Annex I

List of the names, pharmaceutical form(s), strength(s) of the medicinal product(s), route(s) of administration, marketing authorisation holder(s) in the member states

Member State EU / EEA	Marketing authorisation holder	Product name	Strength	Pharmaceutical form	Route of administration
Austria	Servier Austria GmbH Mariahilfer Straße 20/5 Vienna 1070 Austria	Vastarel 35 mg - Filmtabletten mit veränderter Wirkstofffreisetzung	35 mg	Modified-release film-coated tablet	Oral use
Bulgaria	Les Laboratoires Servier, 50, rue Carnot 92284 Suresnes cedex France	Preductal MR	35 mg	Modified-release tablet	Oral use
Bulgaria	Medica AD Industrial area Sandanski 2800 Bulgaria	Prectazidine MR	35 mg	Modified-release tablet	Oral use
Bulgaria	Actavis Group PTC ehf., Reykjavikurvegi 76-78 220 Hafnarfjordur Iceland	Vascotasin	35 mg	Modified-release tablet	Oral use
Bulgaria	ratiopharm GmbH Graf-Arco-Strasse 3 89079 Ulm Germany	Trimetazidine-ratiopharm	35 mg	Modified-release tablet	Oral use
Bulgaria	S.C. Labormed Pharma S.A. 44 B, Theodor Pallady, sector 3 Bucharest Romania	Predozone	20 mg	Coated tablet	Oral use
Bulgaria	Sopharma AD 16 Iliensko shosse str. 1220 Sofia Bulgaria	Trimductal	20 mg	Film-coated tablet	Oral use
Bulgaria	Mylan S.A.S. 117 Allee des Parcs 69800 Saint Priest France	Trimetazigen MR	35 mg	Prolonged - release tablet	Oral use

Bulgaria	Glenmark Pharmaceuticals s.r.o. Hvezdova 1716/2b Prague 4, 140 78 Czech Republic	Apstar	35 mg	Modified-release tablet	Oral use
Bulgaria	Gedeon Richter Plc. Gyomroi ut 19-21 H- 1103 Budapest Hungary	Moduxin MR	35 mg	Prolonged release tablets	Oral use
Bulgaria	Sandoz d.d. Verovskova 57 1000 Ljubljana Slovenia	Trimeluzine	35 mg	Modified-release tablet	Oral use
Cyprus	Les Laboratoires Servier 50, rue Carnot 92284 Suresnes cedex France	VASTAREL 20 mg	20mg	Film-coated tablet	Oral use
Cyprus	Les Laboratoires Servier 50, rue Carnot 92284 Suresnes cedex France	VASTAREL	20mg/ml	Oral drops	Oral use
Cyprus	Les Laboratoires Servier 50, rue Carnot 92284 Suresnes cedex France	VASTAREL MR	35mg	Modified-release film-coated tablet	Oral use
Czech Republic	Les Laboratoires Servier 50, rue Carnot 92284 Suresnes cedex France	PREDUCTAL MR	35 mg	Modified-release tablet	Oral use
Czech Republic	Actavis Group PTC ehf., Hafnarfjördur Reykjavikurvegur 76-78 220 Hafnarfjördur Iceland	TRIMETAZIDIN ACTAVIS 35 MG	35 mg	Modified-release tablet	Oral use
Czech Republic	Mylan S.A.S 117 Alleé des Parcs 69 800, Saint-Priest France	TRIMETAZIDIN MYLAN 35 MG	35mg	Prolonged-release tablet	Oral use

Czech Republic	SANDOZ s.r.o. U Nákladového nádraží 10 130 00 Prague Czech Republic	TRIMETAZIDIN SANDOZ 35 MG	35mg	Prolonged-release tablet	Oral use
Czech Republic	Glenmark Pharmaceuticals s.r.o Hvezdova 1716/2b Prague 4, 140 78 Czech Republic	PORTORA 35 MG TABLETY S PRODLOUŽENÝM UVOLŇOVÁNÍM	35 mg	Prolonged-release tablet	Oral use
Czech Republic	Teva Pharmaceuticals CR, s.r.o. Radlická 3185/1c 150 00 Prague 5 Czech Republic	TRIMETAZIDIN TEVA RETARD 35 MG	35 mg	Prolonged-release tablet	Oral use
Denmark	Les Laboratoires Servier 50, rue Carnot 92284 Suresnes cedex France	Vastarel	20 mg	Film-coated tablet	Oral use
Estonia	Les Laboratoires Servier 50, rue Carnot 92284 Suresnes cedex France	TRIMETAZIDINE MR SERVIER	35mg	Modified-release tablet	Oral use
Estonia	Les Laboratoires Servier 50, rue Carnot 92284 Suresnes cedex France	PREDUCTAL MR	35mg	Modified-release tablet	Oral use
Estonia	Actavis Group PTC ehf Reykjavikurvegi 76-78 220 Hafnarfjördur Island	TRIMETAZIDINE ACTAVIS	35mg	Modified-release tablet	Oral use
Estonia	Teva Pharma B.V. Computerweg 10 3542 DR Utrecht The Netherlands	TRIMETAZIDINE TEVA 35 MG	35 mg	Film-coated tablet	Oral use
Estonia	Sandoz d.d. Verovskova 57 SI-1000 Ljubljana Slovenia	ZIDMETIN	35 mg	Prolonged-release tablet	Oral use

France	BIOGARAN 15, boulevard Charles de Gaulle 92707 Colombes Cedex France	TRIMETAZIDINE ALMUS	20 mg	Film-coated tablet	Oral use
France	BIOGARAN 15, boulevard Charles de Gaulle 92707 Colombes Cedex France	TRIMETAZIDINE BIOGARAN	20 mg	Film-coated tablet	Oral use
France	BIOGARAN 15, boulevard Charles de Gaulle 92707 Colombes Cedex France	TRIMETAZIDINE BIOGARAN	20 mg/ml	Oral solution	Oral use
France	BIOGARAN 15, boulevard Charles de Gaulle 92707 Colombes Cedex France	TRIMETAZIDINE BIOGARAN	35 mg	Modified-release film-coated tablet	Oral use
France	CRISTERS 22 quai Gallieni 92150 Suresnes France	TRIMETAZIDINE CRISTERS	20 mg	Film-coated tablet	Oral use
France	QUALIMED 117, allée des Parcs 69800 Saint-Priest France	TRIMETAZIDINE QUALIMED	20 mg/ml	Oral drops, solution	Oral use
France	QUALIMED 117, allée des Parcs 69800 Saint-Priest France	TRIMETAZIDINE QUALIMED	35 mg	Modified-release film-coated tablet	Oral use
France	Les Laboratoires Servier 50, rue Carnot 92284 Suresnes cedex France	VASTAREL	20 mg	Film-coated tablet	Oral use
France	Les Laboratoires Servier 50, rue Carnot 92284 Suresnes cedex France	VASTAREL	20 mg/ml	Oral drops, solution	Oral use

France	Les Laboratoires Servier 50, rue Carnot 92284 Suresnes cedex France	VASTAREL	35 mg	Modified-release film-coated tablet	Oral use
France	VENIPHARM 4, bureaux de la Colline 92213 Saint-Cloud France	TRANETIZ	35 mg	Modified-release film-coated tablet	Oral use
France	VENIPHARM 4, bureaux de la Colline 92213 Saint-Cloud France	TRIGEMAX	35 mg	Modified-release film-coated tablet	Oral use
France	BIOGARAN 15, boulevard Charles de Gaulle 92707 Colombes Cedex France	TRIMETAZIDINE BGR	35 mg	Modified-release film-coated tablet	Oral use
France	CLL PHARMA Nice Premier - Arénas 455, Promenade des Anglais 06299 Nice Cedex 03 France	TRIMETAZIDINE CLL PHARMA	35 mg	Modified-release film-coated tablet	Oral use
France	SOCIÉTÉ IPSOR GENERIQUES - IGEN 18, avenue des Champs-Elysées 75008 Paris France	TRIMETAZIDINE IGEN	20 mg/ml	Oral drops, solution	Oral use
France	LABORATOIRES IPSOR 18 Avenue des Champs Elysees 75008 Paris France	TRIMETAZIDINE IPSOR	20 mg	Film-coated tablet	Oral use
France	LABORATOIRES IPSOR 18 Avenue des Champs Elysees 75008 Paris France	TRIMETAZIDINE IPSOR	20 mg/ml	Oral drops, solution	Oral use

France	PLUS PHARMACIE SA 26, boulevard Paul Vaillant-Couturier 94200 Ivry-sur-Seine France	TRIMETAZIDINE ISOMED	35 mg	Modified-release film-coated tablet	Oral use
France	CLL PHARMA Nice Premier - Arénas 455, Promenade des Anglais 06299 Nice Cedex 03 France	TRIMETAZIDINE MILGEN	20 mg	Film-coated tablet	Oral use
France	CLL PHARMA Nice Premier - Arénas 455, Promenade des Anglais 06299 Nice Cedex 03 France	TRIMETAZIDINE MILGEN	20 mg/ml	Oral drops, solution	Oral use
France	RATIOPHARM GMBH Graf Arco Strasse 3 89079 Ulm Germany	TRIMETAZIDINE RATIOPHARM	35 mg	Modified-release film-coated tablet	Oral use
France	SUBSTIPHARM 8, rue Bellini 75116 Paris France	TRIMETAZIDINE SUBSTIPHARM	20 mg/ml	Oral drops, solution	Oral use
France	ZYDUS FRANCE 25, rue des Peupliers ZAC Les Hautes Pâtures - Parc d'Activités des Peupliers 92000 Nanterre France	TRIMETAZIDINE ZYDUS	20 mg	Film-coated tablet	Oral use
France	ZYDUS FRANCE 25, rue des Peupliers ZAC Les Hautes Pâtures - Parc d'Activités des Peupliers 92000 Nanterre France	TRIMETAZIDINE ZYDUS	20 mg/ml	Oral solution	Oral use

France	VENIPHARM 4, bureaux de la Colline 92213 Saint-Cloud France	TRIMEVENI	35 mg	Modified-release film-coated tablet	Oral use
France	TEVA SANTE Le Palatin 1 1 cours du Triangle 92936 Paris la Défense Cedex France	TRIMETAZIDINE TEVA	20 mg/ml	Oral solution	Oral use
France	TEVA SANTE Le Palatin 1 1 cours du Triangle 92936 Paris la Défense Cedex France	TRIMETAZIDINE TEVA	20 mg	Film-coated tablet	Oral use
France	TEVA SANTE Le Palatin 1 1 cours du Triangle 9296 Paris la Défense Cedex France	TRIMETAZIDINE TEVA	35 mg	Modified-release film-coated tablet	Oral use
France	SANOFI AVENTIS FRANCE 1-13, boulevard Romain Rolland 75014 Paris France	TRIMETAZIDINE WINTHROP	20 mg	Film-coated tablet	Oral use
France	SANOFI AVENTIS FRANCE 1-13, boulevard Romain Rolland 75014 Paris France	TRIMETAZIDINE WINTHROP	20 mg/ml	Oral solution	Oral use
France	SANOFI AVENTIS FRANCE 1-13, boulevard Romain Rolland 75014 Paris France	TRIMETAZIDINE WINTHROP	35 mg	Modified-release film coated tablet	Oral use
France	AJC INVEST 6, rue de la Rochefoucauld 16000 Angoulême France	RIMETAZE	20mg	Film coated tablet	Oral use

France	AJC INVEST 6, rue de la Rochefoucauld 16000 Angoulême France	RIMETAZE	20 mg/ml	Oral solution	Oral use
France	MYLAN SAS 117, allée des Parcs 69800 Saint-Priest France	TRIMETAZIDINE MYLAN	20 mg	Film coated tablet	Oral use
France	MYLAN SAS 117, allée des Parcs 69800 Saint-Priest France	TRIMETAZIDINE MYLAN	20 mg/ml	Oral solution	Oral use
France	MYLAN SAS 117, allée des Parcs 69800 Saint-Priest France	TRIMETAZIDINE MYLAN	35 mg	Modified-release film-coated tablet	Oral use
France	SANDOZ 49, avenue Georges Pompidou 92300 Levallois-Perret France	TRIMETAZIDINE SANDOZ	20 mg	Film coated tablet	Oral use
France	SANDOZ 49, avenue Georges Pompidou 92300 Levallois-Perret France	TRIMETAZIDINE SANDOZ	20 mg/ml	Oral solution	Oral use
France	ACTAVIS France La Boursidière Centre d'Affaires 92357 Le Plessis Robinson France	TRIMETAZIDINE ACTAVIS	20 mg	Film coated tablet	Oral use
France	QUALIMED 117, allée des Parcs 69800 Saint-Priest France	TRIMETAZIDINE QUALIMED	20 mg	Film coated tablet	Oral use
France	PLUS PHARMACIE SA 26, boulevard Paul Vaillant-Couturier 94200 Ivry-sur-Seine France	TRIMETAZIDINE ISOMED	20 mg	Coated tablet	Oral use

France	EG LABO - LABORATOIRES EUROGENERICS "Le Quintet" - bâtiment A 12, rue Danjou 92517 Boulogne Billancourt Cedex France	TRIMETAZIDINE EG	20 mg	Film coated tablet	Oral use
France	EG LABO - LABORATOIRES EUROGENERICS "Le Quintet" - bâtiment A 12, rue Danjou 92517 Boulogne Billancourt Cedex France	TRIMETAZIDINE EG	20 mg/ml	Oral solution	Oral use
France	EG LABO - LABORATOIRES EUROGENERICS "Le Quintet" - bâtiment A 12, rue Danjou 92517 Boulogne Billancourt Cedex France	TRIMETAZIDINE EG	35 mg	Modified-release film-coated tablet	Oral use
France	ARROW GENERIQUES 26, avenue Tony Garnier 69007 Lyon France	TRIMETAZIDINE ARROW	20 mg	Film coated tablet	Oral use
France	ARROW GENERIQUES 26, avenue Tony Garnier 69007 Lyon France	TRIMETAZIDINE ARROW	20 mg/ml	Oral solution	Oral use
France	RATIOPHARM GMBH Graf Arco Strasse 3 89079 Ulm Germany	TRIMETAZIDINE RATIOPHARM	20 mg	Coated tablet	Oral use
France	RATIOPHARM GMBH Graf Arco Strasse 3 89079 Ulm Germany	TRIMETAZIDINE RATIOPHARM	20 mg/ml	Oral solution	Oral use

France	SANDOZ 49, avenue Georges Pompidou 92300 Levallois-Perret France	TRIMETAZIDINE SANDOZ	35 mg	modified-release film-coated tablet	Oral use
Germany	ratiopharm GmbH Graf-Arco-Str. 3 89079 Ulm Germany	Trimetazidin-ratiopharm 35 mg Retardtabletten	35 mg	Prolonged release tablet	Oral use
Germany	Mepha Investigacao, Desenvolvimento e Fabricacao Farmaceutica, Lda. Lagoas Park, Edificio 5A, Piso 2 2740-298 Porto Salvo Portugal	Mephatrim 35 mg Retardtabletten	35 mg	Prolonged release tablet	Oral use
Greece	HELP ABEE, Valaoritou 10 Metamorfosi Attikis 14452 Greece	NOVAZIDINE	20mg/ml	Oral drops, solution	Oral use
Greece	FOINIXFARM EPE Dervenakion 38 & Sachini Gerakas 15344 Greece	ZIDIN	20mg/ml	Oral drops, solution	Oral use
Greece	SERVIER HELLAS PHARMACEUTICALS Ltd, Ethnikis Antistaseos 72 & Agamemnonos Greece	VASTAREL	20 mg/tab	Film-coated tablet	Oral use
Greece	SERVIER HELLAS PHARMACEUTICALS Ltd, Ethnikis Antistaseos 72 & Agamemnonos Greece	VASTAREL	20mg/ml	Oral drops, solution	Oral use
Greece	SERVIER HELLAS PHARMACEUTICALS Ltd, Ethnikis Antistaseos 72 & Agamemnonos Greece	VASTAREL	35 mg/tab	Controlled release tablet	Oral use

Hungary	Richter Gedeon nyrt. Gyömrői út 19-21. 1103 Budapest Hungary	Moduxin MR	35 mg	Prolonged-release tablet	Oral use
Hungary	Les Laboratoires Servier, 50, rue Carnot 92284 Suresnes cedex France	Preductal MR	35 mg	Modified-release film-coated tablet	Oral use
Hungary	EGIS Gyógyszergyár nyrt. Keresztúri út 30-38. 1106 Budapest Hungary	Adexor MR	35 mg	Modified-release film-coated tablet	Oral use
Hungary	Glenmark Pharmaceuticals s.r.o Hvezdova 1716/2b Prague 4, 140 78 Czech Republic	APSTAR 35 mg retard tabletta	35 mg	Prolonged-release tablet	Oral use
Hungary	ratiopharm GmbH Graf-Arco-Strasse 3 89079 Ulm Germany	TRIMETAZIDIN-RATIOPHARM 35 mg retard tabletta	35 mg	Prolonged-release tablet	Oral use
Hungary	Mylan S.A.S 117 Allee des Parcs 69800 Saint Priest France	TRIMETAZIDINE MYLAN 35 mg retard tabletta	35 mg	Prolonged-release tablet	Oral use
Hungary	Actavis Group PTC ehf., Hafnarfjördur Reykjavikurvegur 76-78 220 Hafnarfjördur Iceland	VASCOTASIN 35 mg módosított hatóanyagleadású tabletta	35 mg	modified release tablet	Oral use
Hungary	Sandoz Hungária Kft. 1114 Budapest Bartók Béla út 43-47. Magyarország Hungary	TRIMETAZIDINE SANDOZ 35 mg retard tabletta	35 mg	Prolonged-release tablet	Oral use

Ireland	Servier Laboratories (Ireland) Ltd First Floor, Block 2 West Pier BusinessCampus Old Dunleary Road, Dun Laoghaire Dublin Ireland	Vastarel	20mg	Film-coated tablet	Oral use
Ireland	Servier Laboratories (Ireland) Ltd First Floor, Block 2 West Pier BusinessCampus Old Dunleary Road, Dun Laoghaire Dublin Ireland	Trimetazidine	35mg	Prolonged-release film-coated tablet	Oral use
Ireland	Servier Laboratories (Ireland) Ltd First Floor, Block 2 West Pier BusinessCampus Old Dunleary Road, Dun Laoghaire Dublin Ireland	Vastarel	35mg	Prolonged-release film-coated tablet	Oral use
Italy	Istituto Farmaco Biologico Stroder S.R.L. Via di Ripoli, 207V - 50126 Firenze Italy	VASTAREL	20 MG	Coated tablet	Oral use
Latvia	Gedeon Richter Plc. H-1103 Budapest Gyömrői út 19-21 Hungary	Moduxin 35 mg ilgstošās darbības tabletes	35 mg	Prolonged-release tablet	Oral use
Latvia	Actavis Group PTC ehf., Reykjavikurvegi 76-78, 220 Hafnarfjorður Iceland	Trimetazidine Actavis 35 mg ilgstošās darbības tabletes	35 mg	Modified-release tablet	Oral use
Latvia	Les Laboratoires Servier 50, rue Carnot 92284 Suresnes cedex France	Preductal MR 35 mg ilgstošās darbības apvalkotās tabletes	35 mg	Modified-release tablet	Oral use

Latvia	Les Laboratoires Servier 50, rue Carnot 92284 Suresnes cedex France	Trimetazidine MR Servier 35 mg ilgstošās darbības apvalkotās tabletes	35 mg	Modified-release tablet	Oral use
Latvia	Teva Pharma B.V. Computerweg 10, 3542 DR Ultrecht The Netherlands	Trimetazidine Teva 35 mg ilgstošās darbības tabletes	35 mg	Prolonged-release tablet	Oral use
Latvia	Sandoz d.d Verovskova 57, SI-1000 Ljubljana Slovenia	Zidmetin 35 mg ilgstošās darbības tabletes	35 mg	Modified-release tablet	Oral use
Lithuania	Sandoz d.d Verovskova 57, SI-1000 Ljubljana Slovenia	Zidmetin	35 mg	Prolonged-release tablet	Oral use
Lithuania	Les Laboratoires Servier, 50, rue Carnot 92284 Suresnes cedex France	Preductal MR	35 mg	Modified-release film-coated tablet tablet	Oral use
Lithuania	Les Laboratoires Servier, 50, rue Carnot 92284 Suresnes cedex France	Trimetazidine MR Servier	35 mg	Modified-release film-coated tablet tablet	Oral use
Lithuania	Teva Pharma B.V. Computerweg 10 3542 DR Ultrecht The Netherlands	Trimetazidine-Teva	35 mg	Prolonged-release tablet	Oral use
Lithuania	Actavis Group PTC ehf., Reykjavikurvegi 76-78 220 Hafnarfjorður Iceland	Trimetazidine Actavis	35 mg	Modified-release tablet	Oral use
Luxembourg	Les Laboratoires Servier, 50, rue Carnot 92284 Suresnes cedex France	Vastarel-20	20mg	Coated tablet	Oral use
Luxembourg	Les Laboratoires Servier, 50, rue Carnot 92284 Suresnes cedex France	Vastarel	20mg/ml	Drops	Oral use

Luxembourg	Les Laboratoires Servier 50, rue Carnot 92284 Suresnes cedex France	Vastarel-35	35mg	Prolonged-release tablet	Oral use
Malta	Les Laboratoires Servier, 50, rue Carnot 92284 Suresnes cedex France	VASTAREL 20 mg	20 mg	Film-coated tablet	Oral use
Malta	Les Laboratoires Servier, 50, rue Carnot 92284 Suresnes cedex France	VASTAREL MR	35 mg	Modified release film coated tablet	Oral use
Poland	Ethifarm Sp. z o. o. ul. Hiacyntowa 39 60-175 Poznań Poland	Cyto-Protectin MR	35mg	Prolonged-release tablet	Oral use
Poland	Przedsiębiorstwo Farmaceutyczne LEK-AM Sp. z o.o. Ostrzykowizna 14A 05-170 Zakroczym Poland	Trimeductan MR	35mg	Prolonged-release tablet	Oral use
Poland	Pabianickie Zakłady Farmaceutyczne Polfa S.A. Marszałka J. Piłsudskiego 5, 95-200 Pabianice Poland	Metazydyna	20 mg	Film-coated tablet	Oral use
Poland	Les Laboratoires Servier, 50, rue Carnot 92284 Suresnes cedex France	Preductal	20 mg	Film-coated tablet	Oral use
Poland	ANPHARM Przedsiębiorstwo Farmaceutyczne S.A. ul. Annopol 6B 03-236 Warszawa Poland	Preductal MR	35 mg	Modified-release film-coated tablet	Oral use

Poland	Gedeon Richter Polska Sp. z o.o. Graniczna str. 35 05-825 Grodzisk Mazowiecki Poland	Protevasc SR	35 mg	Modified-release film-coated tablet	Oral use
Poland	ratiopharm GmbH Graf-Arco-Strasse 3 Ulm, 89079 Germany	Trimetaratio	20 mg	Film-coated tablet	Oral use
Poland	ratiopharm GmbH Graf-Arco-Strasse 3 Ulm, 89079 Germany	Trimetazidine-ratiopharm PR	35 mg	Prolonged-release tablet	Oral use
Poland	Ethifarm Sp. z o. o. ul. Hiacyntowa 39 60-175 Poznań Poland	Cyto-Protectin MR	35mg	Prolonged-release tablet	Oral use
Poland	Glenmark Pharmaceuticals s.r.o. Hvezdova 1716/2b Praga 4 CZ-140 78 Czech Republic	Portora	35 mg	Prolonged-release tablet	Oral use
Poland	Zentiva, k.s. U kabelovny 130 Praga 10, Dolni Mecholupy 10237 Dolni Mecholupy Czech Republic	Trimedal	35 mg	Prolonged-release tablet	Oral use
Poland	Sandoz GmbH Biochemiestrasse 10 A-6250 Kundl Austria	Dimesar	35 mg	Prolonged-release tablet	Oral use
Portugal	Servier Portugal - Especialidades Farmacêuticas, Lda. Av. António Augusto de Aguiar, 128 1069-133 Lisboa Portugal	Vastarel	20 mg	Coated tablets	Oral use

Portugal	Servier Portugal - Especialidades Farmacêuticas, Lda. Av. António Augusto de Aguiar, 128 1069-133 Lisboa Portugal	Vastarel	20 mg/ml	Oral solution	Oral use
Portugal	Sanofi-Aventis - Produtos Farmacêuticos, Lda. Empreendimento Lagoas Park, Edifício 7 - 3º Piso 2740-244 Porto Salvo Portugal	Trimetazidina Zentiva	20 mg	Coated tablets	Oral use
Portugal	Labesfal - Laboratórios Almiro, S.A. Zona Industrial do Lagedo 3465-157 Santiago de Besteiros Portugal	Trimetazidina Labesfal 20 mg Comprimidos Revestidos	20 mg	Coated tablets	Oral use
Portugal	Mylan, Lda. Rua Doutor António Loureiro Borges, Edíficio Arquiparque 1, R/C Esqº 1499-016 Algés Portugal	Trimetazidina Mylan	20 mg	Coated tablets	Oral use
Portugal	Generis Farmacêutica, S.A. Rua João de Deus, 19 2700-487 Amadora Portugal	Trimetazidina Generis 20 mg Comprimidos Revestidos	20 mg	Coated tablets	Oral use
Portugal	Servier Portugal - Especialidades Farmacêuticas, Lda. Av. António Augusto de Aguiar, 128 1069-133 Lisboa Portugal	Vastarel LM	35 mg	Modified-release tablet	Oral use
Portugal	Bluepharma Genéricos - Comércio de Medicamentos, S.A. São Martinho do Bispo 3045-016 Coimbra Portugal	Trimetazidina Bluepharma 20 mg Comprimidos	20 mg	Coated tablets	Oral use

Portugal	Vida - Produtos Farmacêuticos, S.A. Rua da Estação, 42 - Vala do Carregado 2600-726 Castanheira do Ribatejo Portugal	Trimetazidina Vida	20 mg	Coated tablets	Oral use
Portugal	Helm Portugal, Lda. Estrada Nacional n.º 10, Km 140, 260 2695-066 Bobadela - Loures Portugal	Trimetazidina Baldacci 20 mg Comprimidos	20 mg	Coated tablets	Oral use
Portugal	Mepha - Investigação, Desenvolvimento e Fabricação Farmacêutica, Lda. Lagoas Park, Edifício 5 A - Piso 2 2740-298 Porto Salvo Portugal	Trimetazidina Mepha 20 mg Comprimidos Revestidos	20 mg	Coated tablets	Oral use
Portugal	Jaba Recordati, S. A. Lagoas Park, Edificio 5, Torre C, Piso 3 2740-298 Porto Salvo Portugal	Trimetazidina Jaba 20 mg Comprimidos revestidos	20 mg	Coated tablets	Oral use
Portugal	Teva Pharma - Produtos Farmacêuticos, Lda Lagoas Park, Edifício 1 - 3º 2740-264 Porto Salvo Portugal	Trimetazidina Teva	20 mg	Coated tablets	Oral use
Portugal	Les Laboratoires Servier 50, rue Carnot 92284 Suresnes cedex France	Tacirel LM	35 mg	Modified-release tablet	Oral use
Portugal	Cinfa Portugal, Lda. Av.Tomás Ribeiro, 43 - Bloco 1, 4º B - Edifício Neopark 2790-221 Carnaxide Portugal	Trimetazidina Cinfa 20 mg Comprimidos revestidos por película	20 mg	Film-coated tablets	Oral use

Portugal	Ratiopharm - Comércio e Indústria de Produtos Farmacêuticos, Lda. Rua Quinta do Pinheiro - Edifício Tejo - 6º Piso 2790-143 Carnaxide Portugal	Trimetazidina Ratiopharm	20 mg	Film-coated tablets	Oral use
Portugal	Ratiopharm - Comércio e Indústria de Produtos Farmacêuticos, Lda. Rua Quinta do Pinheiro - Edifício Tejo - 6º Piso 2790-143 Carnaxide Portugal	Trimetazidina Ratiopharm	35 mg	Prolonged-release tablets	Oral use
Portugal	Generis Farmacêutica, S.A. Rua João de Deus, 19 2700-487 Amadora Portugal	Trimetazidina Generis	35 mg	Prolonged-release tablets	Oral use
Portugal	Teva Pharma - Produtos Farmacêuticos, Lda Lagoas Park, Edifício 1 - 3º 2740-264 Porto Salvo Portugal	Trimetazidina Teva	35 mg	Prolonged-release tablets	Oral use
Portugal	Labesfal - Laboratórios Almiro, S.A. Zona Industrial do Lagedo 3465-157 Santiago de Besteiros Portugal	Trimetazidina Labesfal	35 mg	Prolonged-release tablets	Oral use
Portugal	Sandoz Farmacêutica, Lda. Alameda da Beloura, Edifício 1, 2º - Escritório 15 2710-693 Sintra Portugal	Trimetazidina Sandoz	35 mg	Prolonged-release tablets	Oral use

Portugal	Mepha - Investigação, Desenvolvimento e Fabricação Farmacêutica, Lda. Lagoas Park, Edifício 5 A - Piso 2 2740-298 Porto Salvo Portugal	Trimetazidina Mepha LP	35 mg	Prolonged-release tablets	Oral use
Portugal	Bluepharma Genéricos - Comércio de Medicamentos, S.A. São Martinho do Bispo 3045-016 Coimbra Portugal	Trimetazidina Bluepharma LP	35 mg	Prolonged-release tablets	Oral use
Portugal	Sandoz Farmacêutica, Lda. Alameda da Beloura, Edifício 1, 2º - Escritório 15 2710-693 Sintra Portugal	Trimetazidina Itraxel	35 mg	Prolonged-release tablets	Oral use
Portugal	Pharmakern Portugal - Produtos Farmacêuticos, Sociedade Unipessoal, Lda. Edifício Atlas II, Av. José Gomes Ferreira, N.º 11 - 3º, Sala 31 - Miraflores 1495-139 Algés Portugal	Lupamadazine	35 mg	Prolonged-release tablets	Oral use
Portugal	Mylan, Lda. Rua Doutor António Loureiro Borges, Edíficio Arquiparque 1, R/C Esqº 1499-016 Algés Portugal	Trimetazidina Mylan	35 mg	Prolonged-release tablets	Oral use
Portugal	Sanofi-Aventis - Produtos Farmacêuticos, Lda. Empreendimento Lagoas Park, Edifício 7 - 3º Piso 2740-244 Porto Salvo Portugal	Zilutra	35 mg	Prolonged-release tablets	Oral use

Romania	MYLAN S.A.S. 117, Allée des Parcs 69800 Saint Priest France	Trimetazidina Mylan	35 mg	Prolonged-release tablet	Oral use
Romania	S.C. TERAPIA S.A. Str. Fabricii nr. 124 Cluj Napoca România	DILATAN MR 35 mg, comprimate filmate cu eliberare modificată, 35 mg	35 mg	Prolonged-release tablet	Oral use
Romania	S.C. TERAPIA S.A. Str. Fabricii nr. 124 Cluj Napoca România	DILATAN 20 mg, comprimate filmate, 20 mg	20mg	Film-coated tablet	Oral use
Romania	S.C. VIM SPECTRUM S.R.L., Şos. Sighişoarei nr. 409, Sat Corunca, Com. Livezeni Jud. Mureş România	TRIMETAZIDIN VIM SPECTRUM 20 mg, capsule	20 mg	Capsule	Oral use
Romania	Les Laboratoires Servier, 50, rue Carnot 92284 Suresnes cedex France	PREDUCTAL MR 35 mg, comprimate filmate cu eliberare modificată	35 mg	Modified-release tablet	Oral use
Romania	Les Laboratoires Servier, 50, rue Carnot 92284 Suresnes cedex France	PREDUCTAL 20 mg, comprimate filmate	20 mg	Film-coated tablet	Oral use
Romania	GEDEON RICHTER ROMÂNIA S. A. Str. Cuza - Vodă nr. 99 – 105 Târgu – Mureş România	MODUXIN MR 35 mg, comprimate filmate cu eliberare prelungită	35 mg	Prolonged-release tablet	Oral use
Romania	GEDEON RICHTER ROMÂNIA S. A. Str. Cuza - Vodă nr. 99 – 105 Târgu – Mureş România	MODUXIN 20 mg, comprimate filmate	20 mg	Film-coated tablet	Oral use
Romania	S.C. TERAPIA S.A. Str. Fabricii nr. 124 Cluj Napoca România	TRIMETAZIDINA 20 mg, drajeuri	20 mg	Coated tablet	Oral use

Romania	LABORMED PHARMA S.A. Bd. Theodor Pallady nr. 44B sector 3, Bucureşti România	TRIMETAZIDINĂ LPH 35mg, comprimate filmate cu eliberare modificată	35 mg	Modified-release tablet	Oral use
Romania	LABORMED PHARMA S.A. Bd. Theodor Pallady nr. 44B sector 3, Bucureşti România	TRIMETAZIDINĂ LPH 20 mg, comprimate filmate	20 mg	Film-coated tablet	Oral use
Romania	LABORMED PHARMA S.A. Bd. Theodor Pallady nr. 44B sector 3, Bucureşti România	Oxcardin 20 mg, comprimate filmate	20 mg	Film-coated tablet	Oral use
Romania	LABORMED PHARMA S.A. Bd. Theodor Pallady nr. 44B sector 3, Bucureşti România	Oxcardin MR 35mg, comprimate filmate cu eliberare modificată	35 mg	Modified-release tablet	Oral use
Romania	GLENMARK PHARMACEUTICALS s.r.o. Hvezdova 1716/2b, Prague 4, 140 78 Czech Republic	APSTAR 35 mg comprimate cu eliberare prelungită	35 mg	Prolonged-release tablet	Oral use
Romania	S.C.SANDOZ S.R.L. Str. Livezeni nr. 7A 540472 Târgu Mureş România	TRIMELUZINE 35 mg comprimate cu eliberare prelungită	35 mg	Prolonged-release tablet	Oral use
Slovak Republic	ratiopharm GmbH Graf-Arco-Strasse 3 89079 Ulm Germany	Trimetazidin-ratiopharm 20 mg	20 mg	Film-coated tablet	Oral use
Slovak Republic	ratiopharm GmbH Graf-Arco-Strasse 3 89079 Ulm Germany	Trimetazidin ratiopharm retard 35 mg	35 mg	Modified-release film-coated tablet	Oral use
Slovak Republic	PRO.MED.CS PRAHA a.s. Telčská 1 140 00 Praha Czech Republic	Angitrim	20 mg	Film-coated tablet	Oral use

Slovak Republic	EGIS Pharmaceuticals PLC Keresztúri út 30-38, 1106 Budapest Hungary	Adexor	20 mg	Film-coated tablet	Oral use
Slovak Republic	Les Laboratoires Servier, 50, rue Carnot 92284 Suresnes cedex France	PREDUCTAL MR	35 mg	Modified-release film-coated tablet	Oral use
Slovak Republic	Mylan S.A.S 117, Allée des Parcs 69800 Saint Priest France	Trimetazidin Mylan 35 mg	35 mg	Prolonged-release tablet	Oral use
Slovak Republic	Deml Group s.r.o. Jeneweinova 51a 617 00 Brno Czech Republic	Trimetazidin - DemlGroup PR 35 mg	35 mg	Prolonged-release film-coated tablet	Oral use
Slovak Republic	Actavis Group PTC ehf Reykjavkurvegi 76-78 220 Hafnarfiroi Iceland	Vascotazin 35 mg	35 mg	Modified-release tablet	Oral use
Slovak Republic	Glenmark Pharmaceuticals s.r.o. Hvezdova 1716/2b 140 78 Praha 4 Czech Republic	Apstar 35 mg tablety s predĺženým uvoľňovaním	35 mg	Prolonged-release tablet	Oral use
Slovenia	Servier Pharma d.o.o. Pot k sejmiscu 33 SI-1231 Ljubljana Crnuce Slovenia	PREDUCTAL MR 35 mg filmsko oblozene tablete s prirejenim sproscanjem	35 mg	Modified-release film-coated tablet	Oral use
Slovenia	Servier Pharma d.o.o. Pot k sejmiscu 33 SI-1231 Ljubljana Crnuce Slovenia	TRIMETAZIDIN SERVIER 35 mg filmsko obložene tablete s prirejenim sproščanjem	35 mg	Modified-release film-coated tablet	Oral use
Spain	LABORATORIOS DAVUR, S.L. C/ Teide, 4- planta baja Polígono Empresarial La Marina 28703 San Sebastian de los Reyes (MADRID) Spain	TRIMETAZIDINA DAVUR 20 mg comprimidos recubiertos EFG	20 mg	Film-coated tablet	Oral use

Spain	RIMAFAR, S.L. Polígono Industrial Malpica Calle C, Nº 4 50016 ZARAGOZA Spain	TRIMETAZIDINA RIMAFAR 20 mg comprimidos recubiertos EFG	20 mg	Film-coated tablet	Oral use
Spain	RATIOPHARM ESPAÑA, S.A. Avda. Burgos, 16 D-5ª planta 28036 MADRID Spain	TRIMETAZIDINA RATIOPHARM 20 mg comprimidos recubiertos con película EFG	20 mg	Film-coated tablet	Oral use
Spain	DANVAL, S.A. Avda. de los Madroños, 33 28043 Madrid Spain	IDAPTAN 20 mg comprimidos recubiertos con película	20 mg	Film-coated tablet	Oral use
Spain	DANVAL, S.A. Avda. de los Madroños, 33 28043 Madrid Spain	IDAPTAN 20 mg/ml solución oral	20 mg/ml	Oral solution	Oral use
Spain	LABORATORIOS CINFA, S.A. C/ Olaz-Chipi, 10 Polígono Industrial Areta 31620 Huarte (PAMPLONA) Spain	TRIMETAZIDINA CINFA 20 mg comprimidos recubiertos con película EFG	20 mg	Film-coated tablet	Oral use
Spain	PENSA PHARMA, S.A.U. C/ Jorge Comín (Médico Pediatra) 3-bajos 46015 Valencia Spain	TRIMETAZIDINA PENSA 20 mg comprimidos recubiertos con película EFG	20 mg	Film-coated tablet	Oral use

Annex II

Scientific conclusions and grounds for variation to the terms of the Marketing Authorisations

Scientific conclusions

Overall summary of the scientific evaluation of trimetazidine containing medicinal products (see Annex I)

Trimetazidine (TMZ) is a metabolic agent whose aim is to protect against ischemia by increasing glucose metabolism relative to that of fatty acids. Its mechanism of action results partly of its effect on cellular metabolism. By decreasing fatty acid oxidation at the level of 3-ketoacyl coenzyme A thiolase, it favours glucose oxidation, which improves the use of the cells' energy reserves in the event of ischaemia. Trimetazidine has no hemodynamic effect on blood pressure or heart rate.

Trimetazidine-containing medicinal products are indicated for prophylactic treatment of angina pectoris crisis, ancillary symptomatic treatment of vertigo and tinnitus and ancillary treatment of visual acuity decrease and visual field disturbances due to vascular reasons.

Trimetazidine medicinal products have been authorised in 21 European Member states. They were first authorised in France in 1978 and are available in three different pharmaceutical forms in the EU: 20 mg tablet, 20 mg/ml oral solution and 35 mg modified release (MR) tablet.

France on 22 April 2011 requested the CHMP to give its opinion under Article 31 of Directive 2001/83/EC on whether the marketing authorisation for trimetazidine-containing medicinal products should be maintained, varied, suspended or withdrawn on the basis of the increased Parkinson's reports.

Of note, all the data submitted and assessed for this referral are newly available data since the first authorisation of trimetazidine.

EFFICACY

Angina pectoris

The clinical experience with trimetazidine dates back to the early 70s.

The CHMP considered all the studies submitted for this indication. However, the TRIMPOL-II study (2001), the study by Sellier (2003) and the revised data from the VASCO study (2011) were the studies providing evidence generated in support of the add-on indication of trimetazidine in symptomatic patients with angina pectoris. These data support the efficacy of trimetazidine in add-on to beta-blockers. In addition the two studies by Manchanda (1997 and 2003) and four other minor studies are considered supportive of the efficacy of trimetazidine in add-on to calcium channel blockers (CCBs).

In a 426-patients randomised, double blind, placebo-controlled study (TRIMPOL-II), trimetazidine (60mg/day) added to metoprolol 100mg daily (50 mg b.i.d) for 12 weeks significantly improved statistically exercise tests parameters and clinical symptoms as compared to placebo: total exercise duration +20.1s, p= 0.023, total workload +0.54 METs, p=0.001, time to 1-mm ST-segment depression +33.4s, p=0.003, time to onset of angina +33.9s, p<0.001, angina attacks/week -0.73, p=0.014 and short acting nitrates consumption/week, -0.63, p=0.032, without hemodynamic changes.

The TRIMPOL-II showed that trimetazidine significantly improves exercise capacity and exercise-induced myocardial ischemia when added to metoprolol. It should be noted that the study was conducted using the Bruce protocol that it is known to underestimate the treatment effect of drugs compared to the modified Bruce protocol. The study results may thus be considered conservative in terms of magnitude of the effect of trimetazidine. Although the methodology followed by the MAH may be regarded as not totally compliant to the currently accepted standards, no major bias affecting the

interpretation of study results appears evident and all analyses show a beneficial effect of trimetazidine combined with metoprolol on exercise tolerance, myocardial ischemia and clinical symptoms. The post-hoc analysis of the study in 298 patients receiving trimetazidine in combination mainly with metoprolol is in line and it is considered useful to better assess the effect of trimetazidine in a population of patients that are often difficult to be treated with haemodynamic agents. Of importance the efficacy was confirmed in patients at maximal dose of metoprolol as well as in patients with recurrent angina.

The aim of the Sellier study (2003) was to assess the efficacy of the combination of trimetazidine MR 70 mg/day in patients suffering from angina pectoris who were insufficiently controlled on 50 mg/day of atenolol after two months of treatment. 223 patients were randomized for this double blind, placebo-controlled study where one 35 mg trimetazidine modified release tablet (b.i.d.) was added to 50 mg atenolol (o.d.) for 8 weeks and produced a significant increase (+34.4s, p=0.03) in the time to 1-mm ST-segment depression in exercise tests, in a sub-group of patients (n=173), when compared to placebo, 12 hours after taking the drug. A significant difference was also evidenced for the time to onset of angina pectoris (p=0.049). No significant difference between groups could be found for the other secondary endpoints (total exercise duration, total workload and clinical endpoints).

In order to show a benefit on daily episodes of angina it is important to adequately assess the baseline occurrence of angina and sublingual nitrate use and to calculate the sample size on the basis of the expected treatment effect. The Sellier study was an exercise study not primarily designed to assess clinical parameters. It is considered that the study is only adequate to show the efficacy of trimetazidine with reference to the primary endpoint, time to onset of angina pectoris, as no significant difference between groups could be found for the other secondary endpoints (total exercise duration, total workload and clinical endpoints).

In a 1962 patients three-month randomised, double-blinded study (VASCO study, 2011) on top of atenolol 50 mg/d, two dosages of trimetazidine (70 mg/d and 140 mg/d) were tested versus placebo. In the overall population, including both asymptomatic and symptomatic patients, trimetazidine failed to demonstrate a benefit on both ergometric (total exercise duration, time to onset of 1mm ST and time to onset angina) and clinical endpoints. However, in the subgroup of symptomatic patients (n= 1574) trimetazidine (140 mg) significantly improved total exercise duration (+23.8 s versus +13.1 s placebo; p=0.001) and time to onset of angina (+46.3 s versus +32.5 s placebo; p=0.005).

The VASCO study was conducted in symptomatic and asymptomatic patients with chronic ischemic heart disease. Less than 50% of patients included in the VASCO study had chronic stable angina despite probable coronary artery disease. The presence of stable angina pectoris is a pivotal inclusion criterion as it identifies the target population for the use of anti-anginal drugs. Indeed, it is well known that patients with proven coronary artery disease who are asymptomatic may not have inducible ischemia and that in these patients anti-anginal treatments are ineffective in improving exercise capacity.

The VASCO study showed a significant difference in the effect on ergometric parameters between trimetazidine at the highest dosage (140 mg) and placebo in the group of symptomatic patients. The analysis performed by the MAH has been repeated independently by the Italian Institutes of Health (ISS). This analysis showed that in patients with chronic stable angina trimetazidine given as add-on to atenolol significantly improved exercise tolerance (p<0.01), time to 1 mm ST segment depression and time to angina. The improvement in the primary end point with trimetazidine was observed in the pooled analysis of patients receiving 35 and 70 mg twice daily and in the analysis of patients receiving either 35 mg twice daily or 70 mg twice daily.

The efficacy of trimetazidine was also summarised in a recent network meta-analysis including 358 clinical trials and 27058 patients. Trimetazidine was shown to have an effect very similar to that of non-heart rate–lowering anti-anginal agents: nicorandil, ranolazine, long-acting nitrates and

dihydropyridines, with less than a few seconds differences in exercise tolerance test (ETT) ergometric parameters. The efficacy of trimetazidine is sufficiently demonstrated as add-on therapy in the short-medium-term (weeks /months) treatment of symptomatic patients with angina who are inadequately controlled by or intolerant to first-line antianginal therapies.

The CHMP considers that the revised indication is in line with the scientific evidence available at present for trimetazidine as add-on therapy and it is supported by trials that became available after the initial authorisation and considered to be of sufficient methodological quality and by meta-analyses that have come to similar conclusions. Recent surveys in patients with coronary artery disease have shown that most patients with angina do not receive adequate anti-anginal therapy because of haemodynamic intolerance or chronotropic incompetence. Therefore, trimetazidine as add-on therapy may represent an optional treatment drug to be used in association with first-line anti-anginal drugs especially in those patients for whom optimally control of symptoms cannot be achieved with other anti-anginal drugs in monotherapy due to haemodynamic intolerance or chronotropic incompetence.

Otology - Ear, Nose and Throat (ENT)

In response to the CHMP request regarding the re-evaluation of the risk/benefit ratio of trimetazidine (all forms and dosages) in the ENT indications, 9 clinical studies (Wayoff, 1984; Sterkers, 2001; Vitte, 2002; Haguenauer, 1980; Kluyskens, 1990; Martini, 1990; Morgon 1990; Coyas 1990 and France cochlea study, 2009 presented as support of safety since the efficacy objective was not reached) were submitted or presented as literature references. Most of these studies included patients presenting very heterogeneous pathologies of various severities with absence of prior stratification on these pathologies, and of very limited duration of treatment (between 2 and 3 months) not in line with what is required by these pathologies that necessitate long term treatments.

Among these studies, five studies were conducted against placebo including the additional study published in 1990 by Coyas. Each study generally included multiple objectives (pharmacodynamic or clinical evaluations). They also mixed ENT pathologies and symptomatologies from different etiologies such as tinnitus, different kinds of vertigo or deafness. The main studies conducted versus placebo were Wayoff study (tinnitus, dizziness, hearing loss) and Morgon study (tinnitus). They are studies whereby the results, often presented as statistically in favour of trimetazidine, are disputable mainly for methodological reasons. Two additional and more recent studies were focused on dizziness but the exploratory nature of the Sterkers study (2001) and the extremely small populations included (28 patients) do not make it possible to give any demonstrative weight to the results reported. In addition, Vitte study (2002) had the same methodological weaknesses as the Wayoff and Morgon studies. Favourable results from ‘Dizziness Handicap Inventory questionnaire’ were suggested by the small Sterckers and Vitte studies. These results were pooled without confirming the beneficial effect . Three studies were conducted against betahistine (Haguenauer, 1980; Kluyskens, 1990; Martini, 1990) to demonstrate a clinical benefit of trimetazidine in the treatment of dizziness. None of these three studies was predefined as non-inferiority study. Therefore, the results which were presented as supporting a similar efficacy than trimetazidine are not reliable. Thus, all of these elements deriving from post-approval data do not demonstrate a relevant clinical benefit of trimetazidine for patients suffering from tinnitus, dizziness or hearing loss.

In conclusion, the data submitted for trimetazidine with respect to ENT indications, insufficiently support the demonstration of a relevant clinical benefit for these patients suffering from tinnitus, vertigo or hearing loss symptomatology who were targeted by the ENT therapeutic indications as mentioned currently in the European marketing authorisations. The studies suggested limited methodology in the ENT field and do not confirm the current methodology of investigation by applying

the basic statistical principles of clinical trials methodology. Of the ten studies submitted, nine do not apply the relevant methodological principles currently required to demonstrate efficacy. Therefore, considering these methodological weaknesses, the dossier is insufficient to conclude that trimetazidine has satisfactorily demonstrated a clinical benefit as adjuvant symptomatic treatment of dizziness, tinnitus or hearing loss.

The CHMP concluded that the limited data generated by the clinical trials submitted for the ENT indication, insufficiently support the demonstration of a relevant clinical benefit of trimetazidine for patients suffering from tinnitus, vertigo or hearing loss and that either the currently ENT registered indication or the newly claimed indications cannot be supported.

Ophthalmology

In response to the CHMP's request regarding the re-evaluation of the risk/benefit ratio of trimetazidine (all forms and dosages) in its ophthalmologic indications, the clinical package submitted comprises of nine studies. Eight of them show inclusions of patients presenting very heterogeneous pathologies of various severities with absence of prior stratification on these pathologies, and short durations of treatment (between 2 and 6 months) while these pathologies are known to progress slowly and to require extended treatments. These pathologies lead ultimately to blindness. Most ophthalmologic trimetazidine clinical trials have been conducted with the 20 mg strength but in some studies the daily doses used (20mg and 40 mg/day) were lower than those recommended in the current marketing authorisation (60 mg or 70 mg), which is also a limit of these studies, particularly in documenting the safety at the registered dosage.

Among these nine studies, three were non-comparative studies (Guillaumat, 1982; Millara, 1988; Nowak, 2007); three were comparative studies of short duration (up to 3 months) conducted against products used at the time of these studies e.g. cinnarizine, piridoxilate which are no more considered as therapies of choice to treat or prevent retinal or glaucoma diseases by the ophthalmologists; two studies were conducted against placebo (Couderc, 1984 and Aron-Rosa, 1988). Finally, the most recent study using an appropriate methodology was submitted only for safety purpose as the efficacy objective was not reached (France ARMD 2, 2008).

The clinical studies supporting ophthalmic field suffer from major methodological flaws.

The non-comparative nature of three studies conducted in patients with heterogeneous ocular disorders, did not allow concluding to the existence of a clinical benefit.

The three studies of short duration (up to 3 months) conducted against reference products of the time (e.g cinnarizine, piridoxilate), included a small number of patients who presented very heterogeneous or poorly defined pathologies (n=19, n=24 and n=8 respectively for the Cornand (1982), Cordella (1982) and Perdriel (1988) studies). Furthermore, these studies present other specific weaknesses: the Cordella study (versus cinnarizine) did not include inter-group comparison. Furthermore, the multiplicity of comparisons was not taken into account in the statistical analyses and the criteria were not presented hierarchically, so this comparison cannot have any demonstrative value; and lastly, the Perdriel single dose electroretinographic study (versus pyridoxilate) used an injectable intravenous form of trimetazidine 20 mg that has not been authorised.

The most recent study conducted with trimetazidine 35 mg from 1999 (France, ARMD 2) related to a higher number of patients monitored for 3 to 5 years. Results from this study did not highlight any clinical benefit of trimetazidine in comparison to the placebo to prevent the bilateralisation of choroidal neovascularisation in patients suffering from age-related macular degeneration, principal criterion of

evaluation chosen to demonstrate the clinical benefit of trimetazidine 35 mg to slow the progression of age-related macular degeneration (ARMD).

Based on the data submitted for the ophthalmologic indications, the CHMP considered that the evidence does not fulfill the requirements and criteria for the evaluation of efficacy currently requested in these pathologies. The submitted data comparing TMZ to either placebo or the other reference products or based on cohorts without comparator provide insufficient demonstration of a relevant clinical benefit of trimetazidine in the ancillary treatment of visual acuity decrease and visual field disturbances due to vascular reasons. The CHMP concluded that following the assessment of all these studies the efficacy of trimetazidine is not proven on the ophthalmological indication.

SAFETY

A prescription study in France showed that trimetazidine was prescribed in patients in cardiovascular indications in 45.3% of cases, in ENT indications in 30% of cases and in ophthalmological indications in 0.4% of cases. In 24.3% of cases, the indication was unknown. Patients with a cardiovascular profile were significantly older (mean age: 74.8 years) than those with an ophthalmological and ENT profile (70.3 years and 63.5 years, respectively).

The main identified serious ADR is related to Parkinson syndrome and related symptoms. This risk has been identified in post marketing setting and in literature based on: positive dechallenge of Parkinson symptoms after the only withdrawal of TMZ, positive rechallenge, significant higher coprescription of antiparkinson drugs in TMZ group compared to control group (IMS study) and significant higher number of patients that begin antiparkinson drugs after the introduction of TMZ compared to control group (IMS study).

The most exposed population based on sales data, is patients aged more than 75 years old, and they received the treatment for very long periods mainly in cardiology indications.

The reporting rate of Parkinson's syndrome plausibly related to trimetazidine is stable over time since the last 8 years, despite the increase, since 2007, in the number of spontaneous reports of Parkinson's syndrome and related symptoms.

It is acknowledged that extrapyramidal symptoms reported in patients receiving TMZ have a low prevalence (incidence of 0.36/100,000 PY) and are generally reversible after TMZ withdrawal. However, some patients had symptoms only partially reversible after TMZ withdrawal, and the connection to TMZ in some cases of non-reversible symptoms cannot be ruled out.

Considering all currently available data, the CHMP concluded that trimetazidine-containing medicines should be contraindicated in patients with Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders. In addition, the SmPC has to be amended to include a warning about trimetazidine induced parkinsonism, its diagnosis and management. These changes are considered adequate to manage the risk of pakinsonian symptoms and tremors.

Elderly patients may have increased trimetazidine exposure due to age-related decrease in renal function. Population pharmacokinetics data indicate that serious adverse events were more frequent in treated elderly patients with high trimetazidine plasma concentrations. The Emeriau PK study has shown high plasma concentrations of trimetazidine in old patients, receiving the usual dose of 35 mg twice daily. Accordingly, the SmPC has been amended to include dose information in the elderly and in patients with moderate renal impairment (creatinine clearance [30-60] ml/min). In addition, a pharmacokinetics study was agreed with the MAH to investigate the effects of renal impairment and age on the trimetazidine safety profile.

Considering all currently available data, the CHMP concluded that trimetazidine-containing medicinal products should be contraindicated in patients with severe renal impairment (creatinine clearance < 30ml/min).

Some new potential, very rare and reversible adverse effects were highlighted during the referral procedure, including trombocytopenia, agranulocytosis and liver dysfunction and have been included in the risk management plan (RMP) and reflected in the relative sections of the SmPC.

The proposed multicentre, randomised, double-blind, placebo controlled long-term study in post-percutaneous coronary intervention (PCI) patients and the prospective and comparative cohort study to assess the prevalence of EPS in patients receiving trimetazidine may be adequate to solve the concerns on long-term efficacy and safety of trimetazidine.

A PASS study to address all important, potential and identified risks, particularly Parkinsonism, and a Drug utilization study to monitor whether the risk minimization measures put in place as results of the referral procedure are effective have been requested by the CHMP.

Overall conclusion

Overall, the CHMP concluded that after assessing the newly available data, the benefits continue to outweigh the risks in patients with angina pectoris but that treatment should be restricted to add-on to existing treatments in patients who are not adequately controlled by or intolerant to other medicines for angina pectoris. The new proposed wording in the angina pectoris indication is in accordance with the available efficacy and safety data assessed. For the remaining two indications of symptomatic treatment of tinnitus, vertigo and of visual field disturbances, the CHMP concluded that in view of the newly available safety data and very limited efficacy, the benefits no longer outweigh the risks under normal conditions of use and therefore these therapeutic indications should be removed.

In patients with moderate renal impairment (creatinine clearance [30-60] ml/min) the recommended dose has been added in the SmPC. Elderly patients may have increased trimetazidine exposure due to age-related decrease in renal function. Dose titration in elderly patients should be exercised with caution. Considering all the currently available data the CHMP concluded that the trimetazidine should be contraindicated in patients with Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders as well as in patients with severe renal impairment (creatinine clearance < 30ml/min).

The CHMP agreed that trimetazidine can cause or worsen parkinsonian symptoms (tremor, akinesia, hypertonia), which should be regularly investigated, especially in elderly patients. In doubtful cases, patients should be referred to a neurologist for appropriate investigations. The occurrence of movement disorders such as parkinsonian symptoms, restless leg syndrome, tremors, gait instability should lead to definitive withdrawal of trimetazidine. These cases have a low prevalence and are usually reversible after treatment discontinuation. The majority of the patients who recovered, had their symptoms disappeared within four months after trimetazidine withdrawal. If parkinsonian symptoms persist more than four months after drug discontinuation, a neurologist opinion should be sought. Caution should be exercised when prescribing trimetazidine to patients in whom an increased exposure is expected moderate due to renal impairment, or in elderly patients older than 75 years old.

The CHMP endorsed a communication, Direct Healthcare Professional Communication (DHPC), to communicate the outcome of the present review.

The CHMP also agreed on a study protocol to assess the effect of renal impairment and age on trimetazidine pharmacokinetics for the study to be conducted. A Post-Authorisation Safety Study (PASS

study) to address all important, potential and identified risks, particularly Parkinsonism and a drug utilization study to verify the compliance of prescribers regarding the restricted indication after marketing authorisation changes was also agreed.

Benefit –risk balance

Therefore, the Committee concluded that the benefit-risk balance of trimetazidine- containing medicinal products in the add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line antianginal therapies, remains positive under normal conditions of use, subject to the restrictions, warnings, changes to the product information, additional pharmacovigilance activities and risk minimisation measures agreed. For the remaining two indications of symptomatic treatment of tinnitus, vertigo and of visual field disturbances, the CHMP concluded that in view of the newly available safety data and very limited efficacy, the benefits no longer outweigh the risks under normal conditions of use and therefore these therapeutic indications should be removed.

Grounds for the variation to the terms of the marketing authorisation

Whereas

- The Committee considered the referral under Article 31 of Directive 2001/83/EC;
- The Committee reviewed all available submitted data from clinical studies, published literature and post-marketing experience on the safety of trimetazidine containing medicinal products, in particular with regards to the Parkinson syndrome and related events. The Committee concluded that trimetazidine is associated with the occurrence of Parkinson syndrome and related symptoms.
- The Committee also considered the cumulative efficacy and safety data submitted for the indications of the prophylactic treatment of attacks of angina pectoris, ancillary symptomatic treatment of vertigo and tinnitus and ancillary treatment of visual acuity decrease and visual field disturbances due to vascular reasons.
- The Committee is of the opinion that the benefits continue to outweigh the risks in patients with angina pectoris but that treatment should be restricted to add-on to existing treatments in patients who are not adequately controlled by or intolerant to other medicines for angina pectoris.
- For the indications of symptomatic treatment of tinnitus, vertigo and of visual field disturbances, the CHMP concluded that in view of the newly available safety data and very limited efficacy, the benefits no longer outweigh the risks under normal conditions of use and therefore these therapeutic indications should be removed.
- Considering all the currently available safety data the Committee concluded that trimetazidine should be contraindicated in patients with Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders as well as in patients with severe renal impairment (creatinine clearance < 30ml/min).
- The Committee also recommended that trimetazidine can cause or worsen parkinsonian symptoms (tremor, akinesia, hypertonia). The occurrence of movement disorders such as parkinsonian symptoms, restless leg syndrome, tremors, gait instability should lead to definitive withdrawal of trimetazidine. These cases have a low prevalence and are usually reversible after treatment discontinuation. Caution should be exercised when prescribing

trimetazidine to patients in whom an increased exposure is expected such as with moderate renal impairment and elderly patients older than 75 years old.

The Committee, therefore, concluded that the benefit-risk balance of trimetazidine- containing medicinal products remains positive under normal conditions of use, subject to the restrictions, warnings, changes to the product information, additional pharmacovigilance activities and risk minimisation measures agreed, only as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line anti-anginal therapies.

Annex III

Amendments to relevant sections of the summary of product characteristics and package leaflet

A. Summary of Products Characteristics

4.1 Therapeutic indications

[the currently approved indications should be deleted and replaced by the following]

Trimetazidine is indicated in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line antianginal therapies.

4.2 Posology and method of administration

[the wording below should be inserted]

The dose is one tablet of 20mg or 1 ml (20 drops) of oral drop solution of trimetazidine three times a day during meals.

The dose is one tablet of 35mg of trimetazidine twice daily during meals.

[...]

Special populations

Patients with renal impairment
In patients with moderate renal impairment (creatinine clearance [30-60] ml/min) (see sections 4.4 and 5.2), the recommended dose is 1 tablet of 20mg or 1 ml (20 drops) of oral drop solution twice daily, i.e., one in the morning and one in the evening during meals.

In patients with moderate renal impairment (creatinine clearance [30-60] ml/min) (see sections 4.4 and 5.2), the recommended dose is 1 tablet of 35mg in the morning during breakfast.

Elderly patients
Elderly patients may have increased trimetazidine exposure due to age-related decrease in renal function (see section 5.2). In patients with moderate renal impairment (creatinine clearance [30-60] ml/min), the recommended dose is 1 tablet of 20mg or 1 ml (20 drops) of oral drop solution twice daily, i.e., one in the morning and one in the evening during meals.
Dose titration in elderly patients should be exercised with caution (see section 4.4).

Elderly patients may have increased trimetazidine exposure due to age-related decrease in renal function (see section 5.2). In patients with moderate renal impairment (creatinine clearance [30-60] ml/min), the recommended dose is 1 tablet of 35mg in the morning during breakfast.
Dose titration in elderly patients should be exercised with caution (see section 4.4).

Paediatric population:
The safety and efficacy of trimetazidine in children aged below 18 years have not been established. No data are available.

[...]

4.3 Contraindications

[the currently approved contraindications should be deleted and replaced by the following]

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders,
- Severe renal impairment (creatinine clearance < 30ml/min).

4.4 Special warnings and precautions for use

[the wording below should be inserted]

[...]

Trimetazidine can cause or worsen parkinsonian symptoms (tremor, akinesia, hypertonia), which should be regularly investigated, especially in elderly patients. In doubtful cases, patients should be referred to a neurologist for appropriate investigations.

The occurrence of movement disorders such as parkinsonian symptoms, restless leg syndrome, tremors, gait instability should lead to definitive withdrawal of trimetazidine.

These cases have a low incidence and are usually reversible after treatment discontinuation. The majority of the patients recovered within 4 months after trimetazidine withdrawal. If parkinsonian symptoms persist more than 4 months after drug discontinuation, a neurologist opinion should be sought.

Falls may occur, related to gait instability or hypotension, in particular in patients taking antihypertensive treatment (see section 4.8).

Caution should be exercised when prescribing trimetazidine to patients in whom an increased exposure is expected:
- moderate renal impairment (see sections 4.2 and 5.2),
- elderly patients older than 75 years old (see section 4.2)

[...]

4.7 Effects on ability to drive and use machines

[the currently approved wording of this section should be deleted and replaced by the following]

Trimetazidine does not have haemodynamic effects in clinical studies, however cases of dizziness and drowsiness have been observed in post-marketing experience (see section 4.8), which may affect ability to drive and use machines.

4.8 Undesirable effects

[the wording below should be inserted]

[...]

System Organ Class	Frequency	Preferred Term
Nervous system disorders	Common	Dizziness, headache
	Not known	Parkinsonian symptoms (tremor, akinesia, hypertonia), gait instability, restlessleg syndrome, other related movement disorders, usually reversible after treatment discontinuation
	Not known	Sleep disorders (insomnia, drowsiness)
Cardiac disorders	Rare	Palpitations, extrasystoles, tachycardia

Vascular disorders	Rare	Arterial Hypotension , Orthostatic hypotension that may be associated with malaise, dizziness or fall, in particular in patients taking antihypertensive treatment, flushing
Gastrointestinal disorders	Common	Abdominal pain, diarrhoea, dyspepsia, nausea and vomiting
	Not known	Constipation
Skin and subcutaneous tissue disorders	Common	Rash, pruritus, urticaria.
	Not known	Acute generalized exanthematus pustulosis (AGEP), angioedema
General disorders and administration conditions	Common	Asthenia
Blood and lymphatic system disorders	Not known	Agranulocytosis Thrombocytopenia Thrombocytopenic purpura
Hepatobiliary disorders	Not known	Hepatitis

[...]

5.1 Pharmacodynamic properties

[the wording below should be inserted]

[...]

Mechanism of action

[...]

Trimetazidine inhibits β-oxidation of fatty acids by blocking long-chain 3-ketoacyl-CoA thiolase, which enhances glucose oxidation. In an ischaemic cell, energy obtained during glucose oxidation requires less oxygen consumption than in the β-oxidation process. Potentiation of glucose oxidation optimizes cellular energy processes, thereby maintaining proper energy metabolism during ischaemia.

Pharmacodynamic effects

In patients with ischaemic heart disease, trimetazidine acts as a metabolic agent, preserving the myocardial high-energy phosphate intracellular levels. Anti-ischemic effects are achieved without concomitant haemodynamic effects.

Clinical efficacy and safety

Clinical studies have demonstrated the efficacy and safety of trimetazidine in the treatment of patients with chronic angina, either alone or when the benefit from other antianginal medicinal products was insufficient.

In a 426-patients randomized, double blind, placebo-controlled study (TRIMPOL-II), trimetazidine (60mg/day) added to metoprolol 100mg daily (50 mg b.i.d) for 12 weeks significantly improved statistically exercise tests parameters and clinical symptoms as compared to placebo: total exercise duration +20.1s, p= 0.023, total workload +0.54 METs, p=0.001, time to 1-mm ST-segment depression +33.4s, p=0.003, time to onset of angina +33.9s, p<0.001, angina attacks/week -0.73, p=0.014 and short acting nitrates consumption/week, -0.63, p=0.032, without hemodynamic changes.

In a 223 patients randomized, double blind, placebo-controlled study (Sellier), one 35 mg trimetazidine modified release tablet (b.i.d.) added to 50 mg atenolol (o.d.) for 8 weeks produced a significant increase (+34.4s, p=0.03) in the time to 1-mm ST-segment depression in exercise tests, in a sub-group of patients (n=173), when compared to placebo, 12 hours after taking the drug. A significant difference was also evidenced for the time to onset of angina pectoris (p=0.049). No significant

difference between groups could be found for the other secondary endpoints (total exercise duration, total workload and clinical endpoints).

In a 1962 patients three-month randomised, double-blinded study (Vasco study) on top of atenolol 50 mg/d, two dosages of trimetazidine (70 mg/d and 140 mg/d) were tested versus placebo. In the overall population, including both asymptomatic and symptomatic patients, trimetazidine failed to demonstrate a benefit on both ergometric (total exercise duration, time to onset of 1mm ST and time to onset angina) and clinical endpoints. However, in the subgroup of symptomatic patients (n= 1574) defined in a post-hoc analysis, trimetazidine (140 mg) significantly improved total exercise duration (+23.8 s versus +13.1 s placebo; p=0.001) and time to onset of angina (+46.3 s versus +32.5 s placebo; p=0.005).

B. Package Leaflet

[the wording below should be inserted in the relevant sections]

1. What <invented name>is and what it is used for

This medicine is intended for use in adult patient, in combination with other medicines to treat angina pectoris (chest pain caused by coronary disease).

2. What you need to know before you take <invented name>

Do not take <invented name>
- if you are allergic to trimetazidine or any of the other ingredients of this medicine (listed in section 6),
- if you have a Parkinson disease: disease of the brain affecting movement (trembling, rigid posture, slow movements and a shuffling, unbalanced walk),
- if you have severe kidney problems.

Warnings and precautions

Talk to your doctor or pharmacist before taking <invented name>

[...]

This medicine can cause or worsen symptoms such as trembling, rigid posture, slow movements and a shuffling, unbalanced walk, especially in elderly patients, which should be investigated and reported to your doctor who could reassess the treatment.
[...]

Children and adolescents
<invented name> is not recommended in children aged below 18 years.

[...]

Pregnancy and breast-feeding
[...]

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
This medicine may make you feel dizzy and drowsy that may affect your ability to drive or use machinery.

3. How to take <invented name>

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose of <invented name> 20mg is one tablet to be taken three times a day during meals.

The recommended dose of <invented name> 20mg/ml solution is 20 drops to be taken three times a day during meals.

The recommended dose of <invented name> 35mg is one tablet to be taken two times a day during meals in the morning and evening.

If you have kidney problems or if you are older than 75 years old, your doctor may adjust the recommended dose.
[...]

4. Possible side effects

[...]
Common:
Dizziness, headache, abdominal pain, diarrhoea, indigestion, feeling sick, vomiting, rash, itching, hives and feeling of weakness.

Rare:
Fast or irregular heartbeats (also called palpitations), extra heartbeats, faster heartbeat, fall in blood pressure on standing-up which causes dizziness, light headiness or fainting, malaise (generally feeling unwell), dizziness, fall, flushing.

Not known:
Extrapyramidal symptoms (unusual movements, including trembling and shaking of the hands and fingers, twisting movements of the body, shuffling walk and stiffness of the arms and legs), usually reversible after treatment discontinuation.

Sleep disorders (difficulty in sleeping, drowsiness), constipation, serious generalised red skin rash with blistering, swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing.

Severe reduction in number of white blood cells which makes infections more likely, reduction in blood platelets, which increases risk of bleeding or bruising.
A liver disease (nausea, vomiting, loss of appetite, feeling generally unwell, fever, itching, yellowing of the skin and eyes, light coloured bowel motions, dark coloured urine).

If you get any side effects, talk to your doctor or pharmacist. This includes any side effects not listed in this leaflet.

Annex IV

Conditions to the marketing authorisations

Conditions to the marketing authorisations

National Competent Authorities (NCAs) of Member State(s) or Reference Member State(s) (RMS) where applicable, shall ensure that the following conditions are fulfilled by the MAH(s):

Conditions	**Date**
DHPC Communication circulation according to the CHMP agreed action plan and conditions.	Within 30 days after Commission Decision
Clinical/safety The MAH should perform a PK study assessing the effect of renal impairment and age on trimetazidine pharmacokinetics according to the CHMP agreed protocol. The final study results will be submitted to NCAs/RMS by:	30 September 2014.
PhV 1 The MAH should perform a drug utilization study to verify the compliance of prescribers regarding the restricted indication after marketing authorisation changes. The final study protocol will be submitted within 60 days from Commission decision to MSs/RMS to be finally agreed prior to starting the study. The final study report will be submitted to NCAs/RMS by:	30 September 2014
PhV 2 The MAH will perform a PASS study to address all important, potential and identified risks, particularly Parkinsonism. The full study protocol for the nested case-control study within the European Society of Cardiology cohort, to investigate the potential association between extrapyramidal symptoms (EPS) and trimetazidine will be submitted to the MSs/RMS within 60 days after Commission Decision to be finalised prior to starting the study. The final study report will be submitted to MSs/RMS by:	31 March 2015:pilot study 31 December 2016: main cohort (1 year results)