



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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
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	

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).



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	<p>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.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	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	<p>This was an application for a group of variations.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	18/12/2014	16/12/2015	SmPC, Annex II, Labelling and PL	Based on four new interaction studies it can be concluded that colesevelam affects the pharmacokinetics of 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	<p>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.</p> <p>In addition, the list of local representatives in the Package Leaflet is updated.</p> <p>Furthermore, the PI is being brought in line with the QRD template version 8.0.</p> <p>The requested variation proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.</p> <p>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</p>	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	28/04/2010	n/a		

	or oral solutions				
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	<p>Update of Summary of Product Characteristics and Package Leaflet.</p> <p>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.</p> <p>Update of Summary of Product Characteristics and Package Leaflet</p>	18/02/2010	23/03/2010	SmPC and PL	<p>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.</p> <p>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).</p> <p>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</p>

					<p>which require administration via divided doses, it should be noted that the required dose of Cholestagel can be taken once a day.</p> <p>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 four hours 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</p>
II/0014	<p>Extension 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</p>	18/02/2010	23/03/2010	SmPC, Annex II and PL	The Scientific discussion of the CHMP Assessment Report will be published.

	<p>on the bioavailability of lovastatin. The Package Leaflet has been amended accordingly.</p> <p>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 updated Annex II to include the version number of the latest Risk Management Plan (version 1.0) agreed with the CHMP.</p> <p>Extension of Indication</p>				
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	<p>The CHMP is of the opinion that the renewal can be granted with unlimited validity.</p> <p>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.</p>
II/0010	Update of Summary of Product Characteristics and Package Leaflet	20/11/2008	22/12/2008	SmPC and PL	<p>The MAH submitted a type II variation to fulfil a follow-up measure (FUM 05) and consequently 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".</p> <p>The Package Leaflet has been updated accordingly.</p>

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	<p>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.</p> <p>The CHMP agreed to update information in the SPC for the combination cholestagel with fenofibrate.</p> <p>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.</p>
II/0007	Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/04/2008	19/06/2008	SmPC, Labelling and PL	<p>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.</p> <p>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</p>

					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	