ANNEX I

LIST OF THE INVENTED NAME, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION AND MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES (EU/EEA)

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Austria	Abbott GmbH Perfektastraße 84A A-1230 Wien Austria	Reductil 10 mg - Hartkapseln	10 mg	Capsule, hard	oral use
Austria	Abott GmbH Perfektastraße 84A A-1230 Wien Austria	Reductil 15 mg - Hartkapseln	15 mg	Capsule, hard	oral use
Austria	Teva Pharma B.V. Computerweg 10 3542 DR Utrecht The Netherlands	Sibutramin Teva 10 mg Kapseln	10 mg	Capsule, hard	oral use
Austria	Teva Pharma B.V. Computerweg 10 3542 DR Utrecht The Netherlands	Sibutramin Teva 15 mg Kapseln	15 mg	Capsule, hard	oral use
Belgium	Abbott SA rue du Bosquet 2 1348 Ottignies/LLN Belgium	Reductil 10 mg	10 mg	Capsule, hard	oral use
Belgium	Abbott SA rue du Bosquet 2 1348 Ottignies/LLN Belgium	Reductil 15 mg	15 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Belgium	Sandoz NV Telecom Gardens Medialaan 40 1800 Vilvoorde Belgium	Sibutramin Sandoz 10 mg	10 mg	Capsule, hard	oral use
Belgium	Sandoz NV Telecom Gardens Medialaan 40 1800 Vilvoorde Belgium	Sibutramin Sandoz 15 mg	15 mg	Capsule, hard	oral use
Belgium	Teva pharma belgium Laarstraat 16 2610 Wilrijk Belgium	Sibutramin Teva 10 mg	10 mg	Capsule, hard	oral use
Belgium	Teva pharma belgium Laarstraat 16 2610 Wilrijk Belgium	Sibutramin Teva 15 mg	15 mg	Capsule, hard	oral use
Bulgaria	Abbott GmbH & Co KG Max-Planck-Ring 2 65205 Wiesbaden Germany	Reductil	10 mg	Capsule, hard	oral use
Bulgaria	Abbott GmbH & Co KG Max-Planck-Ring 2 65205 Wiesbaden Germany	Reductil	15 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Bulgaria	Sandoz d.d., Verovskova 57 SI - 1000 Ljubljana Slovenia	Sibutramin Sandoz	10 mg	Capsule, hard	oral use
Bulgaria	Sandoz d.d. Verovskova 57 SI - 1000 Ljubljana Slovenia	Sibutramin Sandoz	15 mg	Capsule, hard	oral use
Bulgaria	Zentiva k.s. U kabelovny 130 102 37 Prague 10 Czech Republic	Lindaxa	10 mg	Capsule, hard	oral use
Bulgaria	Zentiva k.s. U kabelovny 130 102 37 Prague 10 Czech Republic	Lindaxa	15 mg	Capsule, hard	oral use
Bulgaria	Teva Pharmaceuticals Bulgaria EOOD 15 N.V. Gogol str. Sredetz district 1124 Sofia Bulgaria	Meissa	10 mg	Capsule, hard	oral use
Bulgaria	Teva Pharmaceuticals Bulgaria EOOD 15 N.V. Gogol str. Sredetz district 1124 Sofia Bulgaria	Meissa	15 mg	Capsule, hard	oral use
Czech Republic	Abbott GmbH &Co.KG Max-Planck-Ring-2 65202 Wiesbaden Germany	MERIDIA 10 MG	10 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Czech Republic	Abbott GmbH &Co.KG Max-Planck-Ring-2 65202 Wiesbaden Germany	MERIDIA 15 MG	15 mg	Capsule, hard	oral use
Czech Republic	Zentiva, k.s. U kabelovny 130, 102 37 Prague 10 Czech Republic	LINDAXA 10	10 mg	Capsule, hard	oral use
Czech Republic	Zentiva, k.s. U kabelovny 130, 102 37 Prague 10 Czech Republic	LINDAXA 15	15 mg	Capsule, hard	oral use
Czech Republic	TEVA Pharmaceuticals ČR,s.r.o. Radlická 3185/Ic 150 00 Prague 5 Czech Republic	SIBUTRAMIN-TEVA 10 MG TOBOLKY	10 mg	Capsule, hard	oral use
Czech Republic	TEVA Pharmaceuticals ČR,s.r.o. Radlická 3185/Ic 150 00 Prague 5 Czech Republic	SIBUTRAMIN-TEVA 15 MG TOBOLKY	15 mg	Capsule, hard	oral use
Denmark	Abbott Scandinavia AB Postboks 509 SE-169 29, Solna Sweden	Reductil	10 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Denmark	Abbott Scandinavia AB Postboks 509 SE-169 29, Solna Sweden	Reductil	15 mg	Capsule, hard	oral use
Denmark	1A Farma A/S Herstedøstervej 27-29 DK-2620 Albertslund Denmark	Sibutramin "1A Farma"	10 mg	Capsule, hard	oral use
Denmark	1A Farma A/S Herstedøstervej 27-29 DK-2620 Albertslund Denmark	Sibutramin "1A Farma"	15 mg	Capsule, hard	oral use
Denmark	Sandoz A/S C. F. Tietgens Boulevard 40 DK-5220 Odense SØ Denmark	Sibutramin "Sandoz"	10 mg	Capsule, hard	oral use
Denmark	Sandoz A/S C. F. Tietgens Boulevard 40 DK-5220 Odense SØ Denmark	Sibutramin "Sandoz"	15 mg	Capsule, hard	oral use
Denmark	Teva Danmark A/S Østergade 38 DK-1100 København K Denmark	Sibutramin "Teva"	10 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Denmark	Teva Danmark A/S Østergade 38 DK-1100 København K Denmark	Sibutramin "Teva"	15 mg	Capsule, hard	oral use
Estonia	Abbott GmbH & Co. KG Max-Planck-Ring 2 65205 Wiesbaden Germany	REDUCTIL	10mg	Capsule, hard	oral use
Estonia	Abbott GmbH & Co. KG Max-Planck-Ring 2 65205 Wiesbaden Germany	REDUCTIL	15mg	Capsule, hard	oral use
Estonia	Sandoz d.d. Verovskova 57 1000 Ljubljana Slovenia	SIBUTRIL	10mg	Capsule, hard	oral use
Estonia	Sandoz d.d. Verovskova 57 1000 Ljubljana Slovenia	SIBUTRIL	15mg	Capsule, hard	oral use
Estonia	Zentiva, k.s. U Kabelovny 130 Dolni Mecholupy 102 37 Prague 10 Czech Republic	LINDAXA 10	10mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Estonia	Zentiva, k.s. U Kabelovny 130 Dolni Mecholupy 102 37 Prague 10 Czech Republic	LINDAXA 15	15mg	Capsule, hard	oral use
Estonia	Teva Pharma B.V. Computerweg 10 3542 DR Utrecht The Netherlands	SIBUTRAMINE TEVA	10mg	Capsule, hard	oral use
Estonia	Teva Pharma B.V. Computerweg 10 3542 DR Utrecht The Netherlands	SIBUTRAMINE TEVA	15mg	Capsule, hard	oral use
Finland	Abbott Scandinavia AB P.O. Box 509 16929 Solna Sweden	Reductil	10 mg, 15 mg	Capsule, hard	oral use
Finland	Sandoz A/S C.F. Tietgens Boulevard 40 5220 Odense SØ Denmark	Sibutramin Sandoz	10 mg, 15 mg	Capsule, hard	oral use
Finland	Teva Sweden AB Järnvägsgatan 11 Box 1070 25110 Helsingborg Sweden	Sibutramine Teva	10 mg, 15 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
France	ABBOT France 10, RUE D'ARCUEIL SILIC 233 94528 RUNGIS CEDEX FRANCE	SIBUTRAL 10 mg, gélule	10 mg	capsule	oral use
France	ABBOT France 10, RUE D'ARCUEIL SILIC 233 94528 RUNGIS CEDEX FRANCE	SIBUTRAL 15 mg, gélule	15 mg	capsule	oral use
Germany	Abbott GmbH & Co. KG Max-Planck-Ring 2 65205 Wiesbaden Germany	Reductil 10 mg Hartkapseln	10 mg	Capsule, hard	oral use
Germany	Abbott GmbH & Co. KG Max-Planck-Ring 2 65205 Wiesbaden Germany	Reductil 15 mg Hartkapseln	15 mg	Capsule, hard	oral use
Germany	Abbott GmbH & Co. KG Max-Planck-Ring 2 65205 Wiesbaden Germany	Zelium 10 mg Hartkapseln	10 mg	Capsule, hard	oral use
Germany	Abbott GmbH & Co. KG Max-Planck-Ring 2 65205 Wiesbaden Germany	Zelium 15 mg Hartkapseln	15 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Germany	Abbott GmbH & Co. KG Max-Planck-Ring 2 65205 Wiesbaden Germany	Reduxade 10 mg Hartkapseln	10 mg	Capsule, hard	oral use
Germany	Abbott GmbH & Co. KG Max-Planck-Ring 2 65205 Wiesbaden Germany	Reduxade 15 mg Hartkapseln	15 mg	Capsule, hard	oral use
Germany	1 A Pharma GmbH Keltenring 1 + 3 82041 Oberhaching Germany	Sibutramin - 1A Pharma 10 mg Hartkapseln	10 mg	Capsule, hard	oral use
Germany	1 A Pharma GmbH Keltenring 1 + 3 82041 Oberhaching Germany	Sibutramin - 1A Pharma 15 mg Hartkapseln	15 mg	Capsule, hard	oral use
Germany	HEXAL AG Postfach 1263 83602 Holzkirchen Germany	Sibutramin-HEXAL 10 mg Hartkapseln	10 mg	Capsule, hard	oral use
Germany	HEXAL AG Postfach 1263 83602 Holzkirchen Germany	Sibutramin-HEXAL 15 mg Hartkapseln	15 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Greece	Abbott Laboratories (Hellas) S.A. 512, Vouliagmenis Avenue GR 17456, Alimos Athens Greece	Reductil	10 mg	Capsule, hard	oral use
Greece	Abbott Laboratories (Hellas) S.A. 512, Vouliagmenis Avenue GR 17456, Alimos Athens Greece	Reductil	15 mg	Capsule, hard	oral use
Greece	Teva Pharmaceuticals Europe B.V. European Headquarters Computerweg 10 3542 DR Utrecht The Netherlands	Sibutramine/Teva	10mg	Capsule, hard	oral use
Greece	Teva Pharmaceuticals Europe B.V. European Headquarters Computerweg 10 3542 DR Utrecht The Netherlands	Sibutramine/Teva	15 mg	Capsule, hard	oral use
Hungary	Zentiva k. s. U Kabelovny 130 102 37 Praha 10 Czech Republic	LINDAXA	10mg	Capsule, hard	oral use
Hungary	Zentiva k. s. U Kabelovny 130 102 37 Praha 10 Czech Republic	LINDAXA	15mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Hungary	Teva Magyarország zrt. Rákóczi út 70-72. 1074 Budapest Hungary	MINIMECTIL	10mg	Capsule, hard	oral use
Hungary	Teva Magyarország zrt. Rákóczi út 70-72. 1074 Budapest Hungary	MINIMECTIL	15mg	Capsule, hard	oral use
Hungary	Abbott Laboratories Kft. Teve u. 1/a-c 1139 Budapest Hungary	REDUCTIL	10mg	Capsule, hard	oral use
Hungary	Abbott Laboratories Kft. Teve u. 1/a-c 1139 Budapest Hungary	REDUCTIL	15mg	Capsule, hard	oral use
Iceland	Abbott Scandinavia Gårdsvägen 8 Box 5091 SE-169 29 Solna Sweden	Reductil	10 mg	Capsule, hard	oral use
Iceland	Abbott Scandinavia Gårdsvägen 8 Box 5091 SE-169 29 Solna Sweden	Reductil	15 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Ireland	Teva Pharma B.V. Computerweg 10 3542 Dr Utrecht Netherlands	Sibutramine Teva 10 mg Capsules	10 mg	Capsule, hard	oral use
Ireland	Teva Pharma B.V. Computerweg 10 3542 Dr Utrecht Netherlands	Sibutramine Teva 15 mg Capsules	15 mg	Capsule, hard	oral use
Ireland	Abbot Laboratories Ireland Ltd 4051 Kingswood Drive Citywest Business Campus Dublin 24 Ireland	Reductil 10 mg capsules, hard	10 mg	Capsule, hard	oral use
Ireland	Abbot Laboratories Ireland Ltd 4051 Kingswood Drive Citywest Business Campus Dublin 24 Ireland	Reductil 15 mg capsules, hard	15 mg	Capsule, hard	oral use
Ireland	Rowex Ltd Bantry Co.Cork Ireland	Sitrane 10 mg hard capsules	10 mg	Capsule, hard	oral use
Ireland	Rowex Ltd Bantry Co.Cork Ireland	Sitrane 15 mg hard capsules	15 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Italy	ABBOTT srl Via Pontina Km 52 04010 Campoverde di Aprilia Italy	REDUXATE	10 mg	capsule	oral use
Italy	ABBOTT srl Via Pontina Km 52 04010 Campoverde di Aprilia Italy	REDUXATE	15 mg	capsule	oral use
Italy	ABBOTT srl Via Pontina Km 52 04010 Campoverde di Aprilia Italy	ECTIVA	10 mg	capsule	oral use
Italy	ABBOTT srl Via Pontina Km 52 04010 Campoverde di Aprilia Italy	ECTIVA	15 mg	capsule	oral use
Italy	ABBOTT srl Via Pontina Km 52 04010 Campoverde di Aprilia Italy	REDUCTIL	10 mg	capsule	oral use
Italy	ABBOTT srl Via Pontina Km 52 04010 Campoverde di Aprilia Italy	REDUCTIL	15 mg	capsule	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Latvia	Abbott GmbH & Co. KG Max-Planck-Ring 2 65205 Wiesbaden Germany	Reductil 15 mg hard capsules	15 mg	Capsule, hard	oral use
Latvia	Abbott GmbH & Co. KG Max-Planck-Ring 2 65205 Wiesbaden Germany	Reductil 10 mg hard capsules	10 mg	Capsule, hard	oral use
Latvia	Sandoz d.d. Verovškova 57 1000 Ljubljana Slovenia	Sibutril 15 mg capsules, hard	15 mg	Capsule, hard	oral
Latvia	Sandoz d.d. Verovškova 57 1000 Ljubljana Slovenia	Sibutril 10 mg capsules, hard	10 mg	Capsule, hard	oral
Lithuania	Abbott GmbH & Co. KG Max-Planck-Ring 2 65205 Wiesbaden Germany	Reductil	10 mg	Capsule, hard	oral use
Lithuania	Abbott GmbH & Co. KG Max-Planck-Ring 2 65205 Wiesbaden Germany	Reductil	15 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Lithuania	Zentiva k. s. U kabelovny 130 10237 Prague 10 Dolni Mecholupy Czech Republic	Lindaxa	10 mg	Capsule, hard	oral use
Lithuania	Zentiva k. s. U kabelovny 130 10237 Prague 10 Dolni Mecholupy Czech Republic	Lindaxa	15 mg	Capsule, hard	oral use
Lithuania	Sandoz d.d. Verovskova 57 1000 Ljubljana Slovenia	Sibutril	10 mg	Capsule, hard	oral use
Lithuania	Sandoz d.d. Verovskova 57 1000 Ljubljana Slovenia	Sibutril	15 mg	Capsule, hard	oral use
Lithuania	Teva Pharma B.V. Computerweg 10 3542 DR Utrecht The Netherlands	Sibutramine Teva	10 mg	Capsule, hard	oral use
Lithuania	Teva Pharma B.V. Computerweg 10 3542 DR Utrecht The Netherlands	Sibutramine Teva	15 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Luxembourg	Abbott Laboratoires 2,rue du Bosquet B- 1348 Ottignies L.L.N. Belgium	Reductil	10mg	capsule	oral use
Luxembourg	Abbott Laboratoires 2, rue du Bosquet B- 1348 Ottignies L.L.N. Belgium	Reductil	15mg	capsules	oral use
Malta	Abbott Laboratories Limited Queenborough Kent ME11 5EL United Kingdom	Reductil	10mg	Capsule, hard	oral use
Malta	Abbott Laboratories Limited Queenborough Kent ME11 5EL United Kingdom	Reductil	15mg	Capsule, hard	oral use
Netherlands	Abbott B.V. Siriusdreef 51 2132 WT, Hoofddorp Netherlands	Reductil 10 mg, capsules, hard	10 mg	Capsule, hard	oral use
Netherlands	Abbott B.V. Siriusdreef 51 2132 WT, Hoofddorp Netherlands	Reductil 15 mg, capsules, hard	15 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Netherlands	Sandoz B.V. Veluwezoom 22 1327 AH, Almere Netherlands	Sibutramine HCL monohydraat Sandoz 10 mg, harde capsules	10 mg	Capsule, hard	oral use
Netherlands	Sandoz B.V. Veluwezoom 22 1327 AH, Almere Netherlands	Sibutramine HCL monohydraat Sandoz 15 mg, harde capsules	15 mg	Capsule, hard	oral use
Netherlands	Medcor Pharmaceuticals B.V. Ketelmeerstraat 142-144 8226 JX, Lelystad Netherlands	Reductil 15 mg, capsules	15 mg	Capsule, hard	oral use
Netherlands	Medcor Pharmaceuticals B.V. Ketelmeerstraat 142-144 8226 JX, Lelystad Netherlands	Reductil 10 mg, capsules	10 mg	Capsule, hard	oral use
Netherlands	Pharmachemie B.V. Swensweg 5 2031 GA, Haarlem Netherlands	Sibutramine HCL-monohydraat 10 mg PCH, capsules	10 mg	Capsule, hard	oral use
Netherlands	Pharmachemie B.V. Swensweg 5 2031 GA, Haarlem Netherlands	Sibutramine HCL-monohydraat 15 mg PCH, capsules	15 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Norway	Abbot Scandinavia AB Box 509 169 29 Solna Sweden	REDUCTIL	10 mg	Capsule, hard	oral use
Norway	Abbot Scandinavia AB Box 509 169 29 Solna Sweden	REDUCTIL	15 mg	Capsule, hard	oral use
Norway	Euromedica Norge AS Jerikoveien 28 C 1067 Oslo Norway	REDUCTIL	10 mg	Capsule, hard	oral use
Norway	Euromedica Norge AS Jerikoveien 28 C 1067 Oslo Norway	REDUCTIL	15 mg	Capsule, hard	oral use
Norway	Sandoz A/ Edvard Thomsens Vej 14 2300 København S Danmark	SIBUTRAMIN SANDOZ	10 mg	Capsule, hard	oral use
Norway	Sandoz A/ Edvard Thomsens Vej 14 2300 København S Danmark	SIBUTRAMIN SANDOZ	15 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Poland	Teva Pharmaceuticals Polska Sp. z o.o. 53 Emilii Plater St. 00-113 Warsaw Poland	Afibron	10 mg	Capsule, hard	oral use
Poland	Teva Pharmaceuticals Polska Sp. z o.o. 53 Emilii Plater St. 00-113 Warsaw Poland	Afibron	15 mg	Capsule, hard	oral use
Poland	Zentiva a.s. U Kabelovny 130 Dolni Mecholupy 102 37 Praha 10 Czech Republic	Lindaxa 10	10 mg	Capsule, hard	oral use
Poland	Zentiva a.s. U Kabelovny 130 Dolni Mecholupy 102 37 Praha 10 Czech Republic	Lindaxa 15	15 mg	Capsule, hard	oral use
Poland	Abbott Laboratories Poland Sp. z o. o. ul. Postępu 18A 02-676 Warsaw Poland	Meridia 10	10 mg	Capsule, hard	oral use
Poland	Abbott Laboratories Poland Sp. z o. o. ul. Postępu 18A 02-676 Warsaw Poland	Meridia 15	15 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Poland	Sandoz GmbH Biochemiestrasse 10 A-6250 Kundl Austria	Obesan	10 mg	Capsule, hard	oral use
Poland	Sandoz GmbH Biochemiestrasse 10 A-6250 Kundl Austria	Obesan	15 mg	Capsule, hard	oral use
Poland	1A Pharma GmbH Keltenring 1 + 3 82041 Oberhaching	Sibutramine-1A Pharma	10 mg	Capsule, hard	oral use
Poland	1A Pharma GmbH Keltenring 1 + 3 82041 Oberhaching Germany	Sibutramine-1A Pharma	15 mg	Capsule, hard	oral use
Poland	Biofarm Sp. z o.o. Wałbrzyska 13, 60-198 Poznan Poland	Zelixa	10 mg	Film-coated tablet	oral use
Poland	Biofarm Sp. z o.o. Wałbrzyska 13, 60-198 Poznan Poland	Zelixa	15 mg	Film-coated tablet	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Portugal	ABBOTT LABORATORIOS, LDA Estrada Alfragide 67-AlfraparK- Edifício D, 2610-008 AMADORA Portugal	Zelium	10 mg	Capsule, hard	oral use
Portugal	ABBOTT LABORATORIOS, LDA Estrada Alfragide 67-AlfraparK- Edifício D, 2610-008 AMADORA Portugal	Zelium	15 mg	Capsule, hard	oral use
Portugal	ABBOTT LABORATORIOS, LDA Estrada Alfragide 67-AlfraparK- Edifício D, 2610-008 AMADORA Portugal	Reductil	10 mg	Capsule, hard	oral use
Portugal	ABBOTT LABORATORIOS, LDA Estrada Alfragide 67-AlfraparK- Edifício D, 2610-008 AMADORA Portugal	Reductil	15 mg	Capsule, hard	oral use
Portugal	Teva Pharma – Produtos Farmacêuticos, Lda. Empreendimento Lagoas Park Edifício 1 - 3 2740-264 Porto Salvo Portugal	Sibutramina Teva	10 mg	Capsule, hard	oral use
Portugal	Teva Pharma – Produtos Farmacêuticos, Lda. Empreendimento Lagoas Park Edifício 1 - 3 2740-264 Porto Salvo Portugal	Sibutramina Teva	15 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Portugal	Solufarma - Produtos Farmacêuticos Unipessoal, Lda. Rua do Tejo, 56 - 9º A Esq 2775-325 Parede Portugal	Sibutramina Sibulaite	10 mg	Capsule, hard	oral use
Portugal	Solufarma - Produtos Farmacêuticos Unipessoal, Lda Rua do Tejo, 56 - 9º A Esq 2775-325 Parede Portugal	Sibutramina Sibulaite	15 mg	Capsule, hard	oral use
Portugal	Solufarma - Produtos Farmacêuticos Unipessoal, Lda Rua do Tejo, 56 - 9º A Esq 2775-325 Parede Portugal	Sibutramina Solufarma	10 mg	Capsule, hard	oral use
Portugal	Solufarma - Produtos Farmacêuticos Unipessoal, Lda Rua do Tejo, 56 - 9º A Esq 2775-325 Parede Portugal	Sibutramina Solufarma	15 mg	Capsule, hard	oral use
Portugal	Farmoz - Sociedade Técnico Medicinal, S.A. Rua da Tapada Grande, 2 Abrunheira 2710-089 Sintra Portugal	Sibutramina Farmoz	10 mg	Capsule, hard	oral use
Portugal	Farmoz - Sociedade Técnico Medicinal, S.A. Rua da Tapada Grande, 2 Abrunheira 2710-089 Sintra Portugal	Sibutramina Farmoz	15 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Portugal	Pentafarma - Sociedade Técnico-Medicinal, S.A. Rua da Tapada Grande, nº2 - Abrunheira 2710-089 Sintra Portugal	Sibutramina Egostar	10 mg	Capsule, hard	oral use
Portugal	Pentafarma - Sociedade Técnico-Medicinal, S.A. Rua da Tapada Grande, nº2 Abrunheira 2710-089 Sintra Portugal	Sibutramina Egostar	15 mg	Capsule, hard	oral use
Portugal	Pentafarma - Sociedade Técnico-Medicinal, S.A. Rua da Tapada Grande, nº2 Abrunheira 2710-089 Sintra Portugal	Sibutramina Blixie	10 mg	Capsule, hard	oral use
Portugal	Tecnimede - Sociedade Técnico-Medicinal, S.A. Rua da Tapada Grande, 2 Abrunheira 2710-089 Sintra Portugal	Sibutramina Blixie	15 mg	Capsule, hard	oral use
Portugal	Tecnimede - Sociedade Técnico-Medicinal, S.A. Rua da Tapada Grande, 2 Abrunheira 2710-089 Sintra Portugal	Sibutramina Atrolex	10 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Portugal	Tecnimede - Sociedade Técnico-Medicinal, S.A. Rua da Tapada Grande, 2 Abrunheira 2710-089 Sintra Portugal	Sibutramina Atrolex	15 mg	Capsule, hard	oral use
Portugal	Tecnimede - Sociedade Técnico-Medicinal, S.A. Rua da Tapada Grande, 2 Abrunheira 2710-089 Sintra Portugal	Sibutramina Argam	10 mg	Capsule, hard	oral use
Portugal	Tecnimede - Sociedade Técnico-Medicinal, S.A. Rua da Tapada Grande, 2 Abrunheira 2710-089 Sintra Portugal	Sibutramina Argam	15 mg	Capsule, hard	oral use
Portugal	Tecnimede - Sociedade Técnico-Medicinal, S.A. Rua da Tapada Grande, 2 Abrunheira 2710-089 Sintra Portugal	Sibutramina Orexinib	10 mg	Capsule, hard	oral use
Portugal	Tecnimede - Sociedade Técnico-Medicinal, S.A. Rua da Tapada Grande, 2 Abrunheira 2710-089 Sintra Portugal	Sibutramina Orexinib	15 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Portugal	Tecnimede - Sociedade Técnico-Medicinal, S.A. Rua da Tapada Grande, 2 Abrunheira 2710-089 Sintra Portugal	Sibutramina Snomas	10 mg	Capsule, hard	oral use
Portugal	Tecnimede - Sociedade Técnico-Medicinal, S.A. Rua da Tapada Grande, 2 Abrunheira 2710-089 Sintra Portugal	Sibutramina Snomas	15 mg	Capsule, hard	oral use
Portugal	Tecnimede - Sociedade Técnico-Medicinal, S.A. Rua da Tapada Grande, 2 Abrunheira 2710-089 Sintra Portugal	Sibutramina Arpedex	10 mg	Capsule, hard	oral use
Portugal	Tecnimede - Sociedade Técnico-Medicinal, S.A. Rua da Tapada Grande, 2 Abrunheira 2710-089 Sintra Portugal	Sibutramina Arpedex	15 mg	Capsule, hard	oral use
Portugal	Tecnimede - Sociedade Técnico-Medicinal, S.A. Rua da Tapada Grande, 2 Abrunheira 2710-089 Sintra Portugal	Sibutramina Marcoliz	10 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Portugal	Tecnimede - Sociedade Técnico-Medicinal, S.A. Rua da Tapada Grande, 2 Abrunheira 2710-089 Sintra Portugal	Sibutramina Marcoliz	15 mg	Capsule, hard	oral use
Portugal	Tecnimede - Sociedade Técnico-Medicinal, S.A. Rua da Tapada Grande, 2 Abrunheira 2710-089 Sintra Portugal	Sibutramina Ocram	10 mg	Capsule, hard	oral use
Portugal	Tecnimede - Sociedade Técnico-Medicinal, S.A. Rua da Tapada Grande, 2 Abrunheira 2710-089 Sintra Portugal	Sibutramina Ocram	15 mg	Capsule, hard	oral use
Portugal	Verum Pharma - Produtos Farmacêuticos - Unipessoal, Lda Av. Sidónio Pais, n.º 24, rés-do-chão esq São Sebastião da Pedreira 1000 Lisboa Portugal	Sibutramina Strami	10 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Portugal	Verum Pharma - Produtos Farmacêuticos - Unipessoal, Lda Av. Sidónio Pais, n.º 24, rés-do-chão esq, São Sebastião da Pedreira 1000 Lisboa Portugal	Sibutramina Strami	15 mg	Capsule, hard	oral use
Portugal	Tecnimede - Sociedade Técnico-Medicinal, S.A. Rua da Tapada Grande, 2 Abrunheira 2710-089 Sintra Portugal	Sibutramina Fililex	10 mg	Capsule, hard	oral use
Portugal	Tecnimede - Sociedade Técnico-Medicinal, S.A. Rua da Tapada Grande, 2 Abrunheira 2710-089 Sintra Portugal	Sibutramina Fililex	15 mg	Capsule, hard	oral use
Portugal	Tecnimede - Sociedade Técnico-Medicinal, S.A. Rua da Tapada Grande, 2 Abrunheira 2710-089 Sintra Portugal	Sibutramina West Pharma	10 mg	Capsule, hard	oral use
Portugal	Tecnimede - Sociedade Técnico-Medicinal, S.A. Rua da Tapada Grande, 2 Abrunheira 2710-089 Sintra Portugal	Sibutramina West Pharma	15 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Portugal	Generis Farmacêutica, S.A. Office Park da Beloura, Edifício 4, Quinta da Beloura 2710-444 Sintra Portugal	Sibutramina Generis	8.37 mg	Capsule, hard	oral use
Portugal	Generis Farmacêutica, S.A. Office Park da Beloura, Edifício 4, Quinta da Beloura 2710-444 Sintra Portugal	Sibutramina Generis	12.556 mg	Capsule, hard	oral use
Portugal	Sandoz Farmacêutica, Lda. Alameda da Beloura, Edifício 1, 2º - Escritório 15 2710-693 Sintra Portugal	Sibutramina Sandoz	10 mg	Capsule, hard	oral use
Portugal	Sandoz Farmacêutica, Lda. Alameda da Beloura, Edifício 1, 2º - Escritório 15 2710-693 Sintra Portugal	Sibutramina Sandoz	15 mg	Capsule, hard	oral use
Romania	Abbott GmbH & Co.KG Max-Planck-Ring 2 65205 Wiesbaden Germany	REDUCTIL 10 mg, capsule	10 mg	Capsule, hard	oral use
Romania	Abbott GmbH & Co.KG Max-Planck-Ring 2 65205 Wiesbaden Germany	REDUCTIL 15 mg, capsule	15 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Romania	SANDOZ S.R.L. ROMÂNIA Str. Livezeni nr. 7A, Târgu Mureş, Romania	MINIMACIN 10 mg, capsule	10 mg	Capsule, hard	oral use
Romania	SANDOZ S.R.L. ROMÂNIA Str. Livezeni nr. 7A, Târgu Mureş, Romania	MINIMACIN 15 mg, capsule	15 mg	Capsule, hard	oral use
Romania	S.C. TERAPIA S.A. Str. Fabricii, nr. 124, Cluj-Napoca, Romania	SILUTON 10 mg, capsule	10 mg	Capsule, hard	oral use
Romania	S.C. TERAPIA S.A. Str. Fabricii, nr. 124, Cluj-Napoca, Romania	SILUTON 15 mg, capsule	15 mg	Capsule, hard	oral use
Romania	TEVA PHARMACEUTICALS S.R.L. Str. Domnița Ruxandra nr 12, parter, Sector 2, Bucureşti Romania	SIBUTRAMINĂ TEVA 10 mg, capsule	10 mg	Capsule, hard	oral use
Romania	TEVA PHARMACEUTICALS S.R.L. Str. Domnița Ruxandra nr 12, parter, Sector 2, Bucureşti Romania	SIBUTRAMINĂ TEVA 15 mg, capsule	15 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Romania	ZENTIVA a.s., U kabelovny 130, 102 37 Praga-10 Dolní Měcholupy, Czech Republic	LINDAXA 10 mg, capsule	10 mg	Capsule, hard	oral use
Romania	ZENTIVA a.s., U kabelovny 130, 102 37 Praga-10 Dolní Měcholupy Czech Republic	LINDAXA 15 mg, capsule	15 mg	Capsule, hard	oral use
Slovakia	Zentiva, k.s. Evropská 846/176a 160 00 Praha 6 Czech Republic	LINDAXA 10	10 mg	Capsule, hard	oral use
Slovakia	Zentiva, k.s. Evropská 846/176a 160 00 Praha 6 Czech Republic	LINDAXA 15	15 mg	Capsule, hard	oral use
Slovakia	TEVA Pharmaceuticals Slovakia s.r.o. Teslova 26, 821 02, Bratislava Slovak Republic	Sibutramin - Teva 10 mg kapsuly	10 mg	Capsule, hard	oral use
Slovakia	TEVA Pharmaceuticals Slovakia s.r.o. Teslova 26, 821 02 Bratislava Slovak Republic	Sibutramin - Teva 15 mg kapsuly	15 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Slovakia	Abbott Laboratories Slovakia s.r.o. Karadžicova 10 821 08 Bratislava Slovak Republic	Reductil 10 mg	10 mg	capsule	oral use
Slovakia	Abbott Laboratories Slovakia s.r.o. Karadžicova 10 821 08 Bratislava Slovak Republic	Reductil 15 mg	15 mg	capsule	oral use
Slovenia	Abbott Laboratories d.o.o. Dolenjska c. 242c SI-1000 Ljubljana Slovenia	Reductil 10 mg trde kapsule	10 mg	Capsule, hard	oral use
Slovenia	Abbott Laboratories d.o.o. Dolenjska c. 242c SI-1000 Ljubljana Slovenia	Reductil 15 mg trde kapsule	15 mg	Capsule, hard	oral use
Slovenia	Lek farmacevtska družba d.d., Verovškova c. 57 SI-1000 Ljubljana Slovenia	Sibutramin Lek 10 mg trde kapsule	10 mg	Capsule, hard	oral use
Slovenia	Lek farmacevtska družba d.d., Verovškova c. 57 SI-1000 Ljubljana Slovenia	Sibutramin Lek 15 mg trde kapsule	15 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Spain	ABBOTT LABORATORIES, S.A. Avda. de Burgos 28050 Madrid Spain	REDUCTIL	10mg	Capsule, hard	oral use
Spain	ABBOTT LABORATORIES, S.A. Avda. de Burgos 28050 Madrid Spain	REDUCTIL	15 mg	Capsule, hard	oral use
Spain	TEVA GENERICOS ESPAÑOLA, S.L. Guzmán el Bueno 133 Edificio Britania 4ºIzq. 28003 MADRID Spain	SIBUTRAMINA TEVA	10mg	Capsule, hard	oral use
Spain	TEVA GENERICOS ESPAÑOLA, S.L. Guzmán el Bueno 133 Edificio Britania 4ºIzq. 28003 MADRID Spain	SIBUTRAMINA TEVA	15 mg	Capsule, hard	oral use
Spain	IDIFARMA, DESARROLLO FARMACEUTICO Polígono Mocholí. Plaza CEIN 5, Nave B-14Noain (Navarra) Spain	SIBUTRAMINA IDIFARMA	10 mg	Capsule, hard	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Spain	IDIFARMA, DESARROLLO FARMACEUTICO. Polígono Mocholí. Plaza CEIN 5, Nave B-14Noain (Navarra) Spain	SIBUTRAMINA IDIFARMA	15 mg	Capsule, hard	oral use
Sweden	Abbott Scandinavia AB Box 509 169 29 Solna Sweden	Reductil	10 mg	Capsule, hard	oral use
Sweden	Abbott Scandinavia AB Box 509 169 29 Solna Sweden	Reductil	15 mg	Capsule, hard	oral use
Sweden	Sandoz A/S, C.F. Tietgens Boulevard 40 DK-5220 Odense SØ Danmark	Sibutramin Sandoz	10 mg	Capsule, hard	oral use
Sweden	Sandoz A/S, C.F. Tietgens Boulevard 40 DK-5220 Odense SØ Danmark	Sibutramin Sandoz	15 mg	Capsule, hard	oral use
Sweden	Teva Sweden AB Box 1070 251 10 Helsingborg Sweden	Sibutramine Teva	10 mg	Capsule, hard	Oral use
Sweden	Teva Sweden AB Box 1070 251 10 Helsingborg Sweden	Sibutramine Teva	15 mg	Capsule, hard	Oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented Name**	**Strength**	**Pharmaceutical form**	**Route of administration**
United Kingdom	Abbott Laboratories Limited Queenborough Kent ME11 5EL United Kingdom	Reductil 10mg	10mg	Capsule, hard	oral use
United Kingdom	Abbott Laboratories Limited Queenborough Kent ME11 5EL United Kingdom	Reductil 15mg	15mg	Capsule, hard	oral use
United Kingdom	Teva UK Limited Brampton Road Hampden Park Eastbourne, East Sussex BN22 9AG United Kingdom	Sibutramine Hydrochloride 15mg Capsules	10mg	Capsule, hard	oral use
United Kingdom	Teva UK Limited Brampton Road Hampden Park Eastbourne, East Sussex BN22 9AG United Kingdom	Sibutramine Hydrochloride 10mg Capsules	15mg	Capsule, hard	oral use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE SUSPENSION OF THE MARKETING AUTHORISATIONS

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF SIBUTRAMINE-CONTAINING MEDICINAL PRODUCTS (SEE ANNEX I)

Sibutramine is an orally administered serotonin and noradrenaline reuptake inhibitor that is indicated as adjunctive therapy for adult patients within a weight management programme, including weight loss and maintenance of weight loss. Sibutramine should be used in conjunction with a reduced calorie diet and increased physical activity in
- Patients with nutritional obesity and a body mass index (BMI) of 30 kg/m2 or higher.
- Patients with nutritional excess weight and a BMI of 27 kg/m2 or higher, if other obesity-related risk factors such as type 2 diabetes or dyslipidaemia are present.

In the EU sibutramine was first authorised in January 1999. An Article 31 referral was triggered in March 2002 due to safety concerns based on fatal adverse reactions. No firm conclusion was reached with regards to these reactions and on the basis of the available data on sibutramine, the CHMP therefore considered the benefit-risk balance to be favourable and adopted an Opinion recommending the maintenance of the Marketing Authorisations. However, the MAHs were required to conduct a large cardiovascular outcome study designed to compare sibutramine to placebo under standard care for weight management in overweight or obese subjects aged 55 years or older, who were at risk of cardiovascular (CV) events on the basis of a history of documented disease or the presence of additional CV risk factors such as diabetes. The Sibutramine Cardiovascular OUTcomes (SCOUT) study was initiated in January 2003.

A procedure under Article 107 of Directive 2001/83/EC was triggered in November 2009 based on preliminary results from SCOUT that suggested an increased cardiovascular risk with sibutramine treatment compared with placebo. The CHMP adopted a List of Questions requesting the MAHs to discuss the results of SCOUT, focusing in particular on drop outs, adverse events, statistical data and the implications of the data on the benefit/risk balance and risk minimisation measures. SCOUT was powered as a superiority study with the aim of showing a decrease in the CV primary outcome event (POE, including, non-fatal myocardial infarction (MI), non-fatal stroke resuscitated cardiac arrest and cardiovascular death due to MI or stroke) rate in the sibutramine treated patients compared to placebo. Consequently the CHMP expressed concern that the increase in rates of POEs in the sibutramine arm compared with placebo was in fact sufficient to be statistically significant.

Following the assessment of the MAHs responses, the CHMP considered that the SCOUT results provide evidence of increased cardiovascular and cerebrovascular risks associated with the use of sibutramine in high risk patients. Sibutramine treatment resulted in a higher incidence of POEs (specifically non-fatal myocardial infarction and stroke were the drivers) compared with placebo in patients with a history of a cardiovascular disease (these patients were acknowledged as Summary of Product Characteristics (SPC) non-conformers). In patients treated according to the approved SPC, i.e. conformers, which accounted for less than 10% of enrolled patients, a numerically slightly increased risk of cardiovascular events was observed when compared to placebo, although the numbers are small and the confidence intervals are wide in this subgroup. Sibutramine significantly increased blood pressure (BP) and heart rate (HR) when compared with placebo (although both reduced diastolic blood pressure and heart rate in patients losing weight) which may have contributed to the observed difference in CV event rates.

The CHMP also concluded that the SCOUT study confirms that sibutramine has, on average, only a modest effect on weight reduction in obese patients. The SCOUT data shows a lower benefit compared to previous trials and to the meta-analysis by Rucker *et al.* (2007). With sibutramine treatment, only 30.4% of the patients were responders (defined as patients who lost at least 5% body weight within 3 months), compared with 19.5% of patients treated with placebo. In the Lead-in Phase (during which all subjects were treated with sibutramine), the intent to treat (ITT) population achieved an initial mean weight loss of 2.6 kg with sibutramine treatment. By the end of the Randomization Phase, patients on sibutramine

achieved a further mean reduction in weight of 0.91 kg while the placebo group experienced a mean increase of 1.02 kg compared with baseline Randomization Phase measurements. The mean change in weight from lead-in period baseline to treatment period final visit thus shows that patients receiving sibutramine lost 1.9 kg more weight than those taking placebo (3.5 kg vs. 1.6 kg). Sibutramine treatment of all patients during the Lead-in Phase may have contributed to the smaller difference in weight loss between sibutramine and placebo-treated patients observed in the SCOUT trial compared to previous studies. In all trials including SCOUT the average weight loss with sibutramine was 2-4 kg more than with placebo. After 12 months of treatment no additional mean weight loss was achieved with sibutramine. In addition, the maintenance of weight loss after cessation of treatment is questionable. Although patients on sibutramine as well as patients on placebo experienced decreased CV event rates when losing weight compared to those who did not, CV events were increased with the use of sibutramine compared to placebo suggesting that the weight loss achieved with sibutramine was not sufficient to counter-balance its adverse CV effects.

The CHMP noted that the SCOUT data clearly demonstrates that patients with obesity and known CV disease taking sibutramine are exposed to an increased risk for CV events compared with placebo. Sibutramine-treated patients in SCOUT had a statistically significantly higher incidence of primary outcome events compared with placebo treatment (hazard ratio HR 1.161, p=0.016), driven by non-fatal MI (HR 1.275, p=0.022) and non-fatal stroke (HR 1.354, 0.026). These non-fatal events are considered serious and life-threatening and may be associated with considerable morbidity. The CHMP considered that an increased CV risk may also apply to patients for whom sibutramine can be prescribed since overweight or obese patients are likely to be at risk for cardiovascular disease.

Comparing sibutramine-treated responders and placebo-treated non-responders (although this comparison may be influenced by behavioural differences including compliance to diet and exercise and is not a logical or scientific comparison to make) provides the most favourable benefit/risk for sibutramine. Even in this “best case scenario” approximately 1400 patients would need to be treated with sibutramine to prevent one CV event. On the other hand, comparing sibutramine responders to placebo responders (a comparison that ignores the finding that more patients achieved 5% weight loss on sibutramine compared to placebo) reveals a number needed to be exposed to sibutramine of 347 for one extra CV event to occur.

The CHMP considered that the currently approved indication and contraindications already provide substantial restrictions and that additional restrictions would not be practical. Moreover, although sophisticated CV screening tests are available such tests are neither reliable to predict future CV events nor practical for detection of CV disease prior to sibutramine treatment. During the December 2009 meeting, following the MAHs Oral Explanation, the CHMP therefore adopted a List of Outstanding Issues, asking the MAHs to further discuss, based on the SCOUT data, any potential patient population in which a positive benefit/risk balance could be established, the evidence of any favourable effect of sibutramine treatment compared to placebo and further risk minimisation measures. The CHMP also requested a Scientific Advisory Group (SAG) Diabetes/Endocrinology meeting to be held in January to provide additional expert input.

Data stratified by CV risk group shows that the “CV + DM” (cardiovascular disease plus Type 2 diabetes) group carried the highest risk of POE, followed by the “CV Only” (cardiovascular disease) group and the “DM Only” (Type 2 diabetes) group. However, although there was no evidence of increased risk of POE or mortality within the DM Only group, the evidence of benefit was considered to be weak. In addition, an increase in duration of use tended to increase the risk of non-fatal POE in this subgroup and the point estimate for non-fatal POE tended towards harm at the three year time point. The CHMP also suggested that the influence of gender within this subgroup (61% females compared with 32-37% in the CV Only group and 36% in the CV + DM group) warrants consideration, as the Cox regression analysis suggests that females have a 40% lower risk of primary outcome than males. The Kaplan-Meier curve shows an early increased risk of POE and an even earlier increase for non-fatal POE. The MAHs also emphasised the benefit from weight loss induced by sibutramine during the Lead-in period and suggested that this would bias the placebo group results. This was acknowledged, however the CHMP considered that the

data shows that the risk of CV events for patients continued on sibutramine was higher than if continued on placebo. Additionally, the CHMP noted the exclusion of 231 high-risk patients with increased HR and/or BP during the Lead-in Period, which is likely to dilute and underestimate the true risk of CV events in the sibutramine arm as such regular and careful BP and HR monitoring is unlikely to be fully implemented in clinical practice. The MAHs provided data on improvements in surrogate markers associated with sibutramine treatment but the CHMP noted that despite these effects an increased cardiovascular risk had been observed, and there were no other benefits other than those indirectly related to weight loss.

The CHMP assessed the proposed risk minimisation measures but noted no changes to the current indicated population and no additional testing for covert cardiovascular conditions besides those already listed in the SPC. The CHMP acknowledged that identification and exclusion of patients at risk of CV disease is difficult, as obesity itself is a risk factor for CV disease. The proposed educational measures (including Direct Healthcare Professional Communication (DHPC) letters, Q&A documents, a call centre and a secure website and patient tracking log books) were not considered likely to decrease the risk for patients or allow the identification of patients with covert CV disease as atherosclerotic complications cannot be diagnosed by BP, HR or weight measurements. A revision of the packaging to limit availability to a 1-month supply was not considered to reduce the increased cardiovascular risk associated with sibutramine and restriction to a one month prescription may not be appropriate for a primary care prescribed product for an increasingly prevalent condition. Furthermore, given the clear divergence of risks between sibutramine and placebo treated patients early on in therapy, the CHMP did not agree that the data supports a treatment duration of one year. Similarly, the proposed yearly PSUR reporting cycle was considered unlikely to promote SPC compliance regarding prescription. In conclusion, the CHMP considered that the proposed risk minimisation measures were inadequate to ensure SPC compliance or to adequately minimise the potential cardiovascular and cerebrovascular risks.

Benefit/risk

In conclusion, the CHMP was of the opinion that the results of the SCOUT study are of concern. Although most of the patients included in the SCOUT study would not normally be prescribed sibutramine, as this drug is contra-indicated in patients with known CV disease, an increased CV risk is also relevant to clinical use of sibutramine because overweight or obese patients are likely to be at risk of CV disease. In addition, it is impossible to exclude patients with covert cardiovascular disease from receiving sibutramine even with risk minimisation measures in place. The SCOUT study was powered as a superiority study aiming to show a decrease in the POE rate in the sibutramine treated patients compared to placebo. Given its modest efficacy and the known risks of sibutramine, the statistically robust evidence of an increased risk of non-fatal MI and stroke in patients with CV disease or Type 2 diabetes with sibutramine treatment compared with placebo is therefore of considerable concern. The current use of sibutramine is already substantially restricted by the SPC and no further useful or practical restrictions were identified. In addition, it was not possible, based on the SCOUT data and other published or unpublished studies, to identify patient groups that may derive benefit from sibutramine use without an increased cardiovascular risk. Other beneficial effects on patients with regards to other system organ classes have not convincingly been shown.

In light of the above findings, the CHMP concluded that the benefit/risk ratio for sibutramine-containing medicinal products is not considered favourable and recommended the suspension of the Marketing Authorisations for the sibutramine-containing medicinal products referred to in Annex I.

GROUNDS FOR THE SUSPENSION OF THE MARKETING AUTHORISATIONS

The Committee considered the data from the SCOUT study, the MAHs responses to the CHMP questions, the report from the SAG for Diabetes and Endocrinology and the discussions within the Committee,

Whereas,

- The Committee considered the procedure under Article 107 of Directive 2001/83/EC, as amended for sibutramine-containing medicinal products,
- The Committee concluded that the SCOUT study showed an increased risk of serious cardiovascular events in subjects with cardiovascular disease using sibutramine and because obese subjects are likely to be at risk of cardiovascular disease, the risks identified in the SCOUT study are considered relevant to the clinical use of sibutramine,
- The Committee considered that the cardiovascular safety concerns are not adequately counterbalanced by the beneficial effects of sibutramine as, on average, the weight loss achieved with the drug is modest, and may not be sustained after cessation of treatment,
- The Committee further considered that a patient population in which sibutramine-containing medicinal products have a clear positive benefit/risk cannot be identified based on the current data,
- The Committee considered that the risk minimisation measures proposed by the MAHs will not ensure compliance with the SPC or adequately protect public health,

The CHMP concluded that the benefit/risk balance of sibutramine-containing medicinal products is affected adversely by the results from the SCOUT study and is considered to be negative.

Following the provisions under Article 107(2) of Directive 2001/83/EC, as amended, the Agency's Committee for Medicinal Products for Human Use (CHMP) adopted an opinion recommending the suspension of the Marketing Authorisations for all sibutramine-containing medicinal products (see Annex 1). The CHMP also recommended that temporary measures are needed and therefore recommends to the European Commission that the marketing and use of sibutramine-containing medicinal products be suspended forthwith in all concerned EU Member States awaiting the adoption of the final measures.

For the suspension to be lifted the Marketing Authorisation Holders would need to provide convincing data to identify a patient population in which sustained and clinically-important efficacy of sibutramine-containing products can be demonstrated, and in which the benefit clearly outweighs its risks (see Annex III)

ANNEX III

CONDITIONS FOR LIFTING THE SUSPENSION

For the suspension to be lifted the Marketing Authorisation Holders would need to provide the National Competent Authorities with the following:

Convincing data to identify a patient population in which sustained and clinically-important efficacy of sibutramine-containing products can be demonstrated, and in which the benefit clearly outweighs its risks.