Lyxumia

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
N/0043	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/07/2023		PL	
IB/0041	B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF	12/05/2023	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).

WS/2418	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the SmPC in order to cholelithiasis and cholecystitis to the list of adverse drug reactions (ADRs) with frequency (uncommon). The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor 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	04/05/2023		SmPC and PL	The Product Information is updated to add cholelithiasis and cholecystitis to the list of adverse drug reactions (ADRs) with frequency uncommon. For more information, please refer to the Summary of Product Characteristics.
IA/0040/G	This was an application for a group of variations. 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.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	03/03/2023	n/a		
T/0038	Transfer of Marketing Authorisation	12/12/2022	10/01/2023	SmPC, Labelling and PL	

IA/0037/G	This was an application for a group of variations. B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS 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.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	08/12/2022	n/a		
IAIN/0036	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	22/09/2022	10/01/2023	SmPC and PL	To update section 4.8 of the SmPC and section 4 of the PL to implement the wording agreed by the PRAC following the outcome of the PSUSA procedure EMEA/H/C/PSUSA/00010577/202111.
IA/0035	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder	11/02/2022	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				
N/0034	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/12/2021	10/01/2023	PL	
II/0033	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	02/09/2021	n/a		
IB/0032	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	24/02/2021	26/11/2021	SmPC	
II/0030	Submission of the final report from study TDR14311 listed as a category 3 study in the RMP, and submitted in accordance with article 46. This is a Randomized, double-blind, placebo-controlled, dose escalation, study on safety, pharmacokinetics and pharmacodynamics of lixisenatide in paediatric patients with Type 2 diabetes mellitus not adequately controlled with metformin and/or basal insulin. The RMP version 6.0 has also been submitted. Furthermore, the MAH took the opportunity to make editorial changes in the SmPC (sections 4.2 and 5.1). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	10/12/2020	26/11/2021	SmPC	

N/0031	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/10/2020	26/11/2021	PL	
IG/1282	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	15/09/2020	n/a		
PSUSA/10017 /202001	Periodic Safety Update EU Single assessment - lixisenatide	04/09/2020	n/a		PRAC Recommendation - maintenance
IA/0028/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 B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	11/05/2020	n/a		
N/0026	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/02/2020	26/11/2021	PL	
IB/0025/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.c.1.z - Change in immediate packaging of the AS - Other variation	16/07/2019	n/a		

N/0024	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/05/2019	26/11/2021	PL	
R/0023	Renewal of the marketing authorisation.	20/07/2017	18/09/2017	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 Lyxumia in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10017 /201701	Periodic Safety Update EU Single assessment - lixisenatide	01/09/2017	n/a		PRAC Recommendation - maintenance
IA/0021	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	14/03/2017	18/09/2017	SmPC	
II/0020	Submission of the final clinical study report for study EFC12382, a randomized double-blind, placebo-controlled, 2 arm parallel group, multicentre study with a 24-week treatment period to assess the efficacy and safety of lixisenatide in patients with Type 2 Diabetes Mellitus patients insufficiently controlled with basal insulin or without metformin, in order to fulfil MEA 004. In addition the MAH took the opportunity to update the RMP (version 4.0) accordingly. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	15/12/2016	n/a		

II/0019	Submission of the final clinical study report for a non-interventional PASS: a retrospective database study to estimate the incidence rates of acute pancreatitis, pancreatic and thyroid cancer among adult Type 2 Diabetes Mellitus patients treated with GLP-1 receptor agonists or a DPP4-inhinitor drug versus patients treated with other anti-diabetics, a category 3 study in order to fulfil MEA 007.2. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	15/12/2016	n/a		
PSUSA/10017 /201601	Periodic Safety Update EU Single assessment - lixisenatide	02/09/2016	n/a		PRAC Recommendation - maintenance
IA/0018	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	24/06/2016	n/a		
II/0014	Update of sections 4.2, 4.4, 5.1 and 5.2 of the SmPC in order to update the safety information on Older Patients with Type 2 Diabetes Mellitus Inadequately Controlled on their Current Diabetes Treatment Regimen and on Patients with renal impairment following submission of study EFC12703 in fulfilment of MEA 006. In addition, an updated RMP was submitted (finally agreed version 3.1).	01/04/2016	02/05/2016	SmPC	The efficacy and safety of lixisenatide in people aged ≥70 years with type 2 diabetes was evaluated in a double-blind, placebo-controlled study of 24 weeks duration (study GetGoal-O). Frail patients, including patients at risk for malnutrition, patients with recent cardiovascular events and patients with moderate to severe cognitive impairment were excluded. A total of 350 patients were randomized (randomization ratio 1:1, 176 patients randomised to lixisenatide). Overall, 37% of the patients were ≥75 years

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				old (N=131, 62 patients randomised to lixisenatide) and 31% had moderate renal impairment (N=107). Patients received stable dose(s) of oral antidiabetic drug(s) (OAD) and/or basal insulin as background therapy. Sulfonylureas or glinides were not used with basal insulin as background therapy. Lixisenatide provided significant improvements in HbA1c (-0.64% change compared to placebo; 95% CI: -0.810% to -0.464%; p<0.0001), from a mean baseline HbA1c of 8.0%. In addition, a double-blind, placebo-controlled cardiovascular outcome study (ELIXA) enrolled 6,068 type 2 diabetes patients with previous acute coronary syndrome (3,034 randomised to lixisenatide, including 198 patients ≥75 years of age and 655 patients with moderate renal impairment). Data from the GetGoal-O and ELIXA study indicate that the risks associated with lixisenatide treatment in the geriatric population (including patients>75 years) and the population with moderately increased renal function are not considerably increased compared with the risk associated with this treatment in the overall diabetic population.
II/0013	Update of sections 4.4 and 5.1 of the SmPC in order to update information on patient with congestive heart failure following submission of final study report for study EFC11319 (ELIXA) in fulfilment of MEA 001. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives for Hungary, Italy and Lithuania in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to	01/04/2016	02/05/2016	SmPC and PL	The ELIXA study was a randomized, double-blind, placebo-controlled, multinational study that evaluated cardiovascular (CV) outcomes during treatment with lixisenatide in patients with type 2 diabetes mellitus after a recent Acute Coronary Syndrome. Overall, 6068 patients were randomized 1:1 to either placebo or lixisenatide 20 mcg (following a starting dose of 10 mcg during the first 2 weeks). Ninety-six percent of the patients in both treatment groups completed the study in accordance with the protocol and

	new quality, preclinical, clinical or pharmacovigilance data				the vital status was known at the end of the study for 99.0% and 98.6% of the patients in the lixisenatide and placebo group, respectively. Median treatment duration was 22.4 months in the lixisenatide group and 23.3 months in the placebo group, and the median duration of study follow-up was 25.8 and 25.7 months, respectively. Mean HbA1c (±SD) in the lixisenatide and placebo groups was 7.72 (±1.32)% and 7.64 (±1.28)% at baseline and 7.46 (±1.51)% and 7.61 (±1.48)% at 24 months, respectively. As a whole, the ELIXA study seems well conducted and the main goal of Study EFC11319, to exclude that lixisenatide treatment confers an unacceptable increase (>30%) in cardiovascular risk, was achieved. Moreover, no other unexpected safety issues emerged from this study.
IB/0016/G	This was an application for a group of variations. B.I.z - Quality change - Active substance - Other variation 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 B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	19/01/2016	n/a		
II/0015	B.II.b.3.b - Change in the manufacturing process of the finished or intermediate product - Substantial changes to a manufacturing process that may have a	14/01/2016	n/a		

	significant impact on the quality, safety and efficacy of the medicinal product				
II/0012	Update of section 5.1 of the SmPC in order to update information regarding efficacy and safety of lixisenatide in comparison to that of insulin glulisine once daily and insulin glulisine three times daily in patients with Type 2 diabetes insufficiently controlled with insulin glargine with or without metformin. The data derives from study EFC12626, object of MEA 005. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives for Romania and Italy in the Package Leaflet and to bring the PI in line with the latest QRD template version 9.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/09/2015	02/05/2016	SmPC, Annex II and PL	Patients with type 2 diabetes with basal insulin combined with 1-3 oral anti-diabetic agents were enrolled in an open-label randomised study for insulin intensification. After 12-week of optimal insulin glargine titration with or without metformin, inadequately controlled patients were randomised to add single dose of lixisenatide or a single dose (QD) of insulin glulisine (both before the largest meal) or insulin glulisine administered three times a day (TID) for 26 weeks. The level of HbA1c reduction was comparable between groups. As opposed to both insulin glulisine treatment regimens, lixisenatide reduced body weight. The rate of symptomatic hypoglycaemic events was lower with lixisenatide (36%) compared to insulin glulisine QD and TID (47% and 52%, respectively).
PSUSA/10017 /201501	Periodic Safety Update EU Single assessment - lixisenatide	10/09/2015	n/a		PRAC Recommendation - maintenance
IA/0011/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 B.II.e.7.b - Change in supplier of packaging	11/06/2015	n/a		

	components or devices (when mentioned in the dossier) - Replacement or addition of a supplier				
PSUSA/10017 /201407	Periodic Safety Update EU Single assessment - lixisenatide	12/02/2015	n/a		PRAC Recommendation - maintenance
IA/0009	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	16/12/2014	n/a		
II/0007	Update of section 5.1 of the SmPC in order to mention a recently completed randomized, active comparator-controlled phase 2 study (PDY12625). In addition, the MAH took the opportunity to update section 2 of the SmPC to correct a typo on the content of metacresol and to update the Instructions for Use (IFU) of the Product Information with minor editorial changes. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/10/2014	15/10/2015	SmPC and PL	The effect of lixisenatide on post prandial glucose was confirmed in a 4 week study versus liraglutide 1.8 mg once a day in combination with metformin. Reduction from baseline in the AUC(0:30-4:30 h) of plasma glucose after a test meal was: -12.61 h*mmol/L (-227.25 h*mg/dl) in the lixisenatide group and -4.04 h*mmol/L (-72.83 h*mg/dl) in the liraglutide group. This was also confirmed in an 8 week study versus liraglutide, administered before breakfast, in combination with insulin glargine with or without metformin.
PSUV/0005	Periodic Safety Update	11/09/2014	n/a		PRAC Recommendation - maintenance
IG/0454	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	17/07/2014	n/a		
II/0004	Update of SmPC sections 4.2 and 5.1 to change the	26/06/2014	22/10/2014	SmPC and PL	In a 24 week open label study, lixisenatide administered

	recommended timing of administration of lixisenatide based on the results of Study EFC12261. The Package Leaflet has been updated accordingly. The Post-Authorisation Measure - MEA 003 - is considered addressed with the submission. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				before the main meal of the day was non inferior to lixisenatide administered before breakfast in terms of HbA1c reduction (LS mean change from baseline: -0.65% versus -0.74%). Similar HbA1c decreases were observed regardless of which meal was the main meal (breakfast, lunch or dinner). At the end of the study, 43.6% (main meal group) and 42.8% (breakfast group) of patients achieved an HbA1c less than 7%. Nausea was reported in 14.7% and 15.5% of patients, and symptomatic hypoglycaemia in 5.8% and 2.2% of patients, main meal group and breakfast group, respectively. Therefore, the product information has been revised to reflect that Lyxumia can be administered once daily, within the hour prior to ANY meal of the day. It is preferable that the prandial injection of Lyxumia is performed before the same meal every day, when the most convenient meal has been chosen. If a dose of Lyxumia is missed, it should be injected within the hour prior to the next meal.
II/0003	Update of product SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/06/2014	22/10/2014	SmPC, Annex II and PL	The application proposes an update of section 4.4 of the SmPC in order to implement the recommendations of an Art 5(3) procedure on GLP-1-based therapies and pancreatic safety. The PL is proposed to be updated accordingly. The opportunity is also taken to update the list of the local representatives (from Finland, Malta, Sweden, United Kingdom) in the PL and to correct an inconsistency between the PL and the SmPC by including injection site reactions in the section 4 of the PL to reflect the information provided in the section 4.8 of the SmPC. Additionally, updates to comply with the latest QRD template (version 9.0) are proposed. An update of the RMP

					is also proposed.
PSUV/0002	Periodic Safety Update	05/02/2014	n/a		PRAC Recommendation - maintenance
IA/0001	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	04/10/2013	22/10/2014	SmPC	