Xenical

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
IAIN/0078	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	12/12/2018		Annex II and PL	
IA/0077/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name	17/11/2017	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).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

	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.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 A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites				
T/0076	Transfer of Marketing Authorisation	05/04/2017	02/05/2017	SmPC, Labelling and PL	
IAIN/0075/G	This was an application for a group of variations. 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 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	15/03/2017	02/05/2017	SmPC, Annex II and PL	
PSUSA/2220/	Periodic Safety Update EU Single assessment - orlistat	02/09/2016	n/a		PRAC Recommendation - maintenance

201602					
N/0074	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/08/2016	02/05/2017	Labelling	
IG/0667/G	This was an application for a group of variations. 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.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)	08/04/2016	n/a		
IA/0071/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 or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	10/12/2015	n/a		

PSUSA/2220/ 201502	Periodic Safety Update EU Single assessment - orlistat	24/09/2015	19/11/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2220/201502.
IG/0573	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	01/07/2015	n/a		
IG/0497	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	18/11/2014	n/a		
PSUSA/2220/ 201402	Periodic Safety Update EU Single assessment - orlistat	11/09/2014	n/a		PRAC Recommendation - maintenance
IB/0066	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	12/06/2014	26/08/2014	SmPC, Labelling and PL	
IB/0065	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/04/2014	26/08/2014	SmPC, Labelling and PL	
PSUSA/2220/ 201308	Periodic Safety Update EU Single assessment - orlistat	10/04/2014	n/a		PRAC Recommendation - maintenance
IA/0063	B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms	21/08/2013	26/08/2014	SmPC and PL	
IG/0311	B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	28/06/2013	n/a		

IG/0228	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/11/2012	n/a		
A20/0059	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), Florence, in the United States of America (USA), to assess the impact thereof on the risk-benefit balance of Xenical and to give its opinion whether the marketing authorisation of this product should be maintained, varied, suspended or withdrawn.	19/07/2012	24/09/2012		Please refer to the assessment report : EMEA/H/C/154/A-20/0059
IA/0060	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	05/07/2012	n/a		
A20/0057	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	20/04/2012	SmPC and PL	Please refer to the CHMP Assessment report for Xenical Art 20 procedure EMEA/H/C/154/A-20/0057

	effective use of these products and on whether the marketing authorisations for these products should be maintained, varied, suspended or withdrawn.				
IG/0115/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	16/12/2011	n/a		
IB/0056/G	This was an application for a group of variations. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	07/07/2011	n/a		
IA/0055/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	02/05/2011	n/a	SmPC and PL	

	an already approved manufacturer 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 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				
IA/0054	A.7 - Administrative change - Deletion of manufacturing sites	31/03/2010	n/a		
II/0053	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SPC) to include safety information on hyperoxaluria and oxalate nephropathy and hypothyroidism. Section 4.5 of the SPC was also updated to include information on interactions with anticonvulsivants and update the information on interaction with amodiarone. Section 2 of the Package Leaflet was amended accordingly. Update of Summary of Product Characteristics and Package Leaflet	19/02/2009	25/03/2009	SmPC and PL	During the review of the renewal, the CHMP requested additional information on renal disorders, drug interactions involving levothyroxine, amiodarone and anticonvulsivants. Following the review of this additional information, the CHMP concluded that an update of the Product Information should be made in sections 4.4, 4.5 and 4.8 of the SPC. This variation application was submitted further to this request of the CHMP and the following information was added: - The use of orlistat may be associated with hyperoxaluria and oxalate nephropathy in patients with underlying chronic kidney disease and/or volume depletion; - Rare occurrence of hypothyroidism and/or reduced control of hypothyroidism may occur. The mechanism, although not proven, may involve a decreased absorption of iodine salts

					and/or levothyroxine; - Antiepileptics patient: Orlistat may unbalance anticonvulsivant treatment by decreasing the absorption of antiepileptic drugs, leading to convulsions. Convulsions have been reported in patients treated concomitantly with orlistat and antiepileptic drugs e.g. valproate, lamotrigine, for which a causal relationship to an interaction cannot be excluded. Therefore, these patients should be monitored for possible changes in the frequency and/or severity of convulsions. - Oxalate nephropathy as a postmarketing adverse event. Special warnings and precautions for use related to the concomitant use with amodiarone was also updated to reflect that the clinical relevance of the slight decrease in plasma levels of amiodarone, when given as a single dose, remains unknown but may become clinically relevant in some cases.
IA/0052	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	09/12/2008	n/a		
R/0050	Renewal of the marketing authorisation.	24/04/2008	17/06/2008	SmPC, Labelling and PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of Xenical continues to be favourable. Pancreatitis has been included as an adverse reaction in section 4.8 of the SPC and section 4 of the Package Leaflet.
IA/0049	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	19/12/2007	n/a		
IA/0047	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	05/11/2007	n/a	Annex II and PL	

II/0045	Change(s) to the test method(s) and/or specifications for the active substance	20/09/2007	27/09/2007		
N/0043	The Marketing Authorisation Holder (MAH) applied for the inclusion of the Romanian and Bulgarian local representatives in the Package Leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/05/2007	n/a	PL	
IA/0044	IA_09_Deletion of manufacturing site	19/03/2007	n/a		
IA/0042	IA_09_Deletion of manufacturing site	26/10/2006	n/a		
IA/0041	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	01/06/2006	n/a		
II/0039	Update of Summary of Product Characteristics (SPC) to include safety information regarding rectal bleeding and unintended pregnancy. Update of Summary of Product Characteristics, Labelling and Package Leaflet	27/04/2006	31/05/2006	SmPC, Annex II, Labelling and PL	Following cases of rectal haemorrhage/blood in stool and unintended pregnancy associated with Xenical, the CHMP performed a reassessment of the available data and requested the MAH to submit this type II variation to update the product information for Xenical in order to include this safety information. With regards to rectal haemorrhage/blood in stool, the following information was included in the product information: Section 4.4 of the SPC ("Cases of rectal bleeding have been reported with Xenical. Prescribers should investigate further in cases of severe and/or persistent symptoms") and Section 4.8 of the SPC ("Rarely cases of rectal bleeding, generally of mild intensity have been reported"). The package leaflet was amended accordingly.

					With regards to unintended pregnancy, the following information was included in the product information: Section 4.4 of the SPC (The use of an additional contraceptive method is recommended to prevent possible failure of oral contraception that could occur in case of severe diarrhoea (see Section 4.5)) and section 4.5 of the SPC (The absence of an interaction between oral contraceptives and orlistat has been demonstrated in specific drug-drug interaction studies. However, orlistat may indirectly reduce the availability of oral contraceptives and lead to unexpected pregnancies in some individual cases. An additional contraceptive method is recommended in case of severe diarrhoea (see Section 4.4)). The package leaflet was amended accordingly.
IA/0040	IA_39_Change/addition of imprints, bossing or other markings	16/03/2006	n/a	SmPC	
IA/0038	IA_01_Change in the name and/or address of the marketing authorisation holder	02/02/2006	n/a	SmPC, Labelling and PL	
IA/0037	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	22/07/2005	n/a		
II/0034	Update of section 5.1 of the SPC with data from a clinical trial in obese adolescent patients. Update of Summary of Product Characteristics, Labelling and Package Leaflet	21/04/2005	10/06/2005	SmPC, Labelling and PL	The section 5.1 of the SPC was updated with information from a multi-centre, parallel-group, double-blind, placebo-controlled study in 539 obese adolescent patients, randomised to receive either 120 mg orlistat (n=357) or placebo (n=182) three times daily as an adjunct to a hypocaloric diet and exercise for 52 weeks with a primary endpoint of change in body mass index (BMI) from baseline to the end of the study. The results were significantly

					superior in the orlistat group (difference in BMI of 0.86 kg/m2 in favour of orlistat). 9.5 % of the orlistat treated patients versus 3.3 % of the placebo treated patients lost = 10 % of body weight after 1 year with a mean difference of 2.6 kg between the two groups. The difference was driven by the outcome in the group of patients with = 5 % weight loss after 12 weeks of treatment with orlistat representing 19 % of the initial population. The side effects were generally similar to those observed in adults. However, there was an unexplained increase in the incidence of bone fractures (6 % versus 2.8 % in the orlistat and placebo groups, respectively).
N/0036	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/01/2005	n/a	Labelling	
II/0031	Update of sections 4.1 and 5.1 of the SPC removing the requirement that treatment with orlistat should only be started if diet alone has previously produced a weight loss of at least 2.5 kg over a period of 4 consecutive weeks, with the corresponding change to section 2 of the PL. In addition, the section 4.5 of the SPC was re-organised and the wording on the interaction with cyclosporine strengthened. Update of Summary of Product Characteristics and Package Leaflet	29/07/2004	15/09/2004	SmPC and PL	The section 4.1 of the SPC was updated to delete the pre-treatment 2.5 kg weight loss criterion while maintaining the second level of restriction, i.e. the >5% weight loss criterion at 12 weeks in the indication labelling.Clarification was provided in section 4.5 of the SPC on the recommendation for monitoring during concomittant use of cyclosporine with orlistat. Guidance was also provided on the lack of specific interactions observed in drug-drug interaction studies. The section 5.1 was updated to give more information on the results of the available analyses of the comparative (orlistat vs. placebo) long term response in patients either able or unable to loose at least 5 % of the body weight at 12 weeks.
IA/0035	IA_09_Deletion of manufacturing site	07/09/2004	n/a		

IA/0033	IA_09_Deletion of manufacturing site	06/08/2004	n/a		
N/0032	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/06/2004	n/a	PL	
II/0029	Update of sections 4.4, 4.5, 4.8 and 5.1 of the SPC and corresponding sections of the PL following completion of a clinical trial. Update of Summary of Product Characteristics and Package Leaflet	21/01/2004	02/03/2004	SmPC and PL	The SPC was updated with clinical data following the completion of a double-blind, placebo-controlled, randomised clinical trial (XENDOS study) Over 4 years, orlistat associated with diet significantly decreased body weight and BMI when compared to placebo. Consequently, the effect of orlistat with respect to the currently approved indication was adequately demonstrated over a long-time period. Data from the 4-year clinical trial showed 41% of the orlistat treated patients versus 21% of placebo treated patients lost 3 10% of body weight after 1 year with a mean difference of 4.4 kg between the two groups. After 4 years of treatment 21% of the orlistat treated patients compared to 10% of the placebo treated patients had lost 310% of body weight, with a mean difference of 2.7 kg.Data from the 4-year clinical trial also suggested that weight loss achieved with orlistat delayed the development of type 2 diabetes during the study (cumulative diabetes cases incidences: 3.4% in the orlistat group compared to 5.4% in the placebo-treated group). The great majority of diabetes cases came from the subgroup of patients with impaired glucose tolerance at baseline, which represented 21% of the randomised patients. It is not known whether these findings translate into long-term clinical benefits.
IB/0030	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	27/11/2003	n/a		

R/0027	Renewal of the marketing authorisation.	26/06/2003	08/10/2003	SmPC, Annex II, Labelling and PL	
II/0028	Update of Summary of Product Characteristics and Package Leaflet	26/06/2003	08/10/2003	SmPC and PL	
II/0026	Change(s) to shelf-life or storage conditions	22/05/2003	27/05/2003		
II/0025	Change(s) to the manufacturing process for the finished product	25/04/2003	02/05/2003		
II/0024	Update of Summary of Product Characteristics and Package Leaflet	21/11/2002	04/03/2003	SmPC and PL	
II/0019	Update of Summary of Product Characteristics and Package Leaflet	21/03/2002	20/06/2002	SmPC and PL	
I/0023	12_Minor change of manufacturing process of the active substance 24a_Change in test procedure for starting material/intermediate used in manuf. of active substance	11/01/2002	23/01/2002		
I/0022	12_Minor change of manufacturing process of the active substance	11/01/2002	23/01/2002		
I/0021	12_Minor change of manufacturing process of the active substance	11/01/2002	23/01/2002		
II/0018	Update of Summary of Product Characteristics	27/06/2001	31/10/2001	SmPC	

N/0020	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/07/2001	06/08/2001	PL	
I/0017	15a_Change in IPCs applied during the manufacture of the product	27/06/2001	04/07/2001		
I/0016	16_Change in the batch size of finished product	27/06/2001	04/07/2001		
I/0015	01_Change following modification(s) of the manufacturing authorisation(s)	27/06/2001	n/a	Annex II and PL	
II/0013	Update of Summary of Product Characteristics	25/01/2001	03/05/2001	SmPC	
II/0012	Update of Summary of Product Characteristics and Package Leaflet	25/01/2001	03/05/2001	SmPC and PL	
II/0011	Update of Summary of Product Characteristics and Package Leaflet	19/01/2000	11/05/2000	SmPC and PL	
II/0010	Update of Summary of Product Characteristics and Package Leaflet	29/07/1999	08/12/1999	SmPC and PL	
I/0009	12_Minor change of manufacturing process of the active substance	19/05/1999	25/05/1999		
I/0007	12a_Change in specification of starting material/intermediate used in manuf. of the active substance	13/05/1999	25/05/1999		
I/0005	24_Change in test procedure of active substance	13/05/1999	25/05/1999		

I/0008	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	16/04/1999	18/05/1999		
II/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) Update of Summary of Product Characteristics and Package Leaflet	27/01/1999	11/05/1999	SmPC and PL	
I/0006	15a_Change in IPCs applied during the manufacture of the product	31/03/1999	n/a		
I/0004	11_Change in or addition of manufacturer(s) of active substance	26/02/1999	05/03/1999		
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/03/1999	11/05/1999	Labelling	
I/0003	01_Change following modification(s) of the manufacturing authorisation(s)	13/01/1999	n/a		