alli

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
IB/0069/G	This was an application for a group of variations. B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits B.II.e.2.a - Change in the specification parameters	10/01/2023	n/a		

[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).

	and/or limits of the immediate packaging of the finished product - Tightening of specification limits 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.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.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.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.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation B.II.e.2.z - Change in the specification parameters				

	and/or limits of the immediate packaging of the finished product - Other variation B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation				
IB/0067/G	This was an application for a group of variations. 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 B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site 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.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor	06/12/2022	n/a		

	changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - 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 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.c.z - Change in control of excipients in the Finished Product - Other variation B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.III.1.b.2 - Submission of a new/updated or				

	deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved				

	manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material)				
IB/0068/G	This was an application for a group of variations. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	24/11/2022	n/a		
PSUSA/2220/ 202202	Periodic Safety Update EU Single assessment - orlistat	29/09/2022	n/a		PRAC Recommendation - maintenance
N/0065	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/12/2021		PL	
IB/0063	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting	12/11/2020	n/a		

	material/intermediate				
IA/0064	A.7 - Administrative change - Deletion of manufacturing sites	02/09/2020	n/a		
IB/0062/G	This was an application for a group of variations. 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 C.I.7.a - Deletion of - a pharmaceutical form	22/07/2020	01/07/2021	SmPC, Annex II, Labelling and PL	
PSUSA/2220/ 201902	Periodic Safety Update EU Single assessment - orlistat	03/10/2019	n/a		PRAC Recommendation - maintenance
II/0058	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	29/11/2018	n/a		
T/0059	Transfer of Marketing Authorisation	31/10/2018	26/11/2018	SmPC, Labelling and PL	
IA/0060/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) B.II.b.2.a - Change to importer, batch release	21/11/2018	n/a		

	arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place				
IB/0057	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	10/01/2018	n/a		
IB/0056	B.I.d.1.b.3 - Stability of AS - Change in the storage conditions - Change in storage conditions of the AS	16/08/2017	n/a		
R/0054	Renewal of the marketing authorisation.	21/04/2017	29/06/2017	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of alli in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IA/0055	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	24/04/2017	n/a		
PSUSA/2220/ 201602	Periodic Safety Update EU Single assessment - orlistat	02/09/2016	n/a		PRAC Recommendation - maintenance
II/0052	Submission of PASS study 204675 and a revised RMP in order to update the safety concerns, pharmacovigilance plan and risk minimisations measures. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing	01/04/2016	n/a		The requested variation proposed amendments to the Risk Management Plan (RMP). The MAH submitted the PASS study 204675 and a revised RMP in order to update the safety concerns, pharmacovigilance plan and risk minimisations measures.

	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				
PSUSA/2220/201502	Periodic Safety Update EU Single assessment - orlistat	24/09/2015	23/11/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2220/201502.
N/0051	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/07/2015	23/11/2015	PL	
IA/0050/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.7 - Administrative change - Deletion of manufacturing sites	19/05/2015	n/a		
IA/0048	A.7 - Administrative change - Deletion of manufacturing sites	16/04/2015	n/a		
IAIN/0047/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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	16/04/2015	28/05/2015	Annex II and PL	

	control/testing takes place 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 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				
IA/0046	A.7 - Administrative change - Deletion of manufacturing sites	05/02/2015	n/a		
PSUSA/2220/ 201402	Periodic Safety Update EU Single assessment - orlistat	11/09/2014	n/a		PRAC Recommendation - maintenance
IB/0045	C.I.3.z - 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 - Other variation	16/06/2014	28/05/2015	SmPC	
PSUSA/2220/ 201308	Periodic Safety Update EU Single assessment - orlistat	10/04/2014	n/a		PRAC Recommendation - maintenance
II/0042	Amendments of sections 4.4 and 4.5 of the Summary of Product Characteristics. The labelling and Package Leaflet are updated accordingly. C.I.4 - Variations related to significant modifications	23/01/2014	28/04/2014	SmPC, Annex II, Labelling and PL	Update of sections 4.4, and 4.5 of the SmPC in order to add a warning in case of concomitant use of orlistat with HIV medicinal products. This is based on reports from literature and post marketing experience. The Package Leaflet and Labelling are updated accordingly.

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet of Belgium, Luxembourg and the UK. Furthermore, the PI is being brought in line with the latest QRD template version 9.
N/0041	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/07/2013	28/04/2014	PL	
IG/0279	A.1 - Administrative change - Change in the name and/or address of the MAH	18/04/2013	28/04/2014	SmPC, Labelling and PL	
IG/0275	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/03/2013	n/a		
IA/0038/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	09/11/2012	n/a		
A20/0036	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 15 December 2011, the opinion of the CHMP on measures necessary to ensure the quality and the safe use of the above mentioned medicinal product further to the inspection findings at the manufacturing site Roche Carolina Inc. (RCI),	19/07/2012	24/09/2012		Please refer to the assessment report : EMEA/H/C/854/A-20/0036

	Florence, in the United States of America (USA), to assess the impact thereof on the risk-benefit balance of alli and to give its opinion whether the marketing authorisation of this product should be maintained, varied, suspended or withdrawn.				
R/0037	Renewal of the marketing authorisation.	19/04/2012	21/06/2012	SmPC, Annex II, Labelling and PL	Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of alli remains positive, but considers that its safety profile is to be closely monitored for the following reasons: • Very limited exposure data is available for the 27mg chewable tablet recently introduced. • The CHMP has requested 2 post marketing surveys, which have not been initiated or completed, to monitor the usage pattern and emerging safety profile. Based upon the safety profile of alli, the CHMP decided that the MAH should continue to submit 6-monthly PSURs. Therefore, based upon the safety profile of alli, which requires the submission of 6- monthly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
A20/0029	Article 20 Review Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested the CHMP to assess the risk of serious hepatotoxicity and its impact on the risk-benefit balance of all orlistat-containing medicinal products and to give its opinion on measures necessary to ensure the safe and	16/02/2012	13/04/2012	SmPC and PL	Please refer to the CHMP Assessment report for the Art 20 procedure on Alli EMEA/H/C/854/A-20/0029

	effective use of these products and on whether the marketing authorisations for these products should be maintained, varied, suspended or withdrawn.				
IA/0035/G	This was an application for a group of variations. B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site A.7 - Administrative change - Deletion of manufacturing sites	11/11/2011	30/01/2012	Annex II and PL	
IA/0034	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	12/10/2011	n/a		
IA/0033	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	15/09/2011	n/a		
IA/0032/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.c - Changes to an existing pharmacovigilance	09/09/2011	n/a		

	system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
IA/0031	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	06/09/2011	n/a		
II/0025	Further to CHMP request during assessment of the Environmental Risk Assessment (FUM004), the MAH has applied to update section 5.3 and 6.6 of the SmPC" and introduce consequential changes in the Package leaflet (Annex IIIB). Furthermore, the Annex II has been updated to remove the version number of the RMP. The list of local representatives in Annex IIIB has been also updated by the MAH. 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	23/06/2011	01/08/2011	SmPC, Annex II and PL	Further to CHMP request, an update of section 5.3 and 6.6 of the PI related to studies performed in relation to the environmental risk assessment is accepted. The following statement" The medicinal use of orlistat is unlikely to represent a risk to the aquatic or terrestrial environment. However, any possible risk should be avoided (see section 6.6)" is added to section 5.3 and "Any unused product or waste material should be disposed of in accordance with local requirements" added to section 6.6. The PIL is updated accordingly. In addition, annex II is updated to remove the version number of the RMP and the list of local representatives updated by the MAH.
IA/0028/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new or updated Ph. Eur.	07/07/2011	n/a		

	TSE Certificate of suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer				
N/0027	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/06/2011	n/a	Labelling and PL	
IA/0026/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	17/05/2011	n/a		
IB/0024	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	17/02/2011	17/02/2011	SmPC, Annex II, Labelling and PL	
X/0010	To add a new strength and pharmaceutical form of alli (alli 27 mg chewable tablets). Annex I_2.(c) Change or addition of a new strength/potency	23/09/2010	29/11/2010	SmPC, Labelling and PL	The MAH applied for a new strength (27 mg) and a new pharmaceutical form (chewable tablets) for alli that corresponds to less than half the strength of the current alli 60 mg capsule.

N/0023	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/08/2010	n/a	Labelling and PL	
IB/0022	B.I.c.z - Container closure system of the AS - Other variation	20/05/2010	n/a		
IB/0021	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	20/05/2010	n/a		
IA/0020	C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	18/05/2010	n/a		
IA/0019	C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities	18/05/2010	n/a		
IA/0018	C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV	18/05/2010	n/a	Annex II	
II/0011	To add an additional active substance manufacturing site, which uses different manufacturing conditions. B.I.a.1.c - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer uses a substantially different	22/04/2010	30/04/2010		

	route of synthesis or manufacturing conditions				
IB/0015	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	22/03/2010	22/03/2010	SmPC, Labelling and PL	
IA/0013	B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits	24/02/2010	n/a		
IA/0012	B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling	24/02/2010	n/a		
II/0009	Update of the Summary of Product Characteristics (sections 4.4. 4.5 and 4.8) to align the Product Information to the other orlistat medicinal containing product in relation to warnings on levothyroxine, antiepileptic interactions, hyperoxaluria/oxalate nephropathy and pancreatitis side effects at the CHMP request. Relevant sections of the Labelling and Package Leaflet have been amended accordingly. Update of Summary of Product Characteristics, Labelling and Package Leaflet	22/10/2009	24/11/2009	SmPC, Labelling and PL	Following review from spontaneous reporting, clinical trials and published literature in relation to possible interactions with levothyroxine and antiepileptics and the risk of pancreatitis and hyperoxaluria/oxalate nephropathy and taking into consideration data from the other orlistat containing medicinal product, the CHMP concluded the following: - Forty five cases of hypothyroidism and other thyroid disorders associated with alli were reported .In some cases, the time to onset of hypothyroidism typically occurs two weeks after initiation of orlistat therapy in a patient on long term levothyroxine treatment. This onset time of two weeks is likely related to the known slow response to levothyroxine dose changes as even the normal peak therapeutic effect of regular oral levothyroxine is not achieved for several weeks. In addition, two positive dechallenges upon orlistat withdrawal were reported. The

					CHMP recommended to add warnings in sections 4.4 and 4.5 to reflect that levothyroxine and orlistat may need to be taken at different times and the dose of levothyroxine may need to be adjusted due to possible decreased absorption of iodine salts and/or levothyroxine. - Twelve cases of convulsions were reported with alli including 3 suspected drug interactions between anticonvulsants and alli, and a positive rechallenge. In line with the other orlistat containing medicinal product, the CHMP therefore recommended to add warnings in sections 4.4 and 4.5 to reflect that monitoring for possible changes in the frequency and/or severity of convulsions should be considered when patients are concomitantly taking an antconvulsivant and orlistat due to possible decreased absorption of anticonvulsivants (such as valproate and lamotrigine). - Twenty three cases of pancreatitis were reported with alli. Although no causal relationship can be established in some of the cases due to confounding factors, 2 positive dechallenges were reported. The CHMP therefore recommended to include
II/0007	To add an alternative desiccant canister to be placed in the bottle. Change(s) to container	25/06/2009	06/07/2009		
IA/0008	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	06/05/2009	n/a		
IA/0006	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	01/04/2009	n/a		

IA/0005	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	23/03/2009	n/a		
IA/0004	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	23/03/2009	n/a		
IA/0003	IA_47_b_Deletion of a strength	23/03/2009	n/a	SmPC, Labelling and PL	
X/0001	Annex I_2.(c) Change or addition of a new strength/potency	18/12/2008	20/01/2009	SmPC, Labelling and PL	
IB/0002	IB_02_Change in the name of the medicinal product IA_39_Change/addition of imprints, bossing or other markings	12/09/2008	n/a	SmPC, Labelling and PL	