Glyxambi

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/0046	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	13/04/2022		SmPC and PL	To update section 4.5 of the SmPC and section 2 of the PL to add the drug-drug interaction empagliflozin and lithium and to update section 4.8 of the SmPC and section 4 of the PL to add the adverse reaction tubulointerstitial nephritis with a frequency 'very rare'.

[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).

IG/1501	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	13/04/2022	n/a		
WS/2223/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. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing 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 C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	07/04/2022	n/a		
WS/2171	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To update section 4.8 of the SmPC and section 4 of the PL to include the side effect 'constipation'. In addition, the following ADR have been updated in section 4.8: - for Glyxambi: 'Necrotising fasciitis of the perineum (Fournier´s gangrene)' from 'not known' to 'rare';	24/03/2022		SmPC and PL	

	'Volume depletion', to add a footnote to indicate that studies with empagliflozin in patients with heart failure showed a higher frequency of volume depletion (‘very common’) in patients with heart failure where half of the patients had type 2 diabetes mellitus. - for Synjardy: 'Necrotising fasciitis of the perineum (Fournier´s gangrene)' from ‘not known’ to ‘rare’; 'Angioedema' from ‘not known’ to ‘uncommon’; 'Volume depletion', to add a footnote to indicate that studies with empagliflozin in patients with heart failure showed a higher frequency of volume depletion (‘very common’) in patients with heart failure where half of the patients had type 2 diabetes mellitus. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
IB/0044/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.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	22/02/2022	n/a		
WS/2200	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	10/02/2022		SmPC	To update sections 4.2, 4.4 and 5.1 of the SmPC to propose a modification of the eGFR threshold in the EU PIs for the fixed dose combinations containing empagliflozin, for

	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				Synjardy® (empagliflozin/metformin) and Glyxambi® (empagliflozin/linagliptin) to allow for use of these empagliflozin containing products in patients with T2DM and high cardiovascular risk and an eGFR of ≥30 ml/min/1.73 m2.
R/0039	Renewal of the marketing authorisation.	20/05/2021	16/07/2021	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 Glyxambi in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10539 /202011	Periodic Safety Update EU Single assessment - empagliflozin / linagliptin	10/06/2021	n/a		PRAC Recommendation - maintenance
IB/0036/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.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	22/02/2021	n/a		
IG/1329	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	22/01/2021	n/a		
IB/0035	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	21/12/2020	n/a		

IB/0033/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.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site 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.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.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	28/10/2020	16/07/2021	Annex II, Labelling and PL	
IG/1286/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	19/10/2020	n/a		

	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.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer				
WS/1780	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 4.4. of the SmPC for Jardiance, Synjardi and Glyxambi in the SmPC subsection `Diabetic ketoacidosis' to reflect new data from 2 phase III interventional studies (EASE-2 1245.69 and EASE-3 1245.72) from the clinical trial program of empagliflozin as an adjunct to insulin in patients with type 1 diabetes. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	04/09/2020	15/10/2020	SmPC	Section 4.4. of the SmPC, subsection 'Diabetic ketoacidosis' reflects the increased risk of diabetic ketoacidosis observed for empagliflozin as an adjunct therapy for patients with T1DM. For more information, please refer to the Summary of Product Characteristics.

IB/0032	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	17/07/2020	15/10/2020	SmPC and PL	
WS/1835	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.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	02/07/2020	n/a		
WS/1807	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 4.5 of the SmPC, in order to add interaction information on interference with the 1,5-anhydroglucitol assay in line with the Company Core Data Sheet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/06/2020	15/10/2020	SmPC	Monitoring glycaemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors. Use of alternative methods to monitor glycaemic control is advised.
PSUSA/10539 /201911	Periodic Safety Update EU Single assessment - empagliflozin / linagliptin	11/06/2020	n/a		PRAC Recommendation - maintenance
IA/0031	A.5.b - Administrative change - Change in the name	28/05/2020	n/a		

	and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)				
IG/1239/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.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	20/04/2020	n/a		
WS/1696/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. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved	16/01/2020	n/a		

	manufacturer 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 B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.b.z - Change in control of the AS - Other variation 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.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.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of				

	a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised 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 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 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				
IAIN/0024	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/11/2019	15/10/2020	SmPC	
WS/1601	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2 and 5.1 of the Trajenta SmPC, update of sections 4.2, 4.4 and 5.1 of the Jentadueto SmPC and section 5.1 of the Glyxambi SmPC, based on the final results from study 1218.74 (CAROLINA study) listed as a category 3 study in the RMP of	31/10/2019	15/10/2020	SmPC and PL	The MAH updated sections 4.2 and 5.1 of the Trajenta SmPC, sections 4.2, 4.4 and 5.1 of the Jentadueto SmPC and section 5.1 of the Glyxambi SmPC, based on the final results from study 1218.74 (CAROLINA study). The double-blind parallel group CAROLINA study evaluated the cardiovascular safety of linagliptin versus glimepiride as adjunct to standard care therapy in patients with type 2 diabetes and with increased CV risk. A total of 6033 patients were treated (linagliptin 5 mg: 3023, glimepiride 1

	Jentadueto and Trajenta, in order to fulfil Trajenta MEA 008.1 and Jentadueto MEA 001.1; this is a phase III randomized, parallel group, double blind study to evaluate Cardiovascular safety of linagliptin versus glimepiride in patients with type 2 diabetes mellitus at high cardiovascular risk. The Package Leaflet for Trajenta is updated accordingly. The RMP version 13.1 for Jentadueto and Trajenta and version 5.1 for Glyxambi have also been submitted. In addition, the Worksharing applicant (WSA) took the opportunity to make corrections throughout the product information for Glyxambi and Jentadueto and to make corrections to the Bulgarian, French, Swedish translations for Glyxambi. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				mg to 4 mg: 3010) and followed for a median of 6.25 years. The mean age was 64 years, the mean HbA1c was 7.15 %, and 60 % were male. Approximately 19 % of the population had an eGFR <60 mL/min/1.73 m2. The study was designed to demonstrate non-inferiority for the primary cardiovascular endpoint which was a composite of the first occurrence of cardiovascular death or a non-fatal myocardial infarction (MI) or a non-fatal stroke (3P-MACE). Linagliptin did not increase the risk of the combined endpoint of CV death, non-fatal myocardial infarction or non-fatal stroke (MACE-3) [Hazard Ratio (HR)=0.98; (95 % CI 0.84, 1.14); p<0.0001 for non-inferiority], when added to standard of care in adult patients with type 2 diabetes with increased CV risk compared to glimepiride.
WS/1626/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. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	25/07/2019	n/a		
PSUSA/10539	Periodic Safety Update EU Single assessment -	14/06/2019	n/a		PRAC Recommendation - maintenance

/201811	empagliflozin / linagliptin				
WS/1563/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. B.I.b.1.h - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a specification parameter as a result of a safety or quality issue 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	28/03/2019	n/a		
IG/1077	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	14/03/2019	n/a		
WS/1461	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 , 4.8 and 5.1 of the SmPC to update the warnings related to acute pancreatitis	14/03/2019	06/06/2019	SmPC	The SmPC sections 4.4, 4.8 and 5.1 have been updated to reflect the results of CARMELINA study on acute pancreatitis and bullous pemphigoid and on the efficacy and safety information of linagliptin. CARMELINA study evaluated the cardiovascular and renal safety of linagliptin 5 mg once daily versus placebo as adjunct to standard care

	and bullous pemphigoid and the efficacy and safety information based on final results from study listed as a category 3 in the RMP "A multicenter, international, randomized, parallel group, double blind, placebo-controlled CArdiovascular Safety & Renal Microvascular outcomE study with LINAgliptin, 5 mg once daily in patients with type 2 diabetes mellitus at high vascular risk (CARMELINA)". The RMP have also been updated accordingly for all products (Trajenta and Jentadueto version 12.1, Glyxambi version 4.1) and to be in accordance with the revision 2 of the RMP template. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				therapy in patients with type 2 diabetes and with increased cardiovascular risk evidenced by a history of established macrovascular or renal disease.
IAIN/0020	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/02/2019	06/06/2019	SmPC and PL	
WS/1469	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.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	17/01/2019	n/a		
PSUSA/10539 /201805	Periodic Safety Update EU Single assessment - empagliflozin / linagliptin	29/11/2018	n/a		PRAC Recommendation - maintenance

IAIN/0014	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	03/08/2018	06/06/2019	SmPC	
PSUSA/10539 /201711	Periodic Safety Update EU Single assessment - empagliflozin / linagliptin	14/06/2018	n/a		PRAC Recommendation - maintenance
IG/0935	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	06/06/2018	n/a		
WS/1316	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	31/05/2018	06/06/2019	SmPC and PL	The SmPC was updated to include additional information from trial 1245.25 (EMPA-REG OUTCOME study). In section 4.8 of Jardiance and Synjardy, changes in eGFR associated with empagliflozin treatment were described. In SmPC section 5.1 of the SmPC for Jardiance, Synjardy and Glyxambi, the effect size of risk reduction in renal and heart failure- related endpoints was added, and in SmPC section 4.4 the statement regarding diabetic ketoacidosis for SGLT-2 inhibitors was aligned. The package leaflet was amended accordingly.
PSUSA/10539 /201705	Periodic Safety Update EU Single assessment - empagliflozin / linagliptin	30/11/2017	n/a		PRAC Recommendation - maintenance

WS/1164	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing 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	30/11/2017	n/a		
WS/1201/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. 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.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 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	14/09/2017	n/a		

	material/intermediate				
WS/1173	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.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	13/07/2017	n/a		
II/0005/G	This was an application for a group of variations. C.I.1.a - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a Union referral procedure - The product is not covered by the defined scope of the procedure C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/06/2017	16/03/2018	SmPC and PL	Changes introduced are based on clinical data from the monocomponents of this fixed dose combination. Sections 4.2, 4.4, 4.5, 4.8, 5.1 of the SmPC were updated with data from the trial 1245.25, which analysed the effect of the empagliflozin component of Glyxambi on cardiovascular outcomes in patients with T2DM and high cardiovascular risk. The adverse drug reaction 'thirst' was added with a frequency of common based on post-marketing data from empagliflozin. Several minor changes to the SmPC were added to align with changes introduced for the SmPCs of Jardiance/Synjardy (empagliflozin) and Trajenta/Jentadueto (linagliptin). Section 4.4 was also updated to add a warning on the risk of lower limb amputations of SGLT2 inhibitors as follows: an increase in cases of lower limb amputation (primarily of the toe) has been observed in ongoing long-term clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot-care.

WS/1162	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	01/06/2017	16/03/2018	SmPC	
WS/1135	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	01/06/2017	16/03/2018	SmPC	
IG/0798/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 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	05/05/2017	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites				
WS/1140	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/03/2017	16/03/2018	SmPC and PL	
IG/0771/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 A.7 - Administrative change - Deletion of manufacturing sites 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	19/01/2017	n/a		

	the AS -replacement or addition of a site where batch control/testing takes place				