mg provides a cholesterol lowering efficacy at a similar range to 10mg atorvastatin, 20mg simvastatin or 40mg pravastatin.

Primary and secondary prevention studies

Large-scale clinical trials of lovastatin, pravastatin and simvastatin have shown the benefits of using statins in both primary and secondary prevention of heart disease, as well as long-term prevention. No such data exist for cerivastatin.

CONCLUSIONS OF THE CPMP ON EFFICACY

Cerivastatin effectively and dose-dependently (0.1-0.8mg/day) reduces total cholesterol, LDL-cholesterol, triglycerides and increases HDL-cholesterol. According to the submitted documentation, the 0.4mg daily dose, corresponding to the highest MR approved dose, would provide a cholesterol-lowering efficacy at a similar range to atorvastatin 10mg, simvastatin 20mg or pravastatin 40mg/day. The data suggest that superior efficacy is possible at the licensed higher dosages of atorvastatin or simvastatin. No trials have been completed which examine the efficacy of cerivastatin in either primary- or secondary-prevention of coronary heart disease. However, there is no reason to believe that the beneficial effect observed following treatment with other statins would not also apply to cerivastatin.

OVERVIEW OF SAFETY

A discussion on the safety of cerivastatin containing medicinal products took place at CPMP based on the assessment reports of the Rapporteur and co-Rapporteur and the data presented by the MAH. The main points are summarised below.

Commonly reported adverse drug reactions in association with the statins include gastrointestinal disturbances, headache, myalgia, dyspepsia, central nervous system disturbances and sleep disorders. Hepatotoxicity and myopathies, including rhabdomyolysis are the most clinically serious adverse reactions.

Pre-clinical Data
Toxicology data confirmed the myotoxicity of cerivastatin

Pharmacokinetic data
Cerivastatin is readily and completely (98%) absorbed from the gastrointestinal tract with plasma concentrations peaking within 2-3 hours of dosing and mono-exponential decay thereafter. Cerivastatin pharmacokinetics are linear: maximum plasma concentration (C_{max}) and area under the curve (AUC) increase dose-proportionally over the dose range of 0.05 to 0.8 mg. At 60% the bioavailability of cerivastatin is greater than that of any of the other statins.

Cerivastatin is exclusively cleared by hepatic metabolism. Metabolites M-1 (demethylated) and metabolite M-23 (hydroxylated) represent the two metabolic pathways with M-1 formation catalysed by cytochrome P450 CYP2C8 and CYP3A4 and M-23 catalysed by CYP2C8 alone. A third minor metabolite (M-24) is not detectable in human plasma. All three metabolites are active inhibitors of HMG CoA reductase with similar potency to the parent drug. Approximately 70% of the administered dose is excreted as metabolites in the faeces and 30% in the urine.

Pharmacokinetic effects of interactions
Maximal doses of the potent inhibitors of CYP3A4, erythromycin and itraconazole increased cerivastatin concentrations by up to 50%, without any effects on safety parameters or tolerability in interaction studies. However, the potential for interaction between cerivastatin and CYP2C8 inhibitors, or the effect CYP enzyme inducing agents on the bioavailability of cerivastatin has not been adequately investigated.

In May 2001, the MAH investigated the potential pharmacokinetic interaction with gemfibrozil via a randomised 2-way crossover study assessing the influence of a 3 day pre and co-treatment of 600mg bid of gemfibrozil on the pharmacokinetics of a single oral dose of 0.2mg cerivastatin. The ratio of the AUC on combination therapy to that on monotherapy was 4.22. (3.48 – 5.12) Similarly the ratio for the Cmax was 1.82 (1.52-2.17). In addition, individual plasma concentration / time profiles showed prolonged systemic exposure and altered elimination half lives, indicating a substantial interaction between the two drugs.

Clinical Trial data
The MAH provided a pooled analysis of 19 studies carried out between Summer 1992 and Summer 2000. The studies were all randomised, double-blind with at least one control arm and lasted a minimum of 8 weeks. Six of the studies (3506 patients) had long term extensions (48-100 weeks) and as such constituted a "long term" safety population. The short term safety data were compared with pooled placebo data whilst long term safety was compared with a joint treatment group of pooled lovastatin, simvastatin, fluvastatin and pravastatin data.

As can be seen from table 3, following short term treatment, elevations of CPK >10xULN are similar for patients treated with cerivastatin at doses between 0.2mg and 0.4mg but there is a 7-fold increase for patients treated with 0.8mg.

Table 3: 'Short-term' treatment emergent increase of CPK (normal and low baseline levels)

Level of increase	Cerivastatin					Placebo
	0.1mg	0.2mg	0.3mg	0.4mg	0.8mg	
> 1xULN	13.2%	12.9%	15.9%	16.4%	24.6%	10.4%
> 3xULN	0.9%	1.0%	1.2%	1.7%	3.8%	1.0%
> 5xULN	0.1%	0.5%	0.3%	0.8%	2.3%	0.6%
>10xULN	0.0%	0.2%	0.2%	0.2%	1.4%	0.2%

The most frequently affected body systems in both the long and short-term analyses were body as a whole, digestive system and respiratory system. For most body systems the other statins had a similar incidence of adverse events when compared with cerivastatin. For events which may indicate drug-induced muscle damage (increased CPK, myalgia, leg pain, arthralgia) the incidence of these events with 0.8mg cerivastatin is higher than that for lower dosages of cerivastatin and other statins. For increased CPK the incidence at 0.8mg is approximately twice that seen with other statins. A similar picture is true for adverse events that led to discontinuation**.**

Table 4: Long-term treatment emergent increase of CPK (normal and low baseline levels)

Level of increase	Cerivastatin					Other statins
	0.1mg	0.2mg	0.3mg	0.4mg	0.8mg	
> 1xULN	29.8%	25.8%	30.9%	30.6%	39.2%	27.0%
> 3xULN	2.2%	2.6%	2.4%	3.9%	58.8%	2.6%
> 5xULN	0.2%	1.0%	0.9%	2.1%	3.5%	1.1%
>10xULN	0.0%	0.3%	0.4%	0.6%	2.0%	0.3%

As can be seen from Table 4 following long term treatment the percentage of patients experiencing CPK elevations >10xULN for cerivastatin 0.1mg to 0.3mg are similar to that seen with other statins. This percentage is slightly increased for cerivastatin 0.4mg (~2-fold), while for patients treated with cerivastatin 0.8mg, there is an approximately 7-fold increase. When analysed by age and gender, the highest reporting rate of CPK elevation >5xULN for the 0.8mg group was observed in elderly women (≥ 65 years) which may indicate a potential risk group.

The overall incidences of all adverse events show a dose-dependent increase in the short-term studies. The dose-dependent increase is less pronounced for the long-term studies for which there is no difference between cerivastatin 0.4mg and 0.8mg. This may be due to the small number of higher dose studies. A similar pattern is seen for serious adverse events and adverse events leading to discontinuation.

The incidence of adverse events which may indicate drug-induced muscle damage (CPK increased, myalgia, athralgia, and leg pain), is clearly higher on cerivastatin 0.8mg as compared with the lower dosages or other statins. For cerivastatin dosages ≤ 0.4mg, when patients are treated short term the percentage of patients experiencing elevations of CPK>10xULN is similar across the dosages and comparable with placebo. However, the long term data show a slight increase (~2-fold) for cerivastatin 0.4mg compared with that of the lower dosages or other statins. With long-term treatment the incidence of CPK >10xULN with cerivastatin 0.8mg is approximately 3-fold that with cerivastatin 0.4mg and 7-fold that with other statins. There were no reports of rhabdomyolysis in any of the treatment groups. This is hardly surprising given that this is likely to be a highly-selected, carefully monitored population.

Comparative safety data from published trials

The MAH performed a literature search on safety of the statins and statin-fibrate combinations. The incidence of rhabdomyolysis (confirmed and unconfirmed), elevated ALT/AST adverse events leading

to discontinuation and serious adverse events (SAE) for cerivastatin 0.4mg and 0.8mg and equipotent doses of the other statins is provided in Table 5 and 6.

Table 5: Incidence of rhabdomyolysis (confirmed (c) and unconfirmed (u), raised AST/ALT and Serious adverse events (SAE) for cerivastatin 0.4mg and equipotent dose of the other statins.

Dose (mg/day)	Incidence (%)				
	Rhabdo (C)	Rhabdo (U)	ALT/AST>3xULN	Discontd due to AEs	SAE
Cerivastatin 0.4 mg	0.08	1.67	0.24	0.99	0.79
Atorvastatin 10mg	0.04	0.52	0.24	2.05	0.76
Simvastatin 20mg	0	2.08	0.41	0.78	0.20
Lovastatin 40mg	0.04	1.24	0.65	9.81	5.35
Fluvastatin 80mg	0	0.77	0	5.45	2.7
Pravastatin 40mg	0	2.29	1.23	2.11	5.25

Table 6: Incidence of rhabdomyolysis (confirmed (c) and unconfirmed (u), raised AST/ALT and Serious adverse events (SAE) for cerivastatin 0.8mg and equipotent dose of the other statins.

Dose (mg/day)	Incidence (%)				
	Rhabdo (C)	Rhabdo (U)	ALT/AST >3xULN	Discontd due to AEs	SAE
Cerivastatin 0.8 mg	0.37	1.21	0.44	1.14	0.57
Atorvastatin 20mg	0	1.69	0.22	0.90	1.41
Simvastatin 40mg	0.02	1.22	0.64	2.62	1.48
Lovastatin 80mg	0.09	1.43	0.89	4.16	5.91
Pravastatin80mg*	0	0.62	1.0	1.0	0

*Not licensed in EU

These data suggest that the incidence of confirmed rhabdomyolysis for cerivastatin 0.4mg and 0.8mg in published trials is greater than the other statins. The same is not true, however, for the incidence of unconfirmed cases, which on the whole is comparable with the other statins. For the statin-fibrate combination these data do not suggest any increased incidence of rhabdomyolysis (confirmed or unconfirmed) when any statin is used in combination with any fibrate

The incidence of serious adverse events with cerivastatin 0.4mg is comparable with atorvastatin, but slightly higher than that seen with simvastatin and considerably less than that with lovastatin at equipotent doses. While for 0.8mg cerivastatin the incidence is less than any of the other statins but the data are very limited.

No deaths were reported among the patients treated with cerivastatin. This is compared with 113 (1.4%), 106 (0.6%) and 5 (0.05%) deaths in patients treated with lovastatin, simvastatin and atorvastatin, respectively.

Overall these data suggest that the incidence of confirmed, but not unconfirmed rhabdomyolysis is higher with cerivastatin than with the other statins. The MAH comments that suspected rhabdomyolysis (confirmed and unconfirmed) is the worst case scenario. However, myalgia a commonly reported symptom was classified as unconfirmed rhabdomyolysis unless accompanied by CPK >10xULN, indicators of renal failure or necessitated hospitalisation. The impact of this would be to dilute any increased incidence of unconfirmed rhabdomyolysis with cerivastatin. Therefore, the

most appropriate comparison is that of confirmed rhabdomyolysis. It should be noted that the numbers of cases underlying these assumptions are very low.

Post Marketing Data

Exposure Data
Data suggest that cerivastatin is used much less frequently than the other statins.

Spontaneous reports
Up to 8 August 2001 a total of 5,667 reports containing 11,637 suspected adverse drug reactions associated with the use of cerivastatin have been received by Bayer global drug safety. The majority of the reported reactions (78%) belong to the following COSTART body systems- Musculoskeletal (3,417; 29%), Body as a whole (1,814; 16%), Digestive (1,663; 14%), Metabolic and Nutritional (1,354; 12%), Nervous (914; 8%) and Urogenital (768; 7%). For serious ADRs, 55% belonged to the Musculoskeletal, Urogenital and Metabolic and Nutritional body systems and reflect the reports of rhabdomyolysis.

Rhabdomyolysis
There were 1302 (23%) cases of confirmed and 1603 (28%) cases of unconfirmed rhabdomyolysis. "Suspected" rhabdomyolysis therefore comprises 51% of all spontaneous reports.

With 0.4 mg cerivastatin monotherapy, the reporting rate of rhabdomyolysis is greater than that seen with lower doses of cerivastatin. Reporting rates of rhabdomyolysis with the 0.8mg dose were greatly in excess of those seen with both the 0.4mg and lower doses.

When cerivastatin was used concomitantly with fibrates (primarily gemfibrozil), there was a substantially higher reporting rate with increasing dose, depending on the reporting region. As for monotherapy, the reporting rate for 0.4mg cerivastatin was higher than seen with the lower doses of cerivastatin. The reporting rate for 0.8mg cerivastatin was substantially higher than that with any of the lower doses.

A search of the FDA Adverse Event Reporting System (AERS) database found 6,489 reports worldwide of rhabdomyolysis associated with the use of any statin up to the end of 2000. The reporting rates of confirmed and suspected cases of rhabdomyolysis in association with cerivastatin monotherapy is greater than that seen with any of the other statins.

The WHO database contains 546 reports of rhabdomyolysis associated with the use of cerivastatin. The reporting rate for rhabdomyolysis with cerivastatin is higher than with other statins and contrary to expectations has increased over time. Of the 546 reports of rhabdomyolysis with cerivastatin, 302 (55%) were with concomitant gemfibrozil. The disproportion between the reporting rate on combination treatment compared with the proportion of prescriptions suggests a strong interaction between the two drugs leading to an increased risk of rhabdomyolysis. The interaction between cerivastatin and gemfibrozil also appears to produce an increased risk of renal failure, myositis, myopathy and death.

The data for use of gemfibrozil with the other statins also suggest an increased risk however the disproportion between the reporting rate on combination treatment and the proportion of prescriptions is considerably less than that seen with cerivastatin.

A similar disproportionate risk is also seen when clopidogrel is prescribed concomitantly. Of 45 adverse reaction reports where the two drugs were administered concomitantly, 20 (44%) were of rhabdomyolysis.

Fatal cases

Confirmed rhabdomyolysis cases had a 7.6% fatality rate. From the beginning of marketing to the end of September 2001 ninety-nine fatal cases were reported to Bayer. The majority occurred in the USA (62.63%), 21 cases (21.2%) in the EU with others in Japan and the rest of the world. The majority of reported fatal cases occurred in 2001 (70.51%). Despite contraindications being introduced in the US in 1999, physicians there still continued to prescribe gemfibrozil with cerivastatin.

Death was probably related to the rhabdomyolysis in 52% of cases, possibly related in 33.7% and not related in 14.3% (no temporal relationship, other aetiologies.) There were no sex differences and the mean age was 70.9 years. Of the fatal cases, 36.4% were treated concomitantly with gemfibrozil and 17.7% with clopidogrel. Of note is the fact that for cerivastatin the leading reported cause of death was rhabdomyolysis, while for other statins it was hepatic failure. The reporting rate of fatal hepatic failure with cerivastatin was 2-6 times lower than that of the other statins. Cerivastatin is associated with a higher reporting rate of fatal rhabdomyolysis than atorvastatin and the use of cerivastatin in combination with gemfibrozil increases the reporting rate of fatal rhabdomyolysis at lower doses of cerivastatin.

Post marketing studies

Between 1998 and 1999 several Post-marketing observational (PMO) studies were performed in Germany. In total 43,366 hypercholesterolaemic patients, average age 59 years, were treated with cerivastatin. The median observation period was 10 weeks. The starting doses were 0.1mg/day (15%), 0.2mg/day (56.7%) and 0.3 mg/day (26.3%), with up- and down-titration between these doses. Thirty-two percent of patients had previously been treated with lipid lowering medication, for 15% this was a statin.

One hundred and seventy two of these patients (0.4%) experienced at least one adverse event indicative of myopathy (CPK increased, myopathy, myositis, myalgia, myasthenia, arthralgia). No cases of rhabdomyolysis were observed. The frequency of these adverse events does not appear to be dose-dependent. For patients pre-treated with a statin the incidence of these AEs was twice that in other groups (0.76% vs 0.35%). The incidence of these AEs was also higher in patients taking concomitant lipid lowering medications compared with those who did not (0.58% vs 0.39%).

Two further post-marketing studies have been conducted in Germany, the results of which have not been published.

Pharmacoepidemiological studies

Pacificare

Several pharmacoepidemiological studies were performed using the Pacificare claims database. The first study followed up patients for 180 days after the index prescription of a statin to identify any occurrence of myopathy that fulfilled the case definition. Cases were also required to have occurred within 30 days of a statin prescription and to have stopped or switched statin treatments following diagnosis.

There were 394 myopathy cases fulfilling the study definition amongst a cohort of 133,454 study subjects in study 1. Table 7 provides crude absolute risks by last statin prior to diagnosis and the adjusted Odds Ratios for myopathy with the last statin (with or without gemfibrozil) compared to non-concurrent cerivastatin. Crude absolute rates were similar across the class. Adjusted Odds Ratios for myopathy with the last statin (with or without gemfibrozil) compared to non-concurrent cerivastatin were not significant. Most cases of myopathy were non-serious.

Logistic regression analysis of the risk of myopathy for cerivastatin with concurrent gemfibrozil compared to cerivastatin monotherapy (adjusting for age, gender, diabetes, switching and dose) gave an adjusted odds ratio of 25.5 with a 95% confidence interval of 12.9 to 50.3. Other statins in combination with gemfibrozil were reported not to have an increased risk of myopathy compared to monotherapy.

Table 7: Results of study 1

Last Statin prior to case diagnosis	Absolute Risks of Myopathy % (No. exposed)	Adjusted* Odds Ratios for myopathy with the last statin (with or without gemfibrozil) compared to non-concurrent cerivastatin
Simvastatin	0.2% (5,279)	0.8 (0.4-1.7)
Cerivastatin	0.3% (12,340)	Reference
Fluvastatin	0.3% (31,941)	1.3 (0.8-2.0)
Atorvastatin	0.4% (29,916	1.6 (1.0-2.5)
Lovastatin	0.3% (809)	1.0 (0.2-4.3)
Pravastatin	0.2% (53,169)	1.1 (0.7-1.8)

* Adjusting for age, gender, diabetes, switching and dose

Study 2 was an extension of the first study and covered the same time periods plus an additional 18 months. The results suggested that cerivastatin was associated with the lowest risk of myopathy whilst fluvastatin had the highest. A possible explanation of the increased risk of myopathy with fluvastatin was there was a higher use of erythromycin and azole antifungals in this group.

Study 3 addressed the problems of death, myopathy related hospitalisations and the concern of missed rhabdomyolysis diagnosis. The preliminary results suggested that the overall risk for myopathy was 0.4% and that the hospitalisation rate for myopathy associated with the use of cerivastatin monotherapy was not increased relative to the other statins. There was an 8-fold increased risk of myopathy when cerivastatin and gemfibrozil were taken concomitantly compared with monotherapy.

All of these studies used the same population of patients to varying degrees and as such cannot be considered as independent.

GPRD database

The study used a population based cohort of subjects who were newly diagnosed with hyperlipidaemia and/or who received a prescription for a hypolipidaemic agent. All cases of community acquired renal failure, myotoxicity, fulminant hepatic failure or death were identified.

The cohort comprised 68 374 patients with first-time recorded hyperlipidaemia. Of these subjects, 23707 were untreated for some time during follow-up, 23343 were given statin prescriptions, 2283 were given fibrate prescriptions and 900 were given statin and fibrate prescriptions. Two thousand and fifty three patients reported muscle-related symptoms, no patients had a creatine kinase level of more than 1000 U/l.

Sixteen cases were identified as possible or probable cases of acquired renal failure. The incidence in the statin group overall was 1.6 per 10,000 patient years with an incidence of 0 per 10,000 patient years in the cerivastatin group. For the concurrent statin and fibrate group the rate was 27.2 per 10,000 patient years. No cases of fulminant hepatic failure occurred during follow-up.

A total of 992 deaths from all causes occurred. The crude mortality rates were 8.3 per 1000 person-years for cerivastatin, 7.9 for atorvastatin, 10 for simvastatin, 10.8 for pravastatin and 11.9 for fluvastatin, as compared with 6.3 for fibrates, 4.2 in the untreated group.

Mediplus

This UK database was examined for first time cases of myopathy, myositis or renal failure subsequent to any statin prescription. The analysis was repeated for those patients who had not switched statin. There appeared to be little difference between statins for crude absolute risks of myopathy/renal failure.

Additional data
The review of the original data provided by the MAH elicited several issues for which the CPMP required further information. As a consequence a List of Outstanding Issues was adopted by the CPMP in December 2001.

Interaction between cerivastatin and clopidogrel

In vitro studies
An investigation of the potential pharmacokinetic clopidogrel/cerivastatin interaction was conducted in human liver microsomes. The results suggest that any pharmacokinetic interaction is not due to the inhibition of CYP450 mediated metabolism of cerivastatin

Clinical Trial data
The Princess study was designed to determine whether early acute treatment with cerivastatin after a myocardial infarction would reduce the incidence of cardiovascular morbidity and mortality. Patients were randomised to either 0.4mg or placebo with optional titration to 0.8mg. This study was stopped following the suspension of marketing and distribution of cerivastatin.

Spontaneous data
A reanalysis of spontaneous data reported to the MAH up to 30 September 2001 found 1579 confirmed cases of rhabdomyolysis amongst 7,620 reports. Gemfibrozil or other fibrates had been co-prescribed in 576 (36.5%) of cases and clopidogrel in 246 (15.6%). Six cases had been co-prescribed gemfibrozil and clopidogrel. The majority (85%) of rhabdomyolysis cases reported in association with concomitant clopidogrel use were in patients receiving either 0.4 or 0.8mg of cerivastatin. Seventeen cases had a fatal outcome (17.2% of all fatal cases).

There was an increase in the reporting rate of rhabdomyolysis when cerivastatin was prescribed at doses of 0.4mg or more with clopidogrel compared with monotherapy. At a cerivastatin dose of 0.8mg, reporting rates were similar to those seen at that dose with concomitant gemfibrozil.

There is a large amount of clinical evidence for an interaction between clopidogrel and cerivastatin leading to increased plasma levels of cerivastatin and hence an increased risk of rhabdomyolysis. Based on the in vitro data the mechanism of the interaction does not appear to be due to inhibition of CYP450 mediated metabolism but the exact mechanism remains unknown. Neither of the interactions with gemfibrozil or clopidogrel were predictable based on the metabolism of cerivastatin. The lack of a definite mechanism means that it is difficult to predict how many other possible interactions there may be which could lead to an increased risk of rhabdomyolysis.

MAH Justification that the risk of myopathy with cerivastatin 0.1-0.3mg does not exceed that of other equipotent dosages of the other statins.

Data from 8,804 patients enrolled in clinical studies who received cerivastatin 0.025mg up to 0.4mg for 8-24 weeks suggest that the percentage of patients with elevations of CPK $\geq$ 10xULN are similar at all the dosages and with placebo. Long term exposure (> 24weeks) show a slight increase for cerivastatin 0.4mg compared with that of the lower dosages or other statins. The MAH argued that rhabdomyolysis is most likely to occur in the first 6-12 weeks of therapy and so the short term data are more relevant.

Data from published clinical trials suggest that the risk of unconfirmed rhabdomyolysis (including cases in which increased CPK or muscle symptoms occur alone) with cerivastatin is similar to that of the other statins.

The MAH provided an update of the spontaneous reporting data from the FDA AERS database which included reports up to 7 August 2001 (previously 31 December 2000).

The reporting rates of confirmed cases of rhabdomyolysis in association with 0.2mg to 0.8mg cerivastatin monotherapy are greater than those with any of the other statins. The reporting rates for cerivastatin monotherapy at doses of 0.2mg and 0.4mg are higher than those for equipotent dosages of simvastatin and atorvastatin, respectively. The reporting rates for cerivastatin when used in combination with gemfibrozil at doses of 0.4mg and 0.8mg are greatly elevated compared with equipotent dosages of simvastatin and atorvastatin.

Data on patients receiving concomitant cerivastatin and clopidogrel indicate an increased reporting rate of confirmed rhabdomyolysis. In non-US countries, the total number of confirmed cases of rhabdomyolysis was 16 with combined cerivastatin-clopidogrel use, of which 4 were deaths. No cases of confirmed rhabdomyolysis with clopidogrel co-administration were reported with the other statins, except for 3 cases with simvastatin, but no fatalities. When exposure data are considered, the reporting rate is considerably higher with cerivastatin.

In the US, the total number of confirmed cases of rhabdomyolysis was 49 with combined cerivastatin-clopidogrel use, of which 8 were deaths. The reporting rate for cerivastatin was greatly in excess of that seen with simvastatin and pravastatin in combination with clopidogrel. There were no reports for the other statins

Fatal rhabdomyolysis reported to the FDA before June 26, 2001 and associated with the different statins are summarized in the table 8, recently published in the New England Journal of Medicine.

Table 8: Reported cases of fatal rhabdomyolysis for all statins dispensed in the USA since these products were launched

	Cerivastatin	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin	Total
Date approved	06.26.97	12.17.96	12.31.93	08.31.87	10.31.91	12.23.91	
Fatal cases of rhabdomyolysis	31	6	0	19	3	14	73
Reporting rate (per 1 million prescriptions)	3.16	0.04	0	0.19	0.04	0.12	0.15

Fatal rhabdomyolysis is a rare event among statin users, with reporting rates much lower than 1 death per million prescriptions in the case of most statins. The rate of fatal rhabdomyolysis associated with cerivastatin therapy, however, is 16 to 80 times as high as the rates of any other statin. After the exclusion of the cases in which gemfibrozil was co-administered, the reporting rate of fatal rhabdomyolysis is 1.9 per million prescriptions, 10 to 50 times higher than the rates associated with the other statins. The number of fatal cases without clopidogrel co-medication were not presented in this paper.

Pharmacoepidemiological studies

US PACIFIC HEALTHCARE STUDY

A final study report of the 3rd PacifiCare/Prescription Solutions was received. The preliminary report was included in the MAH's initial submission. The principal difference between the final report and the preliminary study report lies in the definition of renal failure included in the case definition. Whereas all renal failure cases had been included in the preliminary report, the case definition this time was more restricted and resulted in a slightly lower number of cases. There were further details on co-morbidity, co-medications, death, hepatic reactions and mortality. However, overall the results were entirely consistent with previous reports. Co prescribing of gemfibrozil was present in 3.2% of the cohort.

Unadjusted risk of myopathy ranged from 0.59% with lovastatin to 0.27% with pravastatin. The risk for cerivastatin was 0.54%. The adjusted odds ratio for myopathy for concurrent cerivastatin and gemfibrozil compared with pravastatin was 10.5 (95% CI 4.2 to 26.2). None of the other statins had

significantly raised odds ratios compared with pravastatin in concomitant treatment. The adjusted odds ratio for myopathy for monotherapy cerivastatin compared with pravastatin was 1.4 (95% CI 1.09 to 1.74). Fluvastatin and atorvastatin had similarly raised odds ratios compared with pravastatin in monotherapy.

Of the myopathy cases, 6.2% were hospitalised: of those diagnosed as inpatients, the largest proportion (42%) were taking cerivastatin and more likely to have concurrent gemfibrozil than those with hospitalised myopathy and other statins. Of those patients who experienced myopathy on cerivastatin, 61% were on ≤ 0.4mg, with 1% having been titrated from a low to a high dose and 37% switched from another statin to low dose cerivastatin. There was no difference between observed and expected rates of death across different statins.

GPRD

The preliminary report of the study was submitted as part of the MAH's initial response. This final study report included additional patients and increased the person-years available for analysis.

The overall incidence rate for community acquired acute renal failure from all cases was 1.4 per 10,000. The incidence rate of acute renal failure was not statically different among different statins. Only one case of acute renal failure assessed to be due to a crush injury presented with clinical symptoms of rhabdomyolysis. This yielded a community-acquired incidence rate of rhabdomyolysis of 2.9 per million person-years. No cases of fulminant hepatic failure occurred during follow-up in the study population.

A total of 2,826 deaths from all causes occurred. The crude mortality rates were 11.9 per 1000 person-years for simvastatin, 12.2 for cerivastatin, 11.0 for atorvastatin, 10.8 for pravastatin, and 12.1 for fluvastatin, as compared with 7.9 for fibrates, 5.5 in the untreated group and 17.5 during the non-compliance period of patients treaded with hypolipidaemic agents at some point. The mortality analysis was limited by a lack of control for cardiovascular risk factors such as smoking, diabetes and hypertension.

In conclusion, this study did not show a significant statistical difference between the risk of community-acquired acute renal failure or all-cause mortality for cerivastatin when compared with simvastatin. No statin related rhabdomyolysis was identified. However, given the small population exposed to cerivastatin (3,309 patients) and to statins in general, no conclusions can be drawn from this study concerning dose dependent severe myotoxicity or comparison of myotoxicity between the different statins.

DISCUSSION

The most common adverse drug reactions associated with statins are non-serious reactions such as gastrointestinal disturbances, headache, myalgia, CNS disturbances and sleep disorders. Hepatoxicity and myopathies are the most clinically important adverse reactions. The safety profile of cerivastatin, with the exception of the risk of myopathy, appears to be similar to that of the other statins. Comparative data from published clinical trials suggest that the risk of hepatic and serious adverse events may be lower with cerivastatin.

Data from the pooled analysis of cerivastatin clinial trials show that the incidence of adverse events indicative of muscle damage, including CPK ≥ 10xULN increases dose dependently. For 0.8mg cerivastatin the incidence of CPK >10xULN is 3 fold greater than that with cerivastatin 0.4mg (2.0% vs 0.6%) and 6 fold greater than that with other statins (2.0 vs 0.35%).

A review of the safety data from all published trials with the statins suggests that treatment with cerivastatin is associated with an increased risk of rhabdomyolysis compared with the equipotent doses of the other statins. This is particularly marked with the 0.8mg formulation, for which the incidence of rhabdomyolysis is between 4 and 10 fold greater than that of the other statins, though the

incidence of rhabdomyolysis with cerivastatin 0.4mg is 2 fold greater than with other statins. The MAH's point of view that very few cases of rhabdomyolysis have been reported during clinical trials, and therefore the higher incidence seen with cerivastatin compared with the other statins should be interpreted with caution, is accepted. However due to the size of the studies and the patient population (highly selected and carefully monitored) the small number of cases is not unexpected.

The updated data from the FDA database suggests that the reporting rates of confirmed cases of rhabdomyolysis in association with 0.2mg to 0.8mg cerivastatin monotherapy are greater than those with any of the other statins.

The reporting rates for 0.4mg and 0.8mg cerivastatin when used in combination with gemfibrozil are much higher than those seen with equipotent dosages of simvastatin and atorvastatin. Data on patients receiving concomitant cerivastatin and clopidogrel indicate an increased reporting rate of confirmed rhabdomyolysis.

The pharmacoepidemiological studies conducted in the US and the UK do not suggest an increased risk of myopathy with cerivastatin compared with the other statins when used as monotherapy. However, there were some concerns over the methodology which make conclusions regarding the relative risk between statins difficult. The US studies confirm an increased risk of myopathy when cerivastatin was used in combination with gemfibrozil.

The available data from the PRINCESS study and spontaneous reports strongly suggest that the risk of rhabdomyolysis is increased when cerivastatin and clopidogrel are administered concomitantly, and that this increased risk is likely to be due to an interaction between these two substances. Though no formal healthy volunteer studies have been conducted to confirm a pharmacokinetic interaction, there is currently no reason to believe that this is likely to be a pharmacodynamic interaction. Furthermore, the mechanism by which this possible interaction may occur remains unknown.

What is apparent is that the interactions between cerivastatin and gemfibrozil or clopidogrel could not have been predicted based on what is currently known about their metabolism. Despite the cancellation of the cerivastatin licences, the lack of a definitive mechanisms by which cerivastatin induces rhabdomyolysis and interacts with gemfibrozil and clopidogrel does have important implications for the balance of risks and benefits for cerivastatin.

CONCLUSIONS

Cerivastatin effectively and dose-dependently reduces total cholesterol, LDL –cholesterol, triglycerides and apolipoprotein B and increases HDL-cholesterol. Atorvastatin and simvastatin may be more efficacious at the higher licensed dosages. Unlike some of the other statins, there are no data to demonstrate the efficacy of cerivastatin in either primary or secondary prevention of coronary heart disease but there is no reason to assume that it would not be beneficial.

There is convincing evidence that the risk of rhabdomyolysis with cerivastatin is dose-dependent. The analysis of spontaneous data suggests that the risk of myotoxicity increases particularly from 0.4 mg.

Assessment of spontaneous adverse drug reaction reports shows an increased reporting rate of rhabdomyolysis, including fatal cases, with cerivastatin compared with other statins. This finding is maintained even when reports with interacting drugs are excluded.

Data from pharmacoepidemiological studies do not support an increased risk with cerivastatin monotherapy. These studies do, however, confirm an increased risk when gemfibrozil is co-prescribed.

The risk of rhabdomyolysis when cerivastatin is used in combination with gemfibrozil or clopidogrel is greatly increased. The lack of predictability of potential drug interactions with cerivastatin has

important implications for the balance of risks and benefits. Given the US experience, avoiding co-prescription with other potentially interacting products, is considered unrealistic.

The CPMP therefore concluded that the balance of risks and benefits for cerivastatin is negative under normal conditions of use at all previously authorised doses.

GROUNDS FOR WITHDRAWAL OF THE MARKETING AUTHORISATION(S)

Whereas
- Notwithstanding the intention of the Marketing Authorisation Holders to withdraw all Marketing Authorisations for cerivastatin containing medicinal products authorised under the Mutual Recognition Procedure, the CPMP decided to continue the referral made under Article 36 of Directive 2001/83/EC as there was a public health matter to be discussed.

- the Committee agreed that cerivastatin containing medicinal products are effective in the treatment of hyperlipidaemia but do not present a specific therapeutic benefit in relation to comparable compounds.

- the Committee agreed that there were concerns related to the safety profile of cerivastatin containing medicinal products, in particular the risk of rhabdomyolysis.

- the risk of rhabdomyolysis is greatly increased when cerivastatin is used concomitantly with gemfibrozil or clopidogrel. These interactions could not have been predicted on what is currently known about the metabolism of these drugs.

- the CPMP considered that the lack of predictability of potential drug interactions and the difficulties in preventing co-prescription with other potentially interacting products constitutes a continuing risk.

- the Committee, based on present evidence, considered the risk/benefit balance of cerivastatin containing medicinal products to be unfavourable.

- the CPMP has recommended the withdrawal of the Marketing Authorisations for cerivastatin containing Medicinal Products authorised under the Mutual Recognition Procedure (see Annex I) since it considers that such medicinal products are harmful under normal conditions of use.