Xultophy

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
II/0050	Update of section 4.8 of the SmPC in order to add Dizziness and Delayed gastric emptying to the list of adverse drug reactions (ADRs) with frequency common and unknown, respectively, based on the cumulative review of clinical studies data, post marketing data, class labels and biological	07/12/2023		SmPC, Labelling and PL	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).

	plausibility. The Package Leaflet is updated accordingly. In addition, the MAH took this opportunity to introduce editorial changes to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0049	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/06/2023		SmPC and PL	
PSUSA/10272 /202209	Periodic Safety Update EU Single assessment - insulin degludec / liraglutide	12/05/2023	n/a		PRAC Recommendation - maintenance
WS/2357	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	09/02/2023	n/a		
WS/2344	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.e.2 - Introduction of a post approval change management protocol related to the AS	12/01/2023	n/a		
WS/2303/G	This was an application for a group of variations	24/11/2022	n/a		

	following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.4.e - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of an in-process test which may have a significant effect on the overall quality of the AS B.I.a.4.e - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of an in-process test which may have a significant effect on the overall quality of the AS				
WS/2298/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Please refer to the Recommendations section B.I.a.4.e - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of an in-process test which may have a significant effect on the overall quality of the AS B.I.a.4.e - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of an in-process test which may have a significant effect on the overall quality of the AS	17/11/2022	n/a		Not applicable
IB/0043	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a	14/02/2022	n/a		

	biological/immunological medicinal product				
IAIN/0042	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	27/01/2022	n/a		
WS/2063	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.c.3.a.2 - Change in source of an excipient or reagent with TSE risk - From TSE risk material to vegetable or synthetic origin - For excipients or reagents USED in the manufacture of a biol/immunol AS or in a biol/immunol medicinal product	10/06/2021	n/a		
WS/1997	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	11/03/2021	n/a		
IAIN/0039	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	30/09/2020	n/a		
WS/1901	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	24/09/2020	22/09/2021	SmPC, Annex II, Labelling and PL	

	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
WS/1865	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	03/09/2020	n/a		Not applicable
WS/1841	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	02/07/2020	n/a		
II/0034	Update of section 4.2 of the SmPC in order to change the wording "transfer from basal insulin" to "transfer from any insulin regimen that includes a basal insulin component", and to modify the current recommendation of a starting dose of 16 dose steps to a more flexible wording allowing for individual variation of the starting dose, based on data from study NN9068-4184 (DUAL II Japan: A double-blinded trial comparing the efficacy and safety of insulin degludec/liraglutide and insulin degludec both in combination with metformin in Japanese subjects	26/03/2020	04/05/2020	SmPC, Annex II, Labelling and PL	Although limited, the data raise no concerns regarding efficacy when transferring from pre-mix/combination insulin therapies. Hypoglycaemic events were more frequent among subjects switching from pre-mix insulin than switching from basal insulin, but this appears to be related to the further up-titration of the dose. In order to minimise the risk of hypoglycaemias at the time of transfer, individual patient characteristics needs be taken into consideration. Therefore, the current recommendation in the SmPC of a starting dose of 16 dose steps has been amended to reflect the fact that although the

	with type 2 diabetes mellitus inadequately controlled with basal or pre-mix/combination insulin therapy and oral anti-diabetic drugs) as well as data from the post-marketing setting. In addition, the MAH took the opportunity to make a minor correction in SmPC section 5.1 and to implement changes in the annexes in accordance with QRD template 10.1. The MAH provided an updated RMP version 9.0 as part of the application. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				recommended starting dose should not be exceeded, it may need to be reduced to avoid hypoglycaemia in selected cases. The benefit-risk balance of Xultophy, remains positive.
PSUSA/10272 /201909	Periodic Safety Update EU Single assessment - insulin degludec / liraglutide	17/04/2020	n/a		PRAC Recommendation - maintenance
WS/1669	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	07/11/2019	n/a		
IAIN/0033	C.I.12 - Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	11/10/2019	04/05/2020	SmPC and PL	

WS/1635	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	25/07/2019	n/a		
WS/1615	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.z - Quality change - Active substance - Other variation	11/07/2019	n/a		
R/0028	Renewal of the marketing authorisation.	26/04/2019	08/07/2019	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Xultophy in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10272 /201809	Periodic Safety Update EU Single assessment - insulin degludec / liraglutide	11/04/2019	n/a		PRAC Recommendation - maintenance
WS/1478	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	14/02/2019	n/a		

II/0026	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/09/2018	08/07/2019	SmPC	
IB/0025	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	06/07/2018	n/a		
II/0023	Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to include information based on cardiovascular outcomes studies conducted a for each of the monocomponents of Xultophy: LEADER (Liraglutide Cardiovascular Outcomes Trial) and DEVOTE (Insulin Degludec Cardiovascular Outcomes Trial). Section 5.1 was also re-organised to improve reader friendliness. The RMP version 7.0 has also been approved. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	26/04/2018	07/06/2018	SmPC	Please refer to Scientific Discussion 'Xultophy-H-C-002647-II-0023
PSUSA/10272 /201709	Periodic Safety Update EU Single assessment - insulin degludec / liraglutide	12/04/2018	n/a		PRAC Recommendation - maintenance
PSUSA/10272 /201703	Periodic Safety Update EU Single assessment - insulin degludec / liraglutide	26/10/2017	n/a		PRAC Recommendation - maintenance
WS/1222	This was an application for a variation following a	12/10/2017	07/06/2018	SmPC,	The medicine must not be drawn from the cartridge of the

	worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2, 4.4 and 6.6 of the SmPC and relevant sections of the labelling and PL to minimise the potential risk of medication error as requested by the PRAC in the course of a signal assessment (EPITT ref. No. 18893). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data			Labelling and PL	pre-filled pen into a syringe. A new needle must always be attached before each use. Needles must not be re-used. The re-use of insulin pen needles increases the risk of blocked needles, which may cause under- or overdosing. In the event of blocked needles, patients must follow the instructions described in the instructions for use accompanying the package leaflet. The above warnings do not apply to the cartridge presentations of the medicine.
II/0021	Update of section 5.1 of the SmPC in order to reflect data for transfer from insulin glargine U100 to Xultophy as compared to a basal-bolus regimen. The update is based on data from the clinical trial NN9068-4185: A clinical trial comparing efficacy and safety of insulin degludec/liraglutide (IDegLira) versus basal-bolus therapy in subjects with type 2 diabetes mellitus. The MAH has taken the opportunity to make minor editorial and formatting changes throughout the Annexes. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/09/2017	07/06/2018	SmPC, Labelling and PL	
II/0019	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	20/07/2017	n/a		

II/0017	Update of section 4.2 of the SmPC in order to update the information on use of Xultophy in patients with hepatic impairment, based on clinical trial NN2211-1328, the LEAD 1-6 meta-analysis as well as other liraglutide trials. In addition, 'fatigue' has been added to the tabulated list of adverse reactions in Section 4.8 of the SmPC. The Package Leaflet is updated accordingly. RMP version 6.0 has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10. The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/05/2017	13/07/2017	SmPC, Annex II, Labelling and PL	SmPC section 4.2 Posology and method of administration was changed to reflect data obtained from clinical trial NN2211-1328 (a single-centre, open-label trial investigating the pharmacokinetics and the safety profile after a single dose of liraglutide in subjects with hepatic impairment and in subjects with normal hepatic function), the LEAD 1-6 meta-analysis as well as other liraglutide trials. The Posology section now clarifies that "Xultophy can be used in patients with mild or moderate hepatic impairment. Glucose monitoring is to be intensified and the dose adjusted on an individual basis. Due to the liraglutide component, Xultophy is not recommended for use in patients with severe hepatic impairment."
PSUSA/10272 /201609	Periodic Safety Update EU Single assessment - insulin degludec / liraglutide	18/05/2017	13/07/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10272/201609.
PSUSA/10272 /201603	Periodic Safety Update EU Single assessment - insulin degludec / liraglutide	10/11/2016	09/01/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10272/201603.

IB/0015	B.I.a.z - Change in manufacture of the AS - Other variation	24/10/2016	n/a		
PSUSA/10272 /201509	Periodic Safety Update EU Single assessment - insulin degludec / liraglutide	14/04/2016	n/a		PRAC Recommendation - maintenance
II/0012	Update of sections 4.2 and 5.2 of the SmPC in order to updated posology and pharmacology information in type 2 diabetes patients with moderate renal impairment and update of the risk management plan (version 4). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/01/2016	24/02/2016	SmPC	In a 26-week clinical trial, patients with type 2 diabetes and moderate renal impairment (CrCL 30-59 mL/min) had 26% lower liraglutide exposure when compared with a separate trial including patients with type 2 diabetes with normal renal function or mild renal impairment. When Xultophy is used in patients with mild or moderate renal impairment, glucose monitoring is to be intensified and the dose adjusted on an individual basis.
IA/0011	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	23/10/2015	24/02/2016	SmPC	
II/0009	Update of section 5.1 of the SmPC based on the results from 26-week trial assessing efficacy and safety of Xultophy compared to insulin glargine in patients with type 2 diabetes mellitus inadequately controlled on insulin glargine and metformin. Consequently, sections 4.4 and 4.8 of the SmPC have also been updated. Additionally, information on storage conditions (SmPC section 6.4) has also been revised. The Package Leaflet and RMP are updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to	22/10/2015	24/02/2016	SmPC and PL	In this variation the MAH updated the PI with information from open label, 26-week study comparing Xultophy to insulin glargine, both given once daily to patients with type 2 diabetes mellitus inadequately controlled on insulin glargine (20-50 units) and metformin. 54.3% of patients treated with Xultophy reached the HbA1c target of <7% without confirmed hypoglycaemic episodes compared to 29.4% of patients treated with insulin glargine (odds ratio 3.24, p<0.001 confirming statistical significance). The rate per patient year of exposure (percentage of patients) of severe hypoglycaemia was 0.00 (0 patients out of 278) for Xultophy and 0.01 (1 patient out of 279) for insulin

	new quality, preclinical, clinical or pharmacovigilance data				glargine. The rate of nocturnal hypoglycaemic events was statistically significantly lower with Xultophy compared to insulin glargine (estimated treatment ratio 0.17, p<0.001).
PSUSA/10272 /201503	Periodic Safety Update EU Single assessment - insulin degludec / liraglutide	08/10/2015	n/a		PRAC Recommendation - maintenance
WS/0778	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/09/2015	24/02/2016	SmPC	
II/0002	Extension of indication to include the transfer of patients from Glucagon-Like peptide-1 (GLP1) receptor agonist (RA) treatment to Xultophy. Consequently, sections 4.1, 4.2, 4.4, and 5.1 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to include the assigned ATC-code in section 5.1 of the SmPC and to make minor editorial changes in the SmPC. The application included a revised RMP (edition 2.0, version 1.0). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	21/05/2015	25/06/2015	SmPC and PL	Please refer to the Scientific Discussion 'Xultophy-H-C-2647-II-02'.
IB/0008	B.II.h.z - Adventitious Agents Safety - Other variation	24/06/2015	n/a		

II/0001/G	This was an application for a group of variations. B.II.a.3.b.3 - Changes in the composition (excipients) of the finished product - Other excipients - Change that relates to a biological/immunological product B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.f.1.c - Stability of FP - Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol	26/03/2015	25/06/2015	SmPC, Labelling and PL	
IB/0004	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	10/03/2015	n/a		
IB/0006	B.I.a.z - Change in manufacture of the AS - Other variation	27/02/2015	n/a		
IB/0005	B.I.b.z - Change in control of the AS - Other	28/01/2015	n/a		

	variation				
IB/0003	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	28/01/2015	n/a		