Cholestagel

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
IA/0055/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test	14/08/2024		SmPC, Annex II, Labelling and PL	

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	procedure B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)				
II/0053	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	16/05/2024	n/a		
IAIN/0052/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	13/11/2023	n/a		

IAIN/0051	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	03/11/2023		Annex II and PL	
IB/0050/G	This was an application for a group of variations. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	24/08/2023	n/a		
IA/0049/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	21/04/2023	n/a		

	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
IA/0048	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	03/05/2022	n/a		
IA/0047/G	This was an application for a group of variations. B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition) B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	18/03/2022	n/a		
IA/0046/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder	08/11/2021	n/a		

	or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.7 - Administrative change - Deletion of manufacturing sites				
PSUSA/864/202103	Periodic Safety Update EU Single assessment - colesevelam	28/10/2021	n/a		PRAC Recommendation - maintenance
T/0044	Transfer of Marketing Authorisation	29/03/2021	16/04/2021	SmPC, Labelling and PL	
N/0043	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/11/2020	16/04/2021	PL	
N/0042	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/02/2020	16/04/2021	PL	
IAIN/0041	A.1 - Administrative change - Change in the name and/or address of the MAH	13/12/2018	14/11/2019	SmPC, Annex II, Labelling and PL	
PSUSA/864/201803	Periodic Safety Update EU Single assessment - colesevelam	31/10/2018	n/a		PRAC Recommendation - maintenance
N/0039	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/12/2017	14/11/2019	PL	
IB/0038	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	30/06/2017	n/a		

IB/0037	C.I.3.a - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Implementation of wording agreed by the competent authority	05/04/2017	28/04/2017	SmPC, Labelling and PL	
IB/0036	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	26/01/2017	n/a		
N/0035	Update of the package leaflet with revised contact details of the local representatives for Bulgaria and Romania. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/12/2016	28/04/2017	PL	
PSUSA/864/201503	Periodic Safety Update EU Single assessment - colesevelam	08/10/2015	n/a		PRAC Recommendation - maintenance
II/0032	Update of section 4.8 of the SmPC in order to include intestinal obstruction as an adverse reaction following a review of the MAH pharmacovigilance database. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/12/2014	16/12/2015	SmPC and PL	Based on a review performed in the MAH pharmacovigilance database of all solicited and unsolicited cases of intestinal obstruction reported with colesevelam as a suspect drug, the safety signal on intestinal obstruction was identified and a change to the product information was considered necessary. Therefore section 4.8 of the SmPC and section 4 of the package leaflet for colesevelam have been updated to include intestinal obstruction as an adverse reaction.
II/0031/G	This was an application for a group of variations.	18/12/2014	16/12/2015	SmPC, Annex II, Labelling	Based on four new interaction studies it can be concluded that colesevelam affects the pharmacokinetics of

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data			and PL	olmesartan, metformin, glimepiride and glipizide when taken concomitantly. Co-administration of colesevelam and metformin extended release (ER) tablets increases the exposure of metformin. Colesevelam binds to glimepiride and reduces glimepiride absorption from the gastrointestinal tract. No interaction was observed when glimepiride was taken at least 4 hours before colesevelam. Co-administration of colesevelam and glipizide decreases the exposure of glipizide. In this group of variations the product information for colesevelam has been updated in order to include this safety information.
IA/0033	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	20/11/2014	n/a		
IG/0418	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	11/04/2014	n/a		
N/0029	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/11/2013	16/12/2015	PL	
N/0028	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/08/2013	16/12/2015	PL	
IG/0283	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/03/2013	n/a		

N/0026	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/07/2012	16/12/2015	PL	
N/0025	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/05/2012	16/12/2015	PL	
II/0024	Update of section 4.8 of the SmPC in order to update the safety information with adverse event of abdominal distension, dysphagia and pancreatitis. The Package Leaflet is updated in accordance. In addition, the list of local representatives in the Package Leaflet is updated. Furthermore, the PI is being brought in line with the QRD template version 8.0. The requested variation proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	19/01/2012	21/02/2012	SmPC, Annex II and PL	This variation concerns update of section 4.8 with safety information. Based on the assessment of PSUR #12 for Cholestagel, the MAH updated the SmPC to include abdominal distension. Furthermore, based on the provided cumulative overview of cases of pancreatitis and dysphagia, additional update of section 4.8 was agreed. The package leaflet was amended accordingly. The PI was also updated to bring it in line with the QRD template 8.0 and to include updated information on local representatives.
IA/0023	B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings	23/09/2011	n/a	SmPC and PL	
IA/0022	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	10/03/2011	n/a		

N/0021	The Marketing Authorisation Holder (MAH) has updated the package leaflet following a user testing. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/10/2010	n/a	SmPC and PL	
IB/0020	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	07/07/2010	n/a		
IA/0019	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	18/05/2010	n/a		
IB/0016	B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products	12/05/2010	n/a		
IA/0018	B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions	28/04/2010	n/a		
IA/0017	B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	28/04/2010	n/a		

II/0015	Update of Summary of Product Characteristics and Package Leaflet. This type II variation concerns an update of sections 4.2 and 4.5 of the SmPC, upon request by the CHMP following the assessment of PSUR 10, to add information on the posology of Cholestagel in relation to co-administered drugs in general and ursodeoxycholic acid in particular. The Package Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	18/02/2010	23/03/2010	SmPC and PL	The CHMP agreed to the proposed amendments to sections 4.2 and 4.5 of the SmPC to add information on the timing of Cholestagel intake at least four hours before or after concomitantly administered medication. With respect to the interaction with ursodeoxycholic acid, the SmPC was amended with a statement to take Cholestagel at least four hours after the intake of concomitant medicinal products. When a drug interaction cannot be excluded with a concomitant medicinal product for which minor variations in the therapeutic level would be clinically important, Cholestagel should be administered at least four hours before or at least four hours after the concomitant medication in order to minimize the risk of reduced absorption of the concomitant medication (see section 4.5). Cholestagel may affect the bioavailability of other medicinal products. Therefore when a drug interaction cannot be excluded with a concomitant medicinal product for which minor variations in the therapeutic level would be clinically important, Cholestagel should be administered at least four hours before or at least four hours after the concomitant medication to minimize the risk of reduced absorption of the concomitant medication. For concomitant medications which require administration via divided doses, it should be noted that the required dose of Cholestagel can be taken once a day. Ursodeoxycholic acid Cholestagel predominantly binds hydrophobic bile acids. In a clinical study Cholestagel did not affect the faecal excretion of endogenous (hydrophilic) ursodeoxycholic acid.

					However, formal interaction studies with ursodeoxycholic acid have not been performed. As noted in general, when a drug interaction cannot be excluded with a concomitant medicinal product, Cholestagel should be administered at least fours hour before or at least four hours after the concomitant medication to minimise the risk of reduced absorption of the concomitant medication. Monitoring of the clinical effects of
II/0014	Extention of indication, with the addition of Cholestagel as a third-line treatment option for patients with severe forms of primary hypercholesterolaemia who are not adequately controlled on the combination of a statin and ezetimibe, and the addition of Cholestagel as combination therapy with ezetimibe in patients with primary hypercholesterolaemia whom a statin is considered inappropriate or is not well-tolerated. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated. In addition, sections 4.2 and 5.1 were updated to include the information on the results of the clinical study conducted with children. Further, the MAH proposed to update section 4.5 of the SmPC with the information on the effect of Cholestagel on the bioavailability of lovastatin. The Package Leaflet has been amended accordingly. The MAH also took the opportunity to make some minor editorial changes to the annexes and to update the contact details of several local representatives in the Package Leaflet. In addition, the MAH has	18/02/2010	23/03/2010	SmPC, Annex II and PL	The Scientific discussion of the CHMP Assessment Report will be published.

	updated Annex II to include the version number of the latest Risk Management Plan (version 1.0) agreed with the CHMP. Extension of Indication				
N/0013	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/04/2009	n/a	PL	
R/0012	Renewal of the marketing authorisation.	22/01/2009	30/03/2009	SmPC, Annex II, Labelling and PL	The CHMP is of the opinion that the renewal can be granted with unlimited validity. Due to the recent launch of the product in Europe, the MAH should continue to submit 6 monthly PSURs unless otherwise decided by the CHMP.
II/0010	Update of Summary of Product Characteristics and Package Leaflet	20/11/2008	22/12/2008	SmPC and PL	The MAH submitted a type II variation to fulfil a follow-up measure (FUM 05) and consequenlty update Sections 4.4 and 4.5 of the SPC including new recommendations. Based on new clinical data from a healthy volunteer interaction study of Cholestagel with ciclosporin, the main updated information in Section 4.5 of the SPC reads as follows: "Based on theoretical grounds Cholestagel should be administered at least 4 hours after ciclosporin intake". The Package Leaflet has been updated accordingly.
II/0011	Changes in the manufacture of the finished product. Quality changes	23/10/2008	28/10/2008		
II/0008	Update of Summary of Product Characteristics and Package Leaflet	30/05/2008	09/07/2008	SmPC and PL	The applicant submitted results of 2 clinical studies. A clinical efficacy and safety study (WEL-403) examined combined treatment with colesevelam hydrochloride and fenofibrate in patients with hyperlipidaemia and a second

					clinical efficacy and safety study (WEL-408) examining combined treatment with colesevelam hydrochloride and ezetimibe in patients with primary hypercholesterolaemia. The CHMP agreed to update information in the SPC for the combination cholestagel with fenofibrate. However, it was not considered acceptable to update the SPC section 5.1 based on results from the combination with ezetimibe. The applicant was asked to reconsider this when results from the ongoing TRIPLE study become available.
II/0007	Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/04/2008	19/06/2008	SmPC, Labelling and PL	The MAH submitted eight healthy volunteer pharmacokinetics interaction studies between colesevelam hydrochloride and the following possible concurrent treatments: : fenofibrate, glyburide, levothyroxine, combined oral contraceptive pill (norethindrone / ethinylestradiol), pioglitazone, and repaglinide. Based on these studies, the CHMP agreed on amendments to sections 4.2, 4.4 and 4.5 of the SPC. Other minor wording amendments to sections 2, 4.6, 4.8 and 4.9 are introduced. In addition, amendments to the Annex IIIA and IIIB have been made to introduce QRD changes.
IA/0009	IA_28_Change in any part of primary packaging material not in contact with finished product	31/01/2008	31/01/2008	SmPC, Labelling and PL	
IA/0005	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	10/10/2007	n/a		
IA/0004	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	03/08/2007	n/a		

II/0002	Quality changes	21/06/2007	26/06/2007		
IB/0003	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	14/05/2007	n/a	Annex II and PL	
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/06/2005	n/a	Labelling	